A Review on Current Trends and Future Prospectives of Electrospun Biopolymeric Nanofibers for Biomedical Applications

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Abstract

Electrospinning (ES) is considered the most advanced and robust method to make nanoscale materials named nanofibers (NFs) using various polymers. However, due to the hazardous and toxic nature of petroleum based polymers, the trend has shifted toward biopolymers. Conventional techniques to fabricate NFs are nonreproducible, require tedious procedures, and most incorporate toxicity to the final product. ES gained tremendous momentum as it is a crucial solution to the drawbacks of conventional methods. In recent years much prepondering research and review work has been done on ES applications. However, the present paper does not cliche the routine reporting format by review papers in recent years. Instead, it highlights the ignored significant parameters especially solvent related in current research responsible for underutilizing ES and new innovative ES methods. The current review signifies ES's crucial necessity for biomedical applications compared to conventional methods with similar biocomposites. A systematic review of the literature was done to correlate those parameters with the present work to find the gap in the existing literature. The present review is significant in providing a helpful tool to improve further the properties of the NFs biocomposites by ES methods. Significant missing correlations were identified, which, if considered in the future, can drastically improve the future of ES applications.

Keywords

Biopolymers; Electrospinning; Nanofibers; Nanocomposites; Smart polymers

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1. Introduction

The word "biopolymer" is a derivative of the word "polymer," which means "made from" and "bio", meaning "living" hence biopolymers are molecules created by living organisms composed of linear or branching chains of monomeric components such as nucleic acids, saccharides, and amino acids [20]. The primary characteristics of biopolymers include sustainability, low toxicity, biodegradability, ease of availability, and affordability [23, 24], and they are considered green replacements for petroleum-based polymers [25]. Developing cutting-edge technologies that use bio-based materials to lessen reliance on fossil fuels is paramount. They find significant use in ophthalmology, healthcare, horticulture, textiles, paper products, and auto manufacturing [26, 27].

However, increased interest has recently been seen in fabricating biopolymers based nanofibers (NFs) since the fibers have exceptional properties like a high surface area to volume ratio, increased porosity, and controllable morphology (Fig. 2). There are various ways to create nanofibers such as phase separation [28], island in the sea [29], drawing [30, 31], template synthesis [32], and self-assembly [33, 34]. However, ES gained massive momentum in recent years as it is a low-cost, versatile, and quick way to make nanofibers from a wide range of bulk starting materials [35]. The major merits and demerits of various techniques compared to ES are mentioned in Table 1. Biopolymeric nanofibers find their applications majorly in the biomedical field, especially in drug delivery [27], wound healing [36], and tissue engineering [37].

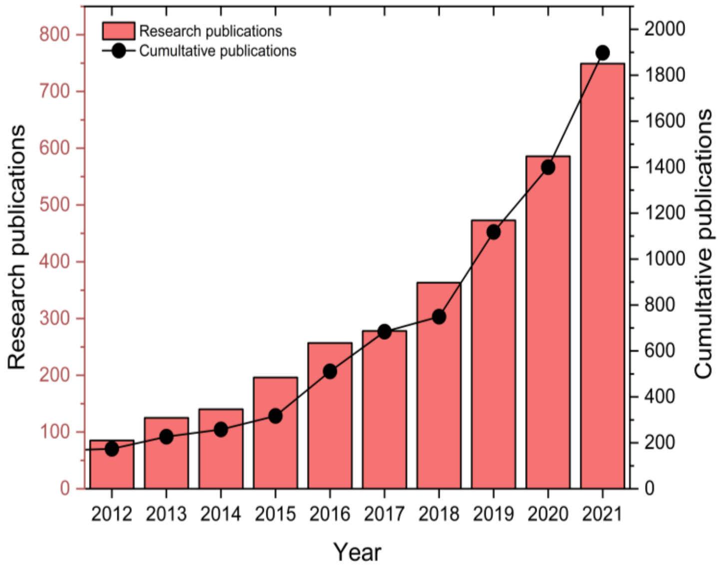


Fig. 1 Researched and cumulative number of publications in ScienceDirect platform in the last decade (2012-21) by using keywords: nanofibers AND biopolymers

Table 1. Major issues with the conventional nanofibers fabrication methods

Methods	**Drawbacks**	**Electrospinning technique merits**	**References**
Drawing method	Results in discontinuous fibers and cannot be used to produce continuous fibers	The electrospinning technique can produce continuous nanofibers	[38]
Template synthesis	This technique lacks the nanofiber diameter control and can produce fibers only with some specific diameters	It gives the control to produce a wide range of diameter nanofibers	[39]
Phase separation method	This method produces fibers only of some specific polymers	It provides the flexibility of combining various biopolymers	[40]
Self-assembly method	The rate of production for this method is relatively slow	The electrospinning technique is rapid in producing nanofibers	[41]

ES was first explained in 1899 and used to fabricate continuous fibers. The growing interest in technology may be traced back to the 1980s but has accelerated in the last decade [42]. The basic ES setup consists of a high-voltage DC power source, a conductive grounded collector, and a syringe (also called a spinneret) [43] (Fig. 2). ES utilizes electrostatic forces to transform a liquid input into ultrafine fiber structures that can dry quickly at ambient temperature during the process. ES is considered a low-cost method for producing dried fibers [44]. The dope (polymer solution to be fabricated) is supplied through a spinneret at a constant, regulated flow rate, this fundamental working of an ES setup [45]. A taylor cone is formed (the cone shape attained by the polymer solution above thresh hold voltage at the jet's origin), and a liquid jet emerges from the cone if the electrostatic forces are strong enough to overcome the surface tension, which causes them to take on fiber like structure; the large surface area of the fibers, typically in submicron size, causes the solvent to evaporate instantly (Fig. 2) [46].

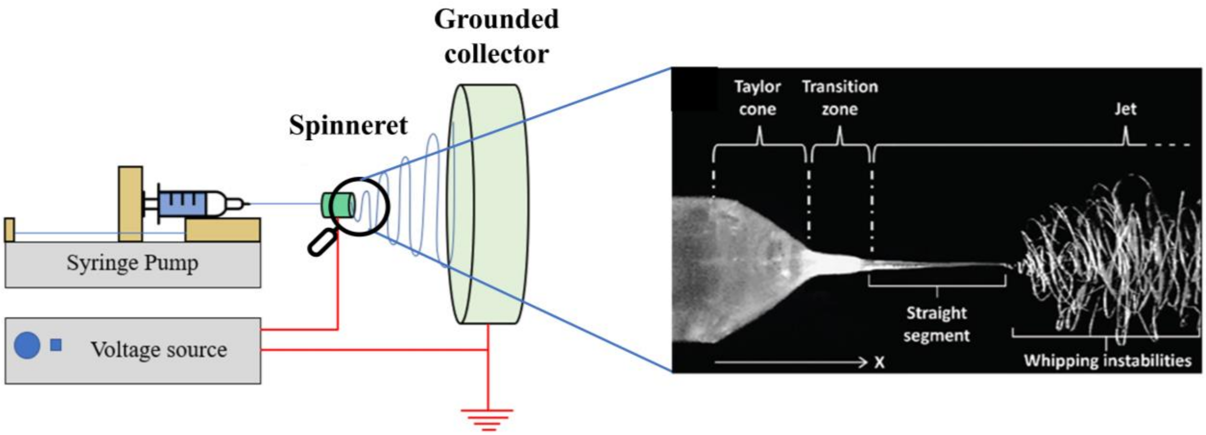


Fig. 2 Basic setup for the electrospinning process (traditional electrospinning)

Since the harmful effects of petroleum-based polymers and their products like carbon foot printing, global warming, and environmental pollution, scientists are looking to make biopolymers based products of all types [47]. ES of biopolymer finds its application in almost all aspects of life as improved goods may be made by combining the inherent features of biopolymers with the fascinating nano-effects provided by ES [48]. However, despite so many advantages, the ES is also a complex process and depends on various parameters for NFs fabrication [49]. The significant parameters are processing, solvent, and ambient which drastically affect the properties, especially the morphology of the NFs. However, significant parameters are mostly ignored or not considered while designing the NFs fabrication in recent years for biomedical applications. These parameters are crucial since morphology is the function of applications [50].

Regardless of the immense work in the field of ES, the major parameters crucial to the fabrication of nanofibers are being ignored and resulting in the hindrance of making generalized methods of ES techniques [51]. Generally, three main parameters of voltage, flow rate, and needle distance are being considered in the current literature. This practice also results in the underutilization of the technique; if the major parameters are considered, it can unlock the full potential of ES. This review highlights the major parameters of the ES procedure being ignored by the researchers, especially the solvent properties like dielectric constant and some innovative ES methods like yarn base NF and radial ES [52]. Furthermore, it also highlights the crucial role of ES in various bio medical applications (wound healing, drug delivery, and tissue engineering) by comparing the properties of the same composition biocomposites fabricated by different methods with nanofibers and how the ES technique itself imparts exceptional properties to the biopolymeric composites.

2. Electrospinning Methods

When it comes to making fibrous materials, ES is among the most popular and diverse methods. Fiber diameter, alignment, volume distribution, and permeability may be adjusted using ES [49]. It is also a low-cost option that does not need specialized equipment [53]. Continuous manufacture of submicron-diameter fibers is possible using ES technology. With the right collector type, complex 3D scaffolds could be created [54]. A significant drawback of ES is consistently replicating the process and the final product after every batch. The process depends on various parameters making it a complex process [55]. Even under identical circumstances, polymers fluidity, electrical conductivity, and other critical characteristics and solutions change throughout ES, causing batch variability [56]. Beads and droplets, low reproducibility, or a total absence of solution spinnability may occur from an unoptimized process [57, 58]. The commonly used ES methods include: traditional electrospinning (TES), wet electrospinning (WES), melt electrospinning (MES), coaxial electrospinning (CAES), tri-axial electrospinning (TAES), multi-needle electrospinning (MNES), and needleless electrospinning (NES). Major ES methods are described in detail in the following sections.

2.1 Basic single needle setup

Three fundamental components required for the primary ES to operate are a powerful voltage power source, an electrical spinneret, and a spinning collector (Fig. 2). This setup may be positioned vertically or horizontally with little effect on the use of setup and the final shape of the fibers [59]. At a steady rate, the polymer in solution form is expelled from an electrospinning needle via a pump. The needle's electric charge attracts charged ions in the polymer solution to the electrode with the opposite charge [60]. After that, a stream of polymer solution is pumped into the grounded collector. Following the operation, the solvent is evaporated, and the fibers are formed [61-63].

The primary issue with the basic configuration is that a small portion of the jet flows in a straight line near the taylor cone, and the jet experiences bending instability, which causes it to spiral in a lateral direction [64]. The spiral loop diameter increases as the jet diameter decrease with each loop. Consequently, the bending instability of the jet plays a crucial role in reducing the width of the fibers [65]. However, if the solvent is non-volatile or the separation between the tip and collector is too short, the solvent may accumulate on the collector's surface [66]. In these cases, it is vital to dry the fiber before use [59]. The major advantages and disadvantages of single needle electrospinning are listed in Table. 2.

Table. 2 Merit and demerits of single needle electrospinning

Advantages	References	Disadvantages	References
1. The presence of a single needle makes the process simple and less complex	[67]	1. Low throughput and time consuming. The setup cannot be used for industrial level	[68]
2. Indeed, the most studied form of electrospinning hence easier to work with new materials	[69]	2. There is a lack of complex structure with smooth morphology in the resultant nanofibers, so in the case of drug delivery, it results in an initial burst and cannot be used for sustained drug delivery	[70]
3. Due to simpler design modifications at any point of the process, especially at the collector end, are easy to make	[71]	3. The overall network of the resultant nanofibers has a highly compact fibrous network because of prolonged fabrication and is not suitable for mammalian cell culture	[72]

One of the major aims of ES is to deliver therapeutics. For this purpose, various polymers or drugs and polymers are mixed in various ratios. A polymer matrix is often used to encase the medication in this manner [73]. Blend electrospinning (BES) has worked effectively with various biological molecules, including antibiotics [74], probiotics [75], anti-inflammatory agents [76], and proteins [77]. It is also an optimal way to create materials for delivering microbiological molecules. So, a sustained DD using electrospun fibers highly depends on the polymer and biomolecule composition [78]. However, the primary issue regarding BES is that the bioactive therapeutics may lose their bioactivity due to the organic solution composition and electric environment during fabrication [79].

Emulsion electrospinning (EES) is advantageous as it combines BES and emulsification. Biomolecules and surfactants are combined to create an emulsion of water and oil, spun to produce NFs using a single-nozzle method [80]. Since, the emulsion is composed of two or more distinct liquid phases, the polymer solutions have a variety of liquid phases [81]. This technology uses a continuous phase to construct the fiber coating in ES, while a droplet phase is used to construct the inner fiber [82].

2.2 Wet electrospinning

The prominent feature of WES is the presence of a coagulation bath for the collection rather than the dry collector (Fig. 3). This type of ES works best when the solvent used for spinning dope is more non-volatile [83, 84].

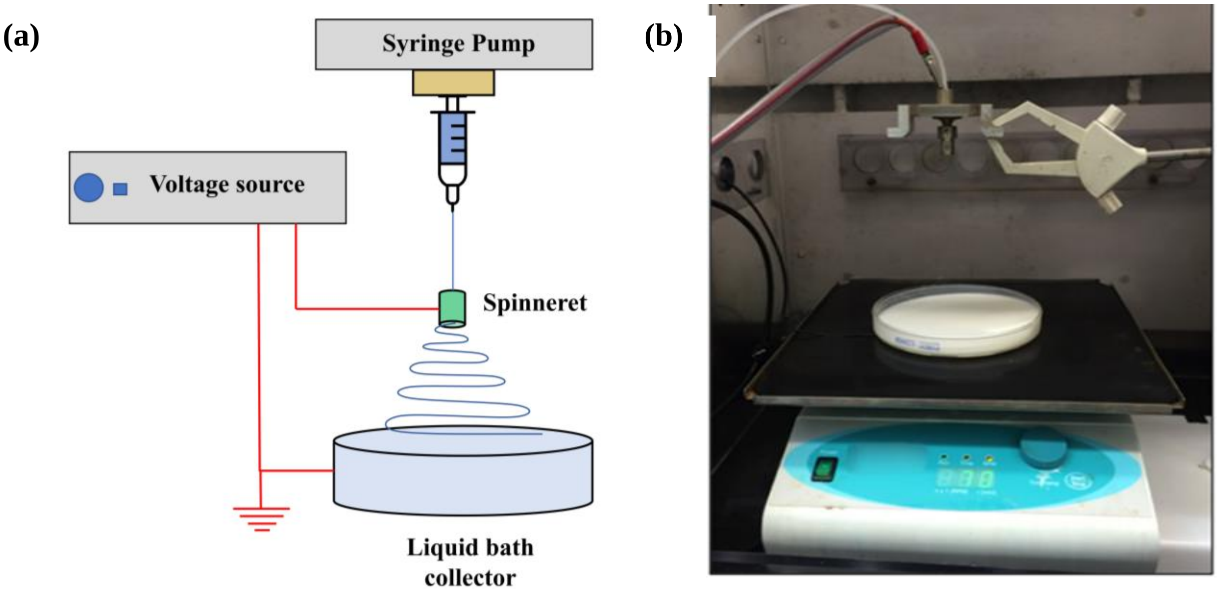


Fig. 3 Wet electrospinning setup, (a) Schematic diagram, (b) Actual setup [9]

This setup removes non-volatile solvents and precipitating fibers in the coagulation bath [85]. The bath must be a poor solvent or nonsolvent for spinning the dope's solute [86]. When selecting a coagulation solution bath, it is vital to consider factors like toxicity, boiling point, latent heat vaporization, and solvent diffusion rates [87]. In WES, the resulting fibers are generally on the micro level rather than the nanoscale, and taking coagulation factors like nature and temperature into account increases the difficulty of the method of design experimentation [88]. As a result of these limitations, wet electrospinning is more complex in designing the procedure than dry electrospinning [89]. The major advantages and disadvantages of wet electrospinning are listed in Table. 3.

