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REVIEW

Electrospun Nanofibers for Periodontal Treatment: A Recent Progress

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Abstract: Periodontitis is a major threat to oral health, prompting scientists to continuously study new treatment techniques. The nanofibrous membrane prepared via electrospinning has a large specific surface area and high porosity. On the one hand, electrospun nanofibers can improve the absorption capacity of proteins and promote the expression of specific genes. On the other hand, they can improve cell adhesion properties and prevent fibroblasts from passing through the barrier membrane. Therefore, electrospinning has unique advantages in periodontal treatment. At present, many oral nanofibrous membranes with antibacterial, anti-inflammatory, and tissue regeneration properties have been prepared for periodontal treatment. First, this paper introduces the electrospinning process. Then, the commonly used polymers of electrospun nanofibrous membranes for treating periodontitis are summarized. Finally, different types of nanofibrous membranes prepared via electrospinning for periodontal treatment are presented, and the future evolution of electrospinning to treat periodontitis is described.

Keywords: periodontitis, electrospinning, barrier membrane, antibacterial, anti-inflammatory, tissue regeneration

Introduction

The oral cavity is a diverse microbial community in the human body, with over 700 species of bacteria. When plaque or biofilm accumulates near the gums and on the teeth, normal oral microbiota become dysregulated, leading to oral diseases, such as periodontitis, caries, and gingivitis.[1] Periodontitis causes inflammation of the periodontal tissue, also known as gum disease. Periodontitis affects nearly 743 million individuals worldwide, with about 11% of them suffering from severe periodontitis.[2] Furthermore, periodontitis is assumed to be the leading cause of adult tooth loss.[3] It also has an interactive relationship with human diseases, such as diabetes,[4] inflammatory bone loss (BL),[5] atherosclerotic cardiovascular disease,[6] rheumatoid arthritis,[7] Alzheimer's disease,[8] adverse pregnancy,[9] and so on. When oral hygiene is poor, bacteria and fungi accumulate on the gums to form a plaque. Among them, Gram-negative anaerobic bacteria, spirochetes, and viruses are the main factors of periodontitis.[10] If not treated on time, periodontal tissues may be damaged, including the alveolar bone, periodontal ligament (PDL), and gums.[11,12]

As a chronic inflammatory disease, periodontitis is an expression of the host's innate immune reaction to pathogens.[13] Periodontitis can lead to unrecoverable soft tissue injury and serious alveolar bone necrosis.[14,15] Therefore, periodontal treatment should eliminate inflammation and achieve periodontal bone regeneration.[16,17] As shown in Figure 1, a number of surgical methods and non-surgical methods can be used to treat periodontitis.[18] Non-surgical periodontal treatment is mainly used to eliminate inflammation and prevent the deterioration of the disease, but the lost periodontal support structure cannot be rebuilt and regenerated.[19] Surgical methods can regenerate damaged periodontal tissue, which is a better treatment at present. Bone transplantation,[20] gene therapy,[21] and local delivery of growth factors[22] are other modes of treatments. However, these methods have drawbacks, such as limited autograft and immune rejection in bone transplantation, weak host immune response and tumor production triggered by gene therapy, and unstable growth factors.[19] Guided tissue regeneration (GTR), as a method of periodontitis surgical treatment, has been applied since the 1980s. The principle of its treatment is to establish a

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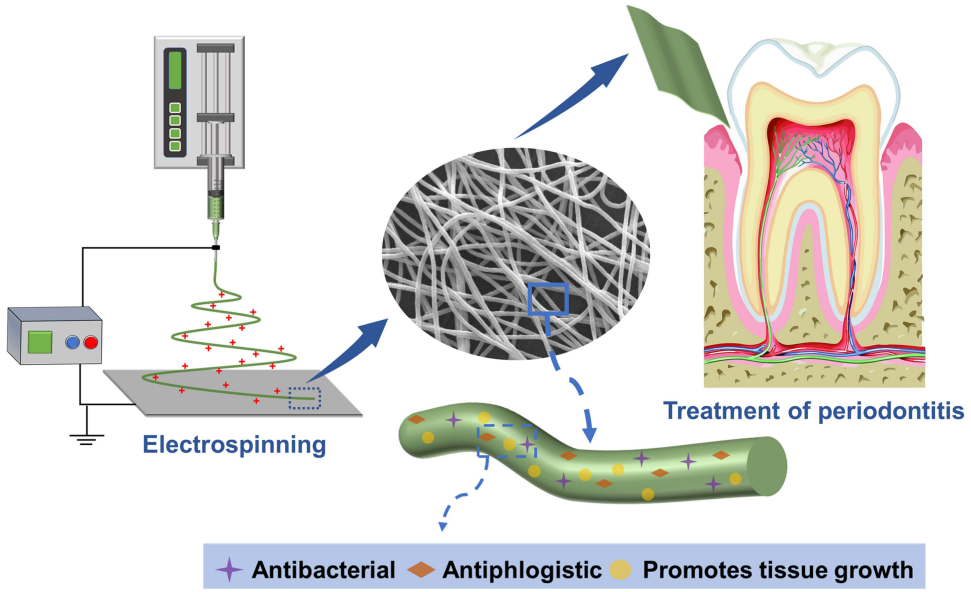
Graphical Abstract



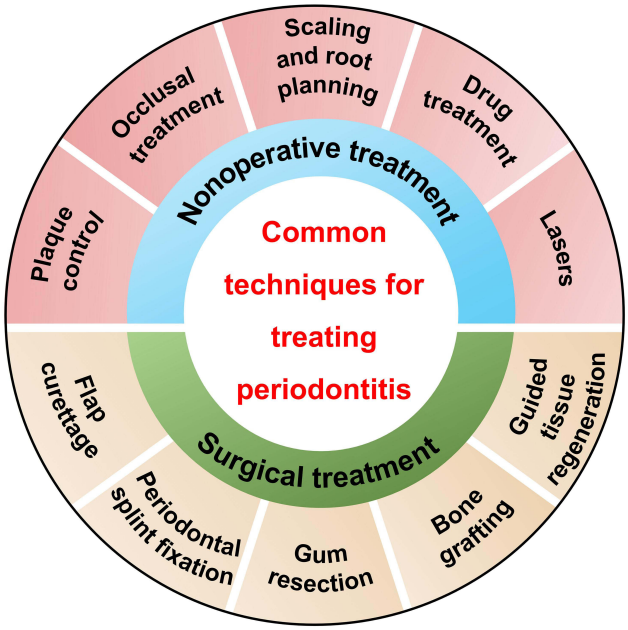


Figure 1 Common methods of periodontal treatment.

mechanical barrier membrane to prevent epithelial and connective tissue growth to address the defect, thereby achieving periodontal tissue regeneration.[23] In addition, the barrier membrane can adhere to the surrounding tissue, thus minimizing bacterial activity and inducing bone differentiation.[24] Therefore, GTR has become a better option for surgical therapy to further promote periodontal tissue regeneration.[25] Considering the particularity of the oral environment, the periodontal barrier membrane for tissue regeneration should have the following properties: 1) absence of cytotoxicity, stimulation, immunogenicity, adverse reactions to tissues, and rejection to the body; 2) good biological compatibility to facilitate cell

adhesion and proliferation; 3) specific surface area and high porosity to facilitate cell tissue and blood vessel growth, thus promoting protein absorption; 4) a certain mechanical strength to meet the mechanical stress generated by the surgical operation and the operation area tissue; 5) evident biodegradability or absorbability, hence avoiding the secondary surgical removal of the barrier membrane, in which the rate of degradation of the barrier membrane can have the same step as the rate of new tissue generation. Therefore, the materials and preparation process of the barrier membrane should be carefully selected.[26]

Researchers have attempted to prepare different types of periodontal barrier membranes via electrospinning, casting membrane utilization, and dynamic filtration. Among them, electrospinning is an efficient method to prepare nanofibrous membranes, and it has found widespread application in biomedicine, especially for wound dressing,[27–31] tissue engineering,[32–36] and cancer treatment.[37] Electrospun nanofibrous membranes can mimic the scale and morphology of extracellular matrix (ECM) proteins, thus facilitating cell attachment, proliferation, and differentiation. The high porosity of nanofibrous membranes allow oxygen permeation, and the relevant high specific surface area can effectively prevent fibroblasts from crossing the fibrous membrane. Nanofibrous membranes can also improve drug loading and local drug delivery in a sustained and controlled manner.[38–40] Therefore, the electrospun nanofibrous membrane is ideal for use as a periodontal barrier membrane.[41,42] On the "Web of Science" portal, the literature from the past ten years was searched under the themes of "treatment of periodontitis" and "electrospinning and periodontitis." The results are shown in Figure 2. Between 2012 and 2021, the number of papers on the theme of "treatment of periodontitis" exceeded 10,000. The trend increases year by year, indicating that the treatment of periodontitis is a hot research topic. However, few related studies have focused on the application of electrospinning in periodontal treatment, indicating that more attention should be paid to this field. This review mainly summarizes the following aspects. 1) introduction of electrospinning; 2) commonly used polymers and related polymer characteristics of electrospun nanofiber membranes adopted for periodontal treatment; and 3) the research status of electrospinning for periodontal treatment, and the future development of electrospinning for treating periodontitis.

Electrospinning

Electrospinning is the direct and continuous preparation of nano-scale fibers via a "bottom–up" method.[43,44] The process has the benefits of having a basic apparatus, simple operation, and cost-effectiveness. Consequently, electrospinning has been widely used in many fields, such as medical engineering,[45–47] environmental treatment,[48,49] biosensors,[50,51] food packaging

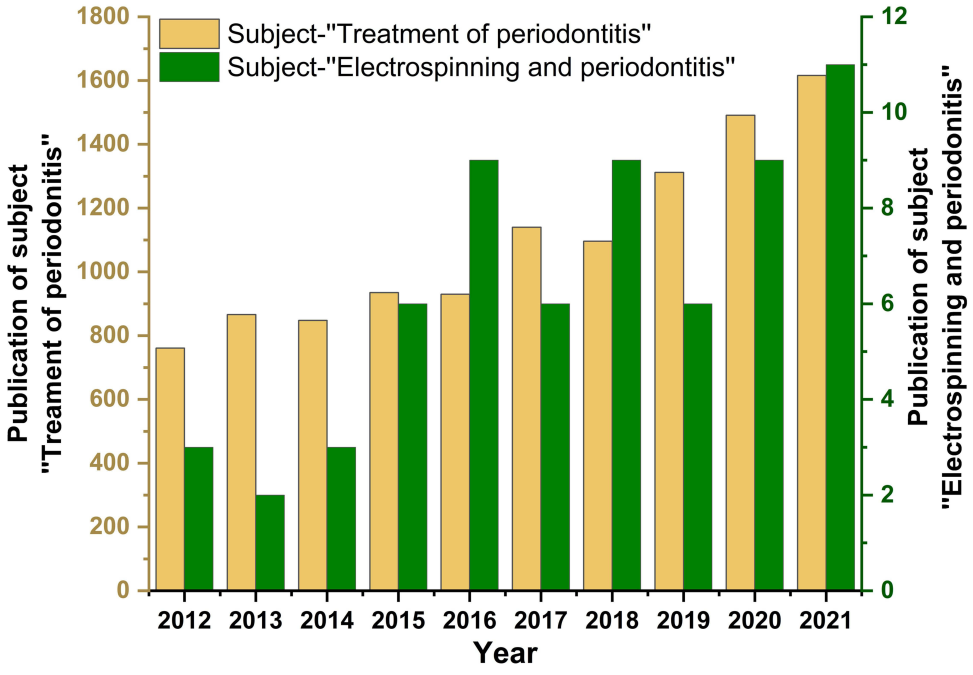


Figure 2 The subjects "Treatment of periodontitis" and "Electrospinning and periodontitis" were used to search the statistics of literature on the "Web of Science" portal.

and herbal medicine.[52,53] The nanofibrous membranes prepared via electrospinning has a small pore diameter, high specific surface area, and easy surface modification, which is highly suitable for use in periodontal barrier membranes.

