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REVIEW ARTICLE

An overview on electrospinning and its advancement toward hard and soft tissue engineering applications

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Abstract

One of the emerging technologies of the recent times harboring nanotechnology to fabricate nanofibers for various biomedical and environmental applications are electrospinning (nanofiber technology). Their relative ease in use, simplicity, functionality and diversity has surpassed the pitfalls encountered with the conventional method of generating fibers. This review aims to provide an overview of electrospinning, principle, methods, feed materials, and applications toward tissue engineering. To begin with, evolution of electrospinning and its typical apparatus have been briefed. Simultaneously, discussion on the production of nanofibers with diversified feed materials such as polymers, small molecules, colloids, and nanoparticles and its transformation into a powerful technology has been dealt with. Further, highlights on the application of nanofibers in tissue engineering and the commercialized products developed using nanofiber technology have been summed up. With this rapidly emerging technology, there would be a great demand pertaining to scalability and environmental challenge toward tissue engineering applications.

Keywords Electrospinning · Spinneret · Feed materials · Wound healing · Tissue engineering · Drug delivery

Introduction

The evolution of nanotechnology in the recent years has provided novel approaches in restructuring materials conferring magnificent physical, chemical, and optochemical properties. Such fine tuning in the properties has given rise to materials of zero-dimensional characteristics that include nanoparticles or quantum dots; one-dimensional nanowires, nanorods, nanofibers, and nanotubes; two-dimensional nanosheets and nanofilms; and three-dimensional forms mostly comprising bundles or dispersions of several nanomaterials [1–4]. Among various nanomaterials, nanofibers have gained popularity as for its wide application is concerned. The outstanding features that make them unique from other nanomaterials are their high surface area to volume ratio, flexibility, mechanical strength, and high porosity. The materials with such characteristics are preferred as a robust candidate for much advanced applications pertaining to tissue engineering, drug delivery and sensors [5, 6]. In addition, they have also been widely employed in textile industries and in aerospace engineering for reinforced clothing. It is the fiber diameter that determines the performance characteristics, processibility, and practicability of the fibrous structures destined to various applications.

Indeed, these were the results of the pioneering works of Professor Darrell Reneker for the introduction, rediscovery, and popularization of the art of electrospinning [7]. It was by electrospinning that a number of materials such as polymers (synthetic and natural), carbon-based materials, semiconducting materials, and even nanocomposites have been recruited to create nanoscale fibers with superior characteristics [8–11]. Although there are several other alternatives in the fabrication and generation of nanofibers, electrospinning is the much preferred one owing to its simplicity, versatility and viability [12]. Most importantly, there has been a rapid progress in the fabrication and functional applications of nanofibers in biomedical, clinical, and healthcare settings.

Here, a critical review on the evolution, challenges, and emerging development of nanofiber technology in biomedical field and regenerative medicine has been elaborated. As

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electrospinning is the most sought after technique for synthesizing specific nanofiber for a wide range of applications including electronics, photonics, environmental treatment, energy generation and storage, a clear description about the timelines, fabrication techniques, and their broad spectrum application in areas encompassing biomedical engineering and healthcare industry have been discussed. Alongside, the current state and future directions augmenting commercialization and implementation have also been highlighted.

The need for fiber-based technology

Tissue engineering represents one of the emerging fields that adopt the principles of bio and chemical engineering in achieving the goal of tissue regeneration. It is for this that the technology utilizes various biomaterials, cells, and growth factors either solely or in combinations to restore, maintain, and improve the functional characteristics. This generally involves fabrication of tissue-like constructs mimicking the functional tissue with structural, topographical, and mechanical properties. Secondly, the construct must facilitate diffusion of nutrients and oxygen and removal of metabolic wastes as well during tissue regeneration. Indeed, there were some fiber-based techniques viz. weaving, knitting, braiding, electrospinning, and direct writing to facilitate the construction of 3D scaffolds and cell laden tissue constructs. Construction of such 3D synthetic frameworks would enable cellular attachment, proliferation, and growth, thus leading to the formation of new tissue. The scope of fabricating scaffolds potentially mimicking the natural human tissue at nanometer scale has drawn much attention owing to their high surface area to volume ratio and typical microporous structure that better suited to achieve desired effects in tissue engineering applications [13].

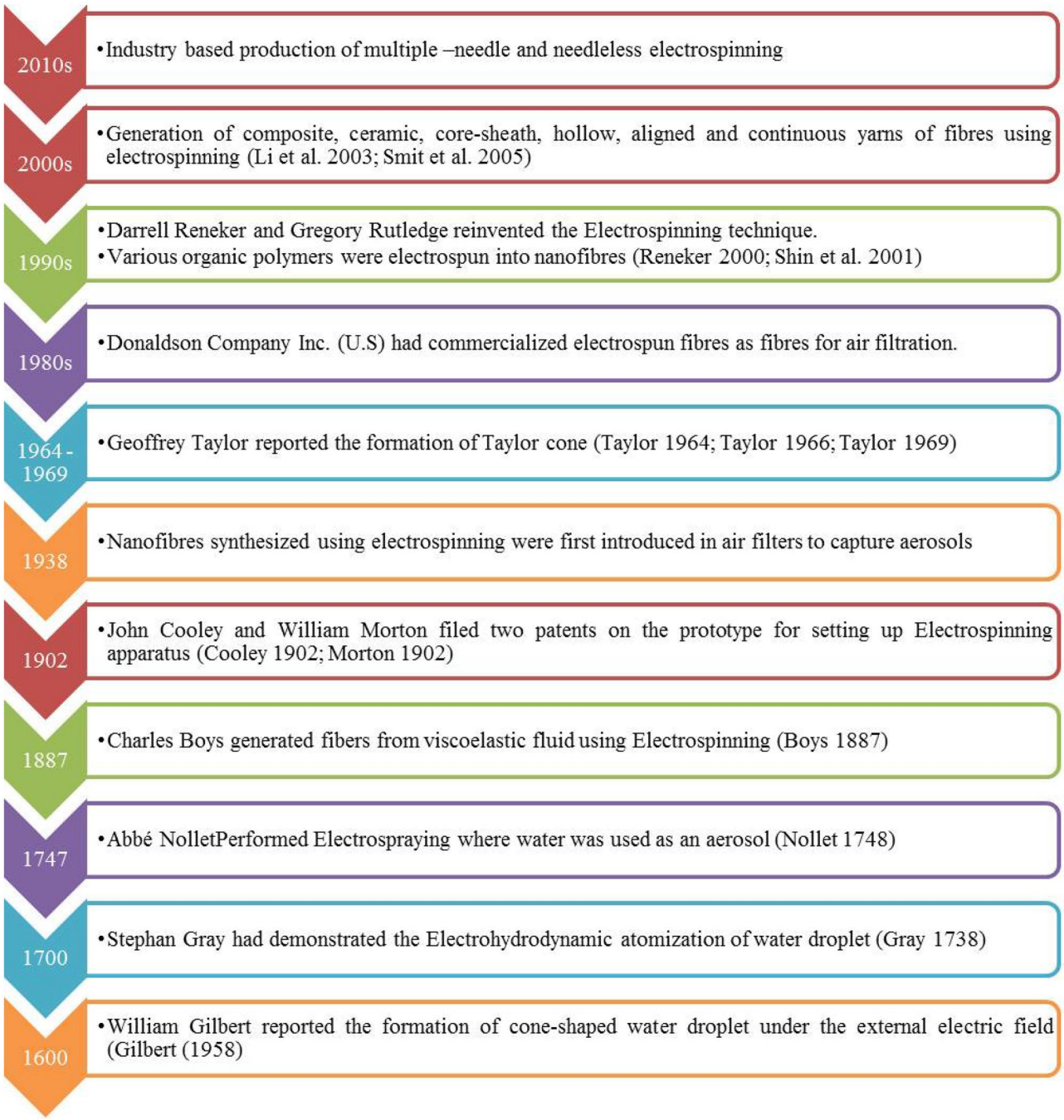
Fiber-based technology and their implications date back to several millennia where the fibrous structures were woven into textiles and used as clothing and for decoration. Their applications have been engineered and extended toward filtration, composite fabrication, energy systems, and microfluidics. In order to fabricate fibers, there are innumerous approaches such as electrospinning, wetspinning, biospinning, interfacial complexation, microfluidic spinning, and meltspinning. Among them, electrospinning seems to be the most promising and attractive technique for tissue engineering applications. It is this technique that offers a better prospect of controlling the thickness, composition of the nanofibers, and porosity with relatively simple protocol. In addition, electrospinning exhibits certain strengths with respect to scaffold fabrication viz. simplicity, efficiency in controlling the flow rate and voltage, and the scaling-up process. However, there are certain challenges associated with electrospinning such as fabrication of thick 3D complex scaffolds, poor control over high fiber packing density leading to small pore size (~ 10–15 μm), and poor cellular infiltration as a result of pore size. Although living cells were encapsulated in electrospun fibers by configuration of the coaxial needle connected to a syringe pump to facilitate constant flow rate, cells could not be accommodated by the fibers owing to porosity issues. Furthermore, cell encapsulated constructs could not be electrospun owing to the lack of control over the distribution of cells in a given volume. Though the cells can be arranged using high electric fields (~ 1–2 kV cm^{-1}), the fate of viability of the cells for tissue reconstruction needs further investigations [14].

Fabrication of biopolymeric fibers with varied topographical properties arranged in a spatiotemporal fashion at micro and/or nanoscale represents the initial step in a fiber-based engineering strategy. These fibers could be used as carriers for biological moieties and microorganisms depending upon the application. Moreover, the biological and mechanical properties of the fibers fabricated determine the functional aspect of the tissue constructs. One of the main characteristic features of the fiber-based technology in tissue engineering is the surface topology, which plays a pivotal role in directing the growth of the cell inside the 3D spatial arrangement [15].

Electrospinning: state of the art

Electrospinning is one of the most widely employed and established techniques used for the generation of specific fibers at different scales [16]. But before man could attempt constructing fibers, he had been greatly inspired by nature where spiders and silkworms served as an important source for the development of artificial fibers [17]. But an interesting fact is that man has already mastered the art of weaving during 5000 BC as evidenced from the fragments of cotton articles unearthed during archaeological excavation. Notably, silkworm cultivation began only during 2700 BC, and around 1300 BC, spindles were invented progressing into production of fabrics and clothes from wool and cotton leading to the establishment of textile industry in 1880s. Plant-based materials namely cotton or wood cellulose fibers were efficiently used by man to create the first synthetic product, Rayon, in 1891 [18].

Notably with the introduction of commercially viable synthetic fiber nylon by DuPont in 1938 by the integration of chemistry and polymeric science, the scope for fiber-based technology saw a great expanse in wide applications [19]. There were many methods developed for producing artificial fibers using polymers under the influence of various physical, chemical, and mechanical processes, where the resultant fibers were found to have



Scheme 1 Timelines in the evolution of electrospinning

limited stretchability and viability. It was Charles V. Boys who in 1887 had reported on the synthesis of fibers using a viscoelastic fluid (beeswax and collodion) under the influence of external electric field [20]. From then on, it was termed electrospinning that facilitated the synthesis of ultrathin fibers having diameters in the nanometer scale. A detailed timeline on the evolution of electrospinning has been schematically represented (Scheme 1).