Table. 3 Major advantages and disadvantages of wet electrospinning

Advantages	References	Disadvantages	References
1. The setup is simple and easy to use for the single polymer system	[90]	1. The presence of a liquid collector makes the process more complex as it adds more factors to the solvent	[91]
2. Results in the solvent free nanofibers	[92]	2. Not good for the biopolymers with water sensitive nature, and during collection, the morphology of the nanofibers is altered	[93]
3. The resultant fibers are at the micro level	[92]	3. It results in the altered therapeutic quantity during the collection process	[93]
		4. The options for the biopolymers solvent and the collectors solvent reduce if working with multipolymers nanofibers	[94]

2.3 Multi-needle electrospinning

Multineedle electrospinning (MNES) development addresses the single spinneret ES productivity limit issue [95]. MNES uses many spinnerets to enhance the fiber output, as shown in the schematic diagram in Fig. 4a. Various dope and even incompatible polymers may fill the spinneret with MNES to create unique composite mats [96]. With MNES, fiber characteristics can be altered, and the production rate of CAES can be increased. Spinneret production may be affected by jet repulsion [97]. Many spinnerets alter the needles tip electric field (EF) and charge density. Fiber diameter and form are out due to the repulsion between the jets and a shifting electric current [98]. MNES electric field homogeneity may be improved by focusing on these critical elements: needle design, number, and spacing [99]. This approach often employs linear or 2D needle arrangements. A linear array of jets behaves considerably differently in bending direction and envelope cone. These disparities become more apparent with a more extensive array [100].

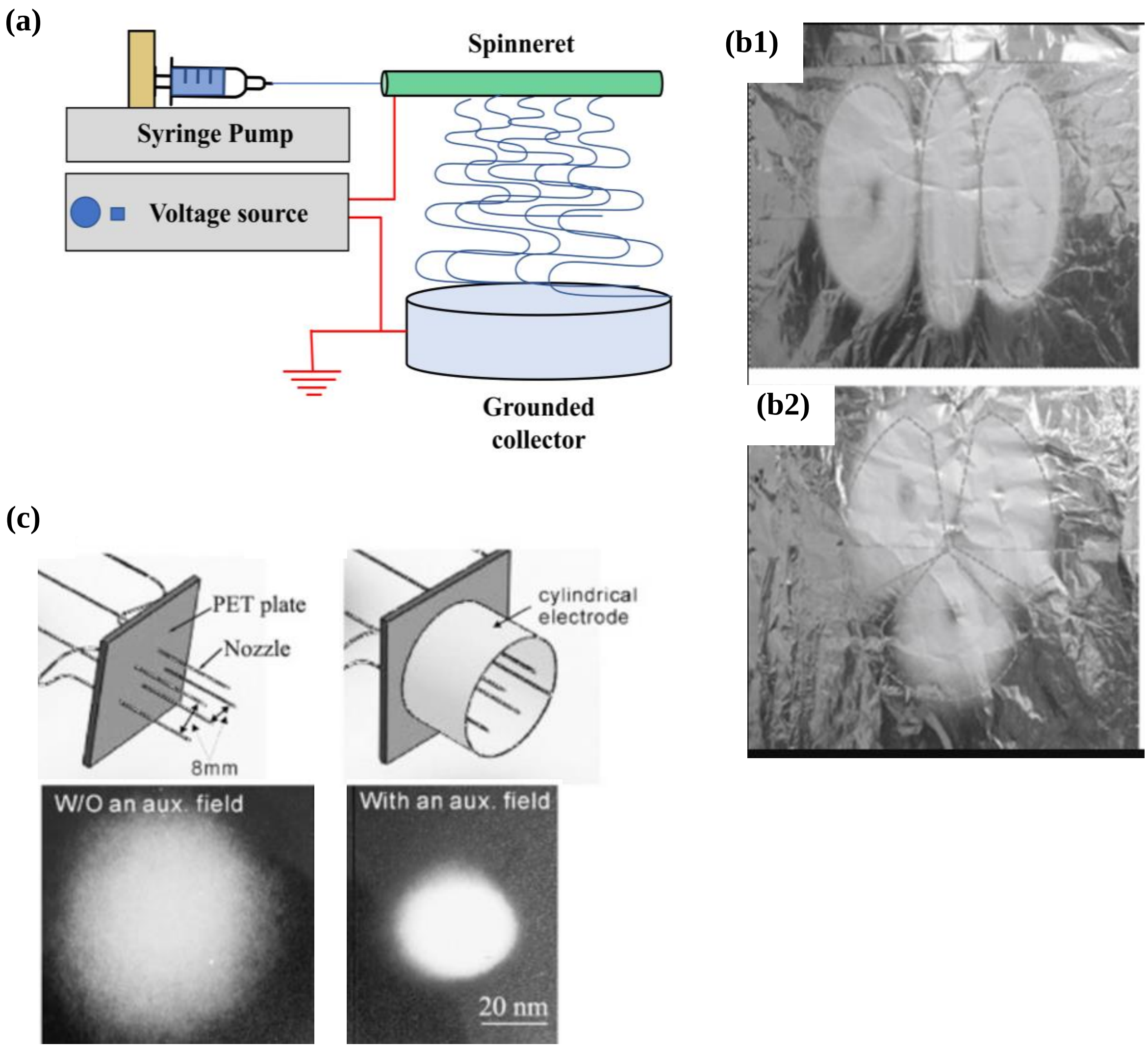


Fig. 4 Multineedle electrospinning, (a) Schematic diagram, (b) Effect of arrangement on nanofiber deposition (b1, in line and b2, in circle) [14], (c) Effect of needles casing on deposition [21, 22]

A concentric 2D needle array is presently thought to be the best layout concerning productivity, process stability, and fiber homogeneity [101]. Trapezoidal needle designs have recently shown favorable outcomes in MNES applications. Unlike a "typical double-line linear" array or an equilateral triangle, trapezoidal waves may produce a more uniform EF (Fig. 4b) [84]. An extra or auxiliary electrode, a cuboidal collector, and a polytetrafluoroethylene (PTFE) jacket surrounding every spinneret are further modifications to boost the homogeneity of the EF (Fig. 4c). The electromagnetic field surrounding the needle tips is amplified by plastic casings, which helps to increase consistency. As a consequence, the diameter of the fibers becomes smaller [102]. Despite its complexities, MNES may produce more consistent, complex, diversified fibers and is more readily modifiable [103]. The major advantages and disadvantages of MNES are listed in Table 4.

Table. 4 Major advantages and disadvantages of multineedle electrospinning

Advantages	References	Disadvantages	References
1. Solves the issue of low throughput faced by most of the basic electrospinning setups with single needle	[104]	1. The major issue of needle based electrospinning is the clogging of the needle, and involving a multineedle system results in difficulty of the system maintenance and increases the frequency of needle clogging	[97]
2. Good potential for the industrial level for a high production rate	[44]	2. Difficult to operate the setup since the nearby needles result in the electrostatic interaction and affect the nanofiber production of the neighboring needles	[105]

2.4 Coaxial electrospinning

Coaxial electrospinning (CAES) constitutes the same setup as TES. It implies a spinneret with double concentric needles, joined to their respective spinning dope and driven by separate syringe pumps rather than a single spinneret [106]. The relative flow rate between the inner and outer dopes is controllable and can be fine-tuned to generate high-quality fibers. This relation should be kept in mind while designing the process [107]. The encapsulating effectiveness of the fibers is greatly influenced by the relative flow rate, with a reduced inner flow rate often boosting this efficiency [58]. Electrical charges develop up at the shell solution's outer layer when higher voltage is supplied to the spinneret tip, which results in the stretching of the shell [108]. The constant drag and friction between the core and the outer shell shear the core solution. As a result, the taylor cone, critical for producing fibers, advances further, passing the critical point [44]. The fibers form a core-shell structure because there is no merging of the spinning dopes throughout the procedure [109, 110]. Fibers with a tubular structure or material with less ES ability may be made by removing the outer shell and the inner core of their respective materials. However, after the process, a post-processing method is required in the case of CES. [111]. A basic schematic diagram of the TAES setup is shown in Fig. 5a, and the resultant nanofibers with core-sheath morphology and nano wire in microtube TEM micrographs are shown in Fig. 5b & c.

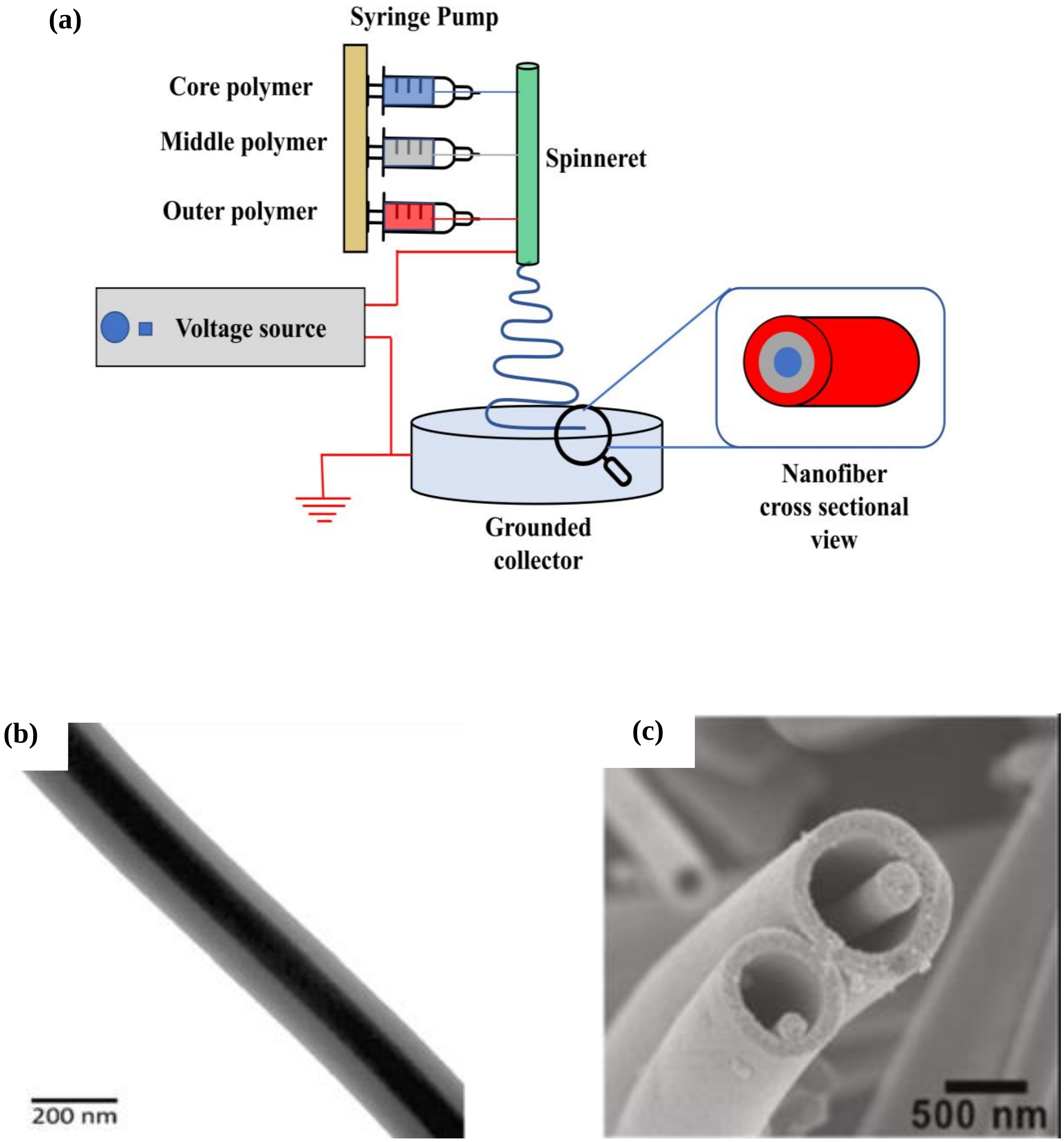


Fig. 5 Coaxial electrospinning setup, (a) Schematic diagram, (b) TEM micrograph for core-sheath structure (c) TEM micrograph of nanowire in microtube structure [8]

A further improvement of CAES is triaxial electrospinning (TAES), which utilizes three concentric needles to spin triple dopes simultaneously. With TAES, fibers can be further customized for their ultimate use by varying the material composition and the fiber configuration are the two advantages of this process over others [112]. A "nanowire in a nanotube" structure can be possible with the TAES (Fig. 5c) [112]. Moreover, TAES is a complicated method, and this technique requires additional work before it is ready for commercial use.

CAES is a well-recognized and recommended ES approach for fabricating polymers for drug release. Co-spinning two distinct polymer solutions create core-shell NF composites [113]. CAES may create synthetic and biopolymer fibers with enhanced physical, chemical, and biological properties [114]. First, the composite's outer shell breaks apart, releasing the medicine from the center. Although the coaxial NFs usually have an equal distribution of proteins, this is not always the case [115]. However, the NFs usually lack sustained drug delivery due to release burst phenomena, the release of the drug at once [112]. Some of the major advantages and disadvantages of CAES are listed in Table 5.

Table. 5 Major advantages and disadvantages of coaxial and triaxial electrospinning

Advantages	References	Disadvantages	References
1. Best option for the non-electrospinnable materials that cannot be directly electrospun due to their chemical structure or process sensitivity	[116]	1. The complex setup of the spinneret increases the overall complexity in designing the protocol as it adds more parameters	[116]
2. The resultant core-sheath nanofibers provide a novel morphology and a good option for the biomedical applications	[117]	2. The core and sheath materials pass through a single needle, so they require much compatibility to retain the structure, and that limits the flexibility of options and different combinations of biopolymers	[118]
3. The issue of burst release faced by the nanofibers of all other techniques can be overcome by using the coaxial electrospinning	[111]	3. Difficult to manage the two biopolymeric systems to produce continues nanofibers. The two polymer solutions could have different solvents and different properties like viscosity, conductivity and hence require different flowrates	[119]

2.5 Melt electrospinning

Melt electrospinning (MES) has become a popular choice because of not require the use of solvent. The basic schematic diagram for the MES is shown in Fig. 6a. ES polymer melt is used instead of the traditional polymer solution and is cooled to harden. Only by accurately controlling the circulation rate of polymer melt at the optimum temperature and rate can fibers with a continuous shape and big diameter be produced [120]. Joo et al. (2011) [22] show the variations in the temperature profile during the MES for polylactic acid, polypropylene, and nylon-6 (Fig. 6b). The fabrication of NFs without solvents until micro concentration makes it optimal for biomedical applications, as solvents may be toxic.

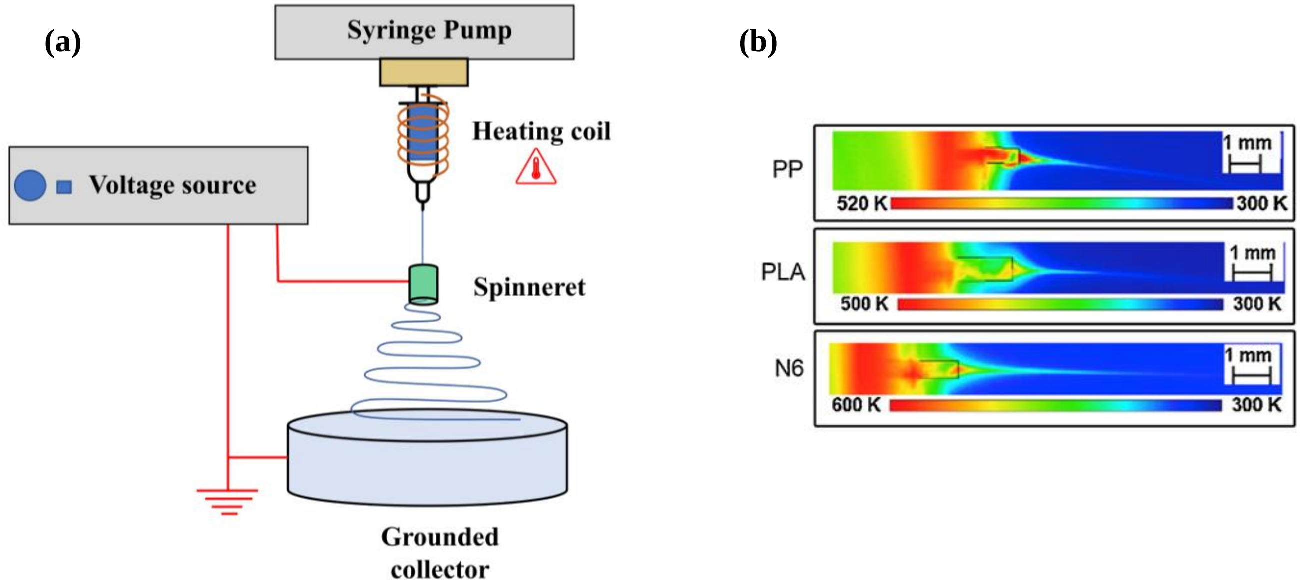


Fig. 6 Melt electrospinning setup, (a) Schematic diagram, (b) Temperature variations around the needle and taylor cone [13]

Pharmaceuticals and other biomolecules like proteins may affect the material's melting point. The viscosity and flow rate influence the kind of fibers produced. The polymer's viscosity and flow rate dictate the fiber's output [121]. The needle size is strongly related to the initial jet diameter and linked to the taylor cone size. If a finer fiber is needed, the cone size should be reduced. These fibers release drugs slower than solution-based NFs polymers and are an ideal candidate for sustained drug delivery [122, 123]. Some of the major advantages and disadvantages of MES are listed in Table 6.