Development of Electrospinning

In the 16th century, William Gilbert[54] reported that when the electrostatic field and a water droplet were sufficiently close to each other, the water drop's tip would eject tiny droplets. From this idea, the concept of "electrospinning" was proposed. In 1882, Lord Rayleigh[55] calculated the highest charge required to exceed the surface tension of a droplet, allowing for the ejection of the droplet of a certain size. In 1902, William Morton[56] and John Cooley[57] introduced the electrospinning process. The first patent was applied for a device that could eject liquid via an electric charge. Between 1907 and 1920, John Zeleny[58] wrote a number of papers about electrical discharges on liquid and solid surfaces. Between 1931 and 1944, Anton Formhals[59] was able to commercialize the technique and published as many as 20 patents. From 1964 to 1969, Taylor[60] explained the process of a liquid drop and the change from hemispheric to cone shape ("Taylor cone") in an electric field by using mathematical language and a model. In 1971, Baumgarten[61] discovered that the fiber diameter depends on various electrospinning parameters, such as solution viscosity and applied voltage. In the 1970s, electrospinning was gradually commercialized.

Many other researchers have ventured into electrospinning since the 1990s. Consequently, the number and quality of research papers have increased exponentially, from only a few papers per year to more than 49,000 papers in 2022 (the term "electrospinning" was searched in the Web of Science portal on March 30, 2022), with the number expected to continuously increase.

Electrospinning Apparatus and Process

Figure 3 depicts the electrospinning apparatus and its electrospinning process. Four parts (syringe pump, spinneret, receiving device, and high-voltage DC generator) constitute the main apparatus system. The syringe pump, which is a fluid-driving system,

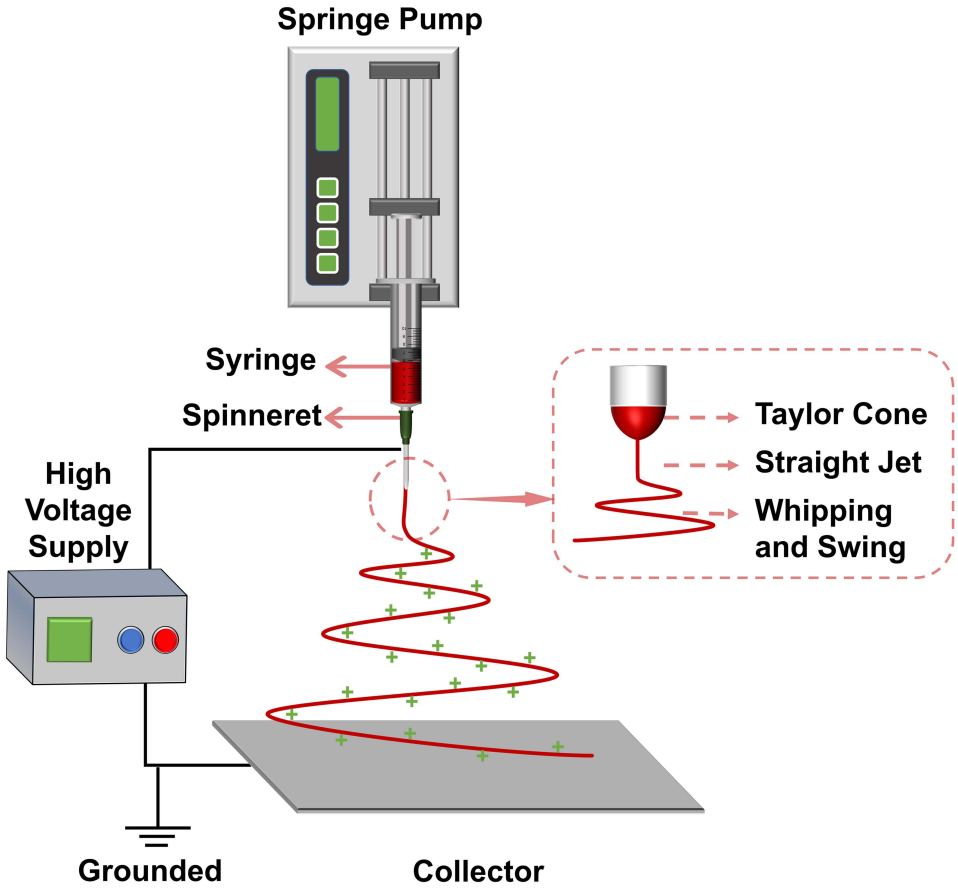


Figure 3 Electrospinning device and the schematic diagram of the electrospinning process.

is designed to accurately control the flow and flow rate of the working fluid. During the electrospinning process, droplets are generated at the top of the spinneret, thereby also allowing the droplets to form into a Taylor cone and spray fluid jets. The spinneret can also control the nanofiber structure. The receiving device can be used to collect the nanofibers. The power supply poles of the high-voltage DC generator are connected to the spinneret and the receiving device, and an electrostatic field is formed between them. The electrospinning process can be divided into three stages. 1) The working fluid in the syringe is driven by the syringe pump and forms a droplet at the spinneret's tip. 2) Under the action of electric field force, the droplets gradually form the Taylor cone. At this time, the droplet is subjected to three forces, namely, its gravity, surface tension, and electrostatic repulsion. When the voltage continues to increase, the charge will reach a critical value, causing the droplet's surface tension to be less than the electrostatic repulsion, and a straight jet will appear at the tip of the cone. 3) Given the Rayleigh Taylor instability and the charge interactions in the electrostatic field, the straight jet can only be maintained for a short period of time. Then, the phenomenon of whipping and swinging will occur. The charged jet is stretched under the interaction of gravity, causing an electrostatic repulsion between charges and a Coulomb repulsion between the layers. The electrospun nanofibers are collected on the receiving device while the solvent in the working fluid rapidly evaporates.

Influencing Factors of Electrospinning

The factors influencing the preparation of nanofibers via electrospinning mainly include three parts, namely, the system parameters, process parameters, and environmental parameters. The system parameters comprise the polymer relative molecular weight, polymer relative molecular mass distribution, polymer solubility, solvent volatility, solvent conductivity, solution concentration, solution surface tension, and solution conductivity. The process parameters comprise the voltage, fluid flow rate, and receiving distance. The environmental parameters comprise the temperature, humidity, and airflow. The analysis of the influencing factors of the electrospinning process is shown in Table 1. In the preparation of the required nanofibers via electrospinning, we need to consider the different parameters because of their interactions.

Classification of the Electrospinning Process

With the continuous development and differentiation of electrospinning modes, a variety of classification methods have been adopted. Single-fluid electrospinning, double-fluid electrospinning, and three-fluid electrospinning are the three types of electrospinning. As shown in Figure 4, the classification is based on the amount of fluid and, partially, by their corresponding electrospun nanofibers.

Single-Fluid Electrospinning

Single-fluid electrospinning mainly includes blend electrospinning[62] and emulsion electrospinning.[63] The working fluid of hybrid electrospinning is usually composed of one or more polymers loaded with model drugs. This process has the advantages of simple operation and easy implementation. Its disadvantage is that the working fluid requires spinnability, but preparing the nanofiber structure is relatively simple. When the nanofiber is applied to the medical field, the model drug inevitably appears on the surface of the monolithic fiber, leading to a burst release. Emulsion electrospinning allows the use of a spinneret with a monolithic structure to prepare nanofibers with a core–sheath structure.[64] Emulsion electrospinning involves the dissolution of the polymer in the oil phase and the drug or protein molecule in the water phase. During electrospinning, the two-phase emulsion is drawn into filaments, forming nanofibers with a core–sheath structure.[65] Zhao et al[66] used hybrid electrospinning, emulsion electrospinning, and coaxial electrospinning to create polycaprolactone (PCL)-loaded L-ascorbic acid-2-magnesium phosphate nanofibers for promoting the osteogenic differentiation of bone tissue-engineered stem cells. When dichloromethane/methanol=7:3 was chosen as the solvent, the nanofibers prepared via hybrid electrospinning and emulsion electrospinning entailed a lesser burst release. At present, most of the preparation methods of barrier membranes for periodontal treatment use single-fluid electrospinning, among which hybrid electrospinning is the primary method.

Double-Fluid Electrospinning

Double-fluid electrospinning includes coaxial electrospinning[67–70] and side-by-side electrospinning.[71–73] Aiming for the smooth progress of electrospinning in traditional coaxial electrospinning, the sheath fluid has to be spinnable. The core

Table 1 Analysis of Influencing Factors of the Electrospinning Process

Influence Parameter		Effect on Nanofibers
System	Polymer relative molecular weight	The higher the relative molecular weight, the larger the fiber diameter, and the smoother the fiber without beads.
	Relative molecular mass distribution	Increasing the polymer's relative molecular mass distribution increases the probability of beaded-on-The-string fiber formation.
	Polymer solubility	The higher the solubility, the more stretched the polymer chain and the entanglement of each other, which is beneficial to the formation of fibers.
	Solvent volatility	When the volatility is too high, the fibers will have a porous structure, and when the volatility is too low, flat fibers are easily obtained, and adhesion occurs.
	Solvent conductivity	The larger the conductivity, the smaller the fiber diameter and the higher the conductivity will affect the stability of the jet.
	Solution concentration	When the concentration increases, the fiber diameter increases. If the concentration is too high, the fiber will be discontinuous. If the concentration is too low, it is easy to get microspheres.
	Solution surface tension	The increase in surface tension leads to the fiber diameter to increase and it may lead to the appearance of beads.
	Solution conductivity	The higher the solution conductivity, the lower the fiber diameter, but the more comprehensive the fiber distribution.
Process	Voltage	The higher the voltage, the easier it is to form uniform fibers with smaller diameters. Too high or too low voltage will lead to an increase in fiber diameter, and the diameter distribution will be uneven.
	Flow rate	The diameter of the fiber increases as the flow rate increases. If the flow rate is too high, the fibers will form beads.
	Receiving distance	The fiber diameter decreases as the receiving distance increases, but when the receiving distance is too small, the solvent is not fully evaporated, and the fibers are flat and not smooth.
Environmental	Temperature	As the temperature increases, the fiber diameter decreases.
	Humidity	When the humidity increases, it is easy to form a porous structure on the fiber's surface. Under higher humidity, it is easy to obtain beads-on-The-string fibers.
	Airflow	Increased airflow will accelerate solvent evaporation, forming porous fibers and increasing fiber diameter.

layer is adequately encapsulated by the sheath layer when the sheath fluid concentration and flow rate are slightly larger than those of the core fluid.[74–76] The traditional coaxial electrospinning can be modified by using a non-spinnable solvent as the sheath fluid to wrap the core fluid and subsequently prepare smooth nanofibers with a monolithic structure.[77] This discovery has further broadened the potential application of electrospinning for preparing core–sheath nanofibers, thus laying the foundation for improving the three-fluid electrospinning to a certain extent.