It was clearly evident from the table that the electrospinning has evolved at a slow pace with the invention of electricity generation and insulation. It was only during the middle of the twentieth century that the development of spinnable polymer solutions and electrostatic work kick started and led to the establishment of markets for artificial fibers. Until 1995, there were considerable activity in patenting aspects and beyond

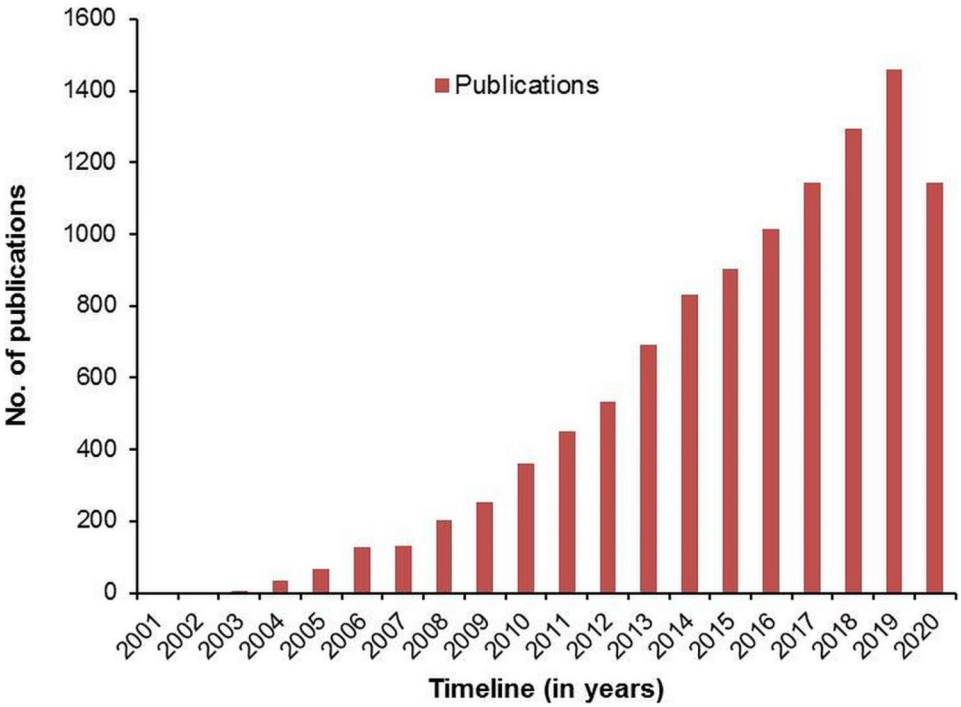


Fig. 1 Scientific evolution of Electrospinning technique in the past two decades. Number of electrospinning publications sourced from PubMed.gov all across the world

which there was significant progress in the volume of publications and scientific investigations. The publication portfolios generated in two decades from 2000 to 2020 have seen an exorbitant growth in the electrospinning technology and application toward biomedical and tissue engineering sectors (Fig. 1). In accordance, there is a positive trend where the technological inputs have been efficiently transformed into product and processes associated with healthcare settings [104, 145–156].

Electrospinning working mechanism

The working mechanism chiefly involves the electrohydrodynamic generation of ultrathin fibers under the influence of high voltage electric supply. In electrospinning process, a liquid drop (polymer/emulsion) is placed under high electric field to generate a jet followed by a sequential stretching and elongation (bending instabilities) resulting in a hyperstretching of the jet called fiber(s) [21, 22]. A schematic representation of the electrospinning process is illustrated in Fig. 2.

In the electrospinning process, there are certain key parameters that determine the efficiency of spun fibers, reproducibility, and consistency which include electric field strength, concentration and viscosity of the polymer solution, and spinning distance. The diameter of the fibers and its regulation is expressed by the following equation [23]:

$$d = \left[\gamma\varepsilon\frac{Q^2}{I^2}\frac{2}{\pi(2\ln\chi - 3)}\right]^{1/3} \quad (1)$$

where d represents the diameter of the fiber, γ corresponds to the surface tension, ε represents the dielectric constant, Q codes for the flow rate, I attributes for the current carried by the fiber, and χ pertains to the ratio of initial jet length to the diameter of the nozzle.

Although, Fridrikh Model tried to emphasize fiber diameter as a function of only some of the independent parameters, dimensionless index i.e. Berry's number was considered [24]. It is given as the product of intrinsic viscosity and the concentration of polymer present in the solution. It is this Berry number that had significantly brought in correlation between the electrospinnability and the fiber diameter [25]. The diameter of the fiber can be estimated using the following equation:

$$d = aB^c \quad (2)$$

where d is the fiber diameter, a represents Mark-Houwink constant, B, the Berry number, and c corresponds to an experimentally determined value related to but not dependent on the crystallinity of the polymer.

Nanofiber generating methods have been categorized based on the spinneret as single-nozzle, co-axial, and multi-nozzle electrospinning as shown in Fig. 3. Single-nozzle electrospinning remains one of the most convenient methods that involves electrification of polymer solution or melt in turn generating fibers mediated through a single orifice (Fig. 3a). This approach facilitates fabrication of composite fibers

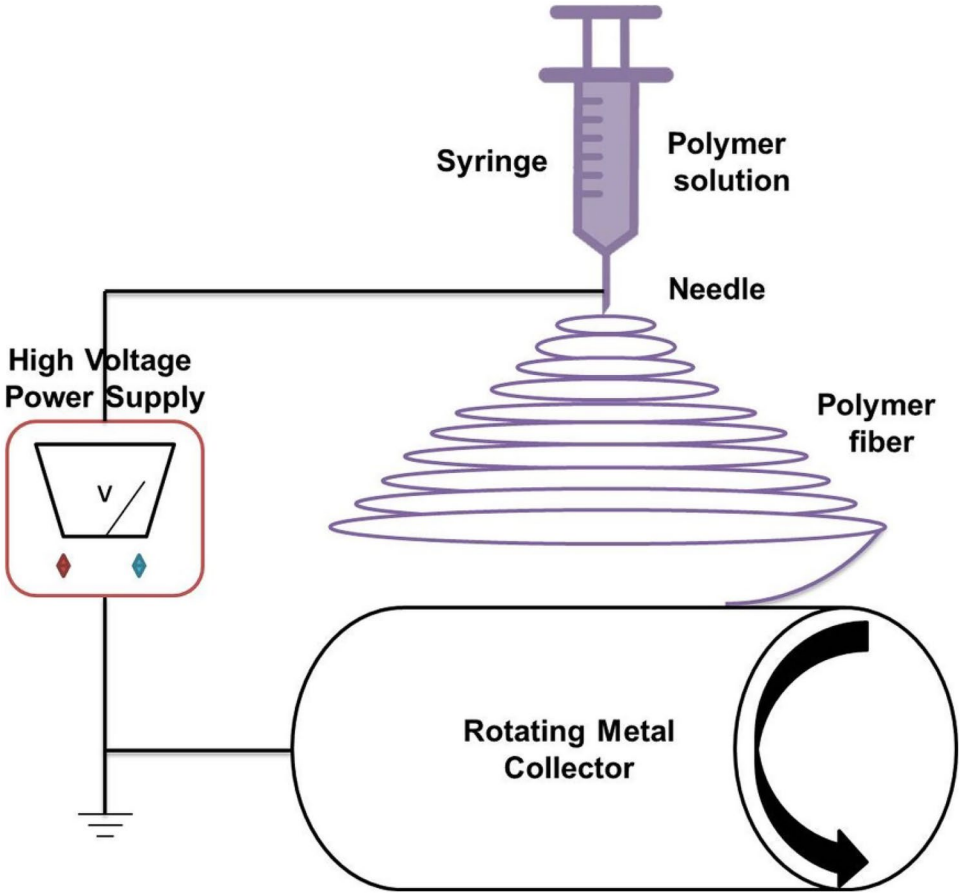


Fig. 2 Electrospinning process. Formation of Taylor cone by the electrification of liquid droplet which leads to the stretching of the charged jet (flying jet) followed by thinning of the jet into finer diameters owing to bending instability, solidification and collection of fine-tuned jet into fiber(s) onto a rotating metal collector

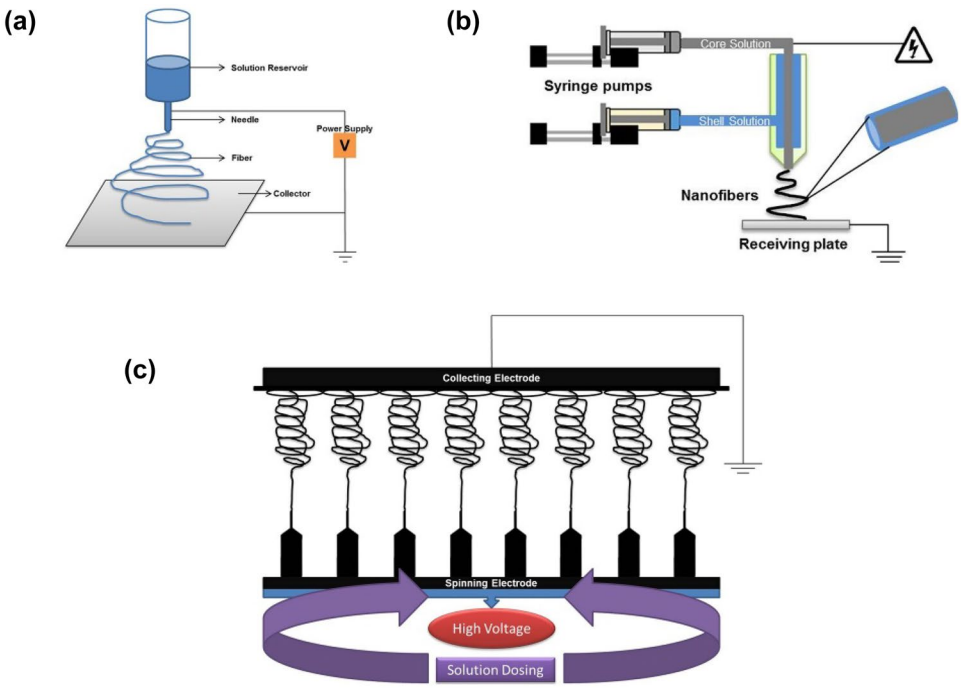


Fig. 3 **a** Single nozzle electrospinning involves generation of fibers through electrification of a polymer or melt flow through a single orifice. **b** Co-axial electrospinning is a modified version of multi-nozzle electrospinning to generate core–shell nanofibers, hollow fibers from non-electrospinnable materials. **c** Multi-nozzle electrospinning involves assembling of composite nanofibers generated from two or more immiscible polymeric solutions

integrating multiple polymer/solvent system. For instance, sodium alginate-polyethylene oxide (PEO) and chitosan-PEO blends were successfully electrospun for tissue regeneration applications. On the other hand, multi-nozzle electrospinning facilitates assembling of composite nanofibers generated from two or more immiscible polymeric solutions. Here, the nozzles (equipped with two power supplies) are placed either side-by-side or in opposite directions to the grounded collector (Fig. 3c). Yet another modification of multi-nozzle electrospinning is co-axial electrospinning (Fig. 3b) in which the spinneret with one nozzle is placed inside a larger nozzle to achieve generation of core–shell nanofibers, hollow fibers, fibers from non-electrospinnable materials for drug delivery, and protein translocation applications [26–28].

