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Chapter

3D Nonwoven Fabrics for Biomedical Applications

Mahesh Kumar Joshi, Rajeshwar Man Shrestha and Hem Raj Pant

Abstract

Fibrous materials are attractive for biomedical applications owing to their structural superiorities, which include large surface-area-to-volume ratio, high porosity, and pore interconnectivity in a controlled manner. Among the various methods of fiber fabrication, electrospinning has emerged as an attractive nanotechnology to produce ultrafine fibrous materials for myriad applications, including tissue scaffolding. In this technique, processing parameters, such as the solution properties, tip-to-collector distance, applied voltage, etc., can be tailored to obtain the fibers of the desired morphology and physicochemical properties. Ideal scaffolds should meet the basic requirements, such as three-dimensional (3D) architecture, proper mechanical properties and biodegradability, and the sufficient surface characteristics for cell adhesion and proliferation. However, most of the electrospun nanofiber-based scaffolds have densely packed two-dimensional (2D) array which hinders the cell infiltration and growth throughout the scaffolds, thereby limiting their applicability in tissue regeneration. To overcome this problem, several attempts have been made to develop a biomimetic three-dimensional, nanofibrous scaffold. This chapter deals with noble techniques including gas foaming (GF), charge repulsion-assisted fabrication, post-processing, liquid-assisted collection, collector modification, and porogen-assisted methods for the fabrication of 3D nanofibrous scaffold for biomedical applications.

Keywords: electrospinning, tissue engineering, nano–/microfiber, 3D scaffold, biomaterials

1. Introduction

The fields of tissue engineering and regenerative medicine aim at promoting the regeneration of tissues or replacing the malfunctioning organs using a scaffold material. The development of scaffolds that mimic the composition and structure of natural extracellular matrix (ECM) is highly demanded in biomedical sciences. A scaffold used for tissue engineering is considered as an artificial extracellular matrix that provides mechanical support for neo-tissue formation in vitro and/or through the initial period after implantation during cell proliferation and differentiation. In addition to contributing to mechanical integrity, the ECM has an important role in signaling and regularity functions in development, maintenance, and regeneration of tissues [1]. It has long been demonstrated that the composition and architecture of a scaffold influence the cell-environment interactions that determine the effectiveness

of the scaffold [2]. The scaffold material must be able to interact with cells in three dimensions and should facilitate the communication. The main goal of tissue engineering is to enable the body to heal itself by regenerating "neo-native" functional tissues [3, 4]. A highly porous scaffold is necessary to control tissue formation in three-dimensional (3D) architecture in a typical tissue engineering approach. The scaffolds provide the microenvironment (synthetic temporary extracellular matrix) for cell attachment, proliferation, differentiation, and neo-tissue genesis. Therefore, the material used for tissue scaffolding must function without interrupting other physiological processes, that is, the scaffold must not promote or initiate any adverse tissue reaction [5]. Furthermore, the scaffold must have an ability to promote normal cell growth and differentiation while maintaining a three-dimensional orientation/space for the cells.

Recently, various materials including ceramics, metals, and polymers have been exploited to develop the scaffolds for tissue regeneration. Although the inorganic/ceramic materials such as hydroxyapatite (HAP) or calcium phosphates are excellent choices for medical implants due to their good osteoconductivity and studied for mineralized tissue engineering, they are disadvantageous due to poor processability into highly porous structures and brittleness. Certain metals have superior mechanical properties and are preferred for medical implants. However, the lack of degradability in a biological environment limits their applications for tissue scaffolding [6]. In contrast, polymers have been extensively studied in various tissue engineering applications, including bone tissue engineering, due to the great design flexibility and structure which can be tailored to the specific needs [6, 7].

Recently, researches in biomaterials have turned to nanotechnology, specifically nanofibers, as the solution to the development of tissue engineering scaffolds and wound repair/care products. At present, few processing techniques are successful in producing nonwoven fibers and subsequent scaffolds on the nanoscale [8]. In basic terms, a nonwoven is a fabric or web composed of fibers. The orientation and properties of the fibers and fabric can be controlled to mimic the native cellular structures, such as collagen fibers of the extracellular matrix. Development and characterization of these nanofibrous structures for tissue engineering applications is crucial in understanding the cell-ECM interactions. Conventional polymer processing techniques are efficient in producing fibers, which are several orders of magnitude larger than the native ECM. Therefore, there has been a concerted effort to develop methods of producing nanofibers that closely mimics to the ECM geometry. In this endeavor, five distinct techniques have proven successful in producing nanofibrous tissue engineering structures: self-assembly, phase separation, melt blowing, drawing, and electrospinning.

Melt blowing and spunbond nonwovens are composed of continuous fiber filaments fabricated by forcing molten thermoplastic polymer through very fine orifices arranged in a spin beam. Melt blowing is a simple, versatile, and one-step process for the production of polymeric fibers in micrometer and smaller scale. During melt blowing and spunbond process, fibers are produced in a single step by extruding a polymer melt through an orifice die. In the melt blowing process, the filaments are drawn and accelerated toward the collector screen via hot air knives, keeping the filaments in a molten state, allowing for fine fiber attenuation. Collected fibers are still in a tacky state, allowing self-bonding between fibers. Conversely, in the spunbond process, as the filaments exit the spin beam, they are rapidly solidified by cool air before being drawn pneumatically. Spunbond and melt blowing techniques can be implemented from lab, pilot, and full production scale. Another method for generation of nonwoven fabric is carding technology. This is a mechanical process that disentangles, cleans, and intermixes fibers to produce a continuous web. In the carding process, short fibers of a few inches

in length (staple fibers) are separated and entangled by a series of specialized combed rollers to form an unbonded web. Unlike spunbond and melt-blown processing that require a thermoplastic polymer for melt spinning, a variety of fiber materials can be processed via carding technology, including natural and synthetic polymers, glass, and metal fibers. The high-speed, repeatable, economical production capabilities of these techniques make them attractive candidates for the commercial production of nonwoven-based tissue engineering scaffolding materials. The main disadvantages of nonwoven webs generated by these techniques are their large fiber diameters which hinder the cell attachment, proliferation, and neotissue generation, thereby limiting their application as tissue scaffolding material.

Among the various techniques, electrospinning is the facile nonwoven manufacturing method and has recently gained significant interest as a method of scaffold fabrication. The size scale of electrospun fibers mimics to the native ECM and provides an ideal environment for cell proliferation, attachment, and differentiation into the target tissue. However, the fabrication of large-scale electrospun scaffolds using conventional technique is time-consuming and difficult to generate 3D microstructures. This chapter focuses on recent advances in the fabrication of the three-dimensional electrospun nanofibrous scaffolds.

2. Electrospinning

Electrospinning employs electrostatic force to draw a fiber from a spinneret. This fiber solidifies and lies down on a collector in the form of a nonwoven fibrous mesh. Recently, electrospinning has attracted much attention because of its low processing cost and tailorable fiber morphology and fiber diameter. Furthermore, synthetic and natural polymers can be processed into the fiber of different diameters at ambient conditions. However the electrospinning technology has been known for a long time; the practice of this technology remained largely dormant until the 1970s. Morton received the first US patent for the electrospinning of artificial fibers in 1902. Zeleny presented one of the earliest studies of the electrified jetting phenomenon in 1914 [9]. Later on, Formhals filed a series of patents on the processing and apparatus in the decades of the 1930s and 1940s to produce electrospun fibers. Only a few publications appeared in electrospinning research during the 1970s and 1980s, notably by Baumgarten and by Larrondo and St. John Manley [10, 11].