Side-by-side electrospinning produces nanofibers with a dual-phase composite structure.[78] Two semicircles in the side-by-side nanofibers contain different phases, and suitable nanofibers can be prepared according to the specifications of specific conditions. Beads-on-The-string nanofibers could be fabricated via side-by-side electrospinning to jointly achieve medication and double-drug controlled release.[79] Coaxial and side-by-side electrospinning have different nanofiber structures, hence their variations in handling drug release properties. Nonsteroidal anti-inflammatory drugs (NSAIDs) can mitigate periodontal inflammation by inhibiting the activity of cyclooxygenase (COX).[80] However, most NSAIDs have poor water solubility and cannot be fully utilized in periodontal treatment. At present, various methods, including solid-dispersible tablets[81–87] and nano-hybrids,[27,46] have been developed to speed up the dissolution rate. In

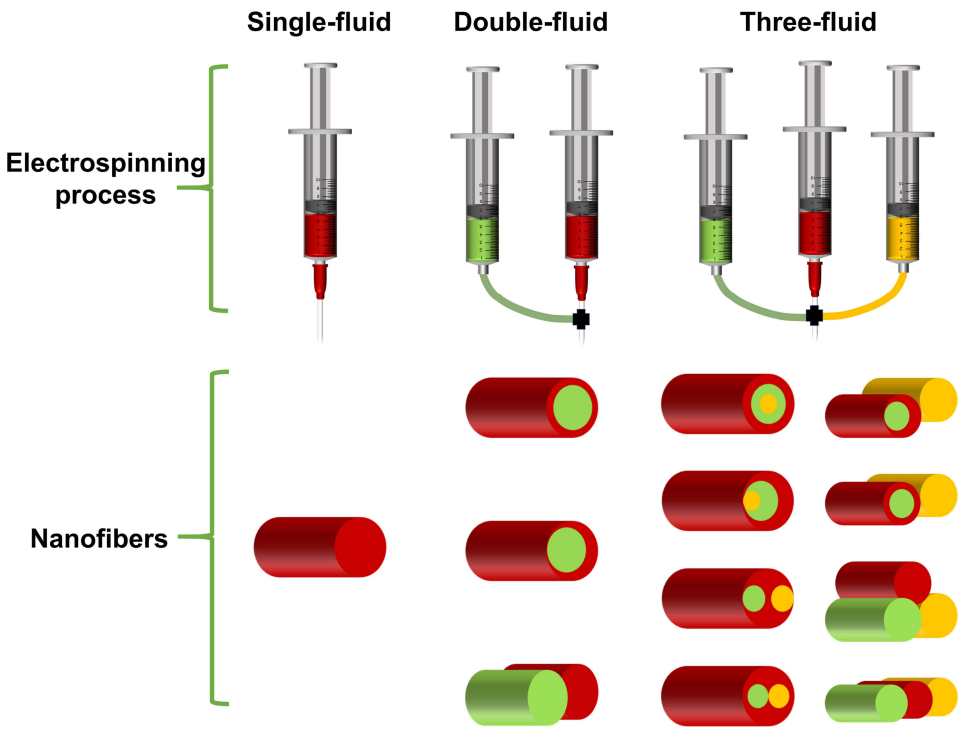


Figure 4 Schematic diagram of the electrospinning process classification and their respective fiber structure.

addition, nanofibers with a good shape, high encapsulation efficiency, and rapid dissolution can be prepared via side-by-side electrospinning, thereby improving the processing of poorly soluble drugs in the oral cavity.

Three-Fluid Electrospinning

Currently, the majority of electrospinning research has concentrated on single-fluid and double-fluid electrospinning, whereas only a few studies have delved into three-fluid electrospinning. Nanofibers with complex structures can be prepared using multi-fluid electrospinning by changing the materials, composition, spatial distribution, and relative size of components.[88,89] In 2007, Zhao et al[90] proposed the preparation of nanofibers with three fluids. Since then, three-fluid electrospinning has received extensive attention. Yang et al[91] used modified triaxial electrospinning to create a pH-sensitive polymer/lipid nanocomposite with a core–shell structure. Liu et al[92] used modified triaxial electrospinning to prepare medicated core–shell nanofibers, and the shell thicknesses were explored to adjust the sustained release profiles of the loaded drug. Currently, the preparation of multifunctional nanofibers with complex structures has become a novel approach in advancing electrospinning technology. As for periodontal treatment, multi-fluid electrospinning can be used in combination with different matrices and model drugs to prepare barrier membranes, further achieving the synergistic effect of multiple drugs.

Polymers Commonly Used in Periodontal Treatment in Electrospinning

The barrier membranes implanted in the oral cavity should have good biocompatibility, stable mechanical properties, excellent antibacterial properties, and controllable biodegradability. At present, the polymers used in periodontal treatment in electrospinning include the natural, synthetic, and composite polymers. Each type has its respective advantages that can be effectively applied to oral barrier membranes. Figure 5 lists a number of polymers commonly used in periodontal treatment via electrospinning.

Natural Polymers

Natural polymers have the advantages of non-toxicity, good biocompatibility, and biodegradability. They promote wound healing and are widely used in drug delivery and regenerative medicine. The natural polymers commonly used in the

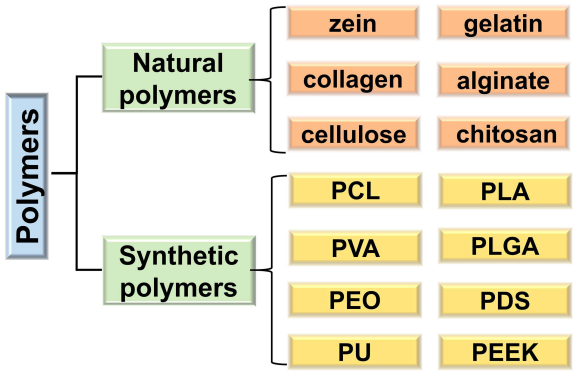


Figure 5 Polymers commonly used in the periodontal treatment in electrospinning.
Abbreviations: PCL, Polycaprolactone; PLA, Polylactic acid; PVA, Polyvinyl alcohol; PLGA, Poly(lactic-co-glycolic acid); PEO, Polyethylene oxide; PDS, Polydioxanone suture; PU, Polyurethane; PEEK, Poly(ether-ether-ketone).

treatment of oral periodontitis are mainly proteins, including zein,[93] gelatin (Gel),[94] and collagen.[95] Polysaccharides, including alginate,[96] cellulose,[97] and chitosan (CS), are also utilized.[98]

Zein

The protein extracted from corn is called zein. Zein has good biocompatibility, natural biodegradability, thermal stability, and renewable properties.[99] When used in drug delivery systems, zein can promote wound healing; it is also adopted for the regeneration treatment of muscle, cartilage, and nerve tissues. However, a large number of hydrophobic amino acids lead to the poor cell affinity of zein.[100] Zein is usually mixed with a hydrophilic polymer in electrospinning to improve biocompatibility. Liu et al[101] prepared highly hydrophilic nanofibers of zein and polyethylene oxide (PEO)-loaded thyme essential oil (TEO) by using a hand-held electrospinning device (Figure 6A). The nanofiber membrane presented good air permeability and absorption capacity for wound exudates. Compared with the untreated Zein/PEO nanofiber groups, Zein/PEO/TEO nanofibers exhibited a more significant inhibition against Escherichia coli and Staphylococcus aureus. Zein/PEO/TEO nanofibers could also prevent wound infection and accelerate wound healing. The electrospun nanofibers prepared using the aforementioned portable device have a potential use in the clinical care of wounds.

Gelatin

Gel is a protein obtained from the partial denaturation or hydrolysis of collagen under the action of acid, alkali, or enzyme. It has solid hydrophilicity, biodegradability, and low-immunity originality.[102] Aytac et al[103] prepared ciprofloxacin (CIP)/hydroxypropyl-β-cyclodextrin (HPβCD)-inclusion complex (IC)-loaded Gel nanofibers via electrospinning (Figure 6B). The dissolution of CIP was significantly enhanced after the complexation with HPβCD. The Gel nanofibers prepared via electrospinning could simulate human ECM, and it promoted the growth of new tissues and accelerated wound healing. As for periodontal treatment, Gel provides a favorable three-dimensional environment for the migration, differentiation, and proliferation of cells, which can guide PDL cells into biological tissues. However, Gel electrospun nanofibers also have drawbacks, including its poor mechanical properties, poor water resistance, and easy deformation. The properties of Gel nanofibers can be improved by mixing them with other polymers or their post-treatment with cross-linking agents. In this manner, a comprehensive range of applications, including clinical applications, of electrospun Gel nanofibers can be promoted.

Chitosan

CS is a natural substance obtained from the deacetylation of chitin. It is a harmless and edible natural polysaccharide.[104,105] CS has many excellent biological properties, including antibacterial, hemostatic, osteogenic, compatibility, and degradability properties, owing to the high reactivity of the CS amino groups.[106] In addition, CS is widely available and inexpensive. Consequently, CS has shown tremendous potential in medical treatments, such as wound healing and bone tissue growth.[107] Although CS is spinnable, its nanofibrous membrane has poor mechanical properties and rapid degradation, which limits its

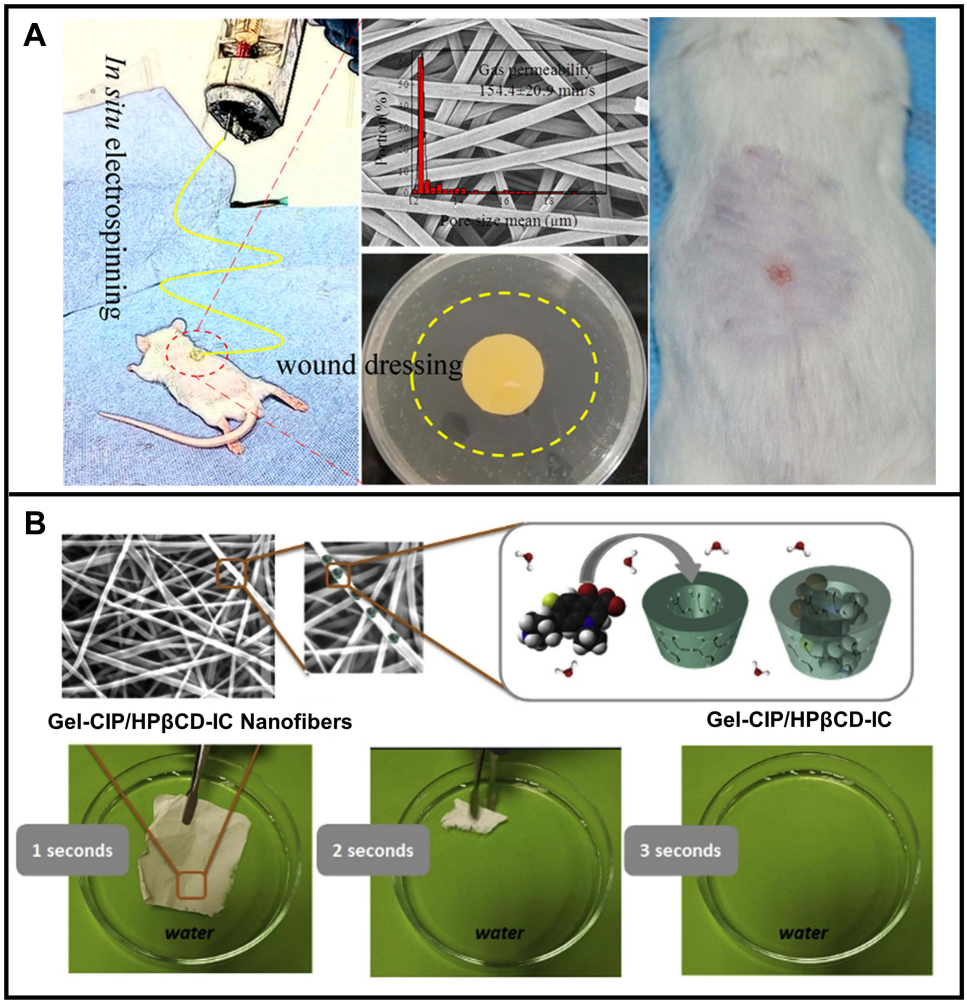


Figure 6 Natural polymers for electrospinning. (**A**) Schematic diagram of in situ electrospinning of Zein/TEO. Reproduced with permission from Liu JX, Dong WH, Mou XJ, et al. In situ electrospun zein/thyme essential oil-based membranes as an effective antibacterial wound dressing. *ACS Appl Bio Mater.* 2020;3(1):302–307. Copyright © 2020 American Chemical Society.[101] (**B**) Schematic diagram of Gel-CIP/HPβCD-IC nanofibers prepared by electrospinning. Reproduced from Aytac Z, Ipek S, Erol I, et al. Fast-dissolving electrospun gelatin nanofibers encapsulating ciprofloxacin/cyclodextrin inclusion complex. *Colloid Surfaces B.* 2019;178:129–136. Copyright © 2019, with permission from Elsevier.[103]

clinical application.[108] Therefore, CS is usually mixed with other polymers in electrospinning to prepare nanofibers with excellent performance.