Scaffold-based electrospinning

The production of electrospun fibrous scaffolds obeys a different hierarchy involving variety of techniques based on the geometric control.

Dual extrusion electrospinning

This dual extrusion electrospinning is a technique used to fabricate multi-layered 3D scaffolds by stacking the microfibrous meshes of the two different feed materials in an alternate fashion to micro/nanomixed meshes. Alongside, this technique enables differential control of two different spatial geometries, namely, the polymeric concentrations and independent solvents. As a result, the micro/nanofibrous structures were made to combine as a single scaffold with definite control over the distribution of electrospun fibers. Hybrid scaffolds of two differently scaled fibers composed of two discrete materials have been fabricated to study the influence on the cellular response of human mesenchymal stem cells seeded on to the scaffold. Further analysis revealed that the electrospun nanofibers could maintain the cellular integrity enabling the deposition of glycosaminoglycan for cartilage regeneration [29]. In a similar fashion, a novel hybrid scaffold was fabricated using electrospinning by arranging the aligned fibers over the random fibers. This well organized scaffold provided uniaxial topographical architecture by the stability and support conferred by the random fibers. These random fibers enable desirable alignment and easy differentiation of cultured C2C12 myoblasts cells [30].

The application of hybrid scaffold for tissue engineering could help surpass the limitation of small pore size, thereby improving the cell migration. For instance, the bone regenerating ability of silk fibroin/poly(ε-caprolactone) nano/microfibrous composite scaffold was found to improve having associated with the nanofiber content in the composite scaffold [31]. Similarly, the cellular response of MC3T3-E1 cells on a micro/nanofibrous mat (PLGA-Col-HA) prepared by dual electrospinning was found significantly higher than on microfibrous PLGA scaffold and micro/nanomixed fibrous PLGA-Col scaffold [32]. Thus, dual extrusion electrospinning technique would be the much sought after approach for fabricating 3D scaffolds with different spatiotopographies and compositions for application toward drug delivery and bone tissue engineering.

Temperature-assisted (cryogenic/melt) electrospinning

Tissue constructs can also be fabricated using temperature driven electrospinning with the help of a temperature controller in order to improve the cell permeability. Cryogenic electrospinning is a technique that uses ice crystals to induce large pores in the electrospun fibers, i.e., it acts as a porogen. This involves the use of low-collecting system to facilitate simultaneous formation of nanofibers and ice crystals resulting in the formation of ice particle implanted fibrous mesh. Then, upon removing the ice particles by freeze-drying, pores are formed inside the electrospun scaffolds. It is by this approach that the porosity and pore sizes are varied by the size and amount of implanted ice crystals. The higher the amount of implanted ice crystals, the greater was the increase in porosity. One of the most important parameters, the humidity, was found to regulate the state of the ice crystals in the electrospinning environment. The scaffold pore size can be adjusted in the range of 10 to 500 µm which enabled the cellular infiltration of NIH 3T3 fibroblasts into a 50-µm-thick porous scaffold under static culture condition within 7 days and proliferated at large within a period of 14 days [33]. This crystal induced scaffold when placed into rat dorsum showed significant improvement in the infiltration of macrophages and collagen-producing fibroblasts in 56 days.

Furthermore, cryogenic electrospinning was recruited in the chemoresistance of cancer cells. For instance, cryogenic electrospun silk fibroin constructs were fabricated to mimic the cancerous extracellular matrix (ECM) onto which HN12 (human head and neck squamous cell carcinoma) cells were seeded to investigate the cell-to-matrix interactions and drug resistance. The highly porous nature of the cryogenic electrospun scaffold significantly supported cellular infiltration in a well-protected fashion. This approach mimicked the 3D culture model facilitating the replication of cells, differentiation, and infiltration interspersing the scaffold [34].

Cryogenic electrospinning mechanism works by blowing the polymer solution into cryogenic solution using pressurized gas channelized through concentric nozzles. Adopting this approach, fibrous scaffolds with controlled porous structures were fabricated by combining thermally induced phase separation and solution blow spinning. These

fibrous scaffolds are as a result of the ice microspheres that lead to the formation of interconnected networks with the fibers assembled directly onto the liquid nitrogen surface. Alongside, they tend to exhibit 3D architecture with interspersed macroscale pores [35]. Recently, porous fibers with extra nanotopography (with diameter 3.29 ± 0.42 µm) have been fabricated using self-made cryogenic electrospinning system. The pores embedded were found to exhibit pits and polygon concaves on their surface. The formation of pits and polygon concaves were induced by phase separation at freezing temperature and solvent interaction with ice crystals [36].

Melt electrospinning on the other hand constitutes another temperature propelled electrospinning technique utilizing higher temperature. This technique harbors a polymer melt in place of polymer solution to enable controlled fibrous deposition of 3D scaffolds with utmost precision in porosity and alignment. In accordance, the polymer placed in a syringe would be subjected to heating at ~ 400 °C and blown using air pressure. This technique is more advantageous as the use of most toxic solvents is circumvented. For instance, melt electrospinning was employed to deposit PCL over structured metallic collector substrates to produce batch-to-batch scaffolds with a mean fiber diameter of 15 µm and a pore size of ~ 250–300 µm on the concave side and ~ 20–80 µm on the convex side. When osteoblasts were seeded onto the PCL scaffolds, there was significant cellular infiltration, growth, and differentiation that mimicked the 3D environment [37].

Recently, Zhao et al. [38] have reported on a self-powered hand-held melt electrospinning device for in situ e-spinning on wounds directly. It is by the use of special high heat transfer insulation unit that the problem of electrostatic interference was surpassed. Moreover, the device is simple to use, reliable, and safe in handling due to its small volume of $24 \times 6 \times 13$ cm^3 weighing about 450 g. Most importantly, biocompatible and biodegradable polymers (polycaprolactone) were successfully e-spun into fibers directly on wounds serving as a dressing gun. Moreover, Großhaus et al. [39] have fabricated medical-grade poly(ε-caprolactone) adopting melt electrospinning by modifying the nozzle. This modification had led to the fabrication of fibers with the smallest mean diameter of $\sim 275 \pm 86$ nm under optimized conditions. This was achieved by positioning a small acupuncture needle to reduce the flow rate up to ~ 0.1 µL h^{-1} and by making the sharp tip protrude beyond the nozzle into the Taylor cone. To retain the material quality, the device was coupled with a dual head printer, and then the melt electrowriting could be performed to produce smallest melt electrospun fibers.

In recent years, melt electrospinning writing (MEW) is gaining popularity as this technique involves solvent-free fabrication of polymeric scaffolds. Moreover, the scaffolds with a large surface area, high porosity, and controlled deposition of the fibers could be fabricated using this technique. This was demonstrated by fabricating cell-scaffold constructs using poly(ε-caprolactone) using MEW for seeding primary human-derived dermal fibroblasts [40].

Needle-less electrospinning

The needle-less electrospinning system has been developed to address the limitations encountered in needle-based electrospinning system. This system is found capable of enhancing the production capacity of fibers by motivating numerous jets simultaneously from the free surface of the liquid or protuberances with the aid of high voltage that typically acts as fiber generators. For instance, Lukas et al. [41] have reported on the self-assembly of charged jets propelled out from the free surface of the liquid. The critical field strength E_c was given by $E_c = \sqrt[4]{4\gamma\rho g/(\varepsilon')^2}$ where γ represents surface tension, ρ corresponds to gravity acceleration, ε' signifies permittivity, and g implies acceleration due to gravity. It has been reported that the more jets produced, the lesser became the distance between individual jets when electric field was made stronger for the given solution. Moreover, the needleless spinning involves strict participation of spinneret and jet initiation from the liquid surface. But the criticality relies on making the electrical forces focus toward the surface of the solution prior to needleless spinning [42]. The parameters involved in needle-less electrospinning on a par with needle-based electrospinning have been enlisted in Table 1.

Ultrasound-enhanced electrospinning (USES)

One of the novel electrospinning techniques employed for the fabrication of nanofibers is ultrasound mediated electrospinning. This was the most recent technology which was patented by Laidmäe et al. in 2016 [165]. It is a continuous orifice-less technique that recruits high-intensity focused ultrasound to enable nanofiber synthesis from a free polymeric solution. The conventional electrospinning technique showcased some limitations such as needle clogging and precision control of the fiber properties which could be overcome by this novel approach. Ultrasound bursts were capable of generating a liquid protrusion with a Taylor cone from the surface of the polymeric solution (e.g., polyethylene oxide). When the polymer has been imparted with a high negative voltage, these nanofibers could jet off from the protrusion tip and successfully land on to the electrically grounded collector. The ease of controlling the ultrasound characteristics facilitated physical modification of the fabricated nanofiber at its topographical level in a non-chemical fashion. There was some phenomena viz. formation of ultrasound fountain relative to applied electric field, generation of capillary waves by ultrasound, cavitation, acoustic streaming, and thermal effects [43]. Similarly, Hakkarainen et al. [44] have investigated fabrication of nanofibers using USES and

Table 1 Needleless Electrospinning parameters involved in the fabrication of nanofibers for biomedical applications

Polymer drug	Technology	Presentation	Property/application	Reference
PCL	Partial immersion of disc spinnert in the polymer solution	Micro- and nanofibrous mats	Drug delivery and scaffolds	Lawson et al. [157]
SFP (silk fibroin protein)	Wire electrode spinneret fed by the solution	Nanofibrous sheet	Bone tissue engineering	Sasithorn et al. [158]
PLA/PEG-CyclosporineA	Nanospider®	Nanofibrous mats	Immunosuppression application	Sirc et al. [159]
PEG/PAN-keratin, collagen, dextran, and poloxamer	Nanospider®	Nanofibrous mats	Biotechnological applications	Böttjer et al. [160]
PLA/PEG-paclitaxel	Nanospider®	Micro-/nanofibrous mats	Localized chemotherapy	Hampejsova et al. [161]
CMC/PEG-diclofenac sodium	Nanospider®	Nanofibrous mats	In vitro sustained drug release	Kurecic et al. [162]
PCL-chlorhexidine acetate	Nanospider®	Nanofibrous mats	Antimicrobial agent	Manikandan et al. [163]
PCL/PVA	Nanospider®	Double-layered nanofibrous scaffolds	Wound dressing/abdominal adhesion and prevention	Klicova et al. [164]

compared with the one synthesized using the traditional electrospinning method for drug delivery applications. The nanofiber generated using USES had higher fiber diameter of 402 ± 127 nm over 77 ± 21 nm fiber synthesized using traditional method. Moreover, the increase in burst count had significantly increased the diameter of the fiber generated using USES up to 555 ± 265 nm with variation in the fiber size. The fibers generated using USES showed promising alternative over aqueous-based fabrication for drug delivery applications. Moreover, this approach confers numerous advantages such as generation of beadless fibers, ease of controlling the fiber diameter by regulating the cycles per ultrasound pulse, and fabrication of amorphous fibers which could not be achieved in traditional electrospinning.