Table. 6 Major advantages and disadvantages of melt electrospinning

Advantages	References	Disadvantages	References
1. Easy and simple process with fewer factors to deal especially solvent system related issues	[124]	1. Only works with the heat resistant biopolymers and can be used for sensitive biopolymers that limit the applications drastically	[125]
2. No requirement to optimize the solvent system and can work with complex polymers system	[126]	2. High heat input is required	[125]
3. The is no extra step for the removal of resultant solvent residues	[124]	3. Requirement of the proper moisture content for the process	[127]
3. The resultant nanofibers are free from any toxic solvent, which is ideal for biomedical applications	[43]	4. Lack of any modifications like encapsulation or any bioactive therapeutics due to the high temperature	[126]

2.6 Comparison of the needle based methods:

The major factor in deciding the ES method is applying the final product being produced. Drug delivery (DD), tissue engineering (TE), and wound healing systems (WHSs) are the major biomedical applications of NFs. Each of these applications requires a different design and morphology of NFs [128]. Figure 3 illustrates various needle based common ES techniques final morphology schemes for resultant NFs. However, each method has its benefits and drawbacks.

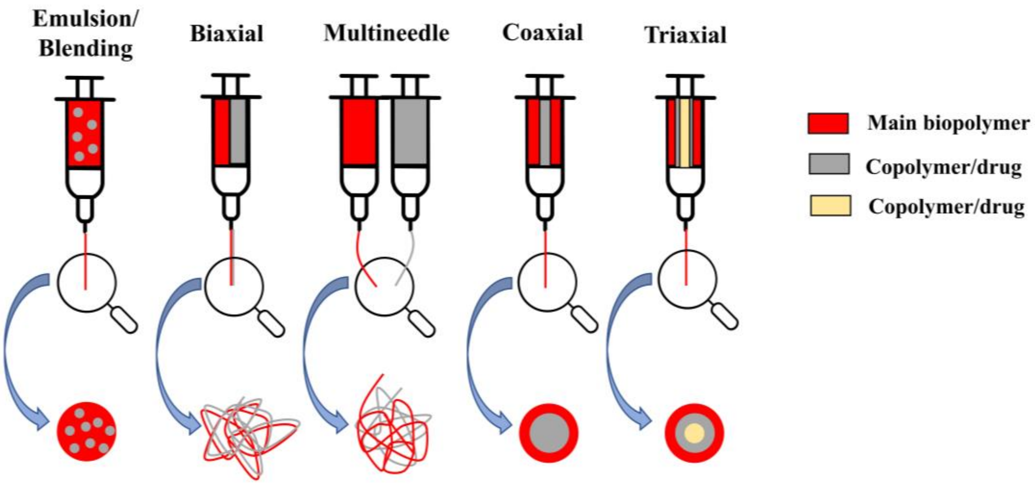


Fig. 7 Cross sectional representation of various methods resultant nanofibers

2.7 Needleless electrospinning

It is increasingly difficult to fabricate fibers as the number of spinnerets causes needle blockage. Therefore, needleless electrospinning (NES) (first patented in 2005) is often preferred over needle based electrospinning techniques for spinning dopes with greater viscosities [63]. The basic schematic diagram of NES is shown in Fig. 8a.

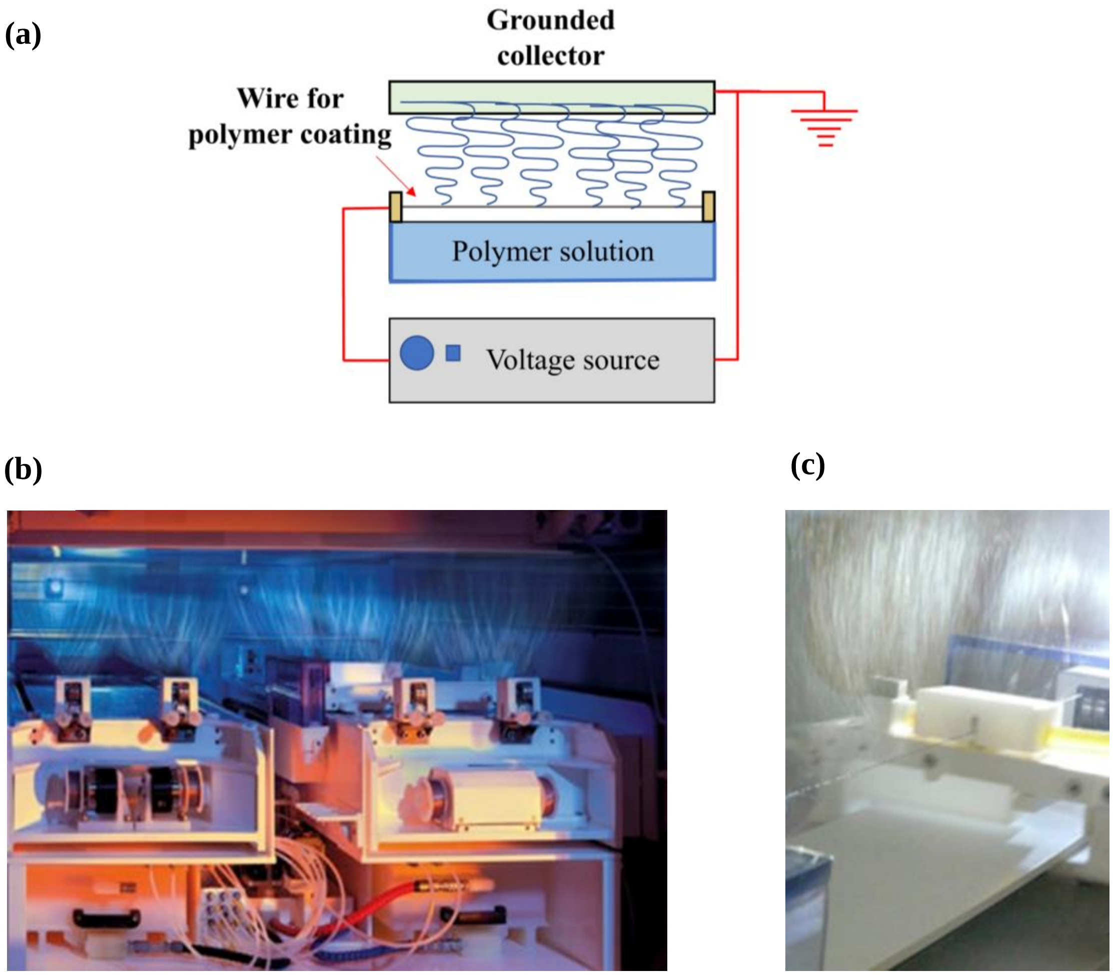


Fig. 8 Needleless electrospinning, (a) Schematic diagram for wire based needless electrospinning, (b) Commercial Nanospider setup [11], (c) Photo of setup in working (source: website www.elmarco.com)

It is an electrospinning system capable of high production while avoiding the problems of MNES [68]. The dope spun is stimulated by the high voltage used in needleless electrospinning. Due to the agitated solution and the EF, taylor cones develop on the spinning dope's free surface [129]. Taylor cones generate polymer jets, which go to the collector and produce nanofibers, as shown in Fig. 8a & b [130]. Many other technology agitation techniques have been needleless, including bubble, disc, ball, spiral coil, slot, and the rotary conical electrospinning condenser [131]. Even though needleless electrospinning considerably increases the pace of fiber production, it has its issues. In NES, solvent evaporation rises because of the greater surface area of the spinning dope exposed to the air [132]. Dope concentrations rise as a consequence of evaporation. The evaporation of the solvent in an industrial setting, depending on the solvent, may pose a significant threat to worker health [44]. Some of the major advantages and disadvantages of NES are listed in Table 7.

Table. 7 Major advantages and disadvantages of needleless electrospinning

Advantages	References	Disadvantages	References
1. High throughput rate and the ability to produce continuous nanofibers make it a better candidate for industry	[133]	1. The nanofibers are usually greater in diameter as compared to the nanofibers produced conventionally by needle based setups	[134]
2. The setup is free from any needle to use, and hence the usage and maintenance are easy since there is no clogging and electrostatic interaction of the neighboring needles	[133]	2. The setup requires high voltage and the cost increase	[118]
3. The throughput can be increased directly by increasing the polymer concentration, which is not possible in the needle based setup as it would result in the clogging of the needle easily	[135]	3. Generation of random and uncontrolled taylor cones results in the non-reproducibility	[71]
		4. The wastage of polymer solution and solvent as a result of random taylor cone is higher as compared to other techniques	[136]

2.8 Other innovative methods

One of the major concerns for biomedical applications like tissue engineering and wound healing is to mimic the extracellular matrix (ECM) for the growth and differentiation of the cells [137]. The matrix pattern is crucial in providing a more growth-friendly environment like ECM [138]. The conventional methods of ES fabricate random nanofibers and hence lack efficiency for cellular growth. However, by modifying the collector, any ES technique setup can be modified at the collecting stage to fabricate nanofibers into different morphologies and patterns [139]. The two major types include radially oriented nanofibers (RON) and yarn like nanofibers (YN).

In the case of RON, a modified collector consisting of the pin-ring structure is employed to obtain the radial pattern (Fig. 9a). The nanofibers are generated in a radial pattern and hence can enhance cell differentiation, growth, and adherence [140]. The SEM analysis from the study of Wu et al. (2023) [5] shows how the pin-ring structure is involved in collecting radially aligned nanofibers. The area around the rings consisted of radially aligned nanofibers, while the area outside the pin-ring structure consisted of randomly aligned nanofibers [5].

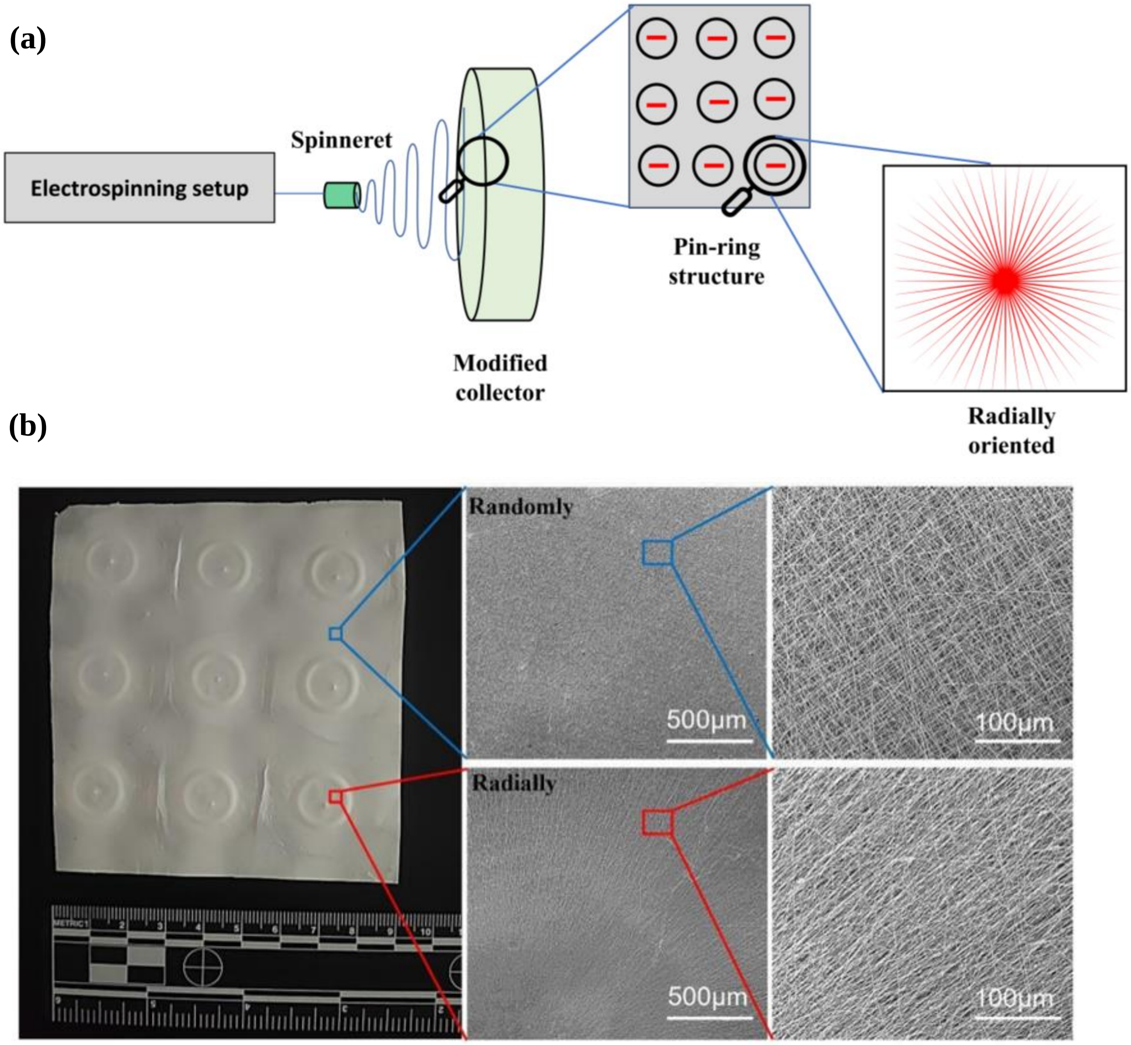


Fig. 9 Radially oriented nanofibers, (a) Basic setup with modification of collector, (b) SEM micrographs of the radial morphology [5]

In the case of YN, the collectors consist of a winding tube to give the yarn like morphology to the nanofibers (Fig. 10). There are normally three forms of the yarn nanofibers, including aligned, twisted, and cover spun, as shown in the Fig. 10 [16].