Natural polymers can be obtained directly from nature. They are one of the leading materials of human ECM, and they are biocompatible and non-toxic. The natural nanofibers produced by electrospinning with high specific surface areas and porous structures can promote cell adhesion and proliferation. Furthermore, natural nanofibers can be used as excellent biomaterials for wound dressings, skeletal tissues, and drug carriers. However, they also have shortcomings, such as high hydrophilicity, low stress, and rapid degradation. When used in oral drug delivery systems, the barrier membrane of natural polymers may be degraded even before the periodontal tissue is fully regenerated, which is highly unfavorable for periodontal treatment. Therefore, the clinical application of natural nanofibers in the oral cavity still needs continuous improvement and optimization.

Synthetic Polymers

Synthetic polymers have good spinnability and thermal stability, and their mechanical properties are better than those of natural polymers.[109] The electrospun nanofibrous membranes of synthetic polymers are widely used in the biomedical

field and polycaprolactone (PCL), polylactic acid (PLA), and polylactic acid-co-glycolic acid (PLGA) are commonly utilized in the treatment of oral diseases.

Polycaprolactone

PCL is a biodegradable organic polymer with good biocompatibility, permeability, flexibility, low production cost, and easy processing and molding. As a material, PCL is popular in biomedical applications.[110] Compared with other degradable synthetic polymers, PCL does not produce acidic byproducts during degradation, and it can maintain the stability of the oral environment. Therefore, PCL is widely used to treat oral diseases and regenerate periodontal tissue.[111]

Batool et al[112] prepared a PCL-loaded ibuprofen (IBU) functional barrier membrane via electrospinning. As shown in Figure 7A, the nanotechnology is combined with a postoperative anti-inflammatory treatment to promote the healing of periodontal wounds, further advancing tissue formation. However, the slow biodegradability of PCL may not perfectly match the rate of new tissue formation, hence the difficulty of controlling the degradation of PCL. Niiyama et al[113] fabricated nanofibers with stable mechanical properties and fast degradation via the hybrid electrospinning of high- and low-molecular weight PCLs without introducing other polymers. In addition, the PCL was modified with natural polymers and bioceramic materials to enhance the bone osteoinductive and osteoconductive capabilities. Their technique can enhance the repair performance of bone tissue, and it allows for PCL to become a more suitable candidate for periodontal implant membranes.

Polylactic Acid

PLA is first extracted from plants and then synthesized via the chemical method. It only produces carbon dioxide and water when degraded.[114] PLA is an environmentally friendly, biodegradable, and easy-to-process polymeric biomaterial with good biocompatibility and mechanical properties.[115] With the deepening of research on PLA, the PLA nanofibrous membranes prepared via electrospinning have become widely used in the treatment of periodontitis. Reise et al[116] prepared PLA-loaded metronidazole (MNZ) nanofibers via electrospinning. MNZ was effectively encapsulated in the PLA matrix, and the drug-loaded nanofibers presented sustained release properties and good antibacterial activity against periodontal pathogens; hence, the approach is beneficial for local periodontal treatment. Cui et al[117] prepared doxycycline hydrochloride (DCH) nanofibers loaded with different contents by using PLA as the matrix (Figure 7B). The nanofibers exhibited cytocompatibility and antibacterial properties; thus, their technique can be used in wound dressings, and it may even improve the effectiveness of traditional small molecule drugs in chronic wound treatment, such as periodontitis.

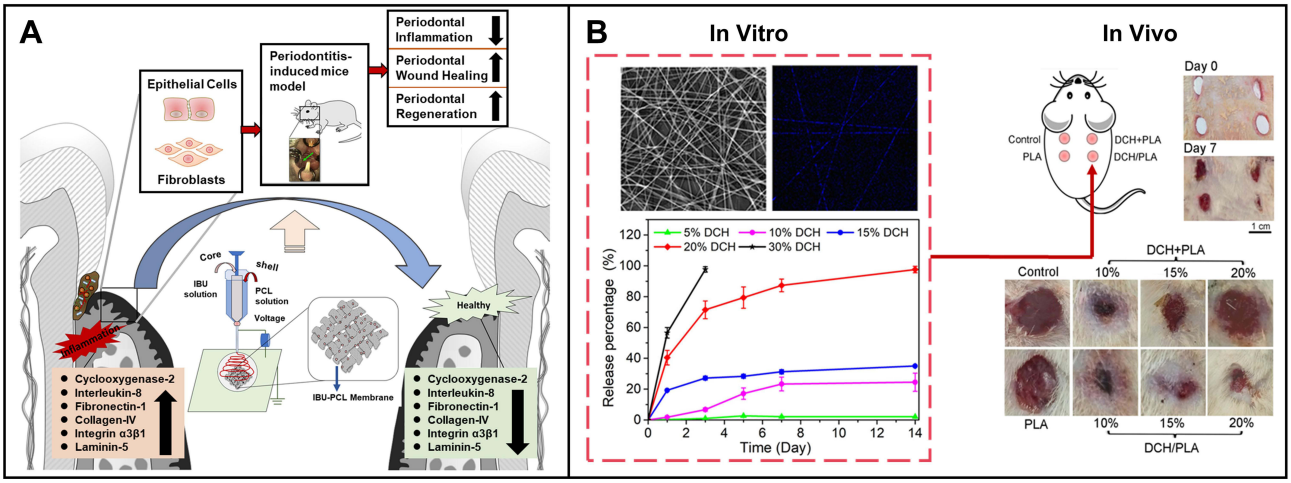


Figure 7 Synthetic polymers for electrospinning. (**A**) Schematic diagram of PCL/IBU anti-inflammatory scaffold used for periodontitis treatment. Reproduced with permission from Batool F, Morand DN, Thomas L, et al. Synthesis of a novel electrospun polycaprolactone scaffold functionalized with ibuprofen for periodontal regeneration: an in vitro and in vivo study. *Materials*. 2018;11(4):580. Copyright © 2018 Materials. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY).[112] (**B**) Schematic diagram of in vitro drug delivery behavior and in vivo healing of wounds from PLA/DCH nanofibers with different DCH contents. Reproduced from Cui SS, Sun X, Li K, et al. Polylactide nanofibers delivering doxycycline for chronic wound treatment. *Mat Sci Eng C-Mater*. 2019;104:109745. Copyright © 2019, with permission from Elsevier.[117]

Polylactic Acid-Glycolic Acid Copolymer

PLGA has good biocompatibility and rapid degradation, and it is commonly applied in the biomedical field, such as for wound dressings, pharmaceutical carriers, and tissue scaffolds.[118] In recent years, PLGA nanofibers prepared via electrospinning have been widely adopted in the therapy of oral diseases, including periodontal disease, pulp disease treatment, and tissue regeneration. The PLGA drug-loaded barrier membrane can provide controlled release and promote bone tissue growth.

Ma et al[119] prepared PLGA-loaded minocycline (MINO) nanofibers via electrospinning. Experimental periodontitis was conducted on mice in vivo. The experimental group prevented the decreased alveolar ridge height and ligation-induced BV/TV decrease, and increased alveolar ridge height. The expression of the nuclear factor receptor activator ligand was also reduced, whereas the expression of the inhibitor osteoprotegerin was facilitated. Therefore, MINO-PLGA membranes can be used for bone regeneration in periodontitis. Liu et al[120] prepared PLGA-loaded dimethyloxalylglycine (DMOG) and nanosilicate (nSi) nanofiber membranes via electrospinning. Their results showed that the DMOG/nSi-PLGA membrane could alleviate the immunoinflammatory response of the defect and promote bone regeneration in periodontal disease after a nanofibrous membrane was implanted into the periodontal defect.

Synthetic polymers have good spinnability, good biocompatibility, excellent mechanical properties, and proper biodegradability. Therefore, they are very suitable for the periodontal barrier membrane for tissue regeneration. However, synthetic polymers have the disadvantages of high surface hydrophobicity and poor heat resistance. They are usually blended with natural polymers or incorporated with bioactive substances for modification.

Composite Polymers

Composite polymers are a mixture of natural and synthetic polymers. They can produce electrospun nanofibers with the desired properties by changing the composition and components of a working fluid. Typically, the respective advantages of natural or synthetic polymers are considered.

The synthetic polymer PCL has strong hydrophobicity, which is not conducive to the proliferation of cells and the adhesion characteristics required by the periodontal barrier membrane. To overcome this shortcoming, Münchow et al[121] demonstrated that synthetic polymer PCL could increase the viscosity by adding natural polymer Gel to achieve a good chain entanglement effect, resulting in more uniform nanofibers compared with PCL nanofibers. The all PCL-based scaffolds had high hydrophobic properties, but the incorporation of Gel resulted in a marked decline in water contact angle and a significant increase in wettability (Figure 8A). Khan et al[122] blended PCL and CS in electrospinning to improve the hydrophilic and adhesive characteristics of nanofibers (Figure 8B). The nanofibrous drug release profile indicated a burst release of 31% of the antibiotic in the first 8 hours, and then a sustained release of up to 18 days. Biphasic drug release was also achieved. Hydrophilic nanofibers have been shown to strengthen cellular affinity for improving cell proliferation and promoting wound healing, which is beneficial for periodontal surgical treatment. In addition to improving the properties of the single polymer, composite polymers can also promote spinnability. Hyaluronic acid (HA) is an anti-inflammatory and antibacterial natural polymer that can promote wound healing, but it is not spinnable. Joshi et al[123] prepared nanofibers with controlled-release behavior and good adhesion properties by mixing HA with polyvinyl alcohol (PVA) to form a stable periodontitis drug delivery system.

Recently, the study on the preparation of composite polymer periodontal barrier membranes via electrospinning has gradually increased, mainly for the following reasons. 1) The number of spinnable natural polymers is limited, but composite polymers can improve the spinnability problem. 2) Natural polymers have the characteristics of weak mechanical properties, strong water solubility, and rapid degradation. Synthetic polymers have the characteristics of good mechanical properties, weak hydrophilicity, and slow degradation. Composite polymers can combine the advantages of the two polymer types to prepare electrospun nanofibrous membranes with excellent comprehensive performance. 3) Several commonly used composite polymers have the advantages of non-toxicity and good biocompatibility, and they are good candidates for oral barrier membranes.