The electrospinning research has gained significant interest when Doshi and Reneker prepared submicron fibers in the 1990s [12]. Since then it has been demonstrated that almost all materials that can be spun from melt or solution by conventional methods can be electrospun into fibers. On account of the remarkable simplicity, versatility, and potential applications of this technique in a variety of fields, the number of publications in this field has been increasing exponentially during the past decade.

The principle of electrospinning involves a high voltage applied between a pendant polymer droplet and a metal target as the counter electrode [13]. Under the electrostatic force, the pendant polymer droplet is deformed from a hemispherical shape to a conical shape which is called as Taylor cone [14]. A thin polymer jet is initiated and travels toward the metal target once the electrostatic force reaches a critical value to overcome the surface tension of the polymer droplet. The charged thin polymer jet is elongated and undergoes a bending instability region where it whips swiftly in the air by the electric field [15]. The thin polymer jet is further stretched due to the evaporation of the solvent during this period and finally deposits on the metal target as a randomly oriented nanofibrous membrane as shown in **Figures 1** and **2**.

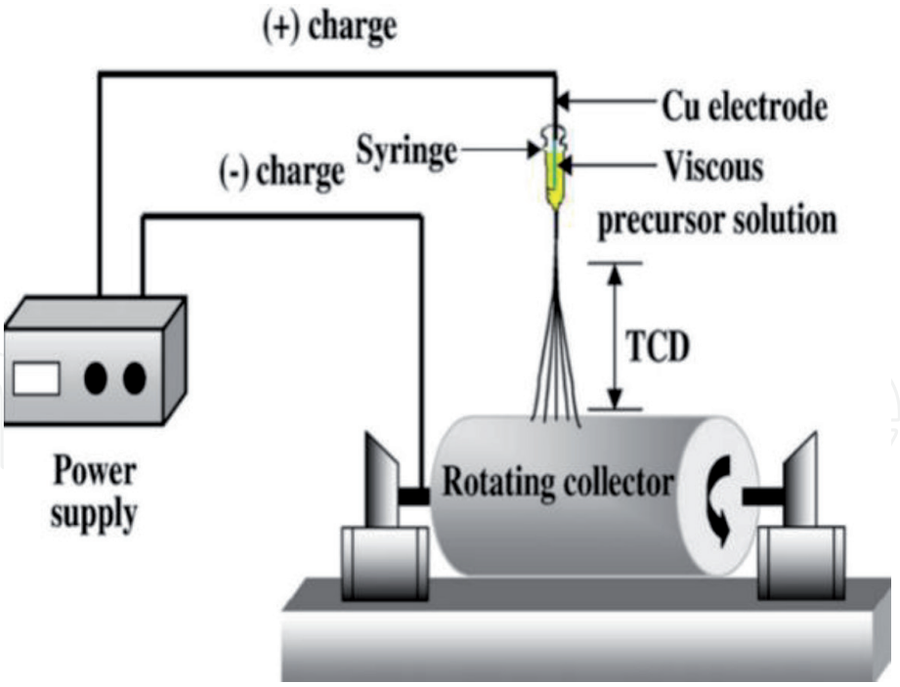


Figure 1.
Schematic illustration of electrospinning setups.

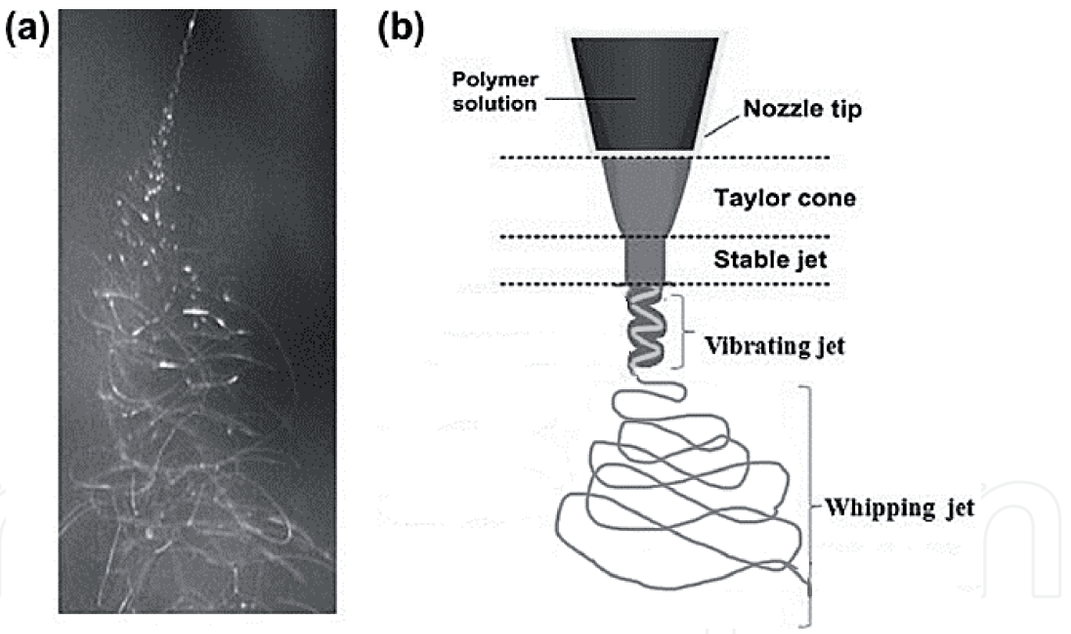


Figure 2.
(a) Photograph of electrospinning jet. (b) Schematic representation for the formation of electrospun nanofibers.

The electrospinning process is characterized by three major regions: (1) the cone region, (2) the steady jet region, and (3) the instability region. A pendant drop of a fluid is charged at the tip of the nozzle at the initial stage of electrospinning which deforms the droplet into a conical shape, just before jetting occurs. The conical shape is called the Taylor cone, named after G. Taylor who has studied this electrified fluid phenomenon [14]. At a critical electrical stress, a fluid jet is ejected from the apex of the cone. The diameter of the jet at the apex is about 100 micrometers. In the steady jet region, the jet can travel in a straight path anywhere from 1 to 20 centimeters. For a fluid that is a solution, real-time spectroscopic data shows that the loss of solvent due to evaporation in this portion of the jet is negligible. In the

final region, the jet deviates from its straight path and undergoes an instability called bending or whipping instability (**Figure 2**) [15].

Several parameters influence the electrospinning process: polymer solution parameters, processing parameters, and ambient parameters. Extensive polymer chain entanglement is necessary for the fiber formation during electrospinning process; otherwise the polymer solution is electrosprayed into small droplets or forms fibers with large beaded polymer aggregates. Low molecular weight polymers are often difficult to electrospun because of their inability for chain entanglements, while higher molecular weight polymers often cause large changes in solution viscosity, thus increasing the surface tension of the droplet and limiting the ability to electrospun. The choice of solvent is another important processing parameter; the solvent should be nontoxic and should evaporate within the distance from the spinneret to the grounded collector. The processing parameters such as distance between spinneret and collector, solution flow rate, humidity, and voltage intensity (~a few kV–40 kV) have substantial influence on the morphology, fiber size and uniformity, and porosity.