Feed materials for electrospinning

Electrospinning involves the utilization of mostly organic polymers in the form of a solution or a melt to generate nanofibers. Besides, small molecules are also efficiently electrospun into fibers, provided that they exhibit the property of self-assembly and chain entanglement. Moreover, the involvement of sol–gel chemistry has taken electrospinning to a different level in generating fibers from composite materials. Notably, materials constituting different dimensions/morphologies such as nanoparticles, nanowires, and nanotubes can also be directly electrospun into fibers.

Polymers

Organic polymers are the most facile materials that can be directly used in electrospinning process. There are certain characteristics such as solubility, viscosity, electrical conductivity, spinnability, stability, reconcilability, dissolution into appropriate solvent system, and the recruitment of high molecular weight polymers that determine the success of electrospinning.

There are two methods, namely, solution and melt electrospinning, that utilize organic polymers as feed. Solution electrospinning is the most common method, where a jet of organic polymer solution is stretched, elongated and thinned by innumerous bending (whipping) instabilities. This is followed by the evaporation of the solvent, solidification of the jet, and deposition of fibers in the form of non-woven mat onto the grounded collector [45]. On the other hand, melt electrospinning involves direct generation of nanofibers from the melts of the solvent insoluble polymers such as polyethylene and polypropylene [46]. Although electrospinning process generates nanofibers with thinner diameter and varied architecture, the choice of the feed materials plays a vital role in deciding the functional aspects for biomedical applications. A list of commonly used polymers and their appropriate solvents used in electrospinning has been shown in Table 2.

Natural polymers

The natural polymers are derived from either plant or animal bodies and are considered excellent renewable resources possessing biodegradability and biocompatibility properties for biomedical and tissue engineering applications. Natural biopolymers such as DNA, silk fibroin, chitosan, chitin, hyaluronic acid, collagen, alginate, and dextran have been successfully electrospun into nanofibers. Besides plant and animal based polymers, the ones derived from sea weeds were also employed; in particular, the alginates with cross links are used as a potential biomaterial in fabricating scaffolds

Table 2 Polymers and their appropriate solvents used in electrospinning for the generation of nanofibers

Polymers (natural/synthetic)	Solvents used	References
Carboxyethyl chitosan/PVA	H_2O	Zhou et al. [166]
Alginate/polyvinyl alcohol	H_2O	Rafienia et al. [167]
Silk fibroin/polyethylene glycol	H_2O	Chutipakdeevong et al. [168]
Chitosan	H_2O/CH_3COOH	Jayakumar et al. [169]
Collagen/chitosan and collagen/zein	CH_3COOH	Chen et al. [170], Lin et al. [171]
Cellulose/polyethylene vinyl acetate	CH_3COOH	Konwarh et al. [172], Jannesari et al. [173]
Collagen and chitin	Hexafluoro-2-propanol	Matthews et al. [174], Rho et al. [175]
PLGA/collagen	Hexafluoro-2-propanol	Liu et al. [176]
Laminin 1	Hexafluoro-2-propanol	Neal et al. [177]
Gelatin	Hexafluoro-2-propanol and trifluoroethanol	Powell and Boyce [142]
Polyurethane/gelatin	trifluoroethanol	Kim et al. [143]
Hyperbranched polyglycerol	CH_3OH / Dimethylformamide	Vargas et al. [144]

and drug cargoes [47]. In this line, an excellent biomaterial chitosan is obtained by the deacetylation of chitin where the extent of deacetylation and pH define its charge density. Notably, the positively charged polymer has increased affinity toward negatively charged drugs or proteins that facilitates its wide applications toward drug delivery [48].

Beyond the incredible features of chitosan based polymeric scaffolds, they still lack sufficient mechanical properties for application toward tissue engineering applications. But, by structural configuration, ease of derivatization, and combination with other polymers, their mechanical properties could be restored. For instance, the surface modification of chitosan with hyaluronic acid had shown significant improvement in mechanical, biological, and non-degrading properties. These properties have extended the application of chitosan-based scaffolds in would dressings, skin grafting, tissue engineering, and drug delivery applications. In a similar fashion, nanofibrous membranes were fabricated by electrospinning chitosan and poly(vinyl alcohol) with antibiotics loaded at different ratios. The volumetric ratio of chitosan-PVA on the nanofibrous structure was found to be 50/50 as revealed by SEM. This composite electrospun scaffold had great potential as wound dressing to prevent infection in skin tissue regenerative procedures [49].

A bicomponent nanofibrous scaffold was fabricated by photocrosslinking of maleilated chitosan-methacrylated poly(vinyl alcohol) via electrospinning with improved water stability. The water stability test revealed that the electrospun photocrosslinked matrix formed in the ratio of 10:90 had excellent integrity of the fibrous structure. Alongside, the cytotoxic studies performed using L929 cells showed that the nanofibrous scaffolds exhibited excellent cytocompatibility for potential wound dressing application [50].

On the other hand, electrospun mats containing PVA-chitosan and PVA-chitosan-tetracycline hydrochloride (TCH) were fabricated by Alavarse et al. [51]. The electrospun fibers had shown even distribution of the drug along the fibers with significant thermal and morphological characteristics. These fibers facilitated burst delivery of the drug during the first 2 h typically exerting antibacterial activity toward *Escherichia coli* and *Staphylococcus aureus*. In vitro studies using rabbit aortic smooth muscle cells (SMCs) were carried out to investigate the cell viability and adherence of the cells over the scaffold by performing indirect contact MTT assay and scratch assay. The results revealed excellent biocompatibility with potential antibacterial action to hasten wound healing serving as a wound dressing.

Chitosan-based nanofibers have also been fabricated for diabetic wound healing applications. In this line, Ahmed et al. [52] have prepared nanofiber mats by electrospinning chitosan-polyvinyl alcohol (PVA)-zinc oxide solutions. These nanofibrous mat had a mean diameter size of 891.72 ± 10.65 nm at the cross over points and 279.34 ± 7.23 nm at the non-crosslinking points but remained finer and smoother. Moreover, the nanofibrous mat exhibited potential antibacterial activity against *E. coli*, *P. aeruginosa*, *B. subtilis*, and *S. aureus*. The wound healing activity of the nanofibrous mat in diabetic animal model showed significant wound closure of $90.5 \pm 1.7\%$ in day 12 showcasing as a promising dressing material for diabetic wounds. In a similar fashion, a wound dressing was fabricated by electrospinning PVA-chitosan-starch into nanofibrous mats and the healing property investigated. The nanofibrous mats exhibited high porosity of 91%, which was further controlled by the addition of starch. The mean surface roughness of the nanofibrous mats were found to be in the range of 262–435 nm. The fabricated nanofibrous mats showed in vitro degradation when immersed in PBS for 21 days characterized by thinning of the fibers pertaining to effective crosslinking of the mats. Moreover, there was a significant antibacterial effect in the range of 60–84% and 47–72% respectively for Gram-positive and Gram-negative strains respectively. The scratch assay demonstrated efficient migration of L929 cells from side to side of the artificial wound within 24 h [53].

Hyaluronic acid is one of the emerging and promising candidates investigated for tissue regeneration application. Hyaluronan is a linear anionic polysaccharide largely found in human tissues in the form of non-sulfated glycosaminoglycans (GAG), mainly involved in the regulation of cell adhesion, proliferation, and differentiation. It is one of the chief components of the extracellular matrix (ECM) having larger interactions with the key proteins present in the ECM. They are widely investigated in the fabrication of scaffolds in tissue engineering. Alongside, due to the polyelectrolytic nature, the solution turns more viscous making electrospinning very difficult. To achieve critical chain entanglement, HA fibers were introduced into sodium hydroxide-dimethylformamide system to generate fibers of 100 nm [54, 55].

In addition, the high surface tension of HA prevents the formation of highly concentrated solutions making the evaporation of water very difficult. In order to resolve, there were numerous attempts made to electrospin HA into nanofibers. One of the common approaches to electrospin polymers with low spinnability is by the use of a dragging polymer, with high spinning characteristics. This approach provides a core–shell nanofiber when HA solution was blended with chitosan [56]. Moreover, the addition of surfactants or a different solvent could help overcome the problem of high surface tension as demonstrated by Malkin et al. [57]. In their study, they concluded that the electrospinning stability could be achieved only below the critical concentration prior to the use of desired intermediate solvent. As a result, there was a positive effect on the spinnability by polymer–solvent demixing solidification mechanism.

Vitková et al. [58] have fabricated nanofiber electrospun using HA combined with PVA and PEO by using two intermediate solvent mixtures (water and isopropanol; water, ethanol, and methanol). Both these solvent mixtures facilitated electrospinning of HA of lower (600 kDa) and higher (1180 kDa) molecular weights, among which the lower molecular weight HA showed higher tendency to form spherical shaped particles. But the best results were acquired when HA at higher molecular weight was used and which was characterized by smooth fibers of a diameter of 100 nm making them promising candidates for tissue engineering applications.

Recently, Fuenteslópez and Ye [59] have fabricated electrospun fibers of HA-chitosan using a portable device. Their work typically demonstrated the electrospinning of HA and chitosan nanoparticles together with polymers such as PCL and gelatin with the aid of a portable device, the Oxford Portable Electrospinner (OPE). The polymeric blends were electrospun at random or aligned fiber arrangements by the device facilitating in situ fiber deposition on the targeted site. The cell viability experiments conducted using these electrospun nanofibers showed cytocompatibility up to 72 h. Moreover, the unidirectional arrangement of fibers helped the cells in guiding the proliferation of cells in a uniaxial fashion corresponding to nerve or muscle tissue repair. Altogether, the HA-chitosan blended polymeric nanofibers exhibited excellent biocompatibility, biodegradability, and non-immunogenicity making them promising carriers for drug delivery and tissue repair applications.

Collagen and its derivatives such as gelatin and other polypeptides are considered natural polymers predominantly found in the connective tissues of humans, spider silk, and mori silk. They are investigated for their multifunctional polymeric properties. Converting collagen into fibers offer good mechanical properties, porosity, and biocompatibility. They have been largely employed in tissue regeneration applications such as artificial skin graft, vasculature, tissue (cartilage) repair, periodontal restoration, and wound dressings [60].

One of the major advantages in fabricating electrospun collagen-based scaffolds is that they readily mimic the microscale architecture of native extracellular matrix present in the dermis. Collagen-based scaffolds are often utilized in wound regeneration and tissue engineering applications. For instance, collagen and chitosan have been electrospun into nanofibers and been applied to enhance angiogenesis and epithelialization of scalds in rat model [61]. In a similar fashion, Türker et al. [62] have fabricated electrospun hybrid scaffold comprising of collagen and poly(l-lactide-co-ε-caprolactone) (PLLCL) for 3D cell culture applications. Co-spinning approach was adopted to fabricate biomimetic scaffold by simultaneously electrospinning collagen and PLLCL, facilitated by a scarifying agent, polyvinylpyrrolidone (PVP). This electrospun hybrid scaffold exhibited 3D network structure with a 300–450-nm diameter for maximized cell adhesion of NIH 3T3 mouse fibroblast cells. Such biomimetic architecture showed a major impact of cell proliferation and viability on a par with 2D systems.