With the continuous research and development of polymers, more and more polymers that can meet the demand may be used for periodontal treatment. At present, the studies should be based on the existing polymers, but they should also be investigated according to the characteristics of drugs and the demand for barrier membranes. This approach is highly

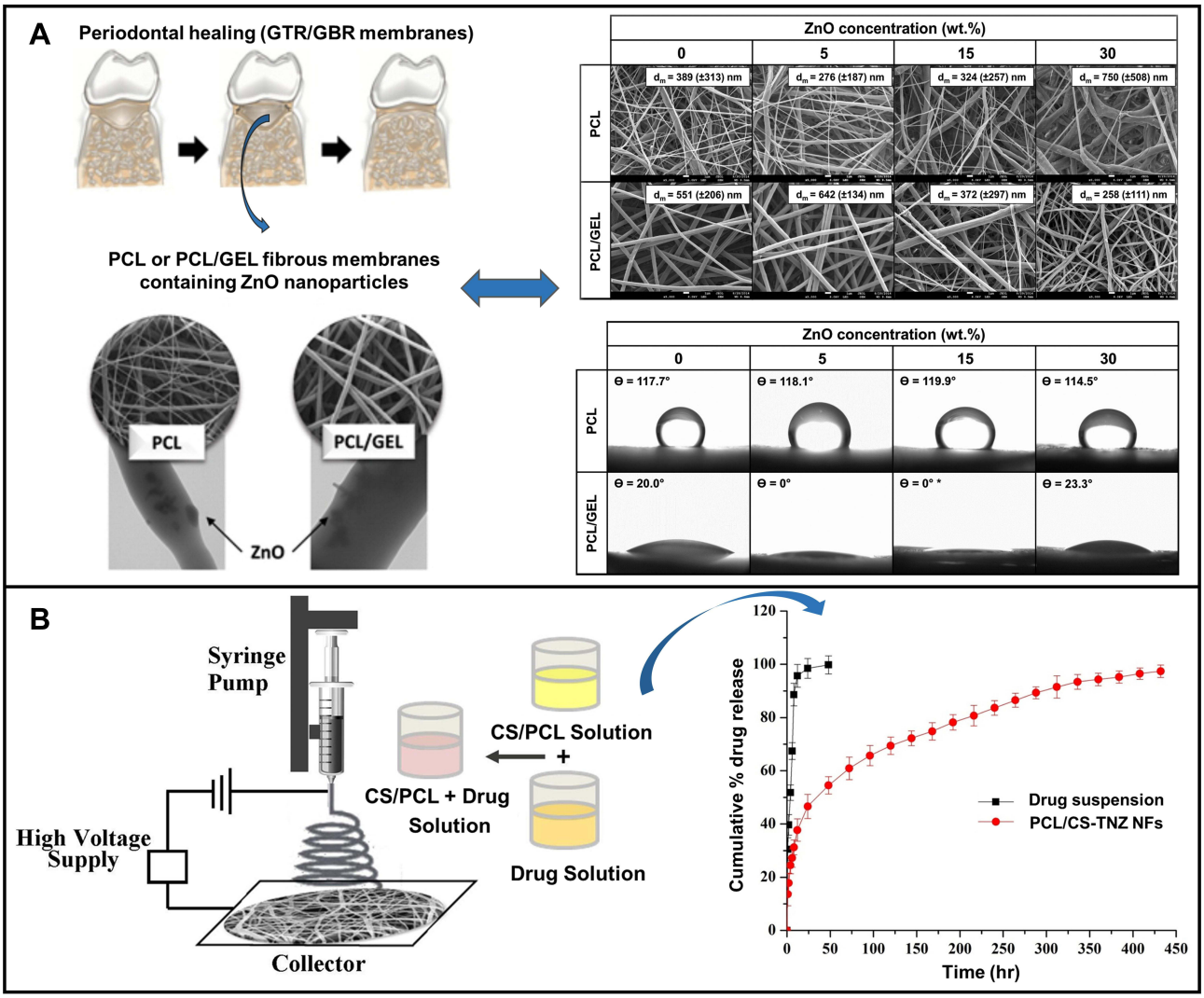


Figure 8 Composite polymers for electrospinning. (**A**) Schematic diagram of the use of PCL and PCL/Gel nanofibers containing ZnO particles for the treatment of periodontitis. Reproduced from Münchow EA, Albuquerque MTP, Zero B, et al. Development and characterization of novel ZnO-loaded electrospun nanofibrous membranes for periodontal regeneration. *Dent Mater.* 2015;31(9):1038–1051. Copyright © 2015, with permission from Elsevier.[121] (**B**) Schematic diagram of the preparation process and drug release of electrospun PCL/CS/TNZ nanofibers. Reproduced from Khan G, Yadav SK, Patel RR, et al. Tinidazole functionalized homogeneous electrospun chitosan/poly (ε-caprolactone) hybrid nanofiber membrane: development, optimization and its clinical implications. *Int J of Biol Macromol.* 2017;103:1311–1326. Copyright ©2017 with permission from Elsevier.[122]

suitable when selecting a suitable polymer as a matrix for electrospinning and preparing a periodontal barrier membrane with excellent performance.

Application of Electrospun Functional Nanofibrous Membrane in the Periodontal Treatment

Electrospun nanofibers can be mimic the natural ECM while providing a favorable environment for cell adhesion, proliferation, differentiation, and migration.[124] Whether the nanofibers are regularly arranged or randomly distributed, they can guide the direction of cell growth, and they favor the precisely oriented tissues, such as stratified periodontal fibers. Therefore, electrospun drug-loaded nanofibrous membranes can be effectively applied in periodontal treatment. Here, we highlight the advanced technologies and methods of electrospinning for treating periodontitis and clarify their research status and related clinical application prospects.

Electrospinning Drug Delivery System

Plaque is one of most major causes of periodontitis. In dentistry, the use of antibacterial biomaterials has become more and more critical. The removal of bacteria and plaque is the foundation of periodontal treatment. In the process of periodontal treatment, the inhibition of infection and the promotion of tissue regeneration are the ultimate goals.[125] As shown in Figure 9, the active substances commonly used in the treatment of periodontitis mainly include antibiotic antibacterial drugs, NSAIDs, natural substances, and inorganic nanoparticles.

Single-Fluid Electrospinning Drug Delivery System

In periodontology, topical administration is considered to be more effective. Topical administration can ensure drug concentration, act on the periodontal pockets constantly and effectively, and can eliminate the side effects caused by systemic administration.[126] In recent years, the nanofiber topical drug delivery system has been mentioned many times for periodontal treatment to enhance periodontal tissue repair.[127] Jia et al[38] fabricated nanofibrous membranes loaded with different concentrations of DCH via single-fluid electrospinning. Their results showed that the fibrous membrane could achieve a sustained release of DCH for over 28 days, and it could inhibit periodontal pathogens for a long time, thus creating a sterile environment for periodontal tissue regeneration and healing. Nasajpour et al[128] prepared a PCL-loaded nano-zinc oxide (ZnO) electrospun nanofibrous membrane to heal periodontitis defects, and it presented tunable mechanical properties and degradation characteristics. When the loading amount of ZnO nanoparticles was 0.5% (w/v), the nanofibrous membrane enhanced the antibacterial and bone conduction properties without compromising biocompatibility. Ekambaram et al[129] prepared the novel sulfonated poly (ether-ether-ketone) (SPEEK)-loaded amine-functionalized zirconia nanoparticles and curcumin (Cur) nanofibrous membrane (Figure 10A). Results showed that their scheme could sustain the release of Cur, improve cell viability from the aspects of antibacterial properties, and promote periodontal wound healing and tissue regeneration. The prepared novel nanofibrous membrane can be used as an effective matrix for periodontal regenerative treatment. Ferreira et al[130] prepared a biodegradable scaffold containing MNZ and tetracycline hydrochloride (TCH) via electrospinning (Figure 10B). Their results showed that the scaffold could increase new bone formation, decrease the BL in the bifurcation area, and decrease the inflammatory cell responses. The scaffold could also eliminate infection and promote periodontal regeneration clinically. Deepak et al[131] prepared a nanofibrous membrane loaded with three drugs via electrospinning. Their results showed that the nanofibrous membrane with silver (Ag) particles, MNZ, and nano-hydroxyapatite (nHA) has better antibacterial and repair potential in animal models compared with the nanofibrous membranes loaded with one or two drugs only. Table 2 summarizes the latest literature on monolithic electrospun nanofibrous membranes used in periodontal treatment.

However, single-fluid electrospinning drug-loading systems also have disadvantages. For example, the working fluid must have spinnability properties. In addition, monolithic electrospun nanofibers usually exhibit a burst release of drug, resulting in the accumulation of drug concentration over a short period, subsequently causing toxicity to the patient's body. Late tailing releases also lead to insufficient drug concentrations. Alternatively, nanofibers with complex structures can be prepared via multi-fluid electrospinning. By regulating the composition, component, relative size, and spatial

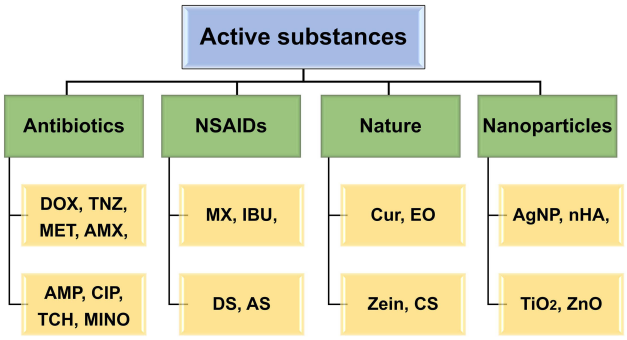


Figure 9 Active substances commonly used in the treatment of periodontitis.
Abbreviations: DOX, Doxycycline Hyclate; TNZ, Tinidazole; MET, Metformin HCL; AMX, Amoxicillin; AMP, Ampicillin; CIP, Ciprofloxacin; TCH, Tetracycline Hydrochloride; MINO, Minocycline; MX, Meloxicam; IBU, Ibuprofen; DS, Diclofenac Sodium; AS, Aspirin; Cur, Curcumin; EO, Essential oil; CS, Chitosan; AgNPs, Silver nanoparticles; nHA, Nano Hydroxyapatite; TiO_2, Titanium dioxide; ZnO, Nano Zinc oxide.

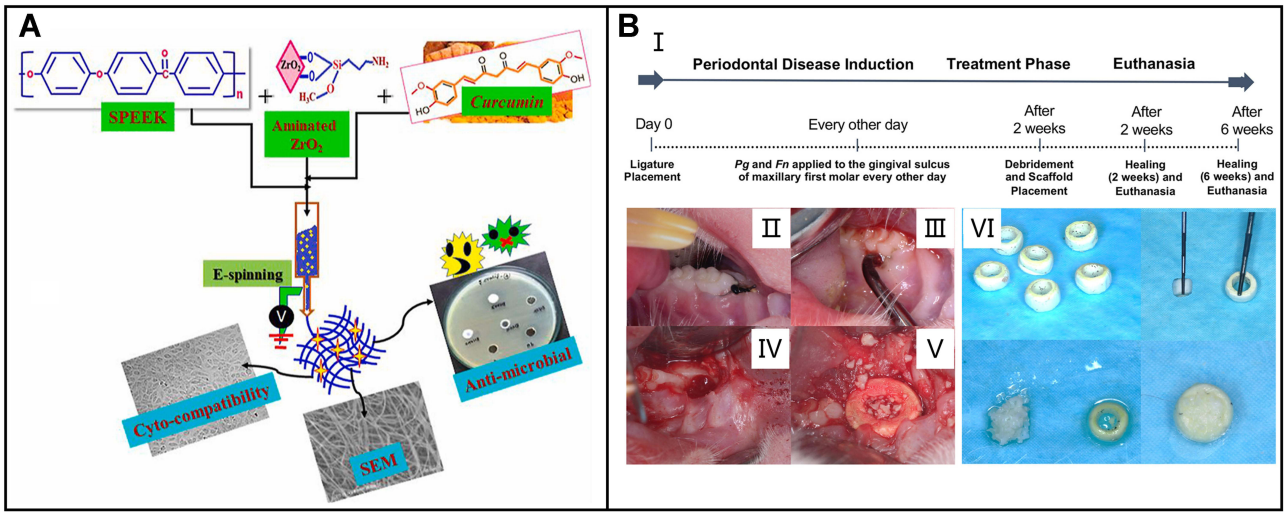


Figure 10 Single-fluid electrospinning for periodontitis treatment. (**A**) Schematic diagram of the SPEEK/NH_2–ZrO_2/Cur nanofiber scaffold for periodontal regeneration. Reproduced from Ekambaram R, Paraman V, Raja L, et al. Design and development of electrospun SPEEK incorporated with aminated zirconia and curcumin nanofibers for periodontal regeneration. *J Mech Behav Biomed*. 2021;123:104796. Copyright © 2021 Elsevier.[129] (**B**) An in vivo model for resolving infection ablation and tissue regeneration: (I) Timeline of different phases of the study; (II) Overview of experimental periodontitis induced by ligation and Pg and Fn infection; (III) Scaling and root planing using a manual curette; (IV) Intraosseous three-wall periodontal defect creation; (V and VI) Antibiotic stent placement. *ACS Appl Mater Inter*. 2021;13(42):49642–49657. Copyright © 2021 Applied Materials. Published by American Chemical Society.[130]

distribution of multiple fluids, the design and development of nanofibers can be further expanded to provide more advanced and effective drug delivery for periodontal treatment.

