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*Review Article*

# Electrospun Nanofibers Applications in Dentistry

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Nanofibrous structures exhibit many interesting features, such as high surface area and surface functionalization and porosity in the range from submicron to nanoscale, which mimics the natural extracellular matrix. In particular, electrospun nanofibers have gained great attention in the field of tissue engineering due to the ease of fabrication and tailorability in pore size, scaffold shape, and fiber alignment. For the reasons, recently, polymeric nanofibers or bioceramic nanoparticle-incorporated nanofibers have been used in dentistry, and their nanostructure and flexibility have contributed to highly promotive cell homing behaviors, resulting in expecting improved dental regeneration. Here, this paper focuses on recently applied electrospun nanofibers in dentistry in the range from the process to the applications.

## 1. Introduction

In the field of dental tissue engineering, a variety of implanted materials and their fabrication techniques have been introduced and excellent outcomes have been revealed. Particularly, the bioceramics have shown their good biocompatibility with dental tissues and teeth since their physicochemical and biological properties such as osteoconductivity and bioactivity are very similar to those of dental tissues [1]. However, these bioceramics are extremely brittle and poor in flexibility, and therefore their own use has shown a severe limitation in the dental applications [2]. To overcome this hurdle, biodegradable polymers with flexibility have been suggested, resulting in increasing some degree of dental regeneration [3]. Examples of these polymers include poly(ethylene glycol) (PEG) and a series of polyesters, such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(D,L-lactide-co-glycolide) (PLGA), polycaprolactone (PCL), and their copolymers [4]. Recent works on bioceramic composites based on these polymers have shown significant results in improving regeneration efficiencies [5]. In particular, nanostructured implants have been expected to improve dental restoration due to the structural similarity to that of natural extracellular matrices (ECMs). Practically, improved cell-favored responses such as cell adhesion, growth, survival, and differentiation have been shown on the nanostructured surface [6], and nanostructured materials have shown increased mechanical stability compared to other typed materials [7].

Among the various types of nanostructured materials, here, we aimed to review the electrospun nanofibrous scaffolds used in dental applications (Figure 1). This paper covers electrospun nanofibrous scaffolds, polymer-based bioceramic composites to enhance their mechanical stability and biological functionality, and their fabrication techniques and processes with the recently studied examples used in the dental applications.

## 2. Cell Behavior on Nanofibrous Structure

Tissue regeneration is initiated by cellular adhesion to the matrix or neighboring cells [8]. Most tissues and also cells are underlain or surrounded by a natural ECM. These tissues are able to organize cells into the ECM, pave a road for cell migrations, activate signal-transduction pathways, and coordinate their cellular functions [9]. In order to mimic the natural ECM, a lot of biomaterials and fabrication techniques