3. Development of 3D scaffolds

The tissue engineering scaffolds should closely resemble to native extracellular matrices (ECMs) that provide structural support to cells. The primary role of the scaffold is to provide the temporary support until the neo-tissue formation. The scaffolds that closely mimics to the topographies and spatial structures of ECM are efficient for the cell proliferation and differentiation. The morphologies of ECMs vary according to the functions of the target tissues. Fibrous structures with 3D orientation and random distribution are found in native ECMs in the breast, liver, bladder, lung, and many other organs and tissues [16]. Therefore, it is reasonable to fabricate scaffolds with particular morphologies and structures according to categories and functions of the original native tissues [17].

Electrospinning is a simple method to fabricate the nano–/microfibers in a continuous process. The electrospinning parameters and instrumental setups can be tailored to fabricate micro–/nanofibers with desired morphologies, such as aligned fibrous array, fiber diameter, and fibrous patterns. Therefore, electrospinning has gained significant attention to fabricate tissue engineering scaffolds composed of nano- or submicrometer fibers from numerous materials [18]. However, the conventional electrospinning method produces two-dimensional (2D) sheet-like membranes with small pore and tightly packed fibrous layers that limits the cell infiltration and growth to the depth of the scaffolds [19–22]; cells mainly spread and distribute on the surface of 2D nanofibrous membrane [23]. Since most human tissues and organs possess three-dimensional microgeometry holding intrinsic functionality, developing three-dimensional structure has drawn a great interest in the search of the tissue surrogates. 3D fibrous scaffolds with macroporous, open structure facilitate the neo-tissue formation, thereby providing biomimetic environment for the cell infiltration, the cell proliferation, and the transportation of nutrients and waste.

4. Gas-foaming technique

Among the process technologies that have been developed and successfully implemented for the design of TE scaffolds, gas foaming (GF) has recently attracted much attention. The gas-foaming technique utilizes the nucleation and

growth of gas bubbles dispersed into a viscous polymer solution for the creation of porosity [24]. The gas bubbles are generated in situ either via chemical reaction or by adding inert gases to the polymer phase at different physical environments. The gas-foaming agents are generally released from a pre-saturated gas-polymer mixture resulting in the formation of 3D porous architectures [24]. A supercritical fluid, that is, a fluid above its critical point, such as carbon dioxide, is commonly used for gas-foaming purpose because of its non-flammability, non-toxicity, and moderate critical point (31.1°C and 73.8 bar). Supercritical fluids can be used to form gas-saturated polymer phase by varying the temperature and pressure [25]. In the process, high-pressure CO2 gas is subjected to solid polymer disks to allow saturation of CO2 in the polymer. In this process, the nucleation and growth of CO2 gas bubbles in the material creates the thermodynamic instability and yields mostly a nonporous surface with closed-pore structure. The main limitation of this technique is that it produces the nonporous surface with closed-pore structure with only 10–30% of interconnected pores [26]. Recently, particulate leaching technique has been combined with the gas-foaming process to improve the inter-pore connectivity, although completely eliminating closed pores remains challenging [26].

Recently, Joshi et al. have developed the novel gas-foaming technique to modify the densely packed 2D electrospun membranes into low-density three-dimensional nanofibrous scaffolds [19, 27]. In this technique, authors put the electrospun nanofibrous mat in an aqueous sodium borohydride (SB) solution where the interconnected pores of a mat were filled with the SB solution. The SB solution undergoes the hydrolysis in situ in the nano–/micropores of the nanofibrous mat and produces the hydrogen gas. As generated H2 gas molecules nucleated to form clusters that reorganize the nanofibers into multilayered 3D scaffold with low-density, macroporous spongy structure (**Figure 3**). In their study, nanofibrous membranes of various polymers were prepared via electrospinning and treated with sodium borohydride solution that was prepared in different solvents. They demonstrate that the solvent for sodium borohydride (either water or methanol) plays a crucial role in the fabrication of 3D scaffolds. The electrospun membranes of polar polymers were processed into 3D architecture in aqueous SB solution, while methanolic solution of SB can be used for both polar and nonpolar polymers. The fabrication process is fast in methanol solution compared to an aqueous solution which is attributed due to the

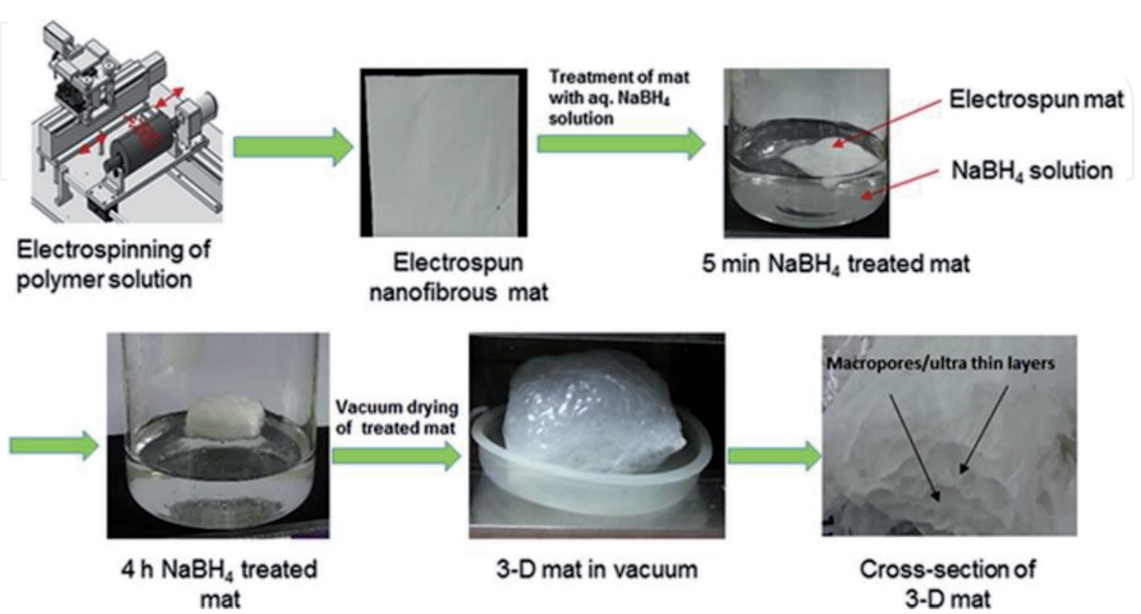


Figure 3.
Schematic illustration for the formation of low-density, macroporous, spongy, and multilayered 3D scaffolds. Reproduced with permission from Ref. [19].

rapid evolution of hydrogen gas from the methanolysis reaction compared to the hydrolysis reaction. This method forms the large pores with multilayered structure that mimics to the ECM. Similarly, Zhao et al. immersed the 2D PCL nanofibrous mat in a NaBH4/methanol solution inside a 3D-printed mold and obtained the 3D nanofibrous scaffolds with controllable geometric shapes [28]. Xie et al. also used the NaBH4 solution as gas source to expand the 2D PCL electrospun mat followed by freeze-drying and obtained 3D PCL scaffolds with highly ordered architecture with controllable gas widths and layered structure as a result [29]. Lee et al. combined electrospinning with salt leaching/gas foaming and developed micro-sized pores in poly(L-lactic acid) (PLLA)/montmorillonite (MMT) nanocomposite fibrous scaffold [30].