Li et al. [63] have fabricated radially aligned electrospun collagen-poly(ε-caprolactone) mats to accommodate gradients of stromal-cell-derived factor-1α (SDF-1α). These gradients were produced continuously in a controlled and reproducible fashion by regulating the collector size and time during the process of electrospinning. Fabricating a long-term gradient was facilitated by using SDF-1α with unique peptide of collagen-binding domain (CBD), capable of specific binding toward collagen. The results revealed that CBD-SDF-1α gradient scaffolds guide the endogenous neural stem cells to migrate from the periphery to the center along the lined up electrospun fibers. Such collagen-based nanofibrous scaffolds find its potential application toward nerve regeneration.

Guo et al. [64] have studied the physiochemical and biocompatibility properties of electrospun collagen-chitosan membranes applied toward guided bone regeneration. Apart from physiochemical characteristics, in vivo calvarial bone defect created on rats and the regenerative efficiency were investigated. The electrospun collagen-chitosan membranes showed higher tensile strength and more stable degradation rate. During the fourth and eighth week, ELISA was performed to quantify the bone alkaline phosphatase and

osteocalcin. The animal model on which the electrospun collagen-chitosan membranes were applied showed higher levels of alkaline phosphatase and osteocalcin in the fourth and eighth week respectively. Alongside, the radiographical and histological results revealed osteogenesis (new bone formation) with characteristic higher bone volume, trabecular number, and lower trabecular spacing.

Synthetic polymers

There are over 100 different types of synthetic polymers used for the direct generation of nanofibers adopting electrospinning. Some of them have been commercially used; in particular, polystyrene and poly(vinyl chloride) were used for environmental applications. Alnaqbi et al. [65] have generated nanofibrous sorbents adopting polymer blending strategy for the removal of various oil spills.

Indeed biocompatible, biodegradable, non-toxic, and mechanically stable synthetic polymers are largely been employed for the generation of nanofibers using electrospinning and used for biomedical applications. Few of them include poly lactic acid (PLA) and PLGA which can be directly spun into fibers and used as scaffolds in tissue engineering [66]. PLA offers the advantage of dissolving easily in different kinds of conventionally used solvents such as acetone, chloroform, dichloromethane, dimethylformamide, and tetrahydrofuran. It is prepared using condensation and ring opening polymerization techniques. As the former method would produce polymer with low molecular weight and poor mechanical properties, the latter would be the most preferred technique that introduces excellent mechanical stability [67, 68]. Alongside, in the derivatives of PLA, namely, poly-L-lactic acid (PLLA) and PLGA, the process occurs via copolymerization with L-lactide and polyglycolic acid respectively [69, 70]. These polymers when converted into nanofibers have profound implications in biosensors and molecular filtrations and been used even in preserving biological specimens [71, 72].

Conducting polymers constitute one of the recently emerged classes of polymers possessing remarkable properties on a par with the conventional polymers. Their characteristic π-conjugated backbone confers enough electrical conductivity upon charge transition by redox reactions. They possess typical characteristics of both the metallic (electrical and optical properties) and polymeric materials (biocompatibility, good processability, chemical stability) [73]. Polyacetylene was the first recognized conductive polymer in the 1970s and has been widely explored for its biophysical properties [74]. Due to the unstable nature and difficulty in processing of this polyene, some of the alternative forms have been introduced such as polyaniline, polypyrrole, polythiophene, and poly(3,4-ethyelenedioxythiophene) with improved thermal stability and conductivity [75]. Moreover, the biodegradable property has been introduced into conducting polymers by the copolymerization of aniline. Notably during electrospinning, these conducting polymers are mixed with biodegradable polymers and electrospun into nanofibers in the fabrication of scaffolds.

Besides innumerous conducting polymers, there are only few polymers that have been successfully developed into nanofibers. For instance, polypyrrole was subjected to pre-processing to attain adequate molecular weight by dissolving it in dimethylformamide and by the addition of di(2-ethylhexyl). Upon electrospinning, the polypyrrole was developed into nanofibers endowed with a thinner diameter of 70 nm [76]. Secondly, direct electrospinning of PANI with PLA/gelatin was developed into nanofibers imparting an electrical conductivity of 4.2×10^{-3} S cm^{-1} and has been used for cardiac tissue engineering applications [77, 78]. There are different functional polymers such as polyvinylidene fluoride and polyvinylidene fluoride-co-trifluoroethylene with enhanced piezoelectric and pyroelectric properties that can be directly electrospun for energy harvesting and biosensor applications [79, 80].

Reactive polymers

Natural and synthetic polymers have been widely used in electrospinning for the development of fibers. In recent years, focus towards the synthesis of reactive and functionalizable nanofibers has drawn much attention. For instance, conjugating appropriate small molecules, ligands, and/or biomolecules into the nanofibers have introduced functional aspects in the generated fibers (Fig. 4). Recent advancement in controlled polymerization techniques has facilitated the fabrication of nanofibers with functional aspects. Moreover, nanofibers developed from polymers with reactive functional groups can undergo post-polymerization modification even under mild conditions. Such fibers offer excellent platform for functionalization of wide variety of polymers intended for desired biomedical applications. The functionalization of the polymers are achieved either by adopting covalent and non-covalent methods. Encapsulation and chemical-mediated attachment facilitate incorporation of active agents (drugs), biological moieties (enzymes, proteins, extracellular matrix etc.), and growth factors for varied applications.

Moreover, fabrication of functionalizable nanofibers is achieved by post-spinning activation of polymers or by direct spinning of reactive and clickable polymers. Conventionally, the surface modification is done by surface activation processes such as plasma treatment or wet chemical methods. This approach poses challenges in achieving homogenous surface activation in turn compromising the fibers stability. To surpass these challenges during post-spinning fiber modifications, recruitment of polymeric precursors possessing specific reactive-functional groups would be the most appropriate strategy in introducing the functional aspects directly into the electrospun fibers. This was facilitated by click chemistry that led to the synthesis of wide variety of reactive polymers. Some

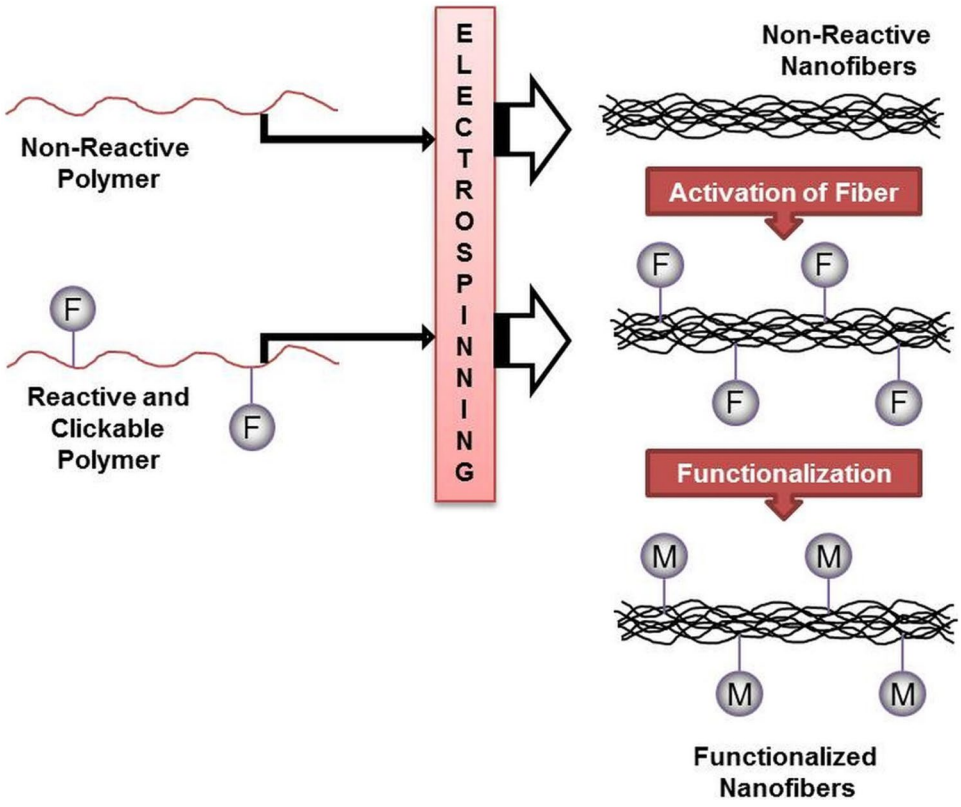


Fig. 4 Typical functionalization of a non-reactive polymer into a reactive polymer mediated by electrospinning and activation

of the most commonly used post-polymerization modification reactions include the following: Huisgen-type copper-catalyzed azide-alkyne cycloaddition (CuAAC), Michael-type nucleophilic thiol-ene conjugate additions, the Diels–Alder, inverse electron demand Diels–Alder cycloaddition, strain-promoted azide-alkyne cycloaddition (SPAAC), and thiol-ene conjugate additions [81–83].

There are instance of fabrication of covalently crosslinked and amine-reactive microcapsules in the form of layer-by-layer assembly of reactive polymers. This has been accomplished by alternating the adsorption of interacting polymers on the surface. Fabrication of such assemblies finds vast application toward catalysis, nanofiltration, preparation of hydrophobic and antimicrobial surface coatings, biomedical device coatings, and drug and gene delivery. This approach was demonstrated by encapsulating high molecular weight FITC-dextran in BPEI/PVDMA (branched poly(ethylene imine)/poly(2-vinyl-4,4-dimethylazlactone)) capsules [84]. Similarly, Broderick et al. [85] have fabricated layer-by-layer assembly of oligonucleotide and protein arrays onto multi-layered reactive polymers comprising PEI and amine reactive, azlactone-functionalized PVDMA. This assembly could efficiently hybridize complementary sequences with high signal intensities and with high sequence specificities. The azlactone groups present in the set up was exploited to immobilize proteins and to fabricate functionalized arrays of proteins and enzymes. Such type of approach has enabled the development of new assay format viz. application toward biomolecular arrays.

Materials fabricated with fascinating properties are most sought in biomedical, environmental, and industrial applications. As with growing incidences of bacterial colonization, infections, and resistance to conventional antibiotics, a novel approach of non-biocidal means has gained significance. Bacterial quorum sensing remains one such target connected with virulence, which need to be countered in order to limit growth and reduce infections. A nanoporous, polymer-based superhydrophobic coatings was fabricated to encapsulate a potent, water-labile peptide-based quorum sensing inhibitors in *Staphylococcus aureus*. The peptide-based quorum sensing inhibitors were released in a controlled fashion over a period of 240 days, and they could strongly inhibit agr-based quorum sensing in *S. aureus*. Fabrication of such materials through electrospinning process has enabled non-bactericidal approaches for the long-term attenuation of quorum sensing–mediated bacterial phenotypes [86].

In a similar fashion, non-woven polymeric nanofibers have been encapsulated with quorum sensing inhibitor to inhibit quorum sensing and virulence in *S. aureus*. This quorum sensing inhibitor (a macrocyclic peptide) has been loaded onto a degradable polymeric nanofibers using electrospinning. As a result, the inhibitor when kept under physiological conditions was found to be released over a period of 21 days, thereby exhibiting agr-based quorum

sensing inhibition in *S. aureus* at least for 14 days and without inducing cell death. Furthermore, these materials were also found to inhibit production of hemolysins, quorum sensing–controlled virulence phenotype, and reduced lysis of erythrocytes. Such quorum sensing inhibitor–based strategy has led to the development of novel anti-infective materials and therapeutic strategies targeting virulence [87].