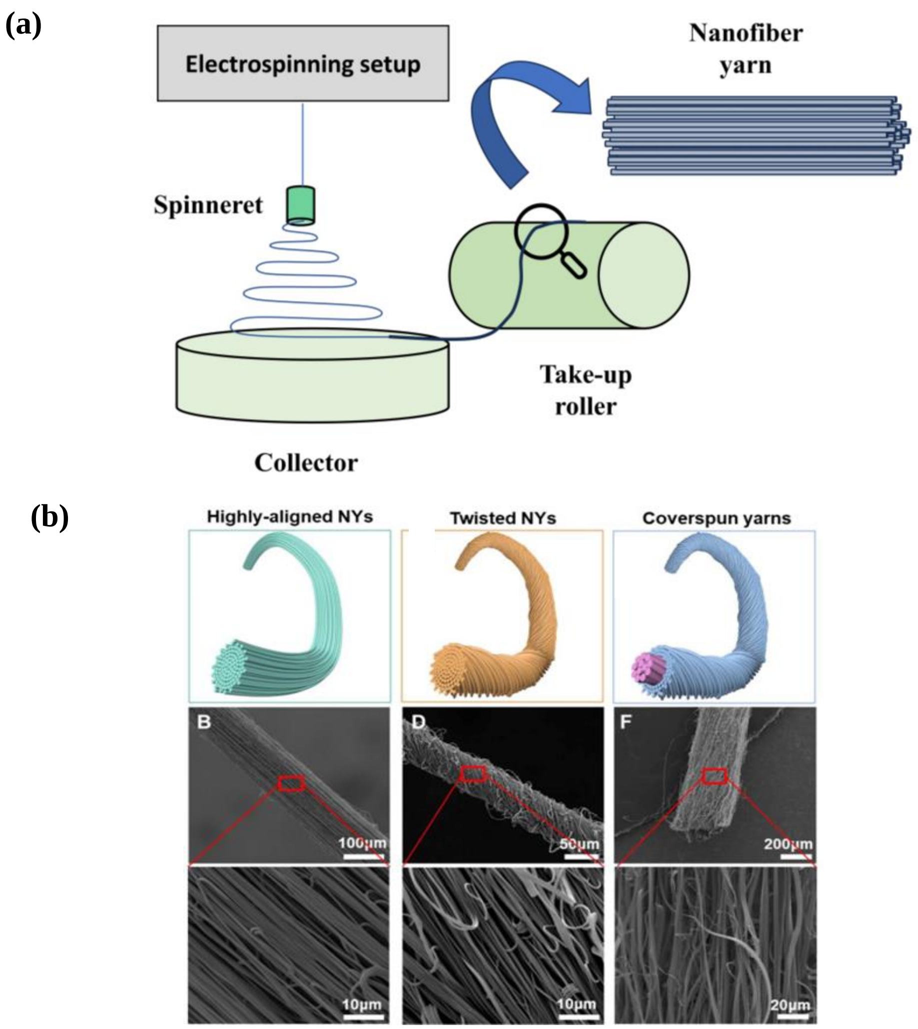


Fig. 10 Yarn nanofibers, (a) Schematic diagram, (b) Types of yarn like nanofibers [16]

The YN can also be weaved or braided into various nanotextiles, as shown in Fig. 11. The densities and porosities of those nanotextiles are tunable depending upon the application requirements [141]. The YN generally has exceptional mechanical strength compared to the randomly fabricated nanofibers. They also provide anisotropic structures and hierarchy in the nanofibers to mimic the ECM, resulting in efficient cell growth and differentiation [142]. These patterns are also well integrated into the biological cues and can result in sustained drug release. These YN find their applications mostly in tissue engineering, surgical structures, actuators, and advanced facial masks [139, 143].

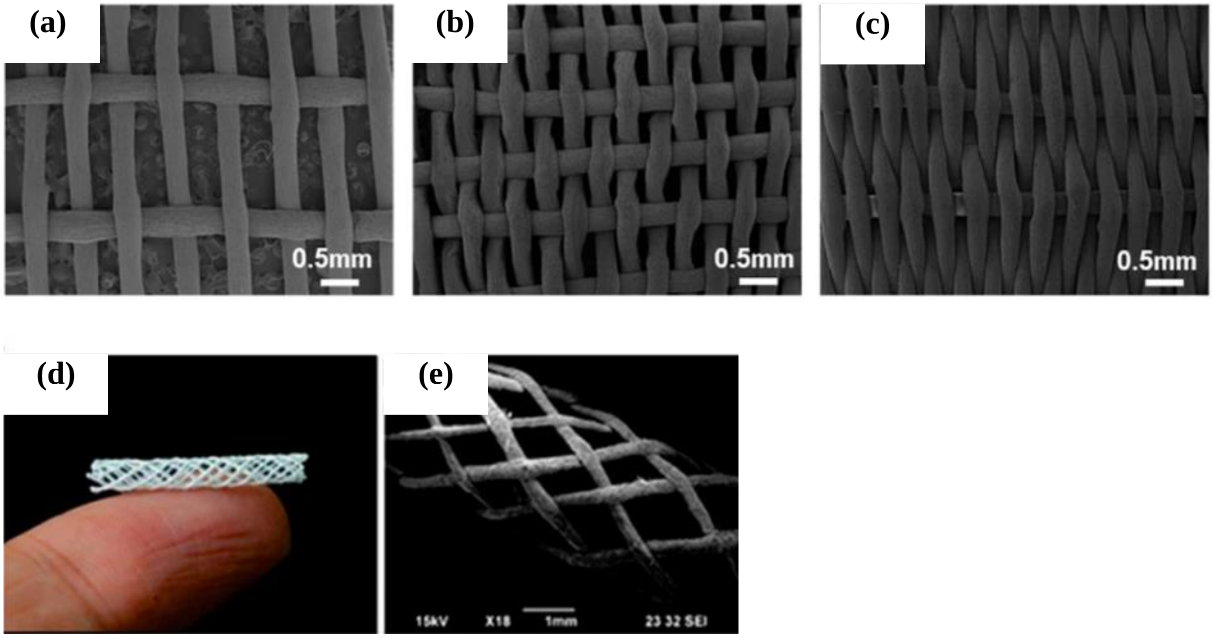


Fig. 11 Examples of nanotextiles, (a-c) Weaved polylactic acid into various densities [3], (d-e) Braided polylactic acid into a tube like structure [18]

Table 8 shows the major advantages and disadvantages of the discussed electrospinning techniques.

Table. 8 Major strengths and drawbacks of various electrospinning techniques

Electrospinning methods	Strengths	Drawbacks	Recent applications	References
Single needle (emulsion/ blend)	High and uniform drug distribution, a high initial burst	The bioactivity of therapeutics is lost due to due voltage and solvent; an initial high dosage burst can cause toxicity	1. Laminin/Polycaprolactone based NFs for TE. 2. Probiotics/pullulan, polycaprolactone/gelatin for DD	[144-146]
Co/tri axial	Hollow fibers formation, two separate solutions for the outer and inner core, saves the therapeutic from the solvents to dissolve biopolymers; the final structure is optimal for the sustained DD since the encapsulation of soluble drugs in core	Consideration of variables like interfacial tension and viscoelasticity makes the procedure designing complex	PCL/5-Fluorouracil and Methotrexate drug delivery system for anti-cancer drug delivery	[147]
Multineedle	Enhanced rate of production	Non-uniform fiber production	No recent potential biomedical application was observed	[148]
Needleless	Superior production rate as compared to TES, no spinneret clogging issue, viscous natured biopolymers can be used	High voltage, non-uniform diameter distribution of fibers, high cost	Spirulina protein/gelatin NFs for wound healing dressing	[149]
Radial nanofibers	Fabricated nanofibers have specific patterns providing biological cues for cells growth and differentiation	The process used a ring and pin structure in the collector while the area without the structure still has random nanofibers, so overall, the technique is complex with low throughput	Gelatin/poly lactic acid based radially aligned nanofibers for diabetic wound healing	[150]
Yarn based nanofibers	The resultant nanofibers show exceptional mechanical strength, surface area and pores mimicking natural extracellular matrix for cell culture	The process is complex as it requires specialized and complex collectors and is not suitable for all biopolymers, limiting the options	Polycaprolactone/silk fibroin based nanofiber yarns for tissue engineering	[139]

3. The factors affecting fibers properties

In the electrospinning process, the parameters used directly influence the fiber quality. The solvent, dope solution, processing, and environmental parameters are examples of these variables

[61, 151-155]. Fig. 12 summarizes the guidelines for the relationship between the fiber and the parameter.

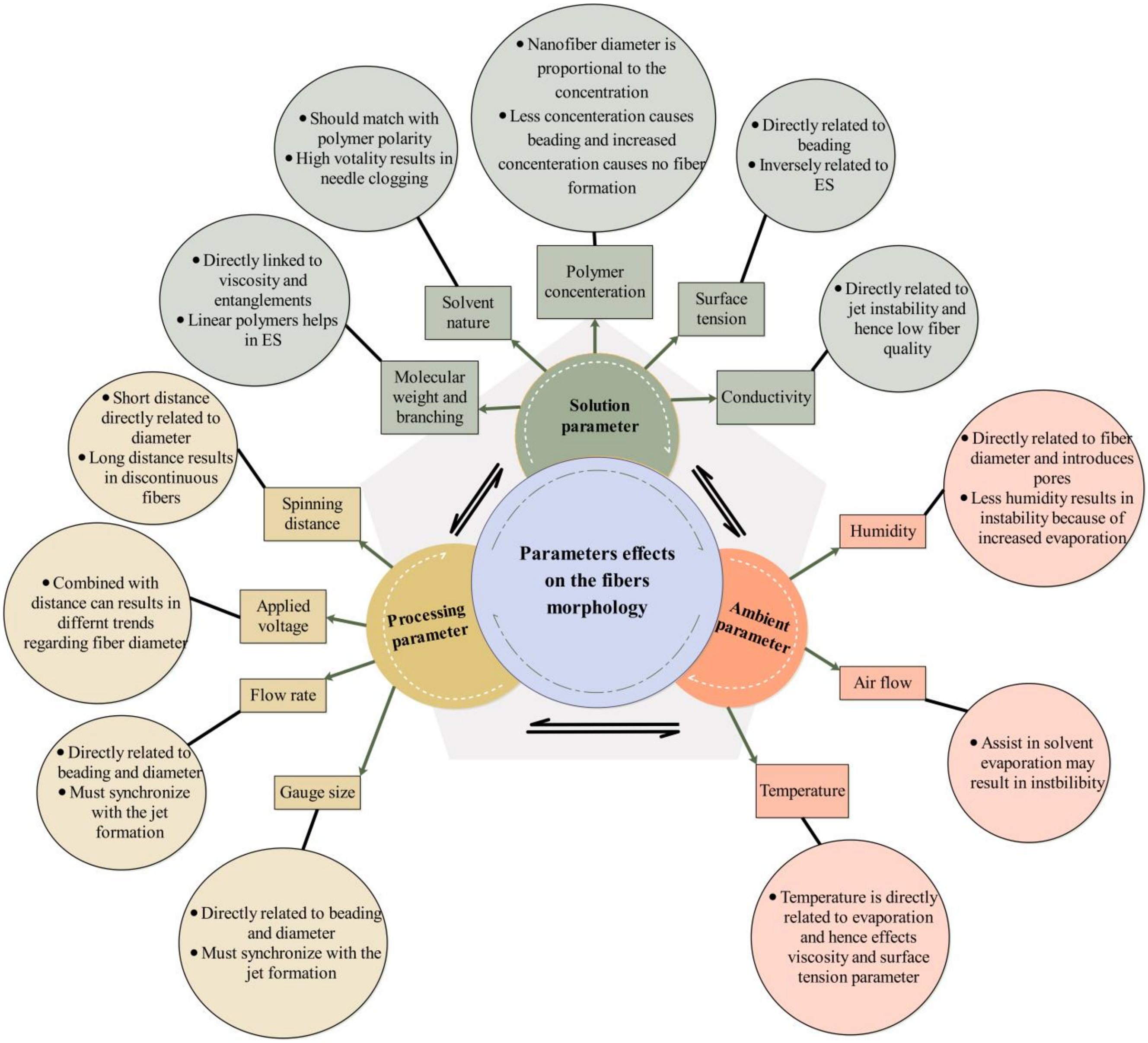
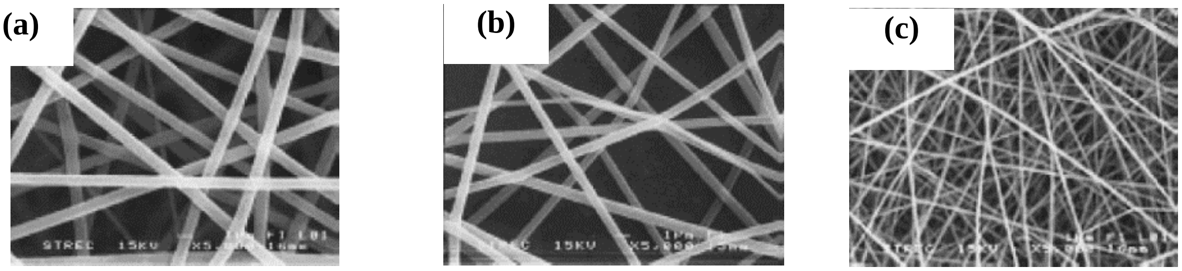


Fig. 12 The relation between the various parameters and the nanofiber morphology

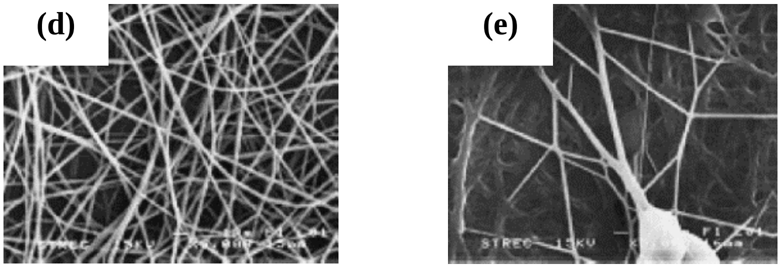
The major parameters responsible for effecting the morphology of NFs include processing, solvent, and ambient parameters [156, 157]. Among the mentioned parameters, processing and ambient parameters are routinely used. However, one of the major fundamental parameters that could play a crucial role in ES is the solvent parameters, which are mostly not considered in current studies. This fundamental parameter is usually not considered in the present context, which could change the fiber properties. Each solvent has specific properties like dipole moment and dielectric constant and interacts specifically with the polymer [158]. By changing the solvent or the biopolymer, significant changes should occur in the final blend, and these properties should be considered further to optimize the fibers properties for the specific application [159]. Choktaweesap et al. (2007) [6] demonstrated the effect of various solvents systems (Glacial acetic acid (AA) (Figure 13a), AA/2,2,2-trifluoroethanol (TFE) (Figure 13b), AA/dimethyl sulfoxide (DMSO) (Figure 13c), AA/ethylene glycol (EG) (Figure 13d), and AA/formamide (F) (Figure 13e)) on the morphology of gelatin NFs. They conducted the ES process under the same processing parameters (voltage: 7.5 kV and the distance between needle and collector 7.5 cm) with the same biopolymer but changed the solvent system to see the direct effect of solvent systems on the final NFs. By changing the solvent systems, the change in the properties of the solution, like surface tension and conductivity, was observed, resulting in the change in morphology and the diameter of the NFs.



Acetic acid 29%,
Conductivity: 342 μS cm^{-1},
Fiber diameter: 839 ± 0.09

Acetic acid:TFE (40:60)
Conductivity: 537 μS cm^{-1},
Fiber diameter: 634 ± 0.13

Acetic acid:DMSO (91:9)
Conductivity: 383 μS cm^{-1}
Fiber diameter: 230 ± 0.03



Acetic acid:EG (93:7),
Conductivity: 250 μS cm^{-1},
Fiber diameter: 264 ± 0.04

Acetic acid:F (91.9),
Conductivity: 490 μS cm^{-1}
Fiber diameter: not applicable

Fig. 13 Effect of different solvent systems on the gelatin nanofibers, (a) Acetic acid, (b) AA:TFE, (c) AA:DMSO, (d) AA:EG, (e) AA:F [6]

Solvent parameters should also be considered while fabricating NFs based biocomposite for a specific application. A few independent research-based studies show solvent parameters' effect on the NFs [160-162]. The current line of research for applications revolves around changing the biopolymer's composition along with the routinely focused parameters [126]. The resultant fiber is characterized for specific applications, and applicability is also demonstrated in Tissue engineering [163, 164], drug delivery [50, 165], and wound healing [166, 167], but the researchers are not taking into account the other parameters. Hence, the ES is not being used to its full potential. Much comparison based research is required to keep the composition and the parameters the same while varying the solvents for specific application studies to make a general guideline for future researchers working on the biopolymers based NFs using ES [168].

4. Trends in biopolymers electrospinning

Petroleum based polymers are primarily toxic and noncyclic. In addition, they are the major contributors to the high carbon footprint and environmental pollution [169]. However, in the past decade, biopolymers have emerged as an eco-friendly alternative to petroleum based polymers [170]. 2. Due to their remarkable properties, they have gained interest as potential candidates for fabrication into NFs, especially for biomedical applications (Fig. 14).