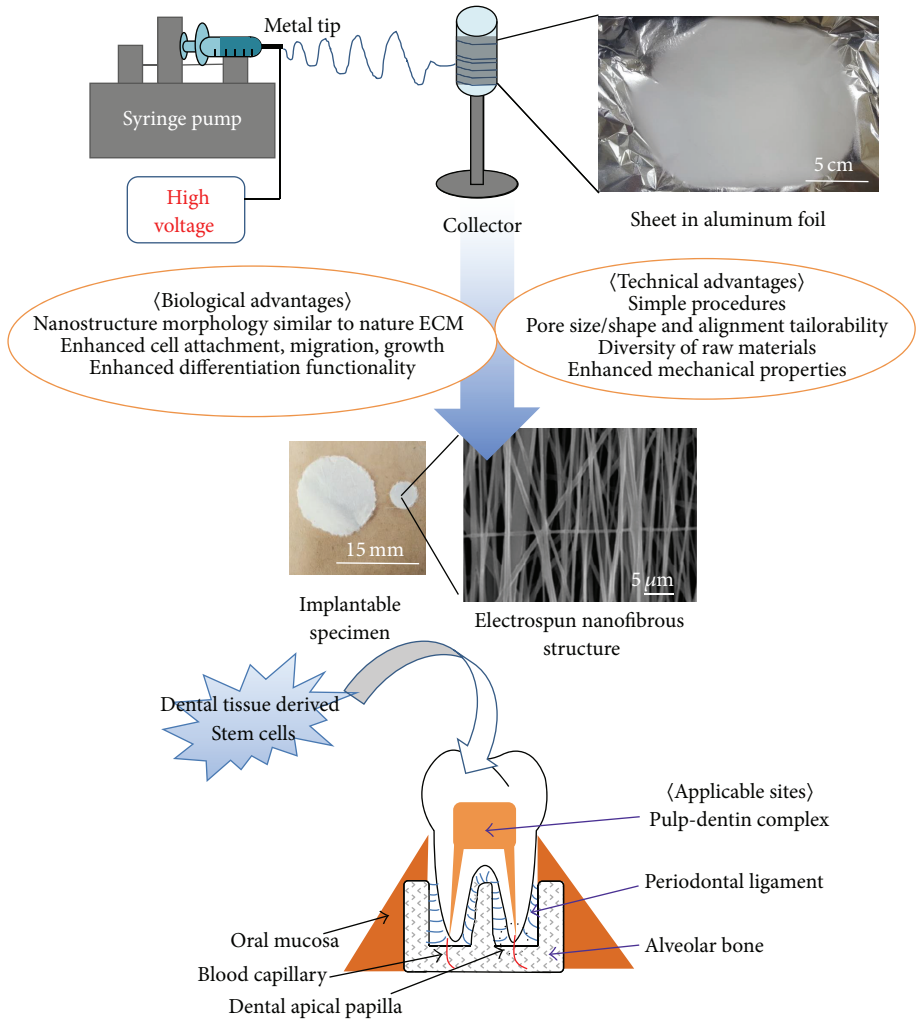


Figure 1: Electrospun nanofibrous scaffold which consisted of polycaprolactone was introduced as an exemplar biomaterial for dental tissue regeneration with various biological and technical advantages.

have been explored and optimized. Of these, nanofibrous scaffolds with nanostructure have gained great attention due to their topographical nanostructure similar to that of natural ECM [6], which has shown a great potential to increase cell adhesion, growth, migration rate, and differentiation into somatic cells from stem [6, 10, 11]. Also, nanofibrous scaffolds have been easily fabricated, and their nanostructure has shown cell-favored properties such as high porosity and surface area, control over alignment of fibrous structure for directing regenerative tissue, and controllability in overall shape, diameter, and pore size [12].

The main fabrication of nanofibrous scaffolds is as follows: self-assembly, phase separation, and electrospinning. Self-assembled formation is prepared and consequently can be directly injected for self-assembled nanofibers. In addition, much smaller diameter can be made in fabrication than when electrospinning is used [13]. However, self-assembled nanofibrous scaffolds do not allow for controlling internal pore shape and may have poor mechanical properties due to their intrinsic limitation in the use of raw materials [14]. Phase separation is the first developed process for the fabrication of nanofibrous scaffolds. In the process of phase separation, nanofibrous structure is made by removing solvent from polymer solutions using thermal treatment, solvent liquefying, porogen leaching, and freeze-drying [15]. PEG, polyesters including PLA, PLGA, and PCL, and other copolymers are the representative materials for the fabrication of nanofibrous scaffolds by phase separation [4]. Despite many advantages such as great reproducibility, low technical sensitivity, and scaffold geometry tailorability, phase separation has been less used than electrospinning due to time consuming complex procedures [16].

Electrospinning predominantly has been used for the fabrication of nanofibrous scaffolds with several advantages such as simple procedure, diameter and alignment tailorability, and raw material diversity [17]. The electrospinning can easily confer nanofibrous structure and control the size of pore and diameter [18, 19] and space between fibers by employing rotating drum collectors [20]. Such control over electrospun fibrous architecture in terms of size and alignment allows cells to migrate on the surface of the scaffold [21]. Representative examples of synthetic polymers for electrospinning include

polydioxanone and a series of polyesters [22]. However, optimization of the electrospinning process depending on the materials for cell growth from their interaction with nanofiber architectures is yet to be fully determined.

