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ELECTROSPUN NANOFIBERS PRINCIPLE, PROCESS AND ORAL APPLICATIONS

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ABSTRACT

The world of nanomaterials comprises a wide range of intriguing materials with outstanding physical and chemical properties and characteristics. These materials include zero-dimensional nanopar-ticles or quantum dots, one-dimensional nanowires, nanorods,nanofibers, and nanotubes, and two-dimensional nanosheets .Widely regarded as nanomaterials with great potential applica-tions, nanofibers stand out among the rest of the nanomaterials.One of the most striking features of nanofibers is their exception-ally high surface area-to-volume ratio and high porosity, making them a robust and attractive candidate for many advanced appli-cations 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. The delivery of biological active ingredients, factors, or drugs can achieve fast and supported regeneration. Nanofibers combined with inorganic ceramics, or polymers with nanoparticles can create functional materials for the speed up wound healing, or osseointegration processes The objective of this article is to review electrospun nanofibers in dentistry in the range from the process to the applications.

KEYWORDS: Nanofibers, nanomaterials; nanotechnology; tissue engineering; regeneration, electrospun nanofibers.

INTRODUCTION

Nanofibers remain an important division of biomaterials due to a wide range of biomedical applications.[1] The fabrication of nanofibers has attracted a lot of researchers due to unique properties required for biomedical applications for example availability of greater surface area for cellular interaction,[2] protein absorption and binding sites to cell receptors Nanofibers can facilitate packing of maximum volume fraction by controlling fibers alignment and orientation hence improving the material strength .The material properties such as surface morphology, porosity and geometrycan be tailored or functionalized for certain applications, for example, bioactive agents for biomedical applications.

Electrospinning is a versatile method for fabrication of submicron sized fibers from biopolymers, ceramics and composite materials. The dental application possibilities of these nanofibers are intensively research areas on the fields of tooth or pulp regenerations, prevention of dental caries, or drug delivery systems. Biopolymers can facilitate the elasticity of created structures, and ensure the similarities to the extracellular matrix. The tailoring of the diameters of the fibers, and pore sizes of the structures ensures the optimal conditions for the proliferation and differentiation of cells.[3] The delivery of biological active ingredients, factors, or drugs can achieve fast and supported regeneration. Composite materials give possibly of adjusting physical, biological, or release properties. Nanofibers combined with inorganic ceramics, or polymers with nanoparticles can create functional materials for the speed up wound healing, or osseointegration processes.

2. 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.[4] 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. Typical electrospinning equipment only requires a high voltage power supply, a syringe with pump, a metal tip needle, and a conducting collector (Figure 1). 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).