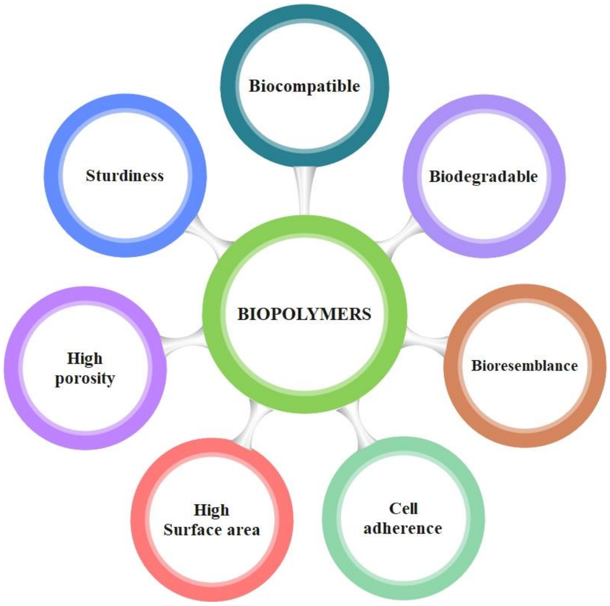


Fig. 14 Properties attained by the nanofibers by the addition of biopolymers

Biopolymers are majorly divided into two main categories of synthetic and natural biopolymers [171]. Synthetic polymers offer mechanical and physical qualities, including tensile strength and elastic modulus, have a low degradation rate, and are highly malleable during synthesis, amenable to chemical manipulation, and repeatable [172]. Synthetic polymers can be mass-produced, and customized scaffolds can be made cheaper than natural biopolymers. The major synthetic biopolymers include polylactic acid (PLA), polyethylene oxide (PEO), and polyvinyl alcohol (PEO) [173]. The fundamental issue with synthetic biopolymers regarding biomedical applications is the lack of cell affinity because of their poor hydrophilicity and cell recognition sites [174].

On the other hand, natural polymers have innate antibacterial characteristics and are more biocompatible and less immunogenic than synthetic biopolymers [175-177]. The natural biopolymers for biomedical applications mostly include chitosan, cellulose, gelatin, and collagen [178]. However, the difficulty in using natural biopolymers is that their structure should not be altered to a great extent as that would result in losing biological activity and their low mechanical strength against physiological conditions [179]. So, to overcome the individual issues of these categories, NFs are mostly fabricated using synthetic and natural biopolymers [84]. Some of the major biopolymers used for ES, along with their merits and demerits, are listed in Table. 9 and a few examples of different biopolymer NFs morphologies are shown in Figure 15.

Table 9. Merits and demerits of commonly used biopolymers in electrospinning

Type	Biopolymers	Advantages	Disadvantages	References
Natural	Cellulose	Good thermal stability and scaffolding for the therapeutics	Activation of the immune system, solubility, limited water holding capacity	[180-182]
	Chitosan	Antimicrobial activity, antioxidation, inflammation regulation, promotion of hemostasis,	Less solubility, biodegradation rate uncontrollable	[183-185]
	Hyaluronic acid	Natural component of the body and actively involves in the clot formation, inflammation, proliferation, and re-epithelialization	High viscosity, even at low concentration	[186-188]
	Collagen	Less immunogenic, good biocompatibility, good for cell proliferation and cell adhesion,	Sudden breakdown during degradability and	[189, 190]
	Silk fibroin	Excellent mechanical properties, controllable rate of biodegradation, and better water and oxygen permeability	The degumming process during the extraction affects mechanical properties	
Synthetic	Polylactic acid	Excellent electrospinnability, good mechanical strength	Hydrophobic in nature and can cause inflammation when staying too longer in the body	[191, 192]
	Polyethylene oxide	Good viscoelastic behavior in a physiological environment improves the electrospinnability as it makes it easy to blend with natural biopolymers	Non-biodegradable within the biological time frame	[193]
	Polyvinyl alcohol	Bio-adhesive, nontoxic, chemical resistance	Bio-inertness and low tensile strength	[194, 195]

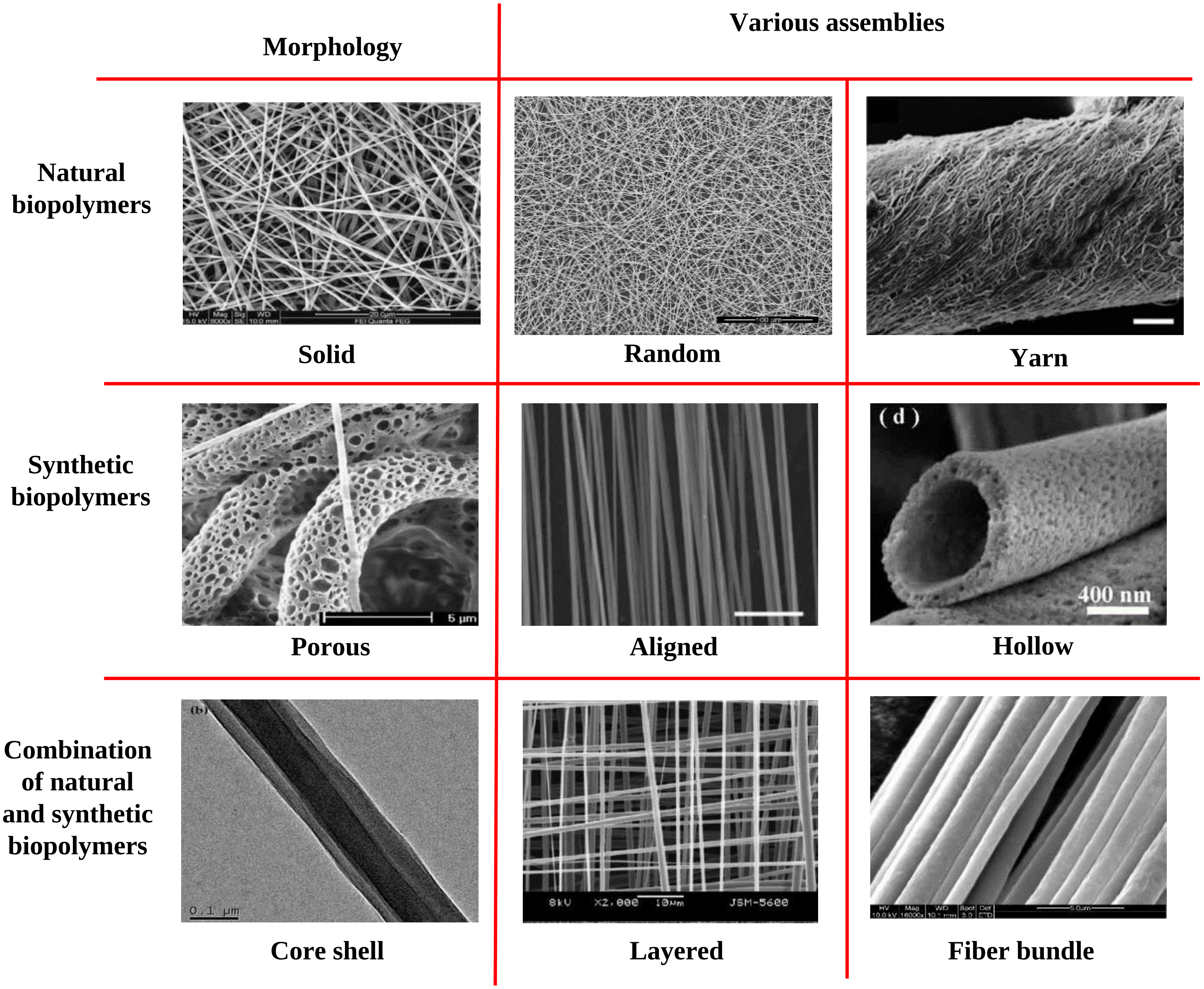


Fig. 15 Various morphologies and assemblies of natural, synthetic or combination of biopolymers [7]

7. Major biomedical applications of biopolymers nanofibers

NFs found their applications in various fields owing to the flexibility of choice in components for their fabrication. However, this article focuses on the biomedical applications of biopolymers based NFs. 5 years based (2017-21). ScienceDirect database literature analysis (Fig. 16) shows the increasing interest of NFs based research for the biomedical applications of tissue engineering (TE), drug delivery (DD), and wound healing (WH).

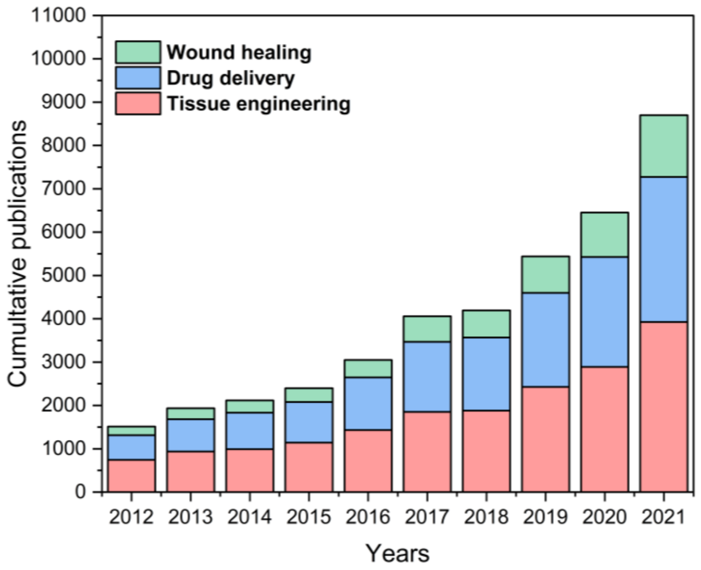


Fig. 16 Research and cumulative number of publications in ScienceDirect platform in the last decade for various nanofibers applications

7.1 Tissue Engineering

Tissue engineering (TE) focuses on the restoration of functional body tissues. This interdisciplinary technique requires coordination from many branches of study, including cell biology, engineering, and medicine [196]. Previously autologous or allogeneic grafts have been used as the primary therapy for severe tissue injury. Allogeneic grafts have several drawbacks, including difficulty obtaining, risk of rejection, and high cost [197]. Allogeneic graft's shortcomings pave the way for technologies that may promote cell renewal by acting like the extracellular matrix and overcoming the drawbacks of allogeneic grafts [198]. To overcome the drawbacks of conventional allogenic grafts, various tissue engineering systems (TES) like hydrogels, 3D printed scaffolds, and nanotechnology based systems (NTBS) are the most practical options available [199].

One of the major TES is hydrogels, with their high hydrophilicity, can precisely replicate the extracellular matrix's (ECM) structural features, making them an excellent habitat for new cell development [200]. In some cases, a new ECM may also be secreted by these cells [201]. Furthermore, injectable hydrogels may be applied to the injured area using non-invasive methods [202]. Despite many advantages, the one major drawback of hydrogels is low mechanical strength due to the lack of natural interaction between the biopolymers [203]. A crosslinker is employed chiefly to overcome low mechanical strength by combining different biopolymers in the network. The crosslinkers make the system toxic, limiting its use in TE applications [204].

The other TES include scaffold printing using 3D printing, which has emerged as a common strategy for creating TES [205]. Scaffolds can be manufactured in a 3D printer and serve as a cell growth and repair platform [206]. The major issue with the scaffolds is the lack of desired porosity (50 to 500 nanometers) since the scaffolds require appropriate porosity for proper cell growth [207]. The next major issue with the 3D-printing is the preparation of bio-inks to make 3D scaffold based TESs. The biopolymers must be prepared to make bio-inks to fabricate TES to promote cell proliferation and differentiation [208]. But natural polymers are not easily processed to make bio-inks, and synthetic biopolymers lack cell proliferation abilities [209]. These are the bottle neck problems for developing 3D printing based TES [210].

However, NFs based TESs have the potential solutions for the issues associated with the previously discussed systems. NFs are porous enough to invade new cells by imitating ECM dimensions in terms of porosity ranging from 50 to 500 nanometers [211]. Ma et al., (2022) [212] prepared CS NFs with PVA for bone tissue engineering. Since pure CS scaffolds lack the mechanical strength for the TE application and modification of CS results in cytotoxicity, the prepared NFs showed excellent porosity (>70%) and high surface area (Fig. 17). The cytocompatibility test also showed their high biocompatibility towards MC3T3-E1 cells and hence they can be used for the TE applications.

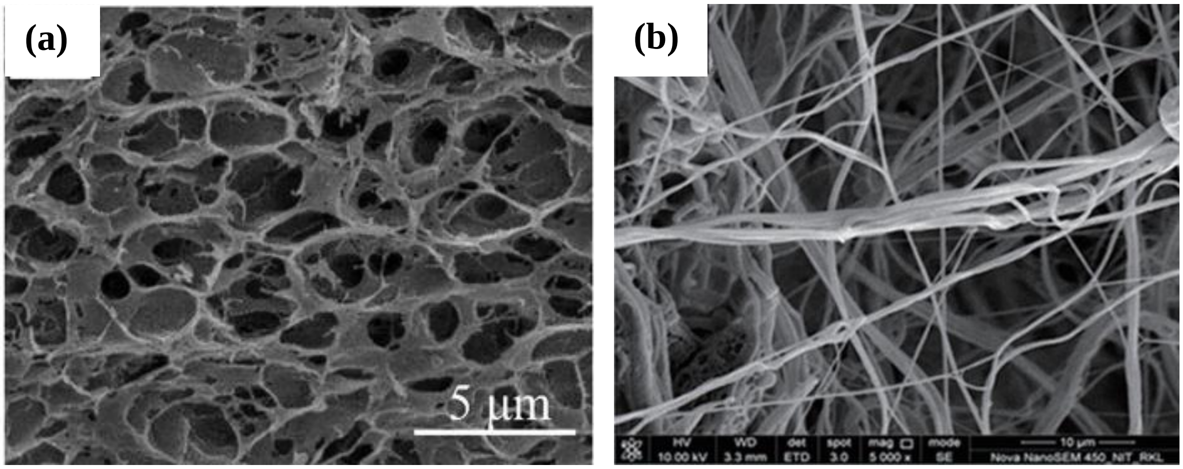


Fig. 17 SEM images of chitosan and polyvinyl alcohol composite fabricated by different methods, (a) Hydrogel based [15], (b) Electrospinning based nanofibers [19]

The other major benefit of the NFSs is their exceptional mechanical strength. NFs are sturdy enough to withstand mechanical stress since they do not rely on the natural interaction of biopolymers, as ES is flexible to combine different biopolymers, which is not possible by other methods [213]. Table. 10 represents the tensile properties of the same material but fabricated into hydrogels [15] and NFs [19]. Increased mechanical strength can be observed in the case of NFs fabricated by ES [214].

Table 10. Comparison of the tensile properties of biocomposites fabricated by hydrogels and electrospinning

Tensile property	Hydrogel	Nanofiber
Strength (MPa)	0.9	6.15
Strain (%)	160	83.44
Elastic modulus (MPa)	0.2	12.38

NFs mimic the natural ECM in terms of the overall 3D environment. ES can play a vital role in tuning topographical properties for the efficient growth of cells since it is quite evident from the literature that cells respond to various topological patterns [215-217]. Chen et al., (2021) [10] prepared HA/PCL based core-shell NFs loaded with platelet rich plasma for the TE of a tendon. They studied the topological effect of the NFs in their study. Two major NFs groups were compared, one having random topology (Figure 18a1) and the other having aligned topology (Figure 18a2). The aligned scaffold showed better mechanical strength (Figure 18c), cell proliferation (Figure 18f), gene regulation (Figure 18d), and protein synthesis (Figure 18e & f).