In biological applications of electrospun nanofibers, it is advantageous for the growth of cells or tissues since their intrinsic structure such as interconnected pores is able to facilitate input or output of nutrient, waste, and cell signaling molecules [23, 24]. In addition, high porosity of the 3D spun network can promote cell-scaffold interaction in terms of focal adhesion formation for attachment and proliferation [15, 25, 26] and thereby invasion of host tissue [27].

In some examples of the limited interaction between a small size of dental tissue and implant and exposure to large biting force and oral bacteria [28], nanofibrous scaffolds have shown these hurdles. In addition, surface alignment of nanofibrous scaffolds can allow cells to migrate on the right direction. For this reason, electrospun nanofibrous scaffolds can be suggested as dental tissue regenerative biomaterial due to size or alignment tailorability, large interfaces between dental cells and material by high porosity and surface area, and its similarity to nanostructured ECM in nature [29].

## 3. Basic Principle and Technique

The electrospinning technique involves a strong potential difference between a polymer-based solution flowing through a capillary metal tip and a metallic collector [30]. When the potential voltage difference between them overcomes the solution surface tension, a jet of charged fluid is split into nanofibers that fall into the metallic collection plate and get solidified with solvent evaporation [31]. Typical electrospinning equipment only requires a high voltage power supply, a syringe with pump, a metal tip needle, and a conducting collector (Figure 1) [32]. This basic setup can be modified for various applications such as dual needle syringe (to make blended or core-shell fibers) or rotating mandrel collectors (to make tube like structure) [33, 34].

In electrospinning, several parameters such as processing, physical, systemic, and solution are involved, which affect the fiber morphology and properties of electrospun fibers [35]. A list of key factors affecting electrospun nanofibers is as follows: process parameters (voltage, flow rate, distance of collector, needle diameter, and motion), systemic parameters (polymer type, molecular weight, polymer architecture, and solvent), solution parameter (viscosity, concentration, conductivity, surface tension, charge of jet, and dielectric constant), and physical parameters (humidity, temperature, and air velocity). Among them, most critically considered process parameters for controlling fiber dimension (voltage, flow rate, distance of collector, and needle diameter) are briefly described.

Inputting voltage, distance of collector, flow rate, needle gauge, and type of collector may affect the electrospinning process as a parameter of processing conditions. Higher voltage induces charges on the solution to cause the jet to emerge from the needle with stronger repulsion [36]. As a result, a decrease in fiber diameter as well as increase of diameter distribution make the control of the process further difficult. Therefore, an optimal voltage is required to inject the solution from the needle.

On the other hand, higher voltage leads to a higher flow rate of solution and faster electrospinning, which may make diameter of fibers higher due to more stretched polymer solution [37]. An increase in flow rate may build up solution at the needle tip because reduced residence time of ions in contact with the needle makes the charge rate into the solution decreased. The flow rate of the solution tailors various features of nanofibers such as diameter, geometry, and porosity [37]. A constant and stable flow rate is essential to minimize the bead formation, which induces large diameter of fibers, nonuniform distribution of fibers, or improper porosity [38]. Generally, slower flow rate results in smaller diameter and a less number of beads compared to faster flow rate [39]. Increased flow rate may also make fibers fused due to improper evaporation of solvent before the fiber collection. Therefore, in order to fabricate nanofiber constantly, the flow rate needs to be optimized.

The reduction of the distance causes flight time for the jet to be shorter, which may not have enough time to evaporate solvent with consequent improper solidification and result in an increase in fibers dimension. It follows a negative power relationship between elongated fibers/decreased fiber diameter and distance from needle to collector because an increase in the distance induces whipping action and bending instabilities [40]. In addition, an increase in gap distance decreases the surface charge density due to diminished magnitude of the electric field [41].

Diameter of the needle orifice also has an effect on fiber dimension. Smaller internal diameter reduces the solution clogging further due to less exposure time of the jet to the environment and an increase in shear stress depending on the flow rate [42]. A decrease in the internal needle diameter increases in the surface tension of the solution resulting in smaller droplet, which induces the jet speed decreased. Therefore, the jet spends more flight time before deposition into collector and is more stretched and elongated, which results in smaller diameter fibers.