5. Multilayering electrospinning

The thickness of the electrospun can be increased by increasing the spinning time during the conventional electrospinning process, leading to the 3D fibrous structure. 3D multilayered fibrous membranes of different materials can be fabricated by a sequential electrospinning or co-electrospinning, and post-processing and sometimes an auxiliary electric field is even used to converge the collected fibers into a confined space to produce 3D fibrous structures [19] (**Figure 4**). Pham et al. [32] prepared layer-on-layer stacks including alternating layers of PCL microfibers and PCL nanofibers. This proposed 3D structure combined the beneficial properties of nanofibers with that of microfibers. The thickness of the nanofiber layers is modulated by electrospinning the nanofiber layers for different lengths of time. They demonstrated that cell infiltration and growth in a multilayered scaffold depends upon the thickness of each layer; increasing the thickness of the nanofiber layer reduced the cell infiltration of the scaffold. Han et al. [33] fabricated the electrospun 3D scaffold of cellulose acetate with three different layers (dense layer, cellular layer, and porous layer) by varying the solutions and processing parameters. In this technique, the total number of layers in multilayered scaffold can be controlled. Furthermore, the composition, the fiber diameter, and the porosity of each electrospun fiber layer can be tailored that affects cell proliferation, migration, and/or differentiation on a scaffold. Erisken et al. [34] reported the functionally graded electrospun PCL and β-tricalcium phosphate (β-TCP) nanocomposites using a hybrid twin-screw extrusion/electrospinning process. Soliman et al. [35] fabricated 3D scaffolds of layered composites with mixed nano- and microscale PCL fibers by modifying the electrospinning setup with two parallel syringes and an actuated collector (co-electrospinning with scalability and modularity from an industrial perspective).

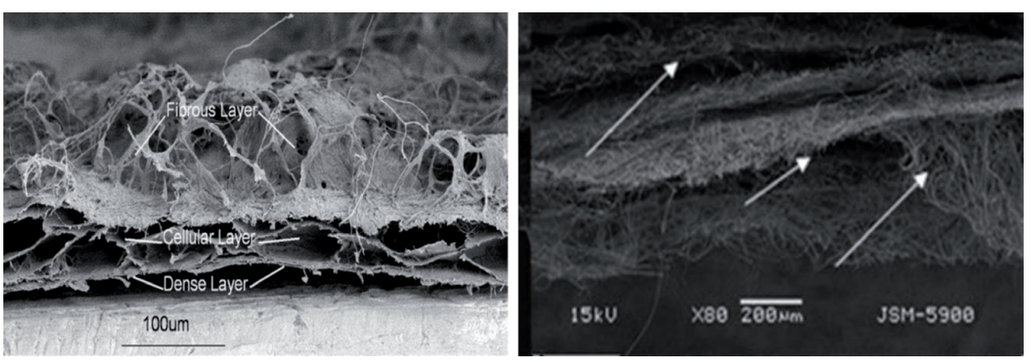


Figure 4.
SEM images showing the cross-sectional view of the multilayered scaffold. Reproduced with permission from [31] and right [19].

6. Post-processing after electrospinning

With a subsequent post-process after electrospinning such as folding/rolling up, the aforementioned 3D multilayer fibrous structures, even the as-spun 2D layer-on-layer mats, can turn into a desired morphology for further application. Recently, Duan et al. [37] reported the ultralight highly porous 3D polymer sponges of extremely low-density and low-specific surface area from dispersions of short electrospun fibers in an attempt to mimic the design principle of natural sponges. Short electrospun fibers were first prepared by cutting of electrospun nonwoven and then dispersed in dioxin in different concentrations. Sponges of different densities were prepared from these dispersions by freeze-drying. Such sponge showed tunable cellular infiltration and growth. Ryu et al. [36] developed a three-dimensional scaffolds of carbonized polyacrylonitrile for bone tissue regeneration. PAN fibers were formed by electrospinning onto a Petri dish containing water, and PAN/water was lyophilized for 48 h. Performing the lyophilization step prior to the carbonization process created the micro-sized pores between the electrospun PAN fibers leading to the cotton ball-like 3D scaffolds (**Figure 5**). The scaffolds were carbonized under 800°C in argon atmosphere and then further modified into a 3D cylindrical geometry. Wang et al. [38] fabricated the electrospun chitosan nano–/microfiber mesh tubes by controlling the spinning parameters. The nonwoven or oriented fibers of the chitosan were deposited and reeled on the bar as the drum rotates. Furthermore, by folding the aligned electrospun nanofibrous meshes several times, a 3D nonwoven macroporous nanofibrous scaffold was manufactured. However, 3D structures generated by this method usually cannot put into use as scaffolds directly because they often have a large space or distance between adjacent fibrous surfaces. 3D electrospun poly(L-lactic acid) (PLLA) microfibrous scaffolds with 5 mm in thickness were fabricated by using a subsequent mechanical expansion process [39]. 3D scaffolds demonstrated a high level of osteoblast proliferation (1.8-fold higher than nanofibrous membranes in a week), actively penetrated the inside of the 3D scaffold, and showed a spatial cell distribution. Sintering after electrospinning is another way to fabricate 3D macrostructures. 3D electrospun scaffolds of pure PLGA and composites of PLGA/hydroxyapatite were