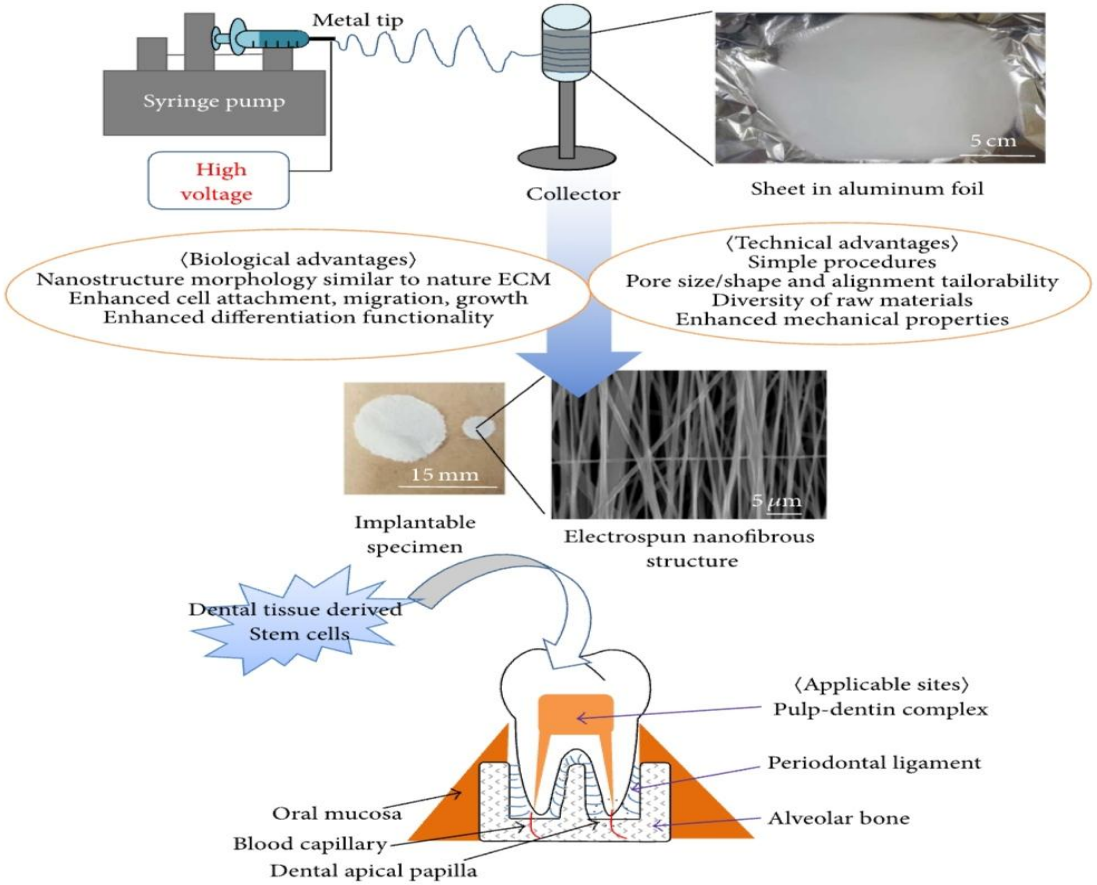

Figure 1: Electrospun nanofibrous scaffold which consisted of polycaprolactone was introduced as an exemplar biomaterial for dental tissue regeneration with various biological and technical advantages.

In electrospinning, several parameters such as processing, physical, systemic, and solution are involved, which affect the fiber morphology and properties of electrospun fibers.

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. 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. An increase in flow ratemay 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. 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. Generally, slower flow rate results in smaller diameter and a less number of beads compared to faster flow rate. Increased flow rate may alsomake 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.[5] It follows a negative power relationship between elongated fibers/decreased fiber diameter and distance from needle to collector because an increase in the distance induceswhipping action and bending instabilities . In addition, an increase in gap distance decreases the surface charge density due to diminished magnitude of the electric field.

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. 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.

Electrospinning process and parameters

The fibers morphology (Figure 2) and the process of the electrospinning are affected by different factors.[4,5,6] the molecular weight of the polymer, source of voltage, concentration of the polymer solution, needle gauge type, and the distance between the needle and the pitch collector. Spinnability, fiber diameters, fiber uniformity, fiber alignment, defects control (e.g. beads, junctions, and pores), and other properties are tunable by adjusting these factors and also including substrate-related parameters (polymer concentration, viscosity, molecular weight, surface tension) and apparatus-related parameters (flow rate and electric field). All these parameters are important to obtain flawless fibers and the choice of a polymer and its production must consider these factors and their modulation. Spinning voltage is related to some defects as bead formation in fibers (Figure 2(a)). However, a low voltage can increase the time of solvent evaporation and high voltages cause the rapid evaporation of solvent, producing a fiber with less pores and defects. Spinning voltage influences also the shape of electrospun fibers in a macroscopical level and in the homogeneity of the generated structures (Figure 2(b) and (c)).