Coaxial Electrospinning Drug Delivery System

In the treatment of periodontitis using electrospun nanofibers, most of the methods involve single-drug loading. However, a single drug cannot achieve the purpose of curing; in contrast, multi-drug synergy is a feasible way for the clinical treatment of periodontitis.[149] The drug can be loaded on the core and sheath layers via coaxial electrospinning to prepare nanofibers with a core–sheath structure. This approach has been adopted in the field of periodontal treatment.

As shown in Figure 11A, He et al[150] prepared dual-drug synergistic nanofibers with core-sheath structure for periodontitis treatment using coaxial electrospinning. The nanofibers used PLGA-loaded MNA as the sheath layer to inhibit bacterial growth, and PVP-loaded naringin (NAR) as the core layer to promote periodontal tissue regeneration. The nanofibrous membrane has good biocompatibility and mechanical properties, facilitated cell adhesion and proliferation, and promoted the active expression of alkaline phosphatase (ALP). In vitro studies demonstrated the short-term and long-term release properties of MNA and NAR, respectively. Moreover, this study achieved multiple functions of antibacterial, anti-infective, and promoting new tissue regeneration. Therefore, the coaxial nanofibrous membrane has a substantial impact on periodontitis treatment. This study will provide a direction for the development of a dual drug delivery system for periodontal regeneration treatment by coaxial electrospinning. As shown in Figure 11B, Liu et al[151] used coaxial electrospinning to prepare degradable nanofibrous membrane with a core-sheath structure, where in the sheath layer was a JNK inhibitors SP600125, and the core layer was the bone morphogenetic protein 2 (BMP-2). This structure can guarantee the sequential release of inhibitors and induced proteins. When the nanofibrous membrane acts on the periodontitis site of animals, it can inhibit the expression of inflammation, avoid alveolar damage and enhance the ability of osteogenic induction. The bone defect was repaired within two months without cytotoxicity, thus making it suitable for the treatment of periodontitis.

Nanofibers entailing the multi-drug synergy of anti-inflammatory and antibacterial characteristics and bone/tissue growth can be prepared via coaxial electrospinning for periodontal treatment. In contrast to monolithic nanofibers, coaxial nanofibers have two chambers that are independent from each other. On the one hand, coaxial nanofibers can avoid the mutual influence between various materials. On the other hand, nanofibers with complex structures, diversified functions, and adjustable performance may be developed. However, the research on the utilization of nanofiber barrier membranes via coaxial electrospinning to treat periodontitis is still rare, suggesting that more attention should be paid to this field.

Table 2 Related Studies on Uniaxial Electrospinning for Periodontitis

Electros-Pinning	Polymer	Bioactive Ingredients	Highlights	References
Single	PCL	DOX	DOX nanofibers achieve sustained release for nearly 20 days.	[38,132]
		TNZ	Prevent alveolar bone resorption and improve the continuity of the interdental papillary epithelium.	[122]
		MNZ	The drug in the nanofibers was released continuously for up to 19 days with very low burst release.	[133]
		IBU	Overcomes inflammatory response and promotes wound healing.	[112]
		ZnO	Antibacterial properties, bone conduction properties.	[128]
		α-TCP	Tensile strength and toughness are significantly improved.	[134]
	PLGA	MINO	Facilitates cell adhesion and proliferation and increases alveolar ridge height in periodontitis models.	[119]
	PLA	MNZ	Sustained antimicrobial properties.	[116]
		DOX	Good cytocompatibility, antibacterial properties, ability to promote wound healing.	[117]
	PDS II®	CIP	The incorporation of antibiotics has obvious inhibitory effects on periodontal pathogens and oral commensal bacteria.	[135,136]
		MET		
Blend	PCL	$AgNO_3$, Aloe Vera Extract	Good biocompatibility, antibacterial properties, guided tissue regeneration	[137]
	PCL, PLGA	AMX, MNZ	Good drug release control and reduced dosing frequency.	[138]
	PCL, PVA	MET	Excellent osteogenic differentiation and bone regeneration properties.	[139]
	PCL, CS	TNZ	Membrane bioactivity, improved mechanical properties, antibacterial properties.	[122]
	PCL, Gel	ZnO	Membrane bioactivity, improved mechanical properties, antibacterial properties.	[121]
		BSS	Nontoxic and antibacterial to human gingival fibroblasts and osteoblasts.	[25]
	PVA	MNZ, $AgNO_3$, nHA	Broad-spectrum antibacterial activity, periodontal treatment potential.	[131]
	PVA, HA	/	Promotes tissue regeneration, anti-inflammatory, and mucoadhesion.	[123]
	PVA, CS	MX, nHA	Has potential anti-inflammatory properties.	[140]
	Gel, PU	AgNPs	The prepared oral wound dressing has excellent antibacterial activity.	[141]
	Gel, Zein	/	Hydrophilicity and cytocompatibility, mechanical properties are significantly increased.	[142]
	PDS	MNZ, TCH	Eliminate inflammation and promote periodontal regeneration.	[130]
		MNZ, CIP	Good biocompatibility and antibacterial properties.	[143]
		MET, CIP, MINO	Good biocompatibility, antibacterial properties, reduce the risk of infection.	[144,145]
	PLGA	DMOG, nSi	It can alleviate the defective immune-inflammatory response, increase macrophages, and ultimately promote bone regeneration in periodontal disease.	[120]
	PLGA, GT	TCH	Enhanced hydrophilicity, increased elastic modulus; good cytocompatibility, and antibacterial properties.	[146]
	PLA	AMP, MNZ	It has a successful inhibitory effect on Fusobacterium nucleatum, Porphyromonas gingivalis, Enterococcus faecalis, and Actinomycetales.	[147]
	SPEEK	NH_2-ZrO_2, Cur	Improves biological activity and promotes periodontal regeneration.	[129]
	PDLLA	AMX	Inhibits bacterial growth while enhancing PDL cells viability. Reduces inflammation and accelerates periodontal treatment at an early stage.	[148]

Note: /, No bioactive ingredients.

Abbreviations: DOX, Doxycycline Hyclate; TNZ, Tinidazole; MNZ, Metronidazole; IBU, Ibuprofen; ZnO, Nano Zinc oxide; α-TCP, α-tricalcium phosphate; MINO, Minocycline; CIP, Ciprofloxacin; MET, Metformin HCL; $AgNO_3$, Silver nitrate; AMX, Amoxicillin; BSS, Bismuth Subsalicylate; nHA, Nano Hydroxyapatite; MX, Meloxicam; AgNPs, Silver nanoparticles; TCH, Tetracycline Hydrochloride; Tetracycline Hydrochloride; CIP, Ciprofloxacin; DMOG, Dimethyloxaloylglycine; nSi, Nano Silicate; AMP, Ampicillin; NH_2-ZrO_2, Aminated Zirconia; Cur, Curcumin; PCL, Polycaprolactone; PLA, Polylactic acid; PLGA, Poly(lactic-co-glycolic acid); PEO, Polyethylene oxide; PDS, Polydioxanone suture; PVA, Polyvinyl alcohol; CS, Chitosan; Gel, Gelatin; HA, hyaluronic acid; PU, Polyurethane; GT, Gum Tragacanth; PEEK, Poly(ether-ether-ketone); PDLLA, Poly(DL-lactide).

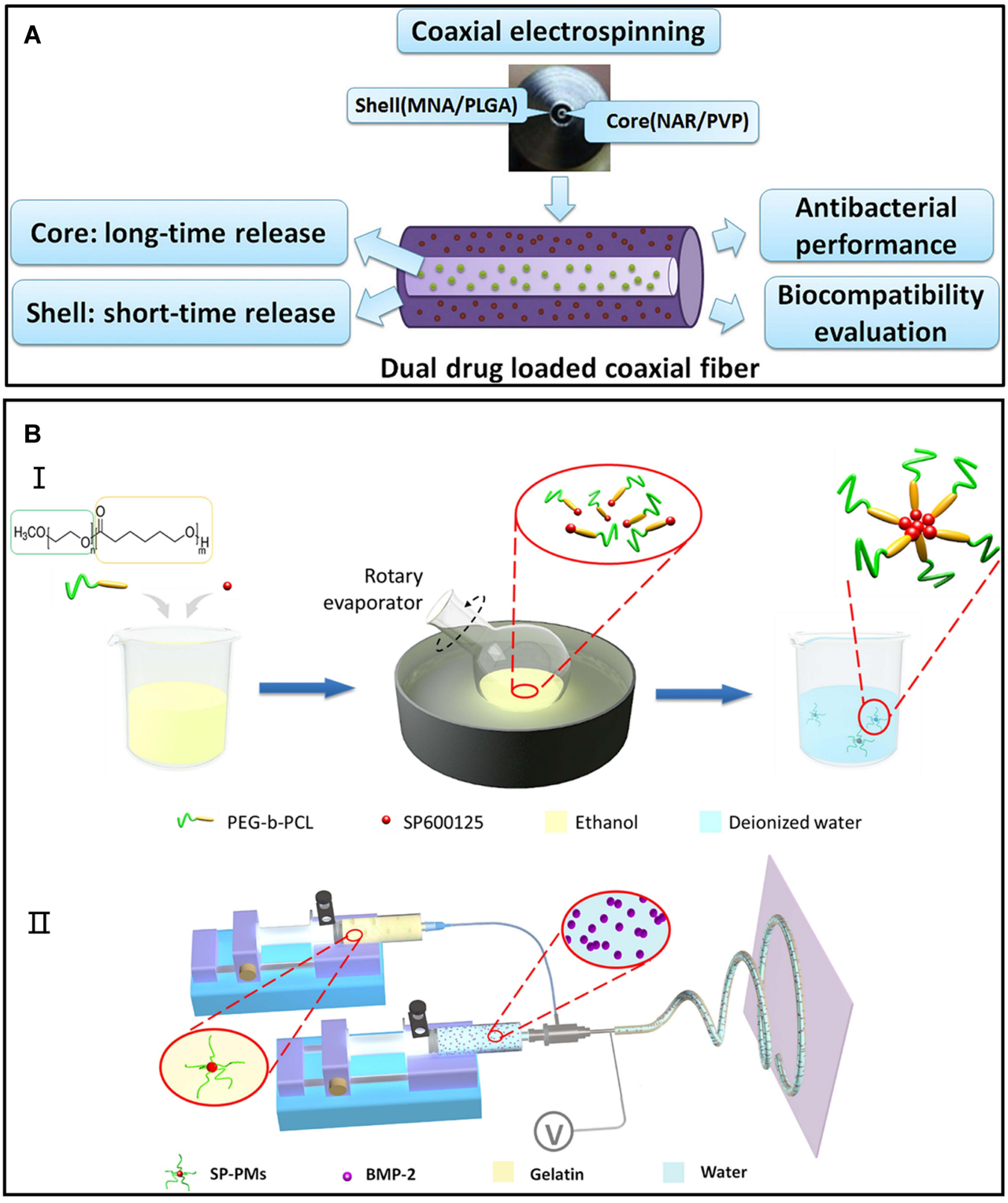


Figure 11 Coaxial electrospinning for periodontitis treatment. (**A**) Schematic diagram of MNA-PLGA//NAR-PVP nanofibers prepared by coaxial electrospinning. Reproduced from He P, Zhong Q, Ge Y, et al. Dual drug loaded coaxial electrospun PLGA/PVP fiber for guided tissue regeneration under control of infection. *Mat Sci Eng C-Mater.* 2018;90:549–556. Copyright © 2018, with permission from Elsevier.[150] (**B**) Coaxial electrospinning to prepare nanofibrous micelle membrane: (I) Schematic diagram of the fabrication process of SP-PMs; (II) Schematic diagram of the coaxial electrospinning process. Reproduced from Liu XC, Zhang WX, Wang YB, et al. One-step treatment of periodontitis based on a core-shell micelle-in-nanofiber membrane with time-programmed drug release. *J Control Release.* 2020;320:201–213. Copyright © 2020, with permission form Elsevier.[151]

Multilayer Nanofibrous Membrane Drug Loading System

In 2003, Gupat et al[152] and Madhugiri et al[153] prepared bilayer nanofibrous membranes to promote the application of electrospinning in multiple fields. Among them, the multifunctional graded membranes prepared via layer-by-layer electrospinning have been widely studied for periodontal treatment.