Small molecules

They are one of the challenging materials which can be directly made into nanofibers using electrospinning. Their unique self-assembling characteristics with a significant chain entanglement capable of stabilizing the electrified jet and suppression of Rayleigh instability could help achieve typical nanofiber. Notably, the small molecules' structure-concentration interrelationship and the type of solvent decide the success of electrospinning for the generation of fibers. Mostly, the small molecules involved in the development of nanofibers constitute amphiphiles and cyclodextrin derivatives [88]. Most importantly, lecithin, a zwitterionic mixture comprising glycerophospholipids and phosphatidic acid, was the first reported small molecule to be developed into nanofibers. Its hydrophobicity and surface tension reduction potential have made them the suitable candidates for regenerative applications, thereby modifying the structure and surface area of the scaffolds [89].

Secondly, their self-assembling properties tend to form spherical micelles above the critical micelle concentration (CMC). By increasing the concentration further, the morphology undergoes a transition from spherical to columnar structures which again overlaps to form chains resembling fibers. The criticality relies on the concentration of lecithin to the amount of solvent used in achieving the desirable fiber diameter. For instance, the ratio of lecithin:$CHCl_3$:DMF at 70:30:43 (wt%) yielded continuous fiber with an average microscale diameter of 2.8 µm whereas the concentration of DMF when increased to 50% (> CMC), the fibers generated had a diameter of 5.9 µm [90]. In addition, Gemini ammonium surfactants N,N′-didodecyl-N,N,N′,N′-tetramethyl-N,N′-ethanediyldiammonium dibromide (12–2-12) in H_2O-CH_3OH have been successfully electrospun into micellar microstructured hydrophilic nanofibers with diameters in the range of 0.9 to 7 µm [91, 92].

Recently, peptide derivatives of the pyrazole-isothiazole scaffold have been specifically fabricated using electrospinning. For instance, phospholipid amphiphiles, tetraphenylporphyrin compounds, and cyclodextrin small molecular system have been successfully electrospun into nanofibers [93]. As mentioned earlier, the type of the CD used and its concentration decide the morphology and the fiber diameter. The disadvantage of the formation of bead-like nanofibers could be overcome by using CD owing to its tendency to form aggregates via hydrogen bonding and exhibiting high solution viscosity and viscoelastic solid-like characteristics [94]. Moreover, the CD offers truncated cone-shaped and relatively hydrophobic cavity in which the drug of choice can form inclusion complex with hydrophobic drugs with hydrophilic exterior, thereby increasing the water-solubility of drugs for prolonged delivery applications [95]. Xiang et al. [96] have developed hydroxypropyl-β-cyclodextrin-polyvinylpyrrolidone-loaded resveratrol nanofibers to enhance the water solubility of resveratrol and to remain stable under UV irradiation. In vitro studies conducted have revealed its slow and sustained release via nanofiber extrusion. The ratio of HP-β-CD to PVP at 1:2 yielded nanofibers with smooth surface and uniform thickness. Further, upon optimizing the concentration of resveratrol to 5%, the solution viscosity corresponded to 4.06 Pa.s attributing for good fiber morphology with an average diameter of 500 nm.

Colloids

Colloidal particles comprises of homogenous non-crystalline substance either found in dispersed or continuous phase. They may include gels, sols, and emulsions where they can be successfully electrospun into nanofibers, once they are capable enough to form entanglement among the dispersed particles to form a jet. This colloid-electrospinning has been a widely used technique to immobilize the particles in fibers at nanoscale dimension. The essential criteria for electrospinning rely on the size and viscosity facilitated by hydrolysis or condensation process. Most importantly, the viscosity tends to be one of the important parameters deciding the size/thickness of the fibers generated. Conversely, sol–gel method was the typical alternative and widely used method for the generation of nanofibers. For instance, by using tetraethyl orthosilicate (TEOS), distilled water, ethanol, and HCl at the molar ratio of 1:2:2:0.01, the silica sol was successfully electrospun into fibers employing acidic catalysis reaction [97]. The thickness of the fibers generated was found to be in the size range of 200–600 nm with an applied voltage of 12–16 kV. Similarly, lithium-cobalt acetate nanofibers with diameter ranging from 0.5 to 2 µm were generated by calcination method [98]. This method was employed to synthesize metal oxide nanofibers comprising aluminum, zinc, nickel, and cobalt at micrometer scale dimension owing to limited control over the size and uniformity of fibers influenced by the rheological properties of the sol [99].

Further, metal nanoparticle comprising silver known for its antimicrobial properties have been electrospun by integrating with synthetic polymers such as PEO, PVA, PVP, and polyacrylonitrile [100] or with natural polymers such as chitosan, gelatin, and N-carboxyethylchitosan [101]. For instance, in situ reduction of silver nanoparticles using formic acid as a solvent was integrated with polyamide 6 and electrospun. This nanoparticle incorporation has attributed for enhanced resonance spectroscopy (SRS)

[102]. It was Chen et al. [103] who unraveled the mechanism behind the nanoparticle-polymer interaction where the π-π co-ordination between the silver moiety and polymer facilitates photoexcitations and charge transfer endorsing optical application.

Applications of electrospinning in biomedical and environmental sector

Prior to thorough understanding on the fundamentals related to physical and functional properties of electrospinning materials, this section attempts to bring out the implications of nanofiber technology toward biomedical and environmental sectors. Nanofibers are mostly applied in fabricating scaffolds for either tissue regeneration or effective drug delivery. Conventionally, tissue regeneration was made possible by involving auto- and allografts. Autograft, although genetically feasible, pose greater challenge toward the availability of donor sites in case of larger affected area. As this could not solve the purpose of grafting and inturn the donor may suffer heavy damage due to the removal of tissues. Besides, the possibility of rejection would be greater when a genetically different material is introduced in case of an allograft due to immunological response. To counterbalance the regeneration and compatibility, this novel tissue regeneration approach has established a biocompatible arena for the host tissues to adhere, proliferate, and differentiate into specific tissues that need to be repaired [105]. This could be achieved by the nanofibers for its enhanced surface area and porosity that drives the regeneration efficacy of the scaffolds [106].

Tissue engineering

The requirements for successful growth of tissues via nanofiber scaffolds produced using electrospinning have made this technology the most preferred one. Properties such as biocompatibility, biodegradability, large surface area, maintaining the structural integrity, high porosity, and high mechanical stability have improved the growth and differentiation of cells [107]. Mostly nanocomposite materials similar to extracellular matrix (ECM) proteins (collagen and glycosaminoglycans) are preferred for their improved cell function and cell–cell/cell-ECM affinity. Notably, thinner fibers with diameter in the range of 50–200 nm have been reported to enhance cell adhesion, proliferation, and alkaline phosphatase activity [108]. Furthermore, the unique properties conferred by these core–shell nanofibers and their ease of manipulation pertaining to mechanical and electrical properties have augmented the scope for tissue engineering. The incorporation of antimicrobial nanoparticles such as Ag, Au, Zn, Ti, Mg, Cu, SWCNT, and graphene [109–111] and polymers (chitosan) [141] into the nanofibers via electrospinning have profound implications in the fabrication of biomedical devices, textiles, and tissue engineering. Some of the nanofiber scaffolds that have been successfully electrospun and extended to tissue engineering applications have been enlisted in Table 3.

In tissue engineering applications, there is a novel in situ approach that holds promise in the regeneration of functional blood vessels following the guidance of vascular scaffolds. The tubular design with multi-layered wall mimicking the native blood vessel architecture has been the most sought after model [112]. It is in this model that the tunica intima takes care of the functional properties by accelerating endothelialization and preventing thrombus. Secondly, the media confers mechanical stability to the vascular scaffold at the anastomotic sites and thereby avoids architecture remodeling. In order to achieve better endothelialization, critical evaluation on the inner and middle layers of the tubular shape needs much consideration. This greatly helps in supporting increased blood flow without leakage in the lumen and checks for anticoagulation properties in preventing stenosis and occlusion that determine the lumen patency [113].

For instance, nanofibers with introduction/loading of heparin or arginine-glycine-aspartic acid have been used to fabricate lumen to evade early thrombosis [114]. Recently, Eilenberg et al. [115] have designed a novel degradable thermoplastic polycarbonate urethane (dPCU) grafts for small vessel replacement in rodents. They have reported an upregulated anti-inflammatory signaling in dPCU conduits offering excellent patency rates of 92.9% without causing any adverse effects in rat model. When compared to expanded polytetrafluoroethylene (ePTFE), dPCU grafts accelerated transmural ingrowth of vascular cells into a structured neovessel around the graft with gradual reduction of graft material. In addition, natural biopolymer silk has shown promise in the fabrication of vascular scaffolds using a bilayered *Antheraea assama* (AA) and *Bombyx mori* (BM) silk. This hybrid model with its inner layer measuring 40 µm and interconnected pores has accelerated cellular infiltration whereas the outer dense layer offers mechanical stability.

Human adipose tissue-derived stromal vascular fraction seeded silk vascular graft was implanted surgically in Lewis rats as an abdominal aortic interposition graft. It was inferred that AA silk laden vascular graft showed superior animal survival and graft patency after 8 weeks. Further, these silk laden vascular grafts degrade into amino acids, and their resorbable byproducts well elucidates its remodeling ability [116]. This approach remains to be the futuristic vascular alternative for bypass and reconstructive surgeries.

The functional properties of the electrospun nanofiber-based scaffold have been improved with respect to architecture and mechanical properties with the advent of 3D electrospinning. Such manipulations find their application toward cartilage, bone, tendon, ligament, skeletal muscle, nerve and cardiac tissue regeneration (Table 4). Fabrication

Table 3 Nanofiber scaffolds and its application in tissue engineering

Nanofiber scaffolds	Tissues	Functional properties	Reference
PLGA	Cartilage (mouse fibroblast cells)	Confers mechanical properties for the desired tissue	Li et al. [178]
PCL	Bone (neonatal rat bone marrow mesenchymal stem cells)	Increase in production of ECM	Yoshimoto et al. [179]
Collagen type II	Cartilage (human articular chondrocytic cell line)	Improves adhesion, proliferation, infiltration of chondrocytes. Establishment of pseudopodia	Shields et al. [180]
Polyurethane (PU)	Ligament/tendon (human ligament fibroblast)	Increases the production of ECM	Lee et al. [181]
Collagen type I, elastin and poly(D,L-lactide-co-glycolide)	Blood vessels (endothelial cells and Smooth muscle cells)	Improvement in the physical properties	Stitzel et al. [182]
poly(ε-caprolactone) and polyethylenimine	Fibroblast cells	High porosity conferred increased adhesion property and mechanical strength	Kim et al. [183]
Polyhydroxyalkanoates (PHA)	Neural stem cells	Strong mechanical properties, good biocompatibility, and non-cytotoxic mimicking the natural extracellular matrix (ECM)	Xu et al. [184]
RADA16-I, self-assembling peptide nanofiber	Brain tissue	Design versatility, high porosity, non-toxic, biocompatible, and biodegradable	Leung et al. [185]
Polycaprolactone/graphene oxide	Mouse marrow mesenchymal stem cells and rat pheochromocytoma (PC12-L) cells	Improved physicochemical properties such as hydrophilicity, surface roughness, and conductivity	Song et al. [186]
Hyaluronic acid/polycaprolactone	SH-SY5Y human neuroblastoma cells	Improved biochemical, biomechanical and biological properties	Entekhabi et al. [187]
Keratin associated PCL	Vascular tissue	Enhanced cell adhesion properties and lower activated thromboplastin time	Li et al. [188]
Graphene oxide/polycaprolactone	Neurite (sciatic nerve defect cells)	Induced pro-angiogenic characteristics. Promotes functional and morphological recovery in peripheral nerve generation	Qian et al. [189]
Bi-layered PCL scaffolds coated with collagen	Bone (human bone mesenchymal stem cells)	Improved internal flexibility, adhesion, proliferation and differentiation. Good candidate for soft tissue replacement	Fouad et al. [190]

of 3D structures confers cell-permeable structure with controlled thickness mimicking biological niches to guide cell growth, differentiation, and tissue regeneration. Characteristic features such as mechanical strength, suture retention strength, and degradability have at large been employed for heavy duty tissues such as muscle, tendon, and ligament.