## 4. Pulp-Dentin Complex Regeneration

Dental caries and trauma would result in the loss of pulp-dentin complex (the mineralized layer and fibrous tissue below enamel). Therefore, various forms of pulp-regenerative dental materials such as calcium hydroxide, ferric sulphate, and mineral trioxide aggregate are aimed at regenerating pulp-dentin complex [43]. For the pulp therapy, electrospun nanofibrous scaffolds have been attempted and resulted in excellent regeneration using dental pulp stem cells (DPSCs), which are an established cell source for the formation of dentin-pulp complex. Odontogenic differentiation of human DPSCs on PLA nanofibrous scaffolds was demonstrated by increased alkaline phosphatase (ALP) activity, dentin related marker gene expression, and mineralization [44]. Mineralized PCL nanofibrous scaffolds have shown promoted odontogenic differentiation and growth of human DPSCs through

collagen type I and the integrin-mediated signaling pathway but they still lack mechanical and biofunctional properties for clinical applications [45]. To increase mechanical and biological properties of electrospun nanofibers, nanoparticles such as bioactive glass nanoparticle, magnetic nanoparticle, and hydroxyapatite nanoparticle were incorporated to polymer matrices before electrospinning. Electrospinning techniques is possible to produce bioactive nanoparticle-polymer composite [46]. For instance, Bottino et al. produced electrospun scaffolds of bioactive nanoparticle-incorporated polydioxanone where antibiotics (i.e., metronidazole and ciprofloxacin) were able to be loaded [47]. It was observed that these scaffolds were able to deliver the antibiotics more effectively than pastes. Kim et al. produced electrospun nanofibrous scaffolds consisting of polyvinyl alcohol and hydroxyapatite nanoparticles, which showed dentin regenerative properties [48]. Collagen or PCL-gelatin-based nanofibrous scaffolds incorporating bioactive glass nanoparticles were developed for dentin-pulp regeneration and showed enhanced growth and odontogenic differentiation from human DPSCs compared to collagen nanofibrous scaffold via integrin-mediated process [5, 49]. Magnetite nanoparticles were incorporated to PCL due to its intriguing physical cues that can tailor the behaviors of DPSCs [50]. The effects of these nanocomposite nanofibers on the adhesion, growth, migration, and odontogenic differentiation of human DPSCs were significantly remarkable compared to those of polymeric nanofibers.

Taken together, the major advantage of electrospinning might be its ability to produce complex geometry of nanofibrous scaffolds for dentin-pulp complex regeneration. The ultimate goal of regenerating dentin-pulp complex is to restore both mechanical and physical attributes of the tooth structure. Therefore, electrospun nanofibers are used for carrying dental derived stem cells for optimum regeneration in the next decade.

## 5. Periodontium Regeneration

Untreated periodontal disease can lead to periodontal tissue destruction and eventual loss of teeth [51]. Regeneration of destructed periodontal tissues has always been a challenge for clinicians. Therefore, periodontal tissue engineering has been of recent interest for the repair of defects in periodontal tissues such as alveolar bone, periodontal ligament (PDL), and cementum. Traditionally, nonresorbable materials such as expanded polytetrafluoroethylene were used as guide tissue regeneration (GTR) membranes but they had the disadvantage of requiring a secondary surgery to remove the membrane. Instead, biodegradable synthetic or natural materials such as collagen, PLGA, PLA, and PCL have been researched but they still lack biological functionality as well as physical properties such as poor control over porosity and surface alignment. Electrospinning has emerged to increase the functionality of these membranes, therefore leading to expecting periodontal regeneration. As a consequence, biodegradable nanofibrous GTR membranes through electrospinning have improved the functionality, such as porosity to attach cells and fiber alignment for orientation of collagen fibers in PDL regeneration, as investigated on the attachment, proliferation, and differentiation of human PDL cells [52, 53].

Electrospun collagen membranes first gained attention in the GTR application due to their intrinsic biological properties such as differentiating potential into osteoblast-like cells [54]. However, since most of the collagen sources are originated from animals, the use of the collagen in human dental applications could be concerned and have conflicted with ethical issues and concerns of cross-infection. As an alternative, synthetic biodegradable polyester membranes are suggested for PDL regeneration.