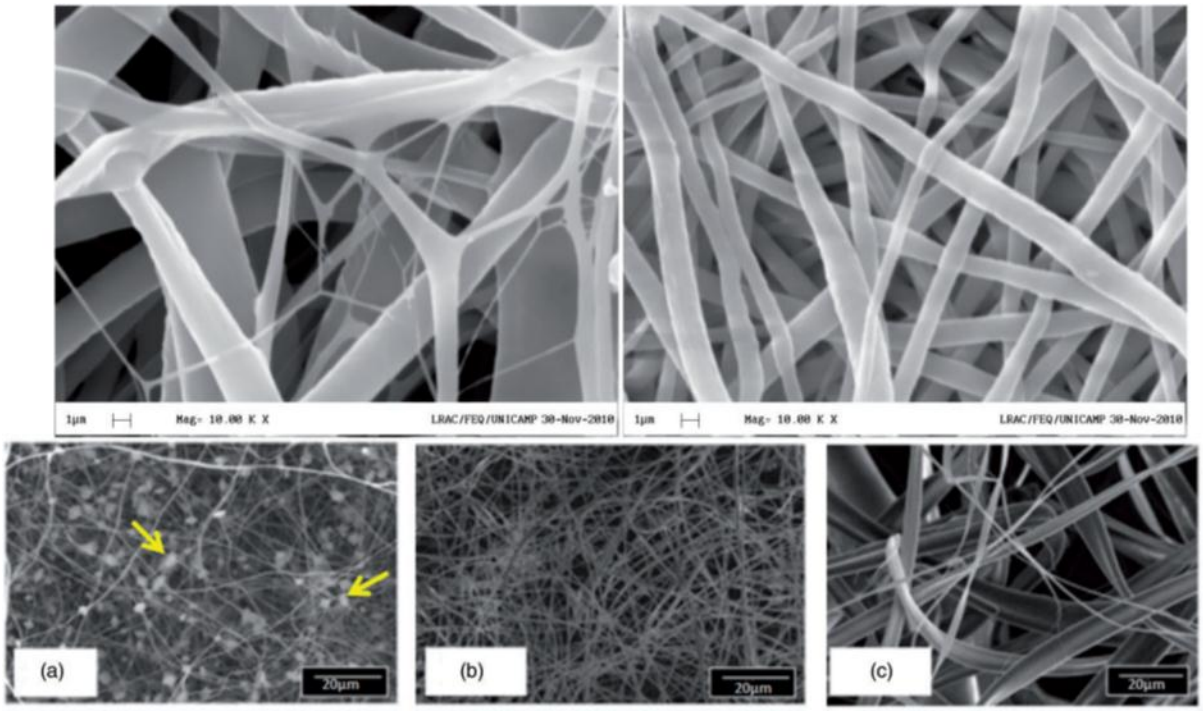

Figure 2: SEM images from electrospun PCL fibers. In (a) is presented beads formation (arrows). In (b) and (c) are presented nanofibers with regular aspect. The upperleft image presents a wider diameter size distribution compared with the image at the upper right, due to the lack of control of the process.

The distance between the needle and the collector field should be carefully adjusted. The fiber morphology is influenced by the distance, which in turn influences in deposition time and evaporation rate of the solvent. The fiber may break before reaching the collector field and create thick fibers with greater distances between them; consequently, the solvent cannot fully evaporate resulting in inaccurate fiber.[7] The diameter of the needle directly affects the diameter of the fiber, and when it is reduced, pore formation decreases. Environmental conditions such as: humidity, atmospheric pressure, and temperature differently influence on all process parameters. The humidity directly affects the polymer solution resulting in changes in the morphology, like

small holes, increased roughness, etc. The effects of relative humidity on electrospun fiber morphology are dependent on polymer hydrophobicity, solvent miscibility with water, and solvent volatility.Too low atmospheric pressure does not allow the process to occur. On the other hand, when working temperature increases, surface tension and viscosity of the fluid decrease and solvent evaporation could be accelerated, terminating the process prematurely. In other cases, when the environment is very cold, the spinning process is hindered.

The viscosity and conductivity of the polymer solution are The main characteristics that influence electrospinning process. The viscosity is related to the polymer molecular weight and the amount of dissolved solids in the solution. Solution concentration is reported to strongly affect fiber size,with fiber diameter increasing with the solution concentration in a power law relationship. In addition, electrospinning from solutions of high concentration is reported to produce fiber sizes with bimodal distribution, reminiscent of distributions observed in the similar droplet generation process of electrospraying. High viscosity can difficult the ejection of the solution from the needle and can also dry before it reaches the metallic collector. The conductivity of the polymer solution influences the diameter of the fiber with direct relation: as the conductivity increases, it produces denser fibers.

Oral Application

Next, main applications of fibers produced by electrospinning in oral areas: drug delivery systems, tissue regeneration and modification of materials, are presented. Functional fibers could be achieved by blending polymers mixtures and active molecules or by dispersing nano or microfillers within fibrous matrix.[8,9] These composites are attractive since novel materials fabricated with electrospinning demonstrated superior mechanical properties, bioactivity and biochemical properties compared to their constituent phases.