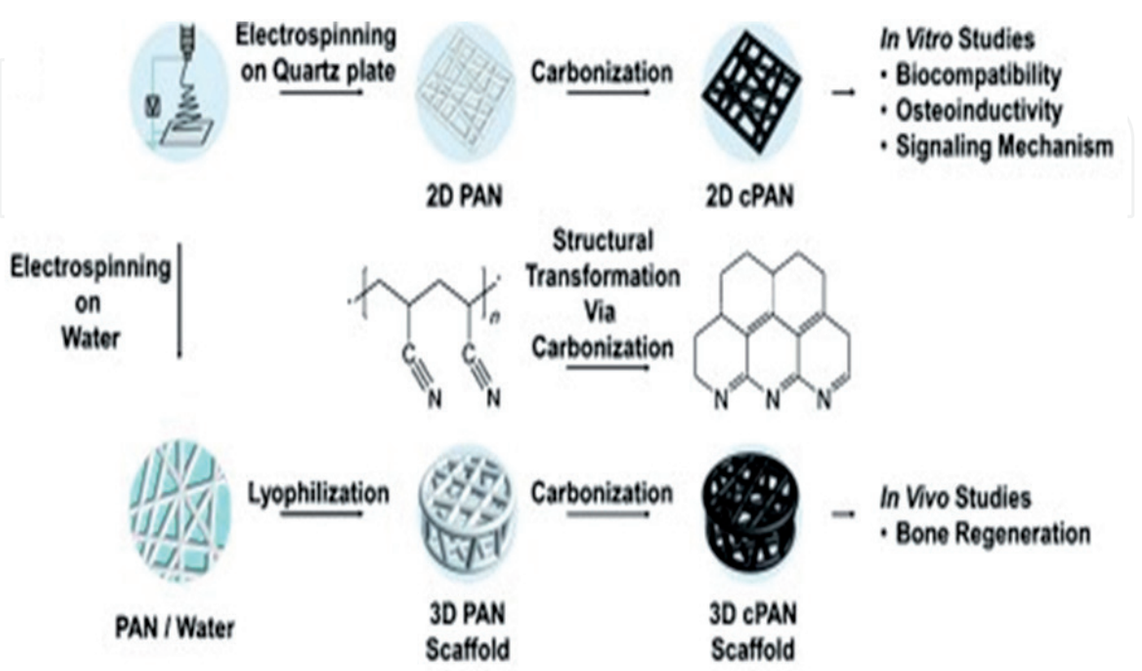


Figure 5.
Schematic illustration showing the fabrication process of cPAN scaffolds. Reproduced with permission from Ref. [36].

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fabricated by a two-step process: electrospun meshes were first stacked and then sintered using pressurized gas which improved the mechanical properties and porosity.

7. Charge repulsion-assisted fabrication

Fabrication of fluffy nanofibrous mesh using the cosolvent that induces the charge repulsion during the spinning has been employed in recent studies [40, 41]. Lee et al. developed a novel strategy to fabricate highly porous poly(L-lactide) (PLLA)-based fibrous scaffold for bone tissue engineering. Blending of PLLA with its monomer, lactic acid (LA) produced the fluffy-type highly porous nanofibrous mesh (**Figure 6**). Their study revealed that the LA component in the blend solution assisted the formation of the macroporous spongy fibrous scaffold. The repulsion between the as-spun fibers occurs due to the interaction between the electric field formed by high voltage and the negative charge on LA due to the functional group (COOH), thereby generating fluffy fibrous mesh [40–42]. Similarly, Xu et al. fabricated a fluffy-type nanofibrous mesh by electrospinning the blend solution of PCL and polystyrene (PS) [42]. In another study, Lee et al. fabricated a core-sheath-type fibrous scaffold (PCL as the core and PS as shell) with fluffy-type architecture using coaxial electrospinning. The PS in the sheath was removed out to avoid its drawbacks associated with scaffold activity [43]. They reported that the negative charge accumulated on the surface of the nanofiber due to the PS (sheath) caused the repulsion between nanofibers under the influence of the strong electric field, thereby generating the fluffy-type nanofibrous mesh [43].

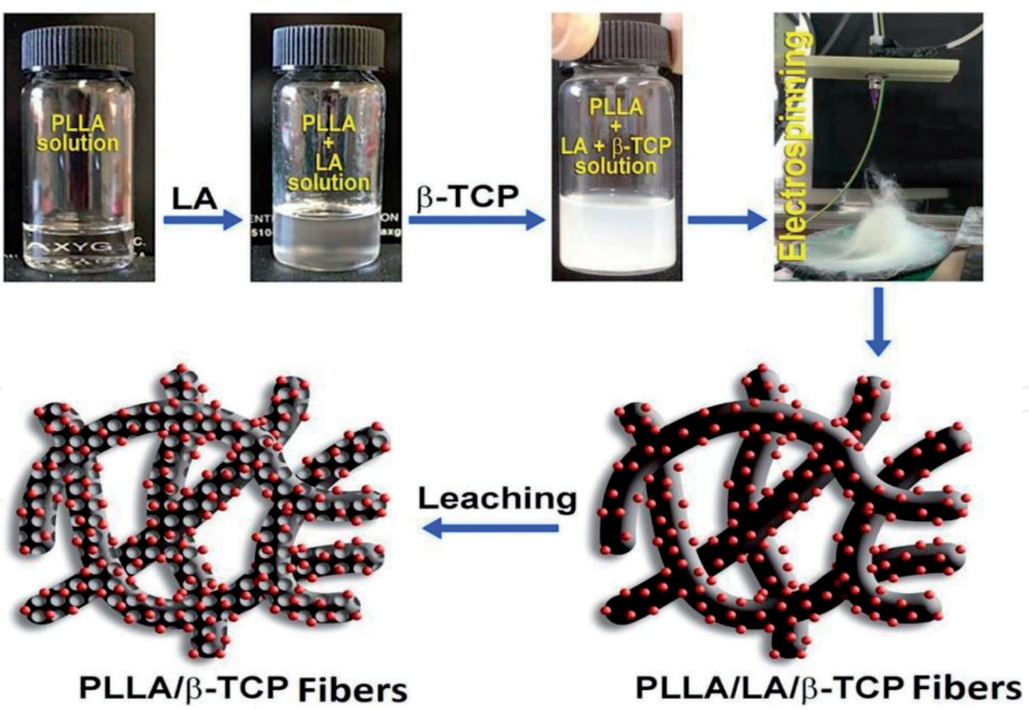


Figure 6.
Diagrammatic representation showing the fabrication of three-dimensional fluffy fibrous scaffolds. Reproduced with permission from Ref. [40].

8. Liquid-assisted collection

The highly porous three-dimensional nanofibrous scaffolds can be obtained using bath collectors containing a low surface tension solvent, and this technique

is also helpful for fabricating 3D fibrous macrostructures. It is known that aligned electrospun micro–/nanofibrous arrays can be collected with the help of a water reservoir collector or a water vortex. Teo et al. [44] fabricated hierarchically organized 3D nanofibrous meshes of PCL using a water vortex. As-collected 3D PCL nanofibrous meshes were either freeze-dried or dried in a mold under ambient condition. The freeze-dried 3D meshes showed visible pores on the surface of the mesh, while the 3D meshes dried in room condition were densely packed without any apparent pores on the surface. Yokoyama et al. [45] fabricated the poly(glycolic acid) (PGA) 3D spongy nanofibrous mesh by combining electrospinning with wet spinning. The spongy-type 3D PGA nanofiber fabric showed a low apparent density and high porosity compared to the usual PGA nanofiber nonwoven mats prepared by conventional electrospinning method.