Orthogonally oriented scaffolds have gained popularity and criticality in engineering of intestinal smooth muscles. Moreover, the directional alignment of the cells either on *x*–*y*, *x*–*z*, and *y*–*z* plane with desired structure and functions have been the most sought after approach. [117] have examined the cellular arrangement on different planes of scaffolds made of two layers of orthogonally oriented fibers. This was one of its kinds where the cells were manipulated to align inside the 3D scaffolds in vivo using a two-layer ePCL scaffold with orthogonally aligned fibers mimicking the intestinal circular and longitudinal muscle layer. Moreover, there was an enhanced regeneration and alignment of the muscle layers not only on the surface but also inside of the ePCL scaffolds viz. at *x*–*z* and *y*–*z* planes.

Similarly, Wang et al. [118] have formulated a serum-free culture methodology to maintain the gut motility and intestinal regeneration with peristaltic function. This approach was adopted to maintain the spontaneous and periodic contractions of murine and human intestinal muscularis cells. A 11% (w/w) poly-caprolactone was subjected to electrospinning and coated with neutralized collagen. The expression of mature marker enabled organized arrangement of the cell sheets facilitating the co-existence of mucosa, muscularis, and serosa. Moreover, the epithelial cells were stretched by the contracting muscularis cells pertaining to gut motility disorders and functional regeneration of the engineered intestinal cells.

Table 4 Scaffold fabricated to support genesis of heavy duty tissues

Scaffold	Heavy-duty tissues	Functional properties	Reference
Collagen and poly-l-lactic acid nanofibers	Cartilage and subchondral bone tissue	Better cartilage formation and functional repair of osteochondral defects. Treatment for deep osteochondral defects	Zhang et al. [191]
Poly(caprolactone)-silk fibroin and polyaniline	C2C12 myoblasts	Formation of core–shell scaffolds, good biocompatibility, and ability to induce 3D cellular alignment and elongation of skeletal muscle regeneration	Wang et al. [192]
Gelatin/PLA 3D porous scaffold	Cartilage tissue	Promotion of cartilage tissue regeneration	Chen et al. [193]
Polyhydroxybutyrate-hydroxyapatite nanofibers combined to protein based hydrogel	Bone tissue	Enhancement in bone regeneration in vivo	Sadat-Shojai et al. [194]
Chitosan-collagen hydrogel aligned PLLA nanofiber	Tendon	Enhanced cell proliferation facilitating good attachment and spreading	Deepthi et al. [195]
Collagen-PVA aligned nanofiber	Cartilage tissue	Enhances articular cartilage repair	Lin et al. [196]
Decellularized meniscus extracellular matrix/polycaprolactone (DMECM/PCL) nanofibers	Meniscus	Promotion of neo-menisci regeneration by the expression of meniscus cells expressing extracellular matrix	Gao et al. [197]
Polycaprolactone-polyethylene glycol	Periodontal ligament stem cells	Improved the release profile of encapsulated proteins, improved osteogenic differentiation, and enhanced osteogenic gene expression. Application toward periodontal regeneration therapy	Lam et al. [198]

Wound healing

An injury hindering the vital functions of the tissues is termed as a wound. Skin remains as the front-line defense of human, and the largest organ is the most susceptible part responding toward physical means of injury. The severity of the wound determines the type of approach adopted to hasten healing process. For instance, minor wounds would heal faster through intrinsic repair mechanism, whereas large-scale or full-thickness wounds (burns, diabetes-related wounds) require scaffolds to aid migration, proliferation, and maturation of repairable cells [119, 120].

Besides wound healing, anti-inflammation, anti-infection, scar formation, and conditions leading to skin cancer need timely resolution. This has been facilitated by the nanofibers generated using electrospinning for faster healing of wounds. These nanofibers with its typical topography mimicking basket weave-like pattern of collagen have been fabricated to accelerate migration and infiltration of repairable cells. Most importantly, the orientation of the fibers play a key role in expediting the process of wound healing. Intercross nanofibers on a par with random or uniaxially aligned fibers exhibit best healing performance by accelerating the infiltration of fibroblasts and keratinocytes [121]. Pal et al. [122] have demonstrated the wound healing efficiency (3 weeks) in rat model by fabricating chitosan-PCL core-sheath fibers using emulsion electrospinning.

Further, the use of 3D scaffold in the regeneration of dermal ECM was found critical. To overcome infiltration intricacies, sandwich-type scaffold was preferred over 3D in skin regeneration application. Here, the radially aligned nanofibers are placed at the bottom, a mat comprising an array of square shaped microwells at the top, and the microlevel skin tissues placed in between the two layers. Their applicability as a promising wound dressing facilitates enhanced cell infiltration, thereby preventing drainage at wound site [123]. Besides 2D nanofibers, fabrication of 3D nanofiber scaffold to promote cellular infiltration with controlled thickness and porosity has been demonstrated by Jiang et al. [124] using depressurized subcritical CO_2 fluid. Such modified 3D scaffold not only formed layered structures but also retained the fluorescent intensity and antibacterial efficacy of coumarin 6 and LL-37 peptide. This helped to surpass nanotopographical cues and significantly accelerated cell infiltration and neotissue formation aided by subcutaneous implantation. Promising results in the formation of blood vessel within 2 to 4 weeks with significant antimicrobial effect and tissue regeneration have been reported using extended 3D scaffolds on a par with the traditional 2D scaffold.

Furthermore, for diabeti-related wound healing, Chen et al. [125] have developed 3D vertical/radially aligned nanofiber scaffolds in bone marrow mesenchymal stem cells (BMSC) transplant. It offers the advantage of shape-recovery upon compression in atmospheric and aquatic conditions fitting in for a variety of type 2 diabetic wounds. These BMSC embedded scaffold has potentially enhanced granulation, angiogenesis, and collagen deposition. In addition, they were also found to inhibit the formation of M1-type macrophage and pro-inflammatory cytokines IL-6 and TNF-α and thereby promoting M2-type macrophage and expression of IL-4 and IL-10.

In yet another study, Lv et al. [126] have reported on the wound healing property of PCL/gelatin nanofibrous scaffold containing silicate based bioceramic particles (NAGEL) fabricated using co-electrospinning process. The uniform distribution of bioceramic particles in the PCL-gelatin nanofibers aided Si ions in sustained release during their degradation. Significantly, they promoted cell adhesion, proliferation, and migration by activating epithelial / endothelial to mesenchymal transition pathway both in vitro and in vivo. Such synergistic effects of the functional biomaterials involving conductive nanocomposite scaffold have opened new vistas in wound healing. Similarly, Ren et al. [127] have reported PILA electrospun nanofiber impregnated with dimethyloxalylglycine-decorated mesoporous silica NPs for wound healing by accelerating the expression of human umbilical vein endothelial cells (HUVECs).

It is noteworthy to mention that several metal nanoparticles with antimicrobial potential are electrospun into nanofiber for counteracting multidrug-resistant bacteria and for wound-healing application. Yang et al. [128] have developed wound dressings using 6-aminopenicillanic acid decorated-gold nanoparticles to inhibit the growth of multidrug resistant (MDR) bacteria. These materials are then electrospun into PCL-gelatin fibers to challenge MDR strains in promoting faster wound-healing. Xi et al. [129] have developed an elastomeric, photoluminescent, biocompatible, and antimicrobial polypeptide based PCE-PCL nanofiber to inhibit MDR bacteria. There was also significant enhancement in skin-thickness wound healing and tissue regeneration in mouse model attributing for competitive multifunctional wound dressing. Some of the developed products patented using nanofiber technology has been shown in Table 5.

Plant based materials, besides their potential medicinal properties, pose great challenge toward electrospinnability and mechanical characteristics in fabricating them in the form of nanofibrous mats. The development of hybrid nanofibrous scaffold has opened new vistas in improving the mechanical properties and retaining the biological efficiency of plant based materials. For instance, *Aloe vera* gel was extracted and blended with two different polymers viz. gelatin and poly(ε-caprolactone) and spun into nanofibrous scaffold under optimized conditions. The electrospun nanofibers were found non-toxic with improved mechanical properties and hydrophilicity for extended application toward skin tissue engineering [130].

A similar study was conducted by Solaberrieta et al. [131], in which the bioactive components from *Aloe vera* skin extract were electrospun into nanofibers using poly(ethylene oxide) solutions. The successful encapsulation and incorporation into poly(ethylene oxide) were determined by changes in the nanofiber morphology with demonstrated bimodal diameter distributions. Besides decreased thermal stability, the encapsulation efficiency was found to be relatively high (92%, 76%, and 105%). These poly(ethylene oxide)-*Aloe vera* electrospun nanofibers with significant antioxidant activity were found to have their application in food packaging industry to help decrease oxidation process during storage of packaged food.

Ghorbani et al. [132] have fabricated *Aloe vera*-loaded nanofibrous scaffold encapsulating zein/polycaprolactone/collagen with the aid of ZnO (1% w) nanoparticles. The nanofibers developed had shown excellent thermal stability and mechanical properties with *Aloe vera* extract at 8% wt and zein/polycaprolactone at 70:30 ratio. Moreover, the nanofibrous scaffolds were found biocompatible and biodegradable upon enhancing the adhesion and proliferation properties of fibroblast cells. The potent antimicrobial activity of the fabricated scaffold was found to have its application toward wound healing by containing the growth of pathogenic bacteria.