Drug delivery systems

The aim of drug delivery systems is to enable the controlled drug releasing towards alleviating medical conditions at a defined rate over a definite period. The promising use of nanofibers in drug delivery systems might result in salient features such as high loading capacity.[6,8,9] Current release of diverse drugs ranging from antibiotics and anticancer agents to proteins, aptamers, DNA has been successfully achieved with electrospun fibers A combination of ampicillin (AMP), MNZ (20/20%w/ w), and PLA single fiber mats were described to suppress periodontopathogenic species A. actinomycetemcomitans within an elution time of 24 h37 and the effect of MNZ (0.1–40% w/w) with electrospun PLA fibers decreased viability of F. nucleatum and P. gingivalis up to 28 days and for A. actinomycetemcomitans up to 2 days.40 In Reise et al., it is described that highly loaded fiber mat with 40% of MNZ (w/w) with a weight of 35mg contains 14mg of MNZ and the amount of MNZ when administered systemically adds up to 8400mg (3_400mg daily over seven days). However, toxic effects are expected if local drug administration provides highly concentrated antibiotics doses. Gradually drug release could be a more biologically friendly approach to be tested such as amounts that promote the elimination of bacteria associated with the reduction of adverse effects.

Tissue Regeneration

Controlled localized delivery of antibacterial agents to dental implants site using a biodegradable electrospun material could be designed in order to prevent bacterial infection, one of the causes of dental implant fail. PCL/ alginate associated with MNZ rings were custom designed and inserted around dental implant prior to their placement procedure. This strategy minimized burst release effects with MNZ release over 30 days.

The synthesis of unique materials to support the regeneration of tissues and lost organs due to trauma and/or diseases and TE remains pivotal to the development and translational impact in regenerative dentistry. TE uses three basic components (cells, scaffolds and biomolecules) to develop biofunctional substitutes for restore and maintenance of tissue function.[10,11]

The regeneration process can be assisted by scaffolds produced by electrospinning method resulting in biocompatible and sometimes biodegradable polymers. However, natural tissue integration with functional neovessels can be also obtained (Figure 3). Scaffolds can convey growth factors as well as cells to the target site to assist the injury regeneration and generate a support to the increase of cell adhesion, growth, migration rate, and differentiation. Biodegradable polymers withdraw surgical implant removal and can improve patient recovery process. Thus, nanostructured materials have been electrospun as mono and multilayered membranes and scaffolds in order to improve tissue regeneration.

Tissue engineering is an interdisciplinary field that applies the principles and methods of engineering and the life sciences toward the development of biological substitutes that restore, maintain, and improve the function of damaged tissues and organs.

Figure 3: In vivo assay via intramuscular scaffolds implantation in rat.

Histological aspect 28 days after implantation of PLGA scaffolds, showing (a) the natural tissue integration capacity and (b) the neovascularization (dark regions) in the implanted region.

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Periodontal regeneration or periodontal tissue engineering is attributed to a complete recovery of periodontal tissues in terms of both structure and function, that is, formation of the alveolar bone, a new connective attachment through collagen fibers functionally oriented on the newly formed cementum Two surgical techniques have been increasingly used to restore/regenerate the different periodontal tissues namely, guided tissue regeneration (GTR) and guided bone regeneration (GBR) . GTR refers to periodontal tissue regeneration, including cementum, the PDL, and the alveolar bone, whereas GBR pertains to the promotion of bone formation. In GTR, an occlusive membrane interfaces with gingival connective tissue/ epithelium and a PDL/alveolar bone tissue to promote periodontal tissue regeneration.[7,10,11]

The membrane acts as a barrier when placed in the surgical site, preventing connective and epithelial tissue migration into the defect. Progenitor cells, located in the remaining PDL adjacent to the alveolar bone or blood, are then able to recolonize the root area and differentiate into a new periodontal supporting apparatus with the formation of new bone, PDL, and cementum. GBR typically refers to ridge augmentation or bone regenerative procedures that pertain to the restoration of deficient alveolar sites (e.g., an extraction site

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.[12]

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 , silk-fibroin-PCL PLA , gelatin- apatite-poly(lactide-co-caprolactone), mesoporous bioactive glass-incorporated PCL-gelatin , mesoporous silica-shelled PCL , and magnetic nanoparticle-incorporated PCL nanofibrous scaffolds . In addition, a number of polymeric nanofibers have been revealed and used for a cellular platformfor 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.