9. Collector modification

3D fibrous macrostructures fabricated by modifying collector are common. Zhang et al. [47] obtained tubular structures through designing the collectors. The collectors used in fabricating the electrospun fibrous tubes are static 3D columnar collectors. The schematic illustration and the photos of the relevant fibrous tubes are separately shown in **Figure 7A** (**a** and **b**). Tubes with different patterned architectures can also be obtained using collectors with two different patterns as displayed in **Figure 7B**(**c–g**). Moreover, crossing tubes with interconnected tubular structures are made using this static collecting method, which are difficult to obtain by other strategies. Similar to 2D assembly, the 3D collecting template is also based on the manipulation of electric field and electric

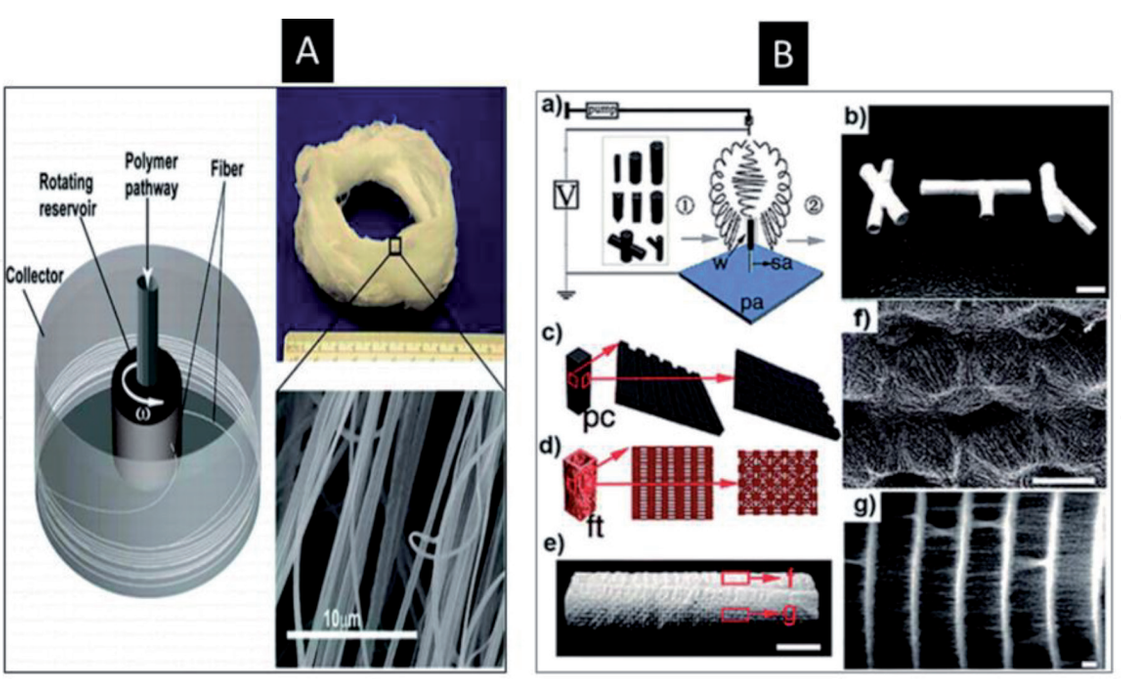


Figure 7.
(A) Schematics of rotary jet-spinning process. Rotary jet spinning consisted of a perforated reservoir. Photographic image of 3D nanofiber structure produced by rotary jet spinning and corresponding SEM image. (B) (a) schematic illustration of collecting process using a cylindrical collector with equally spaced circular protrusions. (b) a fibrous tube with patterned architectures (scale bar = 5 mm). (c) Magnified image of panel b (scale bar = 200 μm). (d) Schematic illustration of collectors with two different patterns and relevant fibrous tube (pc, patterned collector; ft., fibrous tube). (e) a fibrous tube with two different patterns (scale bar = 5 mm). (f,g) Magnified images of two different patterns of panel. Reproduced with permission from Refs. [46, 47].

force. Some key factors, especially the design and configurations of the collector, should be well-tailored, which are critical for tubular structures. Moreover, feasible strategies for fabricating 3D structures are still in demand. Blakeney et al. [20] designed a collector with a network of stainless steel needles on the concave side of a foam half-sphere shell. The fibers were collected randomly between the arrays of needles, thereby generating 3D fluffy, "cotton ball-like" PCL scaffolds. As-fabricated scaffolds showed enhanced cellular infiltration compared with 2D scaffolds produced using traditional collectors [20]. Badrossamay et al. [46] prepared 3D fibrous structure using a rotary jet spinning combined with the hydrostatic pressure with centrifugal pressure, 3D nanofiber structures from poly(lactic acid) (PLA) have been fabricated under a proper rotation speed, and the contained aligned nanofibers were similar to that of the conventional 2D mats (**Figure 7A**). The rotating collector assists the collection of 3D nanofibrous tubular scaffolds. Cai et al. [16] fabricated 3D zein and PEG electrospun scaffolds with three-dimensionally and randomly oriented fibers and large interconnected pores by reducing surface resistivity of materials. The 3D structures are also fabricated via a hybrid technique that combines traditional electrospinning with other methods such as prototyping, polymer/fiber deposition, melt electrospinning, and so on. Park et al. [48] developed a nano- and microhybrid process incorporating direct polymer melt deposition (DPMD) and an electrospinning process. DPMD process was employed to prepare the microfiber layer with computer-aided design modeling data considering some structural points such as pore size, pore interconnectivity, and fiber diameter. The polycaprolactone/collagen nanofiber matrices were deposited between the layers of the three-dimensional structure via an electrospinning process. They found that the polymeric scaffolds with nanofiber matrices provided favorable conditions for cell adhesion and proliferation.

10. Porogen leaching

Another technique for the fabrication of highly porous 3D structure is the use of porogens. Materials such as ice crystals, salt particles, polymers (e.g., poly(ethylene oxide) (PEO)), which acts as porogens, usually are mixed simultaneously with the precursor during electrospinning to enable rapid buildup of the nanofibrous volume and then washed away or dried after a desired thickness is reached [49]. For example, Baker et al. [50] demonstrated that inclusion and subsequent removal of a sacrificial fiber population within a fiber-aligned fibrous scaffold enhance cellular infiltration. Poly(ε-caprolactone) (a slow-degrading polyester) and poly(ethylene oxide) (a water-soluble polymer) were co-electrospun from two separate spinnerets to form dual-polymer composite fiber-aligned scaffolds, and PEO is washed out. Removal of these sacrificial elements (PEO fibers) preserved structural and mechanical anisotropy and tuned to generate composites with varying mechanical properties. Kim et al. [51] fabricated a 3D macroporous and nanofibrous hyaluronic acid (HA) scaffold by combining the electrospinning process with a salt leaching technique (**Figure 8**). The salt particulates, as a porogen, deposited during electrospinning were leached which produced water-soluble HA-based scaffold with macroporous and nanofibrous geometry. Ki et al. [52] developed 3D nanofibrous fibroin scaffold with high porosity by electrospinning. The electrospun SF nanofiber dispersion was collected in 1,4-dioxane having NaCl particles (300–500 μm) as porogen. The scaffold was cross-linked, lyophilized, and washed with PBS solution several times that was effective for cell addition and proliferation.