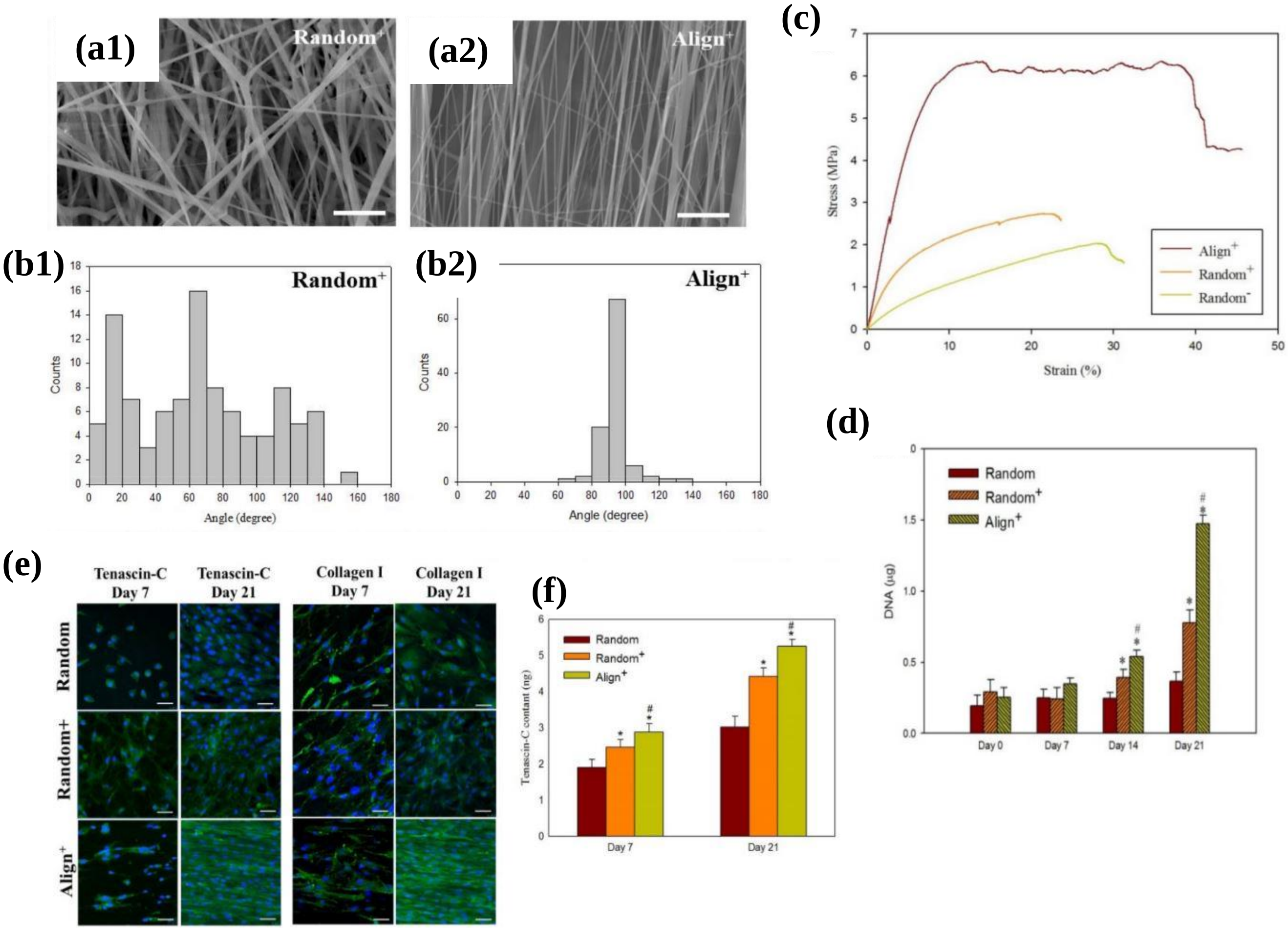


Fig. 18 Topological effect by electrospinning on nanofibers based tissue engineering, (a) SEM images, (b) Fiber angle distribution, (c) Tensile strength, (d) Cell proliferation based on DNA quantification, (e) immunofluorescence staining of tenascin-C and collagen I, (f) Tenascin-C quantification [10]

ES provides the ease of fabricating NFSs according to the needs of the specific tissue by adjusting factors like fiber diameter, surface morphology, and shape, which plays a significant role in cell adherence and proliferation in the case of TE [218]. NFSs can be applied to many cell and tissue types; however, the essential requirement for the TESs remains the same. The systems must be able to mimic the conditions of natural ECM [219]. The system should provide a sturdy framework to generate new cells spontaneously and transmit biological signaling chemicals to the tissue or transport new cells [220]. Various fundamental properties to keep in mind for developing a biopolymer based system are illustrated in Fig. 19. Other than the mechanical strength; ES methods incorporate various exceptional and novel features in the resultant NFs not possible with the other fabrication techniques [221]. Table 11 enlists some recent examples where ES played a crucial role in fabricating the scaffold for unique combinations of biopolymers and the critical properties of resultant NFs in various TE applications.

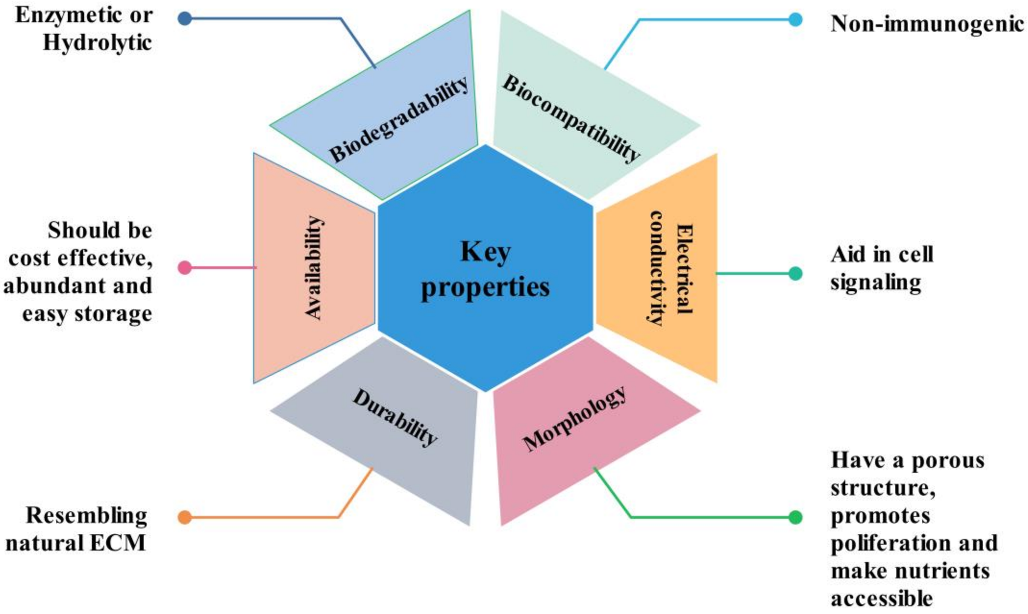


Fig. 19 Key properties for the designing of tissue engineering systems

Table 11. Recent applications of electrospinning methods for biopolymers nanofibers based tissue engineering scaffolds

Electrospinning Method	Biocomposite composition		Role of Electrospinning	Resulting properties in nanofibers	Cells/Tissues	References
	Major biopolymers	Additives				
Immersed*	Chitosan (CS)	Fucoidan and CuS nanoparticles	Difficulty of combining CS and CuS nanoparticles	Increased acid resistance and reduced the swelling rate of CS	Osteoblasts	[222]
Immersed*	CS	Polyvinyl alcohol (PVA) and nano SiO2	No use of toxic organic solvents, uniform NFs diameters	Interconnected pores, high porosity (>70%), excellent swelling properties, and a controllable degradation rate	Osteoblasts	[223]
Adhered*	Gelatin	Growth Factor/ Polycaprolactone	NFs causes the sustained release of growth factor to avoid risk of high concentration	Improved biomechanical properties, enhanced tubular formation of human umbilical vein endothelial cells (HUVECs), and wound healing	Patellar Ligament tissue engineering	[224]
Co-axial	Hyaluronic acid (HA)	Poly lactic acid (PLA)	Combining non-interacting biopolymers for the enhanced biocompatibility	Enhanced cellular activity without cytotoxicity	Pelvic ligament tissue engineering	[225]
Co-axial	HA	Polycaprolactone (PCL)/ L-ascorbic Acid	Encapsulation of ascorbic acid for the synthesis of natural collagen to protect it from the environment	Increased hydrophilicity, and adjustable degradation rate	Skin tissue engineering	[226]
Coaxial	Silk fibroin	Poly methyl methacrylate	Novel composite combination with cell adherence and mechanical stability	Amphophilic nature to work in both dry and wet conditions Porous architecture and improved cell adhesion	Various tissue engineering applications	[227]
Suspension*	Collagen	Polypyrrole/chitosan (CS)	Combining conductive polymer with the natural biopolymer and achieving high surface area with porosity and electrical conductance	Semi-conductive range NFs, improved cell adhesion, growth, and proliferation.	Various tissue engineering applications	[213]
Suspension*	Gelatin	Zinc-Doped Hydroxyapatite/reduced graphene	Electrospun NFs provide a microenvironment for natural differentiation, making it cost-effective	Differentiation of mesenchymal stem cells toward the osteogenic lineage without the need for any external factors Exceptional osteoinductive, angiogenic properties, antibacterial	Osteogenic Differentiation of Mesenchymal Stem Cells	[228]
Suspension*	Silk fibroin	PLA	Micro to nanoscale fibers diameter to mimic the natural ECM	Increased mechanical properties, degradability, and cellular induction	Meniscus Tissue Engineering	[229]
Biaxial*	Collagen	Sodium alginate (SA)/ polyethylene oxide/ GUMS16	Scale up production for industry, collagen based NFs with improved mechanical strength	SA as an absorber of excess wound fluids, and GUMS16 produced exopolysaccharides for antioxidation, Increased cell viability, growth, and proliferation	Various tissue engineering applications	[230]

***Single needle electrospinning**

7.2 Drug Delivery

Electrospun NFs have gained popularity as a drug delivery device in recent years due to their ability to increase the dissolution rate of drug molecules by amorphization, facilitating the absorption of poorly soluble medicines [231]. The solvent's rapid evaporation during ES leads to a solid drug solution in the applied matrix. Because of their homogenous drug distribution within the matrix and their capacity to restrict molecular mobility, the electrospun fiber based amorphous solid dispersions can keep an included active component in the amorphous physical state for extended periods, hence optimal for the sustained DD [232-234]. It is also possible to maintain supersaturation of the drug, which provides a greater driving force for absorption of the drug [235].

NFs based drug delivery systems increase the drug solubility and bioavailability, as well as the capacity to regulate the release and administration, two of the main objectives of modern drug delivery [236]. These days oral and transdermal controlled-release formulations make it possible to provide pharmaceuticals to patients just once or twice a day, increasing patient compliance and decreasing the risk of dangerous plasma peak concentrations that might result from multiple doses of extended release formulations [237]. NFs are the undisputed candidates for achieving oral drug delivery since they can easily dissolve in water and expose a larger surface area to the dissolving media [238].

There are mostly two effective approaches to drug delivery through the NFs. The first one is the incorporation of the drug by making the suspension with the biopolymers before the ES, and the second one is the encapsulation of the drug for delivery [239]. The first approach is used for the drug insensitive to ES parameters (high voltage, temperature, and humidity) and the environment. The schematic illustration for both approaches is shown in Fig. 20.

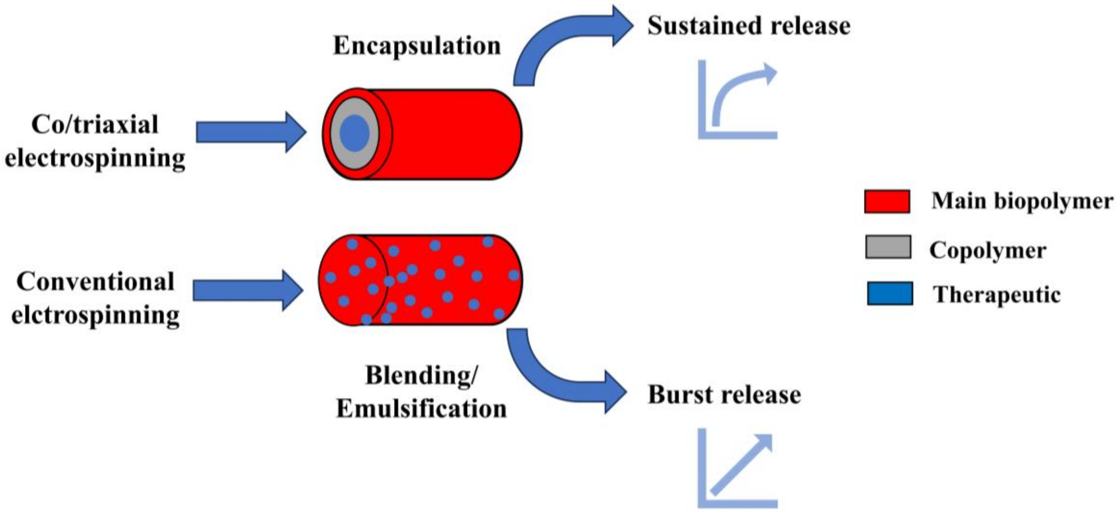


Fig. 20 Schematic representation for drug delivery system strategies of encapsulation and blending

Ekambaram et al. (2022) [240] prepared PCL NFs incorporated with the ZnO NPs, loaded with Docetaxel in the suspension for the ES process. The NFs showed excellent apoptotic activity of 48.84% against the lung cancer cells A549. The retention time of the drug was 11.74 mins with 4.47% of hemolysis. Overall, the system showed promising results for the target drug delivery. The second approach is encapsulation, used for drugs with opposite polarity compared to the matrix or the environmental sensitivity. Encapsulation is also helpful when sustained drug delivery is required. Khalili et al. (2022) [241] prepared a core-shell structure to deliver Indomethacin and Ciprofloxacin. The drugs were encapsulated in the core, while the shell comprised PCL, gelatin, and cellulose acetate. Less degradation and sustained drug release were observed in the NFs compared to the composites without core-shell structure and crosslinking.

One of the major issues with DDSs throughout their development is the rapid drug dissociation from the system, known as burst release [242]. It is a crucial problem for electrospun drug delivery systems as well. The burst release issue is resolved by coating the NFs system with other systems, mostly hydrogels [243] or multiple layering is done [2], or the drug is encapsulated [241, 244-246]. However, using a hydrogel system for the modification is not feasible since dealing with two systems makes the procedure more complex. ES can provide potential solutions to overcome the issue of burst release in the form of multilayering and core-shell structures [247]. In this way, the researcher has to deal with only one system of ES, which makes the procedure less complex and more industrial and upscale friendly one of the major approaches is multilayering. Deng et al., (2022) [2] prepared polylactic glycolic acid based NFs for the delivery of acetylsalicylic acid (Fig. 21a & b). They compared the monolayer NFs with the multi layered NFs. The multilayer NFs showed a 25% reduction in drug release (Fig. 21c).

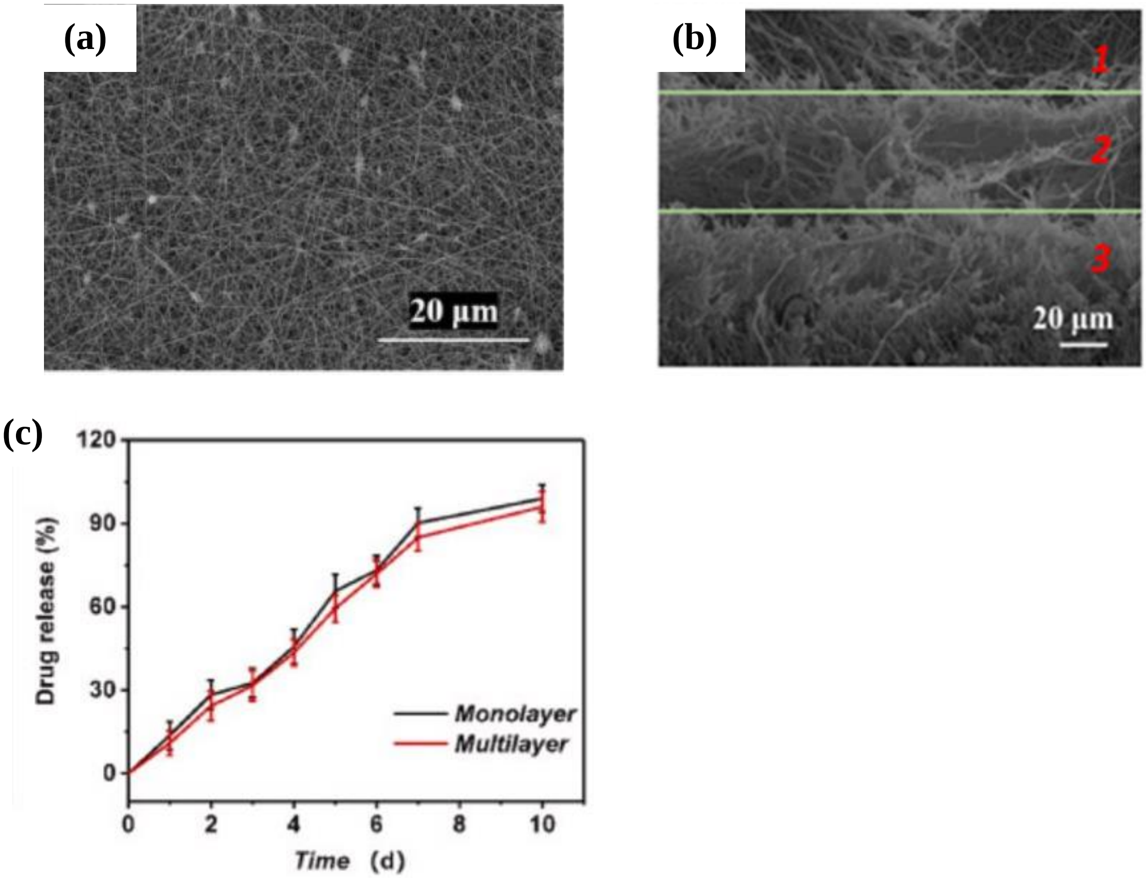


Fig. 21 Multilayered nanofibers based drug delivery system SEM image, (a) Overall biocomposite, (b) Three distinct layers, (c) Drug release comparison between monolayer and multilayer [2]

The other optimal solution is to use the CAES to create core-shell composite nanofibers comprising drugs or bioactive substances [148]. Abdolbaghian et al., (2022) [4] developed PLA/PVA/PVP based core-shell nanofibers for sage drug delivery. The core consisted of the PLA and sage, while the shell comprised PVP and PVA (Fig. 22a & b). They compared drug release of the core, shell, and core-shell structures. Their results showed that the drug release was reduced by 35% in the core-shell structure as compared to the dispersed drug loaded structures (Figure 22c).