Yan et al[154] prepared a stem cell-containing bilayer nanofibrous membrane for periodontal treatment based on stem cell safe therapy by adopting blending and deposition modification techniques. This multilayer nanofiber film is divided into two layers, namely, a barrier layer to resist gingival epithelial cell invasion and a functional layer incorporating dental pulp stem cells to promote the regeneration of structures, such as dentin, cementum, and alveolar bone. In addition, the proposed approach can enhance stem cell differentiation and improve the oral microenvironment. Periodontal repair and stem cell technology were combined, and the multilayer nanofibrous membrane prepared via electrospinning presented excellent characteristics for the repair of periodontal defect tissues. Sundaram et al[155] used the PCL micro-nanofibrous membrane as the top layer and the CS-$CaSO_4$ scaffold as the bottom layer to prepare a bilayer membrane for simulating and reconstructing soft/hard periodontal tissues. The membrane could help the stem cells to attach, infiltrate, multiply, and differentiate into osteoblasts and fibroblasts. Overall, alveolar bone regeneration and PDL were facilitated. Bottino et al[156] prepared a three-layer nanofibrous membrane for optimized periodontal regeneration (Figure 12A). The PLA-Gel-MET acted as a surface layer connected to the epithelial tissue, and it

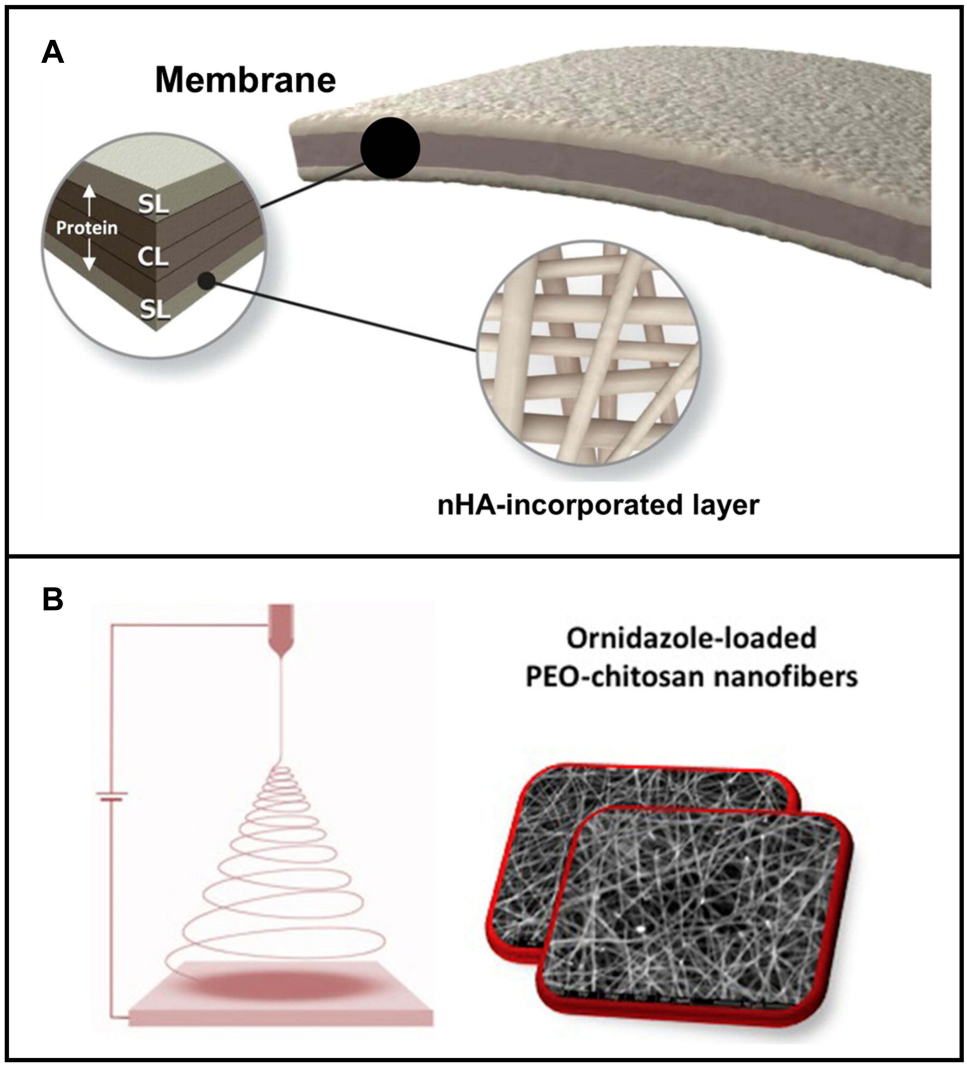


Figure 12 Electrospun multilayer nanofibrous membranes for periodontitis treatment. (**A**) Continuous multilayer electrospinning of novel functionally graded membranes. Reproduced from Bottino MC, Thomas V, Janowski GM. A novel spatially designed and functionally graded electrospun nanofibrous membrane for periodontal regeneration. *Acta Biomater.* 2011;7(1):216–224. Copyright © 2011, with permission from Elsevier.[156] (**B**) PCL/PEO/CS-loaded ornidazole bilayer nanofibers. Reproduced from Tort H, Oktay EA, Tort S, et al. Evaluation of ornidazole-loaded nanofibers as an alternative material for direct pulp capping. *J Drug Deliv Sci Tec.* 2017;41:317–324. Copyright © 2017, with permission from Elsevier.[157]

prevented bacterial colonization. The PLCL-PLA-Gel, PLCL, and PLCL-PLA-Gel constituted the middle layer. The PLA-Gel-nHA constituted the innermost layer, and it was connected to the bone tissue and served to enhance the osteoconductive behavior. Tort et al[157] prepared a bilayer nanofibrous membrane with ornidazole via electrospinning (Figure 12B). Their results showed that the bilayer structure offered an appropriate 3D environment for cell proliferation, thereby presenting potential clinical application in periodontal treatment.

The use of layer-by-layer electrospinning to prepare multilayer nanofibrous membranes is an extension of the single-fluid electrospinning, and it has been adopted to overcome the low performance of monolithic nanofibers with a single structure. The nanofibrous membranes prepared via layer-by-layer electrospinning have the advantages of safety, simple operation, and integrated treatment. This approach is currently a common method for integrating anti-inflammatory, antibacterial, and growth-promoting drugs for treating periodontitis.

Electrospinning-Chemical Modification

Methods for periodontal treatment are constantly being developed with the advancement of science and technology. Among them, the method of changing the properties of fiber membranes via chemical modification has attracted the wide attention of researchers. Two examples are shown in Figure 13.

Santos et al[158] used CS and PVA as a filament matrix to prepare a nanofibrous membrane with a core–sheath structure via coaxial electrospinning and then cross-linked the fiber membrane with genipin. After cross-linking, the fiber membrane not only attained good biocompatibility, but the hydrophilicity and swelling ratio also decreased, indicating the improved mechanical properties of the fiber membrane. The cross-linked nanofiber membrane also presented good stability in an aqueous medium and promoted the sustained release of drugs. Zhu et al[159] prepared metformin (MET)-loaded PCL-CS-MET nanofiber membranes via electrospinning and then cross-linked the fiber membranes with glutaraldehyde. They found that the cross-linked nanofiber membranes enhanced the cell adhesion, proliferation, and differentiation of bone mesenchymal stem cells. This scheme is highly beneficial in the management of alveolar bone defects. Qian et al[160] prepared the Ag-modified/collagen-coated electrospun nanofibrous membrane via in-situ reduction and polydopamine coating with collagen I coating-impregnated Ag nanoparticles (AgNPs) (Figure 13A). The antibacterial properties, biocompatibility, and osteogenic properties of the modified fibrous membrane were enhanced. This scheme is also beneficial for alveolar bone formation. As shown in Figure 13B, Boda et al[20] were the first to describe the use of mineralized nanofibrous fragments in conjunction with calcium-binding BMP-2 as a synthesized graft material. Their results suggest that the mineralized nanofibrous fragments incorporated with peptides may have a tremendous potential for regenerating bone defects in the oral cavity. Chen et al[161] used the ammonolysis method to graft CS on the poly-L-lactic acid (PLLA) electrospun nanofiber membrane surface as a barrier membrane to regenerate periodontal tissues. Their findings revealed that the modification of CS could promote the hydrophilicity of PLLA electrospun membranes, improve the biocompatibility, and promote cell adhesion and proliferation. Simultaneously, the fibrous membrane was able to retain the original characteristics of the natural and synthetic polymers, and it may even be used in the treatment of periodontitis-guided tissue regeneration.

The structure design and surface modification of electrospun nanofibers achieved via chemical methods can create composite materials with multiple functions. This scheme is now commonly used in a number of medical fields, such as bone defect repair, hemostasis, and healing promotion. However, given the diversity and particularity of the oral environment, the treatment of periodontitis is complicated. Therefore, researchers have gradually combined chemical modification with electrospinning to endow the nanofibrous membrane with unique functions for meeting the treatment of periodontitis.