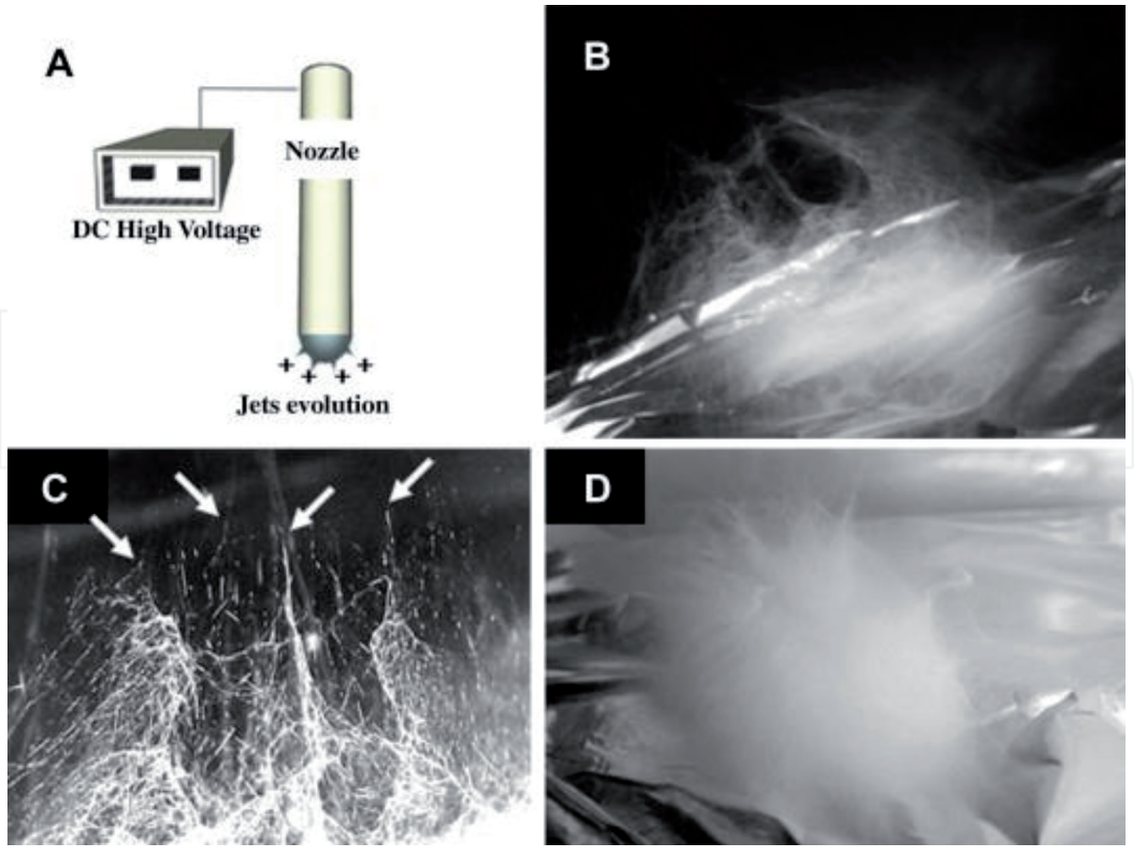


Figure 8.
(A) Diagrammatic illustration showing the polymer jet evolution; (B) digital image showing the vertical growth of solidified fibers; (C) the polymer solution from the needle tip was immediately split into minijets (arrows indicate minijets); and (D) fluffy-type nanofiber mesh. Reproduced with permission from Ref. [50].

11. Conclusion

In conclusion, it is evident from the foregoing examples that the diversity in biomaterials is immense. The utilization of electrospun nanofibers as tissue scaffold is challenging. A great deal of effort has been put in to prepare the biomimetic 3D nonwoven scaffolds based on natural as well as synthetic polymers. Different processing routes have been proposed to produce 3D nanofibrous scaffolds with a great variety of architectures. Many clever approaches to mimicking the structure and, more importantly, the function of the ECM have been devised. Different fabrication methods have their own merits and demerits. However, despite all the extensive literature containing references to the so-called biomimetic three-dimensional scaffolds, it is the authors' opinion that much work is still needed to obtain clinically successful materials. Various types of bioactive components, such as peptides (e.g., RGD) and hydroxyapatite, may be incorporated/integrated to enhance the cellular response and biocompatibility of the 3D nanofibrous scaffolds. More importantly, the real-time monitoring/control systems may be established by integrating either electronic components or magnetic responsive elements with 3D nanofibrous mesh, enabling remote actuation and thus with an active role in the modulation of the host response on implantation that can revolutionize human therapies toward successful regeneration. It is imperative that these important technologies continue to be investigated for their ability to interact in biological systems. It will be most interesting to follow the further progress and the expected and unexpected leaps forward that will be shaping the field in the coming years.

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References

[1] Lavik E, Langer R. Tissue engineering: Current state and perspectives. Applied Microbiology and Biotechnology. 2004;**65**(1):1-8

[2] Joshi MK et al. In situ generation of cellulose nanocrystals in Polycaprolactone nanofibers: Effects on crystallinity, mechanical strength, biocompatibility, and biomimetic mineralization. ACS Applied Materials & Interfaces. 2015;**7**(35):19672-19683

[3] Barnes CP et al. Nanofiber technology: Designing the next generation of tissue engineering scaffolds. Advanced Drug Delivery Reviews. 2007;**59**(14):1413-1433

[4] Maharjan B et al. In-situ synthesis of AgNPs in the natural/synthetic hybrid nanofibrous scaffolds: Fabrication, characterization and antimicrobial activities. Journal of the Mechanical Behavior of Biomedical Materials. 2017;**65**:66-76

[5] Kidoaki S, Kwon IK, Matsuda T. Mesoscopic spatial designs of nano- and microfiber meshes for tissue-engineering matrix and scaffold based on newly devised multilayering and mixing electrospinning techniques. Biomaterials. 2005;**26**(1):37-46

[6] Liu XH, Ma PX. Polymeric scaffolds for bone tissue engineering. Annals of Biomedical Engineering. 2004;**32**(3):477-486

[7] Huang LH et al. Synthesis and characterization of electroactive and biodegradable ABA block copolymer of polylactide and aniline pentamer. Biomaterials. 2007;**28**(10):1741-1751

[8] Tiwari AP et al. Formation of lipophilic drug-loaded human serum albumin nanofibers with the aid of glutathione. Chemical Engineering Journal. 2017;**313**:753-758

[9] Zeleny J. The electrical discharge from liquid points, and a hydrostatic method of measuring the electric intensity at their surfaces. Physical Review. 1914;**3**(2):69-91

[10] Baumgart P. Electrostatic spinning of acrylic microfibers. Journal of Colloid and Interface Science. 1971;**36**(1):71

[11] Larrondo L, St. John Manley R. Electrostatic fiber spinning from polymer melts. I. Experimental observations on fiber formation and properties. Journal of Polymer Science: Polymer Physics Edition. 1981;**19**(6):909-920

[12] Doshi J, Reneker DH. Electrospinning process and applications of electrospun fibers. Journal of Electrostatics. 1995;**35**(2-3):151-160

[13] Han SW, Joshi MK, Kim CS. Fabrication and characterization of silver nanoparticle-incorporated bilayer electrospun–melt-blown micro/nanofibrous membrane AU - Kim, Han Joo. International Journal of Polymeric Materials and Polymeric Biomaterials. 2017;**66**(10):514-520

[14] Taylor G. Disintegration of water drops in an electric field. Proceedings of the Royal Society of London A: Mathematical, Physical and Engineering Sciences. 1964;**280**(1382):383-397

[15] Reneker DH et al. Bending instability of electrically charged liquid jets of polymer solutions in electrospinning. Journal of Applied Physics. 2000;**87**(9):4531-4547

[16] Cai S et al. Novel 3D electrospun scaffolds with Fibers oriented randomly and evenly in three dimensions to closely mimic the unique architectures of extracellular matrices in soft tissues:

Fabrication and mechanism study. Langmuir. 2013;**29**(7):2311-2318

[17] Pant HR et al. Chitin butyrate coated electrospun nylon-6 fibers for biomedical applications. Applied Surface Science. 2013;**285**:538-544

[18] Wang S et al. Electrospun laponite-doped poly(lactic-co-glycolic acid) nanofibers for osteogenic differentiation of human mesenchymal stem cells. Journal of Materials Chemistry. 2012;**22**(44):23357-23367

[19] Joshi MK et al. Multi-layered macroporous three-dimensional nanofibrous scaffold via a novel gas foaming technique. Chemical Engineering Journal. 2015;**275**:79-88

[20] Blakeney BA et al. Cell infiltration and growth in a low density, uncompressed three-dimensional electrospun nanofibrous scaffold. Biomaterials. 2011;**32**(6):1583-1590

[21] Tiwari AP et al. pH/NIR-responsive Polypyrrole-functionalized fibrous localized drug-delivery platform for synergistic cancer therapy. ACS Applied Materials & Interfaces. 2018;**10**(24):20256-20270

[22] Liao N et al. Fabrication, characterization and biomedical application of two-nozzle electrospun polycaprolactone/zein-calcium lactate composite nonwoven mat. Journal of the Mechanical Behavior of Biomedical Materials. 2016;**60**:312-323

[23] Xu T et al. Electrospun Polycaprolactone 3D Nanofibrous scaffold with interconnected and hierarchically structured pores for bone tissue engineering. Advanced Healthcare Materials. 2015;**4**(15):2238-2246

[24] Annabi N et al. Controlling the porosity and microarchitecture of hydrogels for tissue engineering. Tissue Engineering Part B-Reviews. 2010;**16**(4):371-383

[25] Ji C et al. Fabrication of poly-DL-lactide/polyethylene glycol scaffolds using the gas foaming technique. Acta Biomaterialia. 2012;**8**(2):570-578

[26] Harris LD, Kim BS, Mooney DJ. Open pore biodegradable matrices formed with gas foaming. Journal of Biomedical Materials Research. 1998;**42**(3):396-402

[27] Joshi MK et al. Three-dimensional cellulose sponge: Fabrication, characterization, biomimetic mineralization, and in vitro cell infiltration. Carbohydrate Polymers. 2016;**136**:154-162

[28] Gao Q et al. Fabrication of electrospun nanofibrous scaffolds with 3D controllable geometric shapes. Materials & Design. 2018;**157**:159-169

[29] Jiang J et al. Expanding two-dimensional electrospun nanofiber membranes in the third dimension by a modified gas-foaming technique. ACS Biomaterials Science & Engineering. 2015;**1**(10):991-1001

[30] Lee YH et al. Electrospun dual-porosity structure and biodegradation morphology of montmorillonite reinforced PLLA nanocomposite scaffolds. Biomaterials. 2005;**26**(16):3165-3172

[31] Woodfield TBF et al. Polymer scaffolds fabricated with pore-size gradients as a model for studying the zonal organization within tissue-engineered cartilage constructs. Tissue Engineering. 2005;**11**(9-10):1297-1311

[32] Pham QP, Sharma U, Mikos AG. Electrospun poly(epsilon-caprolactone) microfiber and multilayer nanofiber/microfiber scaffolds: Characterization of scaffolds and measurement of cellular infiltration. Biomacromolecules. 2006;**7**(10):2796-2805

[33] Han D, Gouma P-I. Electrospun bioscaffolds that mimic the topology of extracellular matrix. Nanomedicine: Nanotechnology, Biology and Medicine. 2006;**2**(1):37-41

[34] Erisken C, Kalyon DM, Wang HJ. Functionally graded electrospun polycaprolactone and beta-tricalcium phosphate nanocomposites for tissue engineering applications. Biomaterials. 2008;**29**(30):4065-4073

[35] Soliman S et al. Multiscale three-dimensional scaffolds for soft tissue engineering via multimodal electrospinning. Acta Biomaterialia. 2010;**6**(4):1227-1237

[36] Ryu S et al. Three-dimensional scaffolds of carbonized Polyacrylonitrile for bone tissue regeneration. Angewandte Chemie International Edition. 2014;**53**(35):9213-9217

[37] Duan G et al. Ultralight, soft polymer sponges by self-assembly of short electrospun Fibers in colloidal dispersions. Advanced Functional Materials. 2015;**25**(19):2850-2856

[38] Wang W et al. Influences of mechanical properties and permeability on chitosan nano/microfiber mesh tubes as a scaffold for nerve regeneration. Journal of Biomedical Materials Research Part A. 2008;**84A**(2):557-566

[39] Shim IK et al. Novel three-dimensional scaffolds of poly(L-lactic acid) microfibers using electrospinning and mechanical expansion: Fabrication and bone regeneration. Journal of Biomedical Materials Research Part B: Applied Biomaterials. 2010;**95B**(1):150-160

[40] Lee S et al. Lactic acid assisted fabrication of bioactive three-dimensional PLLA/β-TCP fibrous scaffold for biomedical application. Chemical Engineering Journal. 2018;**347**:771-781

[41] Hwang TI et al. Facile fabrication of spongy nanofibrous scaffold for tissue engineering applications. Materials Letters. 2018;**219**:119-122

[42] Sun B et al. Self-assembly of a three-dimensional fibrous polymer sponge by electrospinning. Nanoscale. 2012;**4**(6):2134-2137

[43] Lee S et al. Highly Moldable electrospun clay-like fluffy nanofibers for three-dimensional scaffolds. ACS Applied Materials & Interfaces. 2014;**6**(2):1082-1091

[44] Teo WE et al. Remodeling of three-dimensional hierarchically organized Nanofibrous assemblies. Current Nanoscience. 2008;**4**(4):361-369

[45] Yokoyama Y et al. Novel wet electrospinning system for fabrication of spongiform nanofiber 3-dimensional fabric. Materials Letters. 2009;**63**(9-10):754-756

[46] Badrossamay MR et al. Nanofiber assembly by rotary jet-spinning. Nano Letters. 2010;**10**(6):2257-2261

[47] Zhang D, Chang J. Electrospinning of three-dimensional Nanofibrous tubes with controllable architectures. Nano Letters. 2008;**8**(10):3283-3287

[48] Park SH et al. Development of dual scale scaffolds via direct polymer melt deposition and electrospinning for applications in tissue regeneration. Acta Biomaterialia. 2008;**4**(5):1198-1207

[49] Sun B et al. Advances in three-dimensional nanofibrous macrostructures via electrospinning. Progress in Polymer Science. 2014;**39**(5):862-890

[50] Baker BM et al. The potential to improve cell infiltration in composite fiber-aligned electrospun scaffolds by the selective removal of sacrificial fibers. Biomaterials. 2008;**29**(15):2348-2358

[51] Kim TG, Chung HJ, Park TG. Macroporous and nanofibrous hyaluronic acid/collagen hybrid scaffold fabricated by concurrent electrospinning and deposition/leaching of salt particles. Acta Biomaterialia. 2008;**4**(6):1611-1619

[52] Ki CS et al. Development of 3-D nanofibrous fibroin scaffold with high porosity by electrospinning: Implications for bone regeneration. Biotechnology Letters. 2008;**30**(3):405-410

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