Recent studies have shown good attachment and proliferation of PCL cells as well as tissue formation on electrospun PLGA [55], hydroxyapatite-coated electrospun PCL [56], and silk membranes as confirmed by promoted deposition of the main PDL ECM components such as collagen type I and type III [57, 58]. Silk membranes after incorporating graphene oxide [59] or hydroxyapatite nanoparticles [60] have shown human PDL cell attachment and proliferation and tissue formation into cementum and bone tissue.

Although electrospinning has added exciting new prospects to the field of periodontal tissue regeneration, much work is still required to validate the use of electrospun nanofibrous scaffolds in the clinical stage in terms of mechanical properties and *in vivo*/clinical biological properties as well as the underlying mechanisms.

## 6. Bone Tissue Regeneration

While tissue-engineered bone grafts have been investigated for years, challenges still lie in achieving *in vivo* mechanical/biological properties and vascularization for the treatment of patients who suffer from degeneration or diseases such as periodontitis, trauma, oral cancer, and anatomical abnormality in nature. Electrospun nanofibers may be one of the ideal solutions due to their ECM similarity, since they provide control over nanopores similar to the small blood vessel for the cell survival. Electrospun nanofibers have been studied in a variety of the *in vitro* and *in vivo* tests, such as mesenchymal stem cell- (MSC-) seeded implantation into a rat calvarial defect model [61, 62].

For bone regeneration, Kim's group has shown various electrospun nanofibrous scaffolds made of synthetic and natural polymers with or without mineral deposition such as gelatin-PCL [63], silk-fibroin-PCL [64, 65], PLA [66], gelatin-apatite-poly(lactide-co-caprolactone) [67], mesoporous bioactive glass-incorporated PCL-gelatin [68], mesoporous silica-shelled PCL [69], and magnetic nanoparticle-incorporated PCL nanofibrous scaffolds [70]. In addition, a number of polymeric nanofibers have been revealed and used for a cellular platform for bone, but they lack bioactivity and other biofunctionalities to accelerate bone tissue regeneration. For this, artificial mineralization after fabrication or loading additives (i.e., bioactive nanoparticles and growth factors) to scaffolds during electrospinning process was introduced and resulted in the induction of osteogenesis by accelerating natural mineralization or vascularization [68, 69, 71–73].

These nanofibrous scaffolds would be employed as a carrier for bone-associated growth factors due to their 3D networked pores to facilitate control over drug release [71–73]. Recently, electrospun nanofibrous scaffolds were designed to hold a capacity by loading and releasing dual growth factors for the target of bone regeneration. For example, a core-shell structure of a biopolymer fiber made of polyethylene oxide/PCL was shown to facilitate loading and control releasing properties of these growth factors [33].

To increase cell attachment, biofunnctional materials have been used for electrospinning. Silk nanofibers having the Arg-Gly-Asp (RGD) sequence which act as receptors for cell adhesion [64] were shown to accelerate MSC attachment, proliferation, and differentiation into osteoblastic lineage [65].

## 7. Concluding Remarks

In the field of dental tissue engineering, a number of dental materials have been advanced to create a suitable microenvironment for dental regeneration. Of these, electrospun nanofibrous scaffolds could be one approach suitable to dental applications due to the ease of fabrication, control over scaffold size, and fiber alignment. Electrospun nanofibers have provided mechanical properties and functionalities biologically favored to biological aspects in dental applications. In addition, electrospun nanofibers have played a versatile role in controlled release of biomolecule therapeutics (i.e., growth factors) or modification with adhesive biomolecules (i.e., fibronectin and RGD sequence) and contributed to further improved dental regeneration. Although a number of experiments on nanofibrous scaffolds in the *in vitro* and *in vivo* study have been conducted, clinically, customization to each patient's defect is still difficult. For the reason, the clinical practice of nanofibrous scaffolds is still scarce. In addition, since dental tissue degeneration may come from biological disorders, further studies of biological interplay between electrospun nanofiber and compromised dental tissue derived cells are essential. These studies will be expected to help to understand the biological effect of nanofibers. Conclusively, further elaborated techniques to customize nanofiber scaffolds are imperative, and clinical defects must be categorized into several groups for their customization.

## Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

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