Electrospinning-3D Printing

Santos et al[162] combined 3D printing technology with coaxial electrospinning to produce a bilayer and dual delivery system loaded with Cur and DCH for periodontal treatment. As shown in Figure 14A, a 3D honeycomb model with a size of 25 mm × 15 mm × 0.5 mm is prepared using PLA; then, its surface is modified via the film casting method. As further shown in Figure 14B, the 3D structure is immersed in a DMSO solution containing Zein and Cur, washed, and dried to deposit electrospun nanofibers. Figure 14C shows the process of preparing the core–sheath nanofibers via coaxial

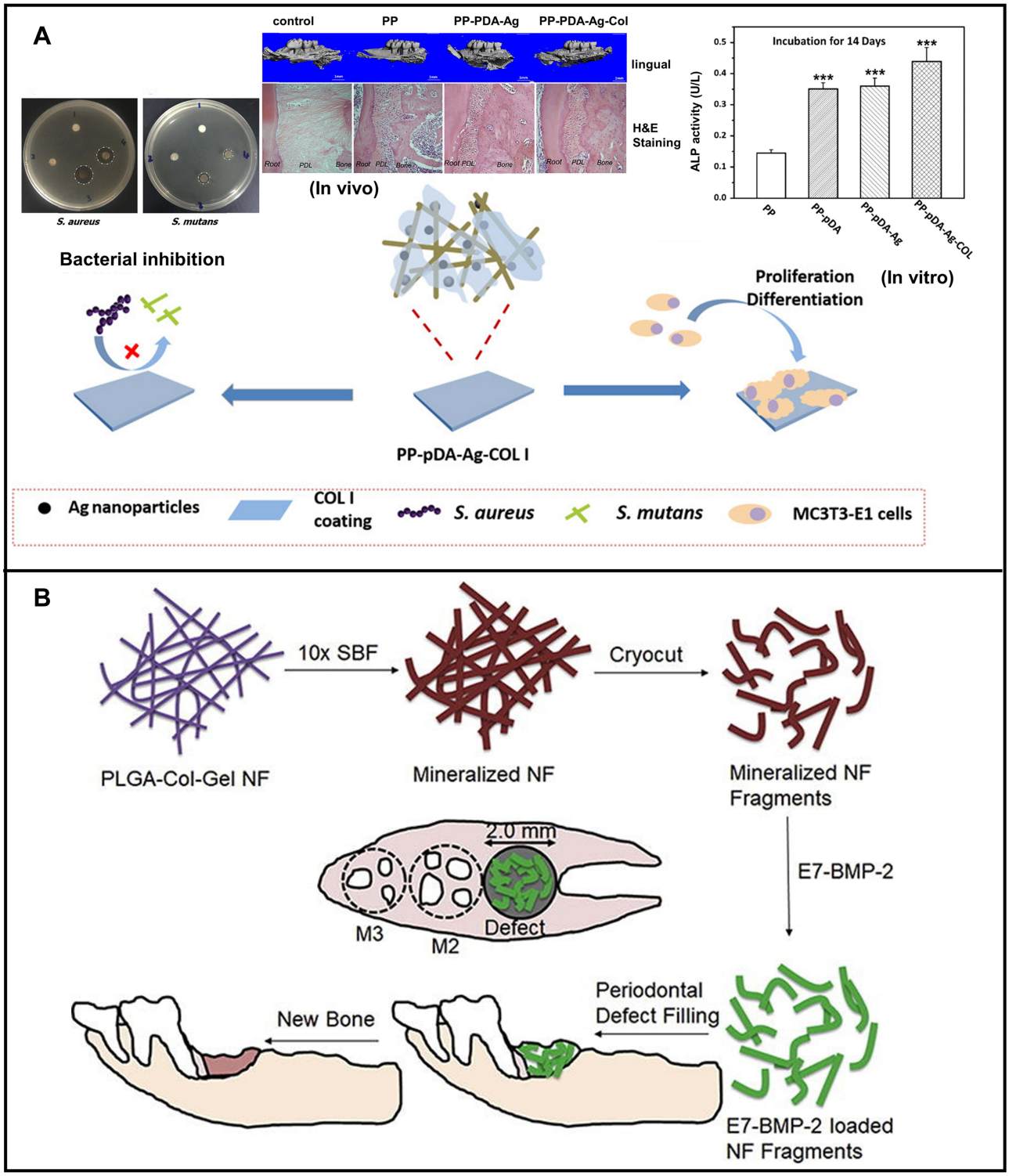


Figure 13 The chemical modifications of electrospun nanofibers for periodontitis treatment. (**A**) Electrospun PLGA/PCL scaffold (PP-pDA-Ag-COL) by silver modification/collagen coating for alveolar bone regeneration. Reproduced with permission from Qian YZ, Zhou XF, Zhang FM, et al. Triple PLGA/PCL scaffold modification including silver impregnation, collagen coating, and electrospinning significantly improve biocompatibility, antimicrobial, and osteogenic properties for orofacial tissue regeneration, *ACS Appl Mater Inter.* 2019;11(41):37381–37396. Copyright © 2019 American Chemical Society.[160] The expression levels were calculated by densitometry analysis relative to GAPDH, ***Indicates a value of $p<0.001$ when compared with PLGA/PCL. (**B**) Application of electrospun mineralized nanofibers BMP-2 conjugated as a synthetic graft material. Reproduced from Boda SK, Almoshari Y, Wang HJ, et al. Mineralized nanofiber segments coupled with calcium-binding BMP-2 peptides for alveolar bone regeneration. *Acta Biomater.* 2019;85:282–293. Copyright © 2019, with permission from Elsevier.[20]

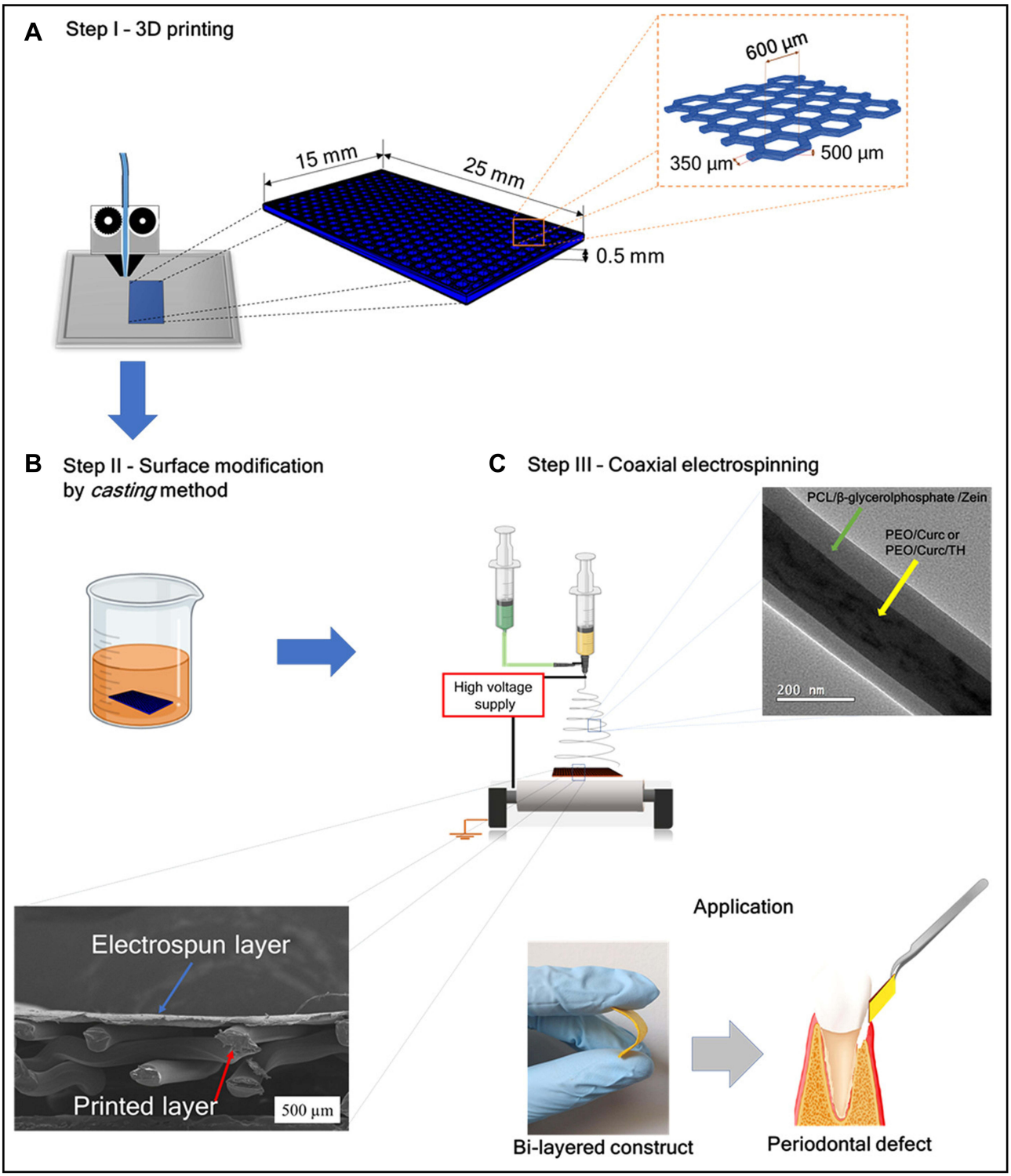


Figure 14 Design of electrospinning and 3D printing bilayer structure. (**A**) The first step of PLA 3D printing honeycomb platform. (**B**) In the second step, the honeycomb walls were modified with a zein-based membrane using the casting method. (**C**) The third step deposits a coaxial electrospun fiber layer on one surface of the 3D printed modified structure. Reproduced with permission from dos Santos DM, de Annunzio SR, Carmello JC, et al. Combining coaxial electrospinning and 3D printing: design of biodegradable bilayered membranes with dual drug delivery capability for periodontitis treatment. *ACS Appl Bio Mater.* 2022;5(1):146–159. Copyright © 2022 American Chemical Society.[162]

electrospinning, in which the sheath fluid is a mixed solution of PCL/Zein/β-GP, whereas the core fluid is a mixed solution of PEO/Cur/TCH. The composite membrane presented numerous advantages, including good wettability, mechanical properties, cytocompatibility, antibacterial properties, and stability, and it offered excellent potential in periodontal regeneration therapy.

3D printing, also known as additive manufacturing, is achieved through digital printing and high-temperature extrusion molding. The prepared 3D scaffolds with its small pore size and complex features can be used in oral implantation, cardiac implantation, and spinal cord implantation. This scheme has numerous applications in the biomedical field. However, the simple 3D printing process can hardly load active ingredients when treating periodontitis. The reason is that high-temperature conditions accelerate the degradation of active ingredients, including drugs. Consequently, the drugs cannot act on the pathological site for a long time, and the treatment effect of periodontitis cannot be achieved. If the electrospinning technology and 3D printing are combined, then the drug-loading performance of the compound fibers can be improved, thereby broadening the application of 3D technology in periodontal treatment.

Conclusions and Prospect

Electrospun nanofibers have high porosity and high specific surface area, which facilitates the growth of cell tissues and blood vessels and promotes protein absorption; the high-density porous structure of nanofibers can allow oxygen to permeate; it is similar to the scale and morphology of extracellular matrix (ECM), which is facilitate cell adhesion, proliferation, and differentiation. Nanofibrous membranes prepared by electrospinning are non-toxic, non-irritating, good biocompatibility, excellent mechanical properties, and degradable. It can meet the special environment of the oral cavity, so it can be used in the treatment of periodontitis.

Although there are many kinds of polymers, the number of polymers that can be directly used for electrospinning is limited. At the same time, there are fewer polymers that satisfy non-toxicity, good compatibility, excellent mechanical properties, and degradability, thus limiting the application of electrospun nanofibers in the treatment of periodontitis. Secondly, it is difficult to achieve a comprehensive treatment of periodontitis with a single drug. The pharmacological properties of the drug and the release mechanism of the drug in the nanofibers also affect the therapeutic effect of periodontitis. Therefore, developing multi-fluid electrospinning or combining electrospinning with chemical post-processing and 3D printing can improve the shortcomings of polymers. On the other hand, the preparation of complex-structured electrospun nanofibers with multiple drug synergistic effects and controlled drug release properties can provide a broader development space for periodontitis treatment.

At present, electrospun nanofibrous membranes are used for periodontitis treatment, mainly in the stage of in vitro experiments and less in vivo experiments in animals. There are still many challenges to achieving clinical treatment of patients. Such as control of the rate of degradation of the nanofibrous membrane in vivo and reduce the risk of surgery transmission of other diseases. Therefore, it is necessary to improve animal experiments and lay the foundation for the safe and effective conduct of human experiments. For example, in animal experiments, the effects of the dynamic and humid oral environment on drug release should be fully considered, and the effects of different ligation protocols and bacterial inoculation on periodontal disease models also should be considered, so as to establish an evaluable clinical study. At the same time, the industrialization and scale of electrospun nanofibrous membranes are very important. Therefore, the improvement of the production efficiency of electrospun nanofibrous membranes still needs to be continuously explored, so as to prepare standardized, multifunctional, and large-scale electrospun nanofibrous membranes. To provide a safe and reliable comprehensive solution for the clinical treatment of periodontitis.

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Author Contributions

All authors made a major contribution to this work, including the conception, study design, execution, data collection, analysis and interpretation; participated in drafting, revising, and reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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