Nanofibers in drug delivery

Electrospinning has enabled easy encapsulation of bioactive molecules/drugs and has prevented its loss facilitating sustained release to exhibit its maximum activity. The objective in delivering a predetermined dose of drug efficiently, specific to tissue/cell for a defined period of time, has been achieved using electrospinning for drug delivery applications. They have also been applied to treat various diseases via oral and topical routes of administration of poorly soluble or insoluble drugs. Typically, drugs that undergo rapid metabolism, extensive degradation, and with low solubility and instability (mostly anti-inflammatory and antioxidant drugs) have been electrospun into fibers for sustained release [133]. The electrospun nanofibers fabricated scaffolds are delivered either by viral or non-viral nucleic acids. Subsequently, immobilizing the drugs onto the nanofibers remains a great challenge and which is overcome by the most commonly adopted entrapment method. In case of nanofibers, the drugs are entrapped through the crosslinking of the polymeric fibers or by an intermediate carriers attributing for core-sheath encapsulation. For instance, alginate when crosslinked with calcium acts as common polymer for entrapment of drugs in bulk [134]. In core-sheath approach, polymers (PCL/PLGA)

Table 5 Patent products of Nanofiber enabled technology for biomedical and environmental applications

Product	Specifications	Country	Patent ID / year
A nanofiber product for wound dressing	A mesh comprising oxidized polysaccharide (polyanhydroglucuronic acid) and a fiber-forming polymer (PVA)	Dublin	WO2008010199A2 / 2007
Electrospun nanofibrous wound dressing	Three nanofibers were electrospun with three different functionalities. The middle layer comprises herbal extract of *Melilotus officinalis*. Various additives are added to control the release profile of the extract	United States	US9101508B2 / 2011
Bioactive nanofibers	One or more nanofibers electrospunned by the integration of active agents comprising plant extracts for the prevention of skin diseases	Australia	AU2012305986A1 / 2012
Biocompatible apitherapeutic nanofibers	Fabrication of nanofibrous highly porous scaffolds (100–1000 nm) including chitosan and honey for drug delivery, bacteriophage, wound dressing, cancer treatment, and antibacterials	United States	WO2015003155A1 / 2014
Antimicrobial and antifungal polymer fibers and fabrics	Fibers prepared by a masterbatch of polymer pellets (PET), silver, and copper salts. Potent inhibitors of Athlete's foot, antibacterial effective against drug resistant strains	United States	US9908987B2 / 2014
Nanofiber cover for wounds	A hybrid mixture of polyvinyl alcohol-pure water-natural honey electrospun into fibers. The nanofibers comprised only honey molecules and are applied for covering wound and ambustion	Konya, Turkey	WO2015183228A1 / 2015
Bioactive oil based polyesteramide nanofibers	Absorbable polymers such as PLA, PGA, and PCL were used for their biocompatibility and biodegradability along with oil based polyesteramide integrated with a pharmaceutical drug for faster wound healing	India	WO2015159305A1 / 2015
Nanofiber ultrafiltration unit	Electrospun nanofiber ultrafiltration membrane for application in tangential filtration mode. Purification of biological materials	United States	US10675588B2 / 2016
Aloe vera hybrid nanofibers	Hybrid nanofibers comprising *Aloe vera* and synthetic polymer viz. poly-3-hydroxybutyrate-co-3-hydoxyvalerate (PHBV), PLLA, and polydioxanone (PDS). The mean diameter ranges from 0.3 to 1.5 µm. Applied for tubular prostheses prior to peripheral nerve axotomy, dressings and sutures. They are also applied for enhanced recovery from lesions	Spain	ES2579161B2 / 2016

would encapsulate the drugs with BSA-dextran/chitosan core to confer stability [135].

Multidrug delivery, a novel approach comprising multiple drugs with or without similar remedial properties, has been electrospun into desirable polymers. Wang et al. [136] have developed a novel controlled drug release system using Chitosan NPs-PCL polymer electrospun fibers. Further, small molecule rhodamine B and naproxen have been successfully loaded in the core-sheath region for sustained release. In this line, MPEG-b-PLA micelles-chitosan-PEO has been electrospun with both hydrophobic and hydrophilic drugs viz. 5-FU and Cefradine. This model exhibited the final release proportion of about 91.4% prior to continuous exposure for 109 h. HepG-2 cells treated with the micellar-loaded nanofibers showed 45.9% viability prior to 3 days of exposure with 21.6 µg 5-FU [137]. With the core–shell nanofibers composed of PVA crosslinked PAN, water- and organic solvent-soluble drugs namely diclofenac sodium and gentamicin sulfate have been loaded successfully at concentrations 1–2% w/w PAN/GEN that enabled deep penetration of PAV/DS into the nanofibers [138].

Recently, Nagiah and co-workers have developed high tensile tripolymeric triaxial electrospun fibrous matrix for delivering multiple drugs. The polymers used were PCL as core and PLGA as sheath with an intermediate gelatin layer. They have demonstrated the dual release of small molecule rhodamine B and a model protein FITC-BSA

Table 6 Nanofiber system with polymer drug/active moiety for drug delivery applications

Nanofiber system	Polymer	Drug or active moiety	Reference
Monolithic	Poly(acrylic acid)	Doxycycline	Khampieng et al. [199]
Monolithic	Shellac	Ferulic acid	Wang et al. [200]
Monolithic	Hydroxypropyl methylcellulose	Piroxicam	Paaver et al. [201]
Matrix type system	Polycaprolactone (monolithic)	Irgasan, cis-diamminedichloroplatinum dexamethasone	Mu and Wu [202]
Blended	Polyvinyl alcohol and sodium alginate	Ciprofloxacin	Kataria et al. [203]
Blended	Polycaprolactone and gelatin	7-Ethyl-10-amino-hydroxy camptothecin	Zhu et al. [204]
Blended	Polycaprolactone and chitosan	Cisplatin	Aggarwal et al. [205]
Blended	Thermoplastic carboxymethyl cellulose and polyethylene oxide	Tetracycline	Esmaeili and Haseli [206]
Blended	Gellan and polyvinyl alcohol	Ofloxacin	Vashisth et al. [207]
Blended	Silk fibroin and gelatin	Thyme essential oil/doxycycline monohydrate	Dadras Chomachayi et al. [208]
Core–shell: reservoir type	Polyethylene oxide, thiolated chitosan core, and polylactic acid shell	Tenofovir at core	Meng et al. [209]
Reservoir	Polycaprolactone core and shell	Ampicillin at core	Sultanova et al. [210]
Reservoir	Cyclodextrin core and polylactic acid shell	Curcumin at core	Aytec and Uyar [211]
Multi-matrix	Polyvinyl alcohol core and polycaprolactone shell	Doxycycline at core and shell	Song et al. [212]
Multi-matrix	Polyvinylpyrrolidone core and poly(lactic-co-glycolic acid) shell	Naringin at core and metronidazole at shell	Ping et al. [213]

Monolithic, composed of single polymer; blended, composed of polymeric blend; reservoir, nanofibers exhibit reservoir structure capable of controlled release of the drug/active moiety; multi-matrix, contains multi-layered chambers for loading drug

incorporated in the sheath and the intermediate gelatin layers. They were able to support the adhesion, migration, and proliferation of mesenchymal stem cells. By this approach, the shrinkage encountered in conventional electrospinning technique was reduced with additive biomechanical stability [139]. Some of the polymeric nanofibers used for effective drug delivery have been enlisted in Table 6.

Conclusion and future outlook

After reviewing several techniques, forms, materials used in electrospinning for the generation of nanofiber materials, and their potential biomedical applications, a paradigm shift toward fabrication of 3D architecture constitutes one of the key elements for clinical implications. This is on a par with the conventional electrospun fiber mats produced by direct deposition of fibers onto the substrate. With 3D intervention, the solubility, low porosity, swelling, and collapsing of the 2D fibers hindering cell infiltration shall be overcome. As 3D nanofiber facilitates the typical in vivo settings for cells to adhere, proliferate, and differentiate within the matrix, their applications in tissue regeneration are the most promising. Moreover, these electrospun nanofibrous scaffolds have been much sought after approach in wound healing as a wound dresser. The typical alignment of the fibers helps fix the drug and release them in a controlled fashion thereby expending the process of healing. Furthermore, the increase in migration efficiency of cells seeded onto fibers helps greatly in tissue repair and regeneration. These advancements have been achieved with the thorough understanding of the spinneret, its control, and mechanism involved in the electrospinning for a better control suiting various applications. It is this understanding that had sown seeds to involve diverse materials including polymers, small molecules, nanoparticles, and colloids to be electrospun in to fibers. Besides innovation, technology transfer, expansion, and commercialization of post-electrospinning product remain the need of the hour. The list of commercialized products manufacturing using nanofiber technology has been enlisted in Table 7. One of the commercially successful products developed was nanofiber-based respiratory mask capable with a filtering efficiency up to 95%. This is in response to encounter COVID-19, where nano-filtered face mask was developed with nanofibers (in the diameter range of 100–500 nm) arranged in orthogonal/unidirectional directions to relieve the challenges. For instance, PVP/TiO_2 nanofibers have been electrospun for potential application toward filtration and environmental remediation

Table 7 Commercial products developed using nanofiber technology

Product	Specification	Manufacturer	Country
Respiratory mask	Highly br cellulose nanofiber-based material with disposable filter cartridge capable of removing virus-size nanoparticles and high breathability	Queensland University of Technology (QUT)	Australia
Nano-filter	Excellent filtering efficacy (94%). Reusable. Nanofibers with diameter of 100–500 nm arranged orthogonally. Water resistant	Kim Il-Doo Research Institute (A start-up company) https://statnano.com/news/67527/Nanofiber-based-Face-Mask-Preserves-Its-Filtering-%E2%80%8EFunction-and-Sturdiness-After-20-Washes	Korea
YAMASHIN Nano Filter™	Fibers developed from synthetic polymers. The 3D structure of the extremely thin nanofibers attributes for super-high trapping properties	Yamashin-filter corp http://www.yamashin-filter.co.jp/eng/	Japan
Nano-coco-carbon™ filter	They are made of natural, organic, and sustainable nanofibers. It comprises coconut shell carbon and nanofiber matrix producing < 1-mm thickness membrane trapping 99.99% toxic compounds from entering the body	Metamasks https://www.metamasks.com/	New Zealand
Nanopoli Nanofiber mask	A water repellent layer made of non-woven fabric with two layers providing high filtration efficiency of 98.75%	Avalon Nanofiber https://www.avalon-nanofiber.com/product/nanopoly-nanofiber-mask/	Taiwan
Nanohack (face mask)	Novel modular filtration system with nanocomposites of PLACTIVE® and MDflex®. It includes non-woven polypropylene impregnated with 5% CuO NPs exhibiting high antibacterial and antiviral properties	Copper 3D Antibacterial Innovations https://copper3d.com/	Chile
Antiradiation fabric for pregnant women	Antibacterial, antiodor, antistatic, and radiation resistance. AgNPs of size 2 nm have been woven into fabric to confer remarkable properties	Beijing Landingji Engineering Tech Co., Ltd. https://product.statnano.com/company/beijing-landingji-engineering-tech-co.,-ltd	China

[140]. In addition, antimicrobial nanoparticles were also introduced into the nanofibers to increase the filtration efficacy and which is possible only through electrospinning.

There is no doubt that this technology enabled nanofibers would hit the global market by the end of 2022. In order to meet out the demand, there needs to be an increased scalability without compromising the quality, diversity, functionality, and environmental sustainability. The use of chemicals and their disposals need to be critically handled with regard to environmental safety. Studies pertaining to toxicity and environmental burden need to be conducted owing to address respiratory problems related to the inhalation of solvents/short electrospun nanofibers (Ag/inorganic) and to draw to a conclusion facilitating the clearance of nanofibers from the human system.

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Declarations

Conflict of interest The author declare no competing interests.

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