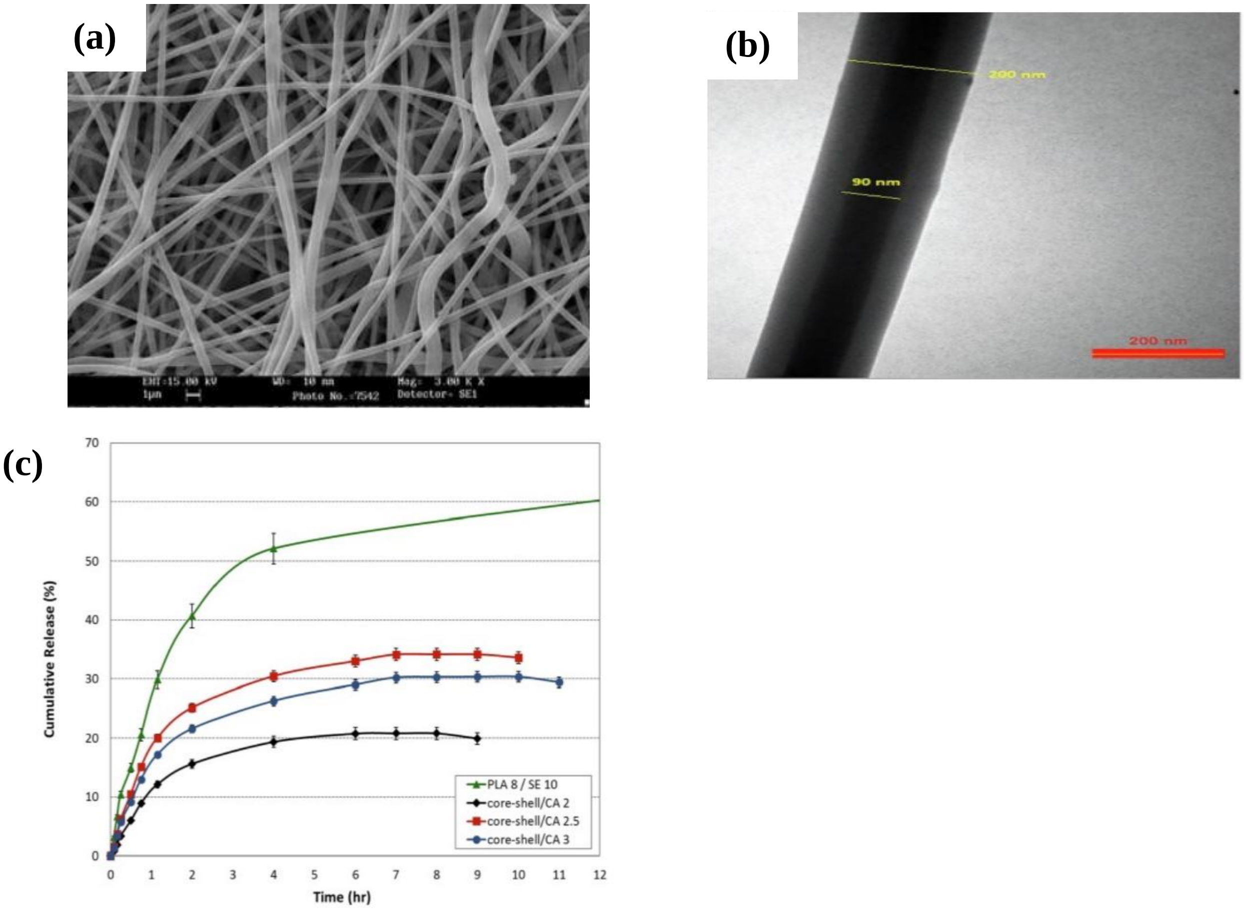


Fig. 22 Core-shell nanofibers based drug delivery system (a) Overall biocomposite SEM image, (b) Single nanofiber TEM image, (c) Drug release comparison between core-shell and simple morphology [4]

Different ES methods for the NFs based drug delivery system incorporating various properties and overcoming different issues of fabricating the system are enlisted in Table 12.

Table 12. Recent applications of electrospinning methods for biopolymers nanofibers based drug delivery systems

Electrospinning method	**Biocomposite composition**			**Drug loading strategy**	**Role of electrospinning technique**	**Reference**
	Drug **	Major biopolymers	Additives			
Suspension*	Ibuprofen+	Dextran	Polyvinylpyrrolidone (PVP)	Dispersion	Enhanced dissolution of poor soluble drugs	[248]
Suspension*	Naproxen+	Dextran	PVA	Dispersion	Degree of orientation and alignment improvement	[249]
Suspension*	Meloxicam+	PVA	Honey and acetylsalicylic acid	Dispersion	Fast dissolving drug delivery system	[250]
Suspension*	Amoxicillin++	pullulan	Poly lactic co-glycolic acid	Multilayering	The issue of burst release was overcome using sandwich technique for the drug layer	[251]
Suspension*	Docetaxel++++	PCL	ZnO nanoparticles	Dispersion	Incorporation of components in the biocomposite not possible by conventional techniques and sustained drug delivery	[240]
Coaxial	Indomethacin+/ ciprofloxacin	Gelatin/ cellulose acetate	PCL	Encapsulated	Improved biological response and controlled drug delivery due to encapsulation	[241]
Coaxial	Ciprofloxacin++	PCL	Gelatin	Encapsulated	Improved cell adhesion and hydrophilic interaction due to combining synthetic and natural biopolymer	[244]
Coaxial	Acyclovir+++	PLA	PEG	Encapsulated	Sustained drug delivery due to encapsulation	[252]
Coaxial	Doxorubicin++++	CS	PVA and PCL	Encapsulated	High drug encapsulation efficiency, sustained release, lower adsorption capacity	[253]

***Single needle electrospinning; ** Chemical name of the drug**

++ Anti-inflammatory; ++ Antibiotic; +++ Antiviral; ++++ Anticancer

7.3 Wound healing

Wounds only manifest once an external force has breached the skin's protective barrier (physical, chemical, microbiological, or immunological). Accidental skin damage is inevitable, and because an infection caused by the patient's germs is the most prevalent problem, treating the wound is crucial [254]. ES is critical in fabricating wound healing dressing using different biopolymer combinations and loading therapeutics. Drug loading in nanofibrous scaffolds is also possible via many methods, from incorporating bio-agents into the biopolymers scaffolds to encapsulating secondary drug delivery carriers [255]. In addition to these features, NFs biocomposites mimic the skin's ECM, which is crucial in maintaining cell adhesion, penetration, and proliferation [256, 257]. The NFs matrix porous morphology promotes nutritional and gaseous exchanges, adsorption of injury exudates, and prevention of microbial infection [258].

The stages of wound healing are illustrated in Fig. 23a [12]. Various factors affecting the process (Fig. 23b) include moisture, contamination, and oxygenation [259]. Different types of wounds follow various types of necrosis, and the WHS is decided according to the type of necrosis [260]. The optimal dressing system should have qualities like protecting against external factors like water and other physical factors, maintaining a moist medium at the wound site, allowing gaseous exchange, and draining excess exudate, hypoallergenic, non-toxic, non-adherent, and easily removed without damaging the wound are all critical functions of a wound dressing [261, 262].

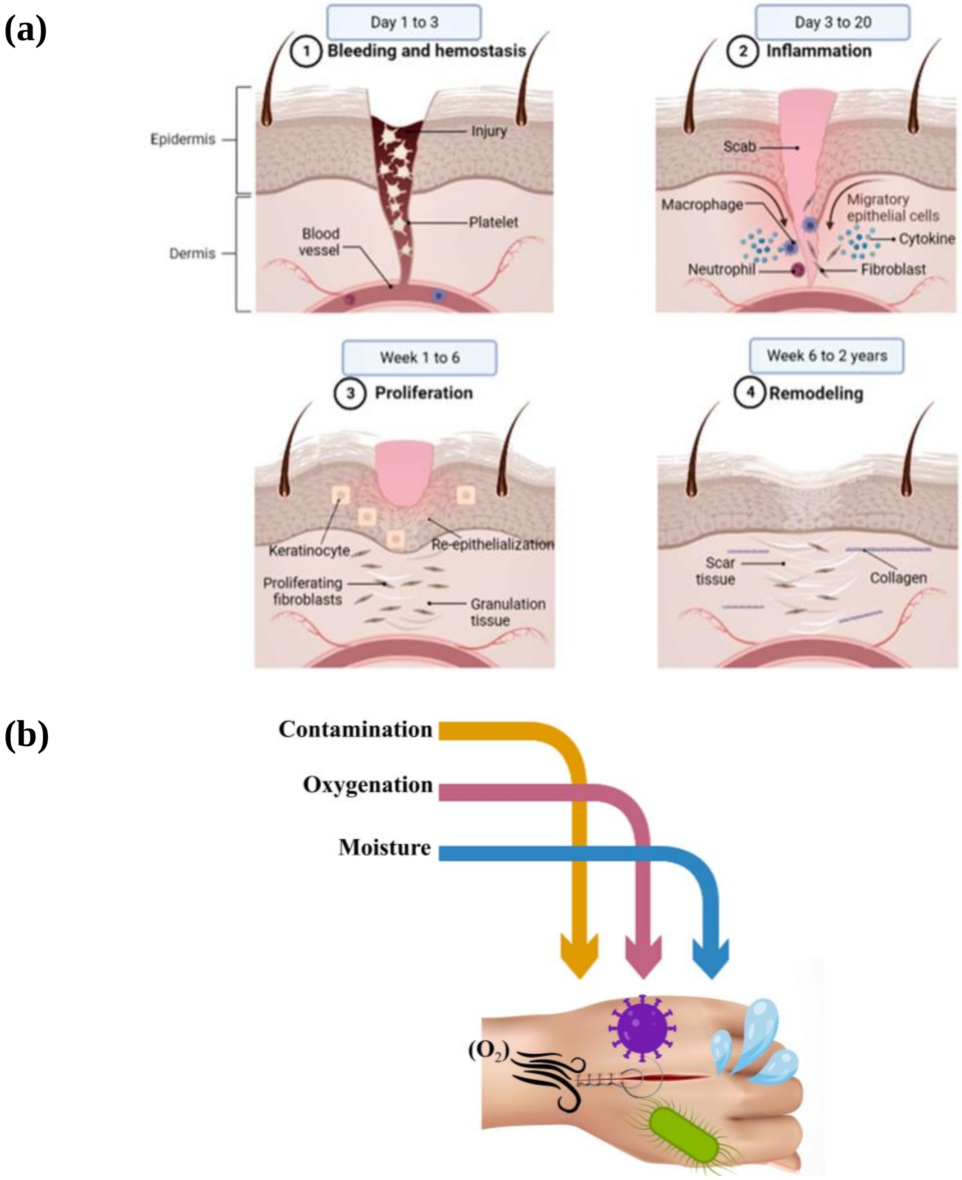


Fig. 23 Wound healing process (a) Different stages along with the time during wound healing [12], (b) Various factors affecting the wound healing

There are four major wound healing dressings (WHDs), and their significant features are shown in Fig. 24. The conventional wound dressings (passive, interactive, and advance) have one major drawback: they are not ideal for rapid recovery from chronic wounds [263]. WHS research focuses on the modern form of WH dressing, known as bioactive dressing, to heal chronic wounds. This WHS combines various dressing materials of certain qualities [264] or integrates drugs [265], nanoparticles [266], and other therapeutics [267] to boost the functioning (i.e., wound healing capabilities) of these dressings.

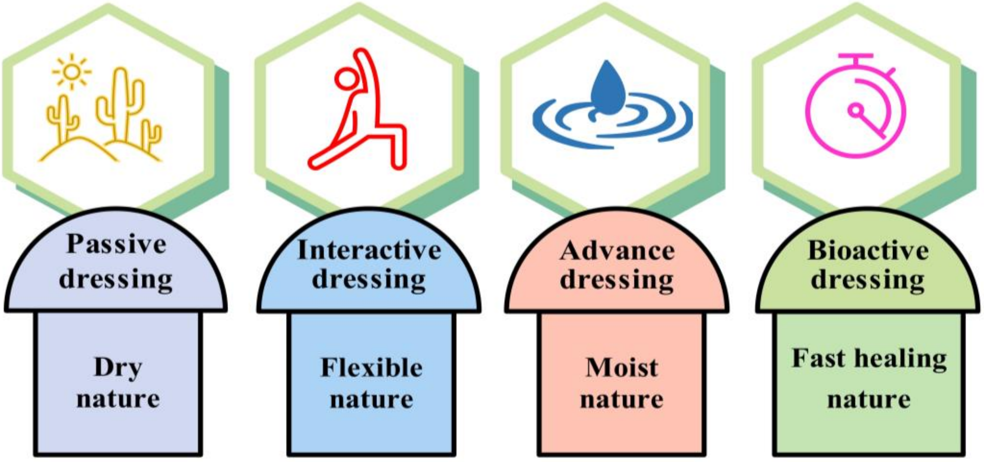


Fig. 24 Types of wound healing dressings

The development of the bioactive dressing is only possible through the ES efficiently. Since ES is the only option for combining various biopolymers, they cannot be prepared using conventional methods, even if their natural interaction is impossible [268]. These NFs based bioactive dressings are intended to respond to the wound's unique physiological environment. Through this interaction, wounds heal more quickly, with less scarring, and over a more extended period than possible without it [269]. The major requirement for chronic wound healing is the sustained drug release incorporating bioactive components and long-term interaction with the wound. All these objectives are mostly not possible by the other techniques. ES provides the flexibility of a novel combination of biopolymers and bioactive components. The issue of sustained release and long interaction is solved using the core-shell NFs based on novel systems for wound healing [270]. Liu et al., (2022) [1] prepared a CS and PEO based biocomposite (Fig. 25) with bioactive components, including curcumin and AgNPs. Due to the nano particle, the dressing showed antibacterial activity against gram-positive and negative bacteria. Curcumin, on the other hand, promotes enhanced wound closure and uniform collagen distribution compared to the commercially available AquacelAg. This NFs based WHS proved to be an excellent dressing for chronic wounds.

In Fig. 25, a hydrogel based WHS prepared by Hady et al., (2020) [17] has the same components as Liu et al., (2022) [1] NFs based WHS. The SEM images (Fig. 25a & d) showed the overall morphology of the dressings. In the case of NFs, a far superior porosity and high surface to area ratio can be observed, which is ideal for wound healing [271]. The TEM images (Fig. 25b & e) show the excellent dispersion of the AgNPs along with each fiber using the maximum surface area of the NP. However, in the case of hydrogel, NPs are embedded in the composite, reducing the surface area of NPs, thus, their antimicrobial effect. In comparing the systems swelling, the hydrogel showed a rapid increase in the swelling, indicating rapid drug release (Fig. 25c), while the NFs showed far better slow swelling, indicating sustained drug release (Fig. 25f) which required for the chronic wound healing treatment. The same composition based systems showed different properties and features just due to the change of technique and ES proved to be the superior technique.