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. 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. 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 were shown to accelerate MSC attachment, proliferation, and differentiation into osteoblastic lineage.

Dental implants have emerged as options for dental prostheses; however, the presence of biofilm can cause periimplantitis and lead to dental implant loss. Scientists have been studying some strategies for creating implants that have an osteointegrative surface while reducing biofilm formation and establishment. PCL/tetracycline nanofibers (5, 10 and 25% wt) were evaluated for their antimicrobial ability against periimplantitisrelated microorganisms such as P. gingivalis, F. nucleatum, P. intermedia and A. actinomycetemcomitans. Nanofibers incorporated with 25% wt tetracycline were responsible for inhibiting 100% of the biofilm of these bacteria . These nanomaterials may emerge as new implant surface treatments in the future. Another recurring problem in dentistry is fungal infections. These opportunistic infections usually caused by C. albicans mainly affect patients who wear full dentures, patients who have some systemic condition that reduces the potential of the immune response, or even patients who use antibiotics that contribute to the reduction of the commensal oral microbiota.[13,14,15] Hence, nanofibers may emerge as a drug-delivery option for antifungals. Fibers containing polyvinylpyrrolidone (PVP) and poly(methyl methacrylate) (PMMA), incorporated with cetylpyridinium chloride (CPC) (5% wt) or miconazole (5% wt) showed in vitro antimicrobial activity through zones of inhibition against C. albicans after 48 h of treatment. In another study, Tonglairoum et al. developed nanofibers composed of various polymers such as PVP, CS and PVA incorporated with clotrimazole. These researchers observed that clotrimazole was released (80%) in a saliva and buffer solution within 4 h and these nanofibers were able to completely inhibit C. albicans growth after 3 h of incubation. Moreover, these nanofibers were not able to reduce the cell viability of human gingival fibroblasts after 24 h of incubation.

Therefore, there is still a barrier between in vitro and clinical studies regarding the application of nanofibers both in dental implants and in prostheses. However, these new possibilities can contribute to the development of implants with antimicrobial characteristics, or antifungal mucoadhesive nanofibers to be coupled between the prosthesis and the oral mucosa.

CONCLUSION

Nanofibers are flexible materials and can carry diverse antimicrobial molecules, as well as other nanostructures. Besides, electrospinning has established itself as the most effective and widespread method to produce nanofibers.

This technique can contribute to the expansion of new 3D bioprinting possibilities. Also, the diversity of polymers used opens gaps for the discussion of cost, degradation, hydrophobicity, and interaction with the incorporated antimicrobial molecules. Given this, each area of dentistry presents specific demands that may facilitate or hinder its implementation.

Thus, in the face of discussions about the barriers to the development of in vivo experiments, new 3D models of tissues present in the oral cavity may appear as options for improving in vitro tests and bringing them closer to the clinical reality.

Expert opinion From the 2000 s, new proposals have appeared in health areas as promising alternatives for the delivery of drugs, antimicrobials and biomolecules. In this context, dentistry has advanced mainly with new conservative or even regenerative therapeutic concepts.

Current proposals discuss not only the use of inert materials but also the development of materials that permit interaction with microorganisms, biofilms, immune system cells and stem cells. Thus, nanotechnology may collaborate with the development of smart, non-cytotoxic treatments that contribute to specific actions in sites not reached by conventional medications applications presented here, it is possible to conclude that the electrospinning technique is increasingly advantageous in oral applications. The improvement of the mechanical properties, the promotion of cell proliferation and differentiation, the degradation rate of different electrospun materials, and the possibility of controlled drug delivery proved the effectiveness of materials produced by this technique. However, some of the analyzed studies require further investigation in order to enable direct human applications. The interaction of nanofiber with biomolecules in animal models may be different in humans and induce different toxic effects. In vivo studies for testing electrospun nanofiber are very low in number compared with in vitro studies. In addition, both in vitro

and in vivo toxicity tests must follow well established regulatory guidelines. This will enhance the performance of products made from fibers and develop new trends and possibilities in oral treatments.

Although, few human studies have been developed, these biomaterials have great potential to reach the clinic and contribute directly to dental approaches in different areas, becoming promising biomaterials for routine use in clinical practice in the future.

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