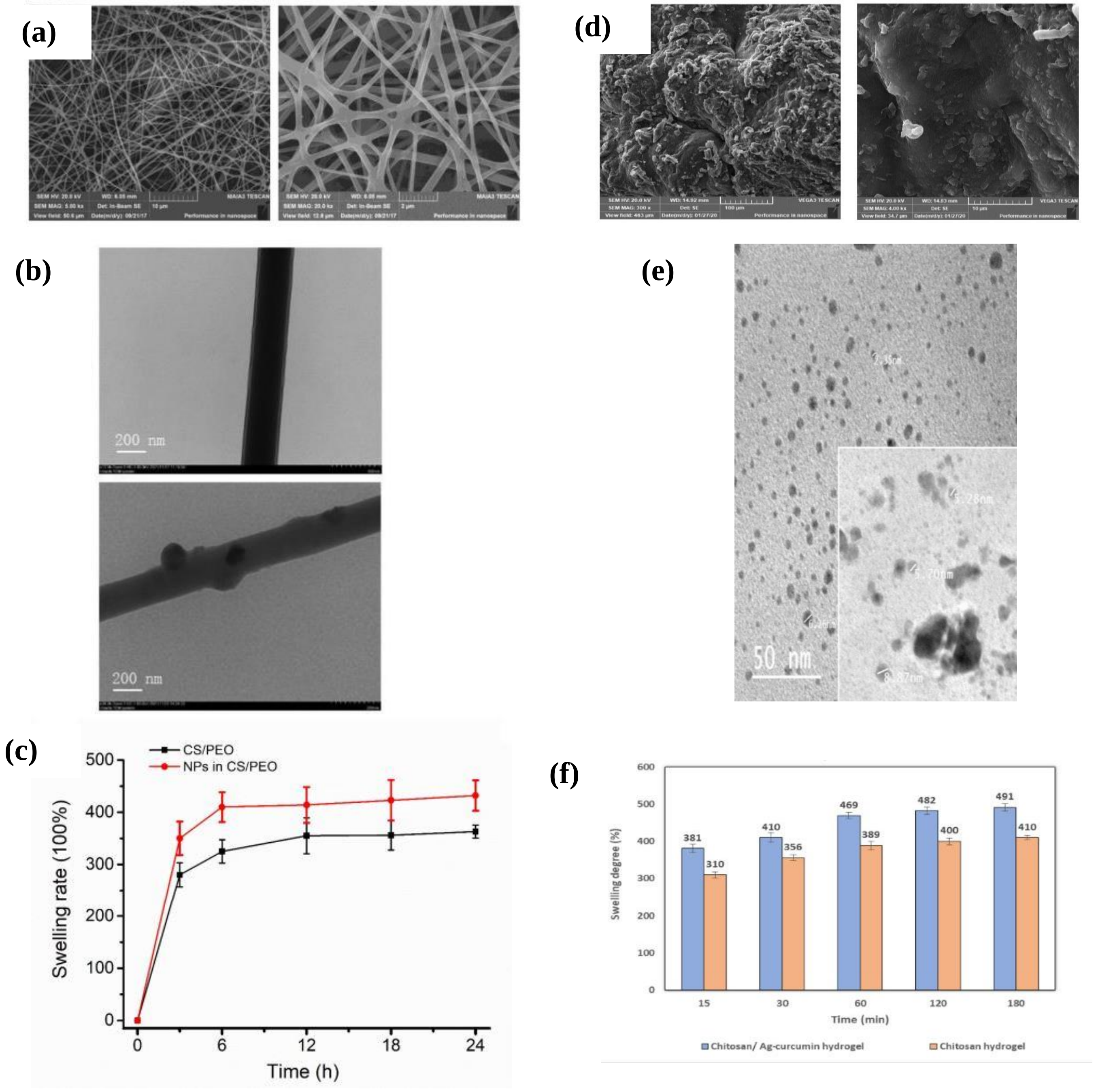


Fig. 25 Comparison of same composition based wound healing systems, hydrogels (a-c) and nanofibers (d-f), (a), (d) SEM images, (b), (e) TEM images, (c), (f) Swelling rates [1], [17]

In another study, Wu et al. (2022) [150] developed wound healing patch wo diabetic patients. The study was primarily based on the effect of biocomposite patterns on the development and differentiation of the cells. In the study, they fabricated a nanofiber and hydrogel based bi-layered dressing for the wounds. Their developed wound healing patches consisted of the radially aligned nanofibers of gelatin and polylactic acid for the biological cues. The developed patches showed enhanced cell recruitment and guidance ability to differentiate the human dermal fibroblasts (HDFS). Fig. 26a & b shows the graphical representation and fluorescent imaging of the migration of HDFS along the radially aligned nanofibers from day 3 to 7. Fig. 26c shows the cell viability test for the developed patches and confirms the successful differentiation environment mimicking the natural ECM.

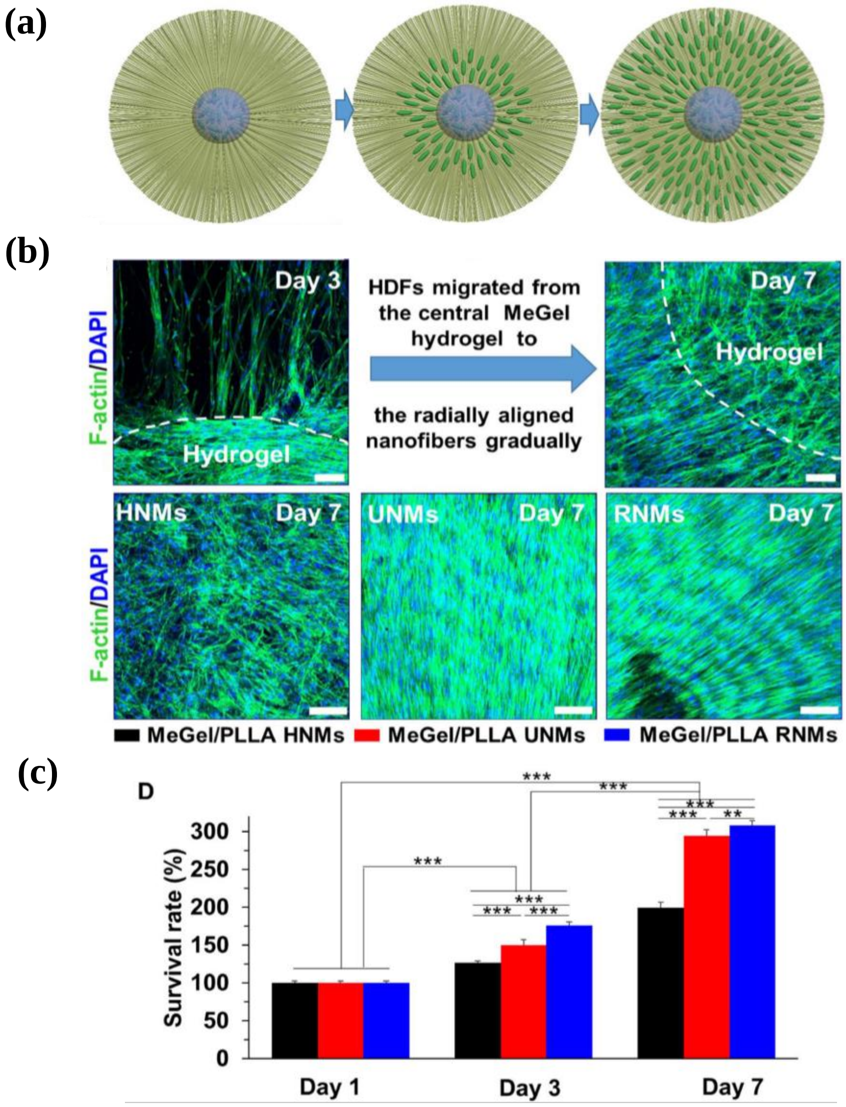


Fig. 26 Radially aligned nanofibers based wound healing patches, (a) Graphical representation of the phenomena, (b) Fluorescent microscope analysis, (c) Cell viability test

Table 13 enlists the recent applications of biopolymer based nanofibers for developing bioactive dressings and highlights the importance of ES in developing new features and improving natural properties in the biopolymers for wound healing applications.

Table 13. Recent applications of electrospinning methods for biopolymers nanofibers based wound healing system

Electrospinning method	Composite composition		Role of electrospinning	Resulting properties in nanofibers	Reference
	Major biopolymers	Additives			
Immersed*	AG	Silk fibroin/ exosomes	Improved mechanical strength of the biocomposite	Nominal water vapors permeability and excellent swelling properties	[272]
Coaxial	HA	Keratin/PCL/PEO	Effective drug loading and sustained release of the active component	No cytotoxic effects, increased cell viability, and proliferation	[273]
Multineedle/ spraying	HA	Polyethylene Oxide/various active components	HA based biocomposite formation with toxic crosslinker	Improved Antioxidant activity, cytocompatibility, and antimicrobial properties Water vapor transmission rate in the range suitable range for the prevention of infections or dehydration of wound	[274]
Immersed*	Cellulose	Gold and silver nanoparticles	Higher dispersion of the nanoparticles and high surface area	Enhanced antimicrobial activity as compared to the individual biopolymers	[275]
Suspension	CS	Sodium nitroprusside doped prussian blue NPs, and Type I collagen, PVA	Less aqueous stability of HA issues was resolved without toxic crosslinkers by ES with PVA	Excellent mechanical strength and water resistance over 14 days	[276]
Coaxial	CS	Silver@curcumin nanoparticles	Hydrophobic active component curcumin loading with hydrophilic CS, sustained release of NP due to encapsulation	Enhanced antibacterial property due to dual effect, uniform collagen distribution in the wound region	[277]
Suspension*	CS	Polyurethane/ linezolid	High mechanical strength, porosity, and surface area to volume ratio	Improved cell attachment, differentiation, and proliferation Excellent permeability for water, oxygen, and nutrient exchange	[278]
Immersed*	Silk fibroin (SF)	Collagen/sino menine hydrochloride/ kaempferol hydrate	Increased surface area of nanofibers results in the increased collagen coating for the deposition	Reduced inflammation and enhanced collagen deposition	[279]
Suspension*	SF	Magnesium nanoparticles	Better dispersion and sustained release of the NPs	Improved mechanical properties, optimal blood clotting ability, and better *In vitro* degradability	[280]
Suspension*	SF	Chondroitin sulfate and silver sulfadiazine	Novel combination of the biopolymers not previously possible	Better electrospinnability, one-time only application avoiding the pain and inconvenience due to changing of dressing	[281]
Suspension/ electro spraying	Collagen	Nanophase hydroxyapatite	Better mechanical strength resulting in the proper architecture for mimicking ECM	Passive differentiation in both osteogenic and adipogenic lineages, mechanically fit and local calcium delivery	[282]

***Single needle electrospinning**

8. Commercial products

Much research is being done on electrospinning, which is growing rapidly. Any research aims to upscale it to the industry level and commercialization of the product to reach the masses. However, in the case of electrospinning, the major issue with all the techniques is the reproducibility of the nanofibers and variations in every batch of nanofibers [283]. This is one of the reasons that most the electrospinning has not reached the industrial or commercialization level, especially in biomedical applications. A few recent electrospinning based products for various biomedical applications are listed in Table 14.

Table 14. Recent applications of electrospinning methods for biopolymers nanofibers based wound healing system

Product category	Brand name	Manufacturer	Main component	Key features	References
Face masks	SWASA®	E-Spin NanoTech Pvt. (India)	---	More filtration and clean breathability as compared to conventional masks	[72]
			---	Specialized face masks during surgery for the medical doctors	[72]
Surgical sutures and wound healing dressings	Surgiclot®	St. Theresa Medical Inc. (Eagan, USA)	Dextrin and fibrin	Sealent for the bone bleeding	[284]
	ReBOSSIS®	Ortho ReBirth (Yokohama-shi Kanagawa pref., Japan)	TCP (β-Tricalcium Phosphate), Bioabsorbable Polymer and SiV (Silicone-containing Calcium Carbonate	Bone filler that promotes the bone formation	[285]
	PK Papyrus®	Biotronic (Berlin, Germany)	Polyurethane	Thin and elastic membrane for stent coating	[286]
	HealSmart™	PolyRemedy®, Inc. (Concord, MA, USA)	Hyaluronic acid	Antimicrobial Dressings	[287]
	ReDura™	MEDPRIN (Guangzhou, China)	Polylactic acid	Material is similar to extracellular matrix (ECM) and promotes rapid repair and regeneration.	[288]
	Zeus Bioweb™	Zeus Industrial Products, Inc. (Orangeburg SC, USA)	Polytetrafluoroethylene	Ultrasmall fibers with the least chemical reactivity	[289]
Drug delivery patches	Rivelin® patch	Bioinicia (Valencia, Spain)	---	The system is specially designed for mucosal surface unidirectional drug delivery.	[290]

9. Conclusions and future prospectives

Biopolymers are now the center of attention for replacing petroleum-based polymers. Various conventional methods for fabricating biocomposites are available, but they lack nano-level tuning, biocompatibility, eco-friendliness, and reproducibility. ES emerged as the robust and tunable replacement for the conventional methods of fabricating biopolymers based NFs. However, in the present study, it was observed that the researchers primarily optimized the routine processing parameters (voltage, distance, and flow rate) or focused on changing biopolymers in the biocomposites. These routine parameters influence the properties and diameter of the nanofibers but they are just a small part of a large picture. Most of the other ignored parameters highlighted in section 3 can prove to be crucial especially the solvent related. The blend prepared for the ES has more to it; as the composition changes, so do the properties like dielectric constant, conductivity, surface tension, boiling point, and dipole moment changes, but these properties are not being considered in the current literature while designing the ES method for the specific applications in most of the studies. Different solvent interacts differently with the biopolymers and could play an essential role in the morphology and topology, significantly affecting application utilization. These properties are directly linked with the NFs morphology, as shown in section 3. While using conventional methods, solvent parameters could be ignored. However, these parameters should also be considered in the ES technique. This specific line of research is completely missing in the recent research for various applications presented in most current works, and ES is underutilized.

Various types of ES methods specifically depend upon the application type as every application requires a specific composition and morphology of biocomposite, and most of the time, the conventional methods cannot meet all the key requirements. TE requires a 3D environment for the proper proliferation and growth of tissues. TE scaffold should be biocompatible and sturdy enough to provide a 3D environment for the cells to grow. With the help of ES, we can fabricate a sturdy, nano-level tuned scaffold optimum for TE. The drug delivery system requires sustained drug release and protection for environmentally sensitive therapeutics. ES solves this requirement by encapsulating sensitive therapeutics by making core-shell assembly. This morphology helps protect and plays a crucial role in sustained drug delivery. Finally, the WHSs require sustained drug release and the environment for cell proliferation to heal the wound. The modern form of WH dressing, bioactive dressing, is only possible using the ES technique. Other than this, NFs also help in providing the porosity for the proper aeration and absorption of exudates by using biopolymers. But in all three major biomedical applications, researchers mostly vary the biopolymers or processing parameters and ignore the other crucial parameters, especially the solvent parameters.

Despite the major research in the electrospinning area to develop new instruments and products, the technique and its products still lack the industrial or commercialization reach. Nanospider is the only commercially available instrument with confirmed pharmacological uses. The core reason for this hindrance is the lack of universal procedures or experimental designs for the fabrication of nanofibers. Although many simulation models have been studied, no one has yet created a model that can reliably forecast the needle-based or needleless electrospinning characteristics. Parametric research and a lack of established thorough studies underpin the bulk use of the electrospinning process.

ES is currently the frontline technique to tackle biomedical issues but is being undermined. A rigorous study is required to examine the effect of various solvent parameters on the same biopolymer blend with the same setup parameters, which is lacking in the current line of research. These issues should be addressed in future research to get more benefits from this technique, and in this way, a general guideline can be established for the particular applications. That guideline would be helpful to take this technique to the industrial level and more commercialization of the products.

Conflict of Interest

The authors state that no potential conflicts of interest or personal ties might have influenced the work reported in this research.

Data and code availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary information

Not Applicable

Ethical statement

Not applicable

Authors contribution

All authors contributed towards drafting and critically revising the paper and agree to be accountable for all aspects of the work. The authors confirm that this manuscript has not been previously published and is not currently under consideration by any other journal.

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