IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 20, Issue 9 Ser.4 (September. 2021), PP 15-22
www.iosrjournals.org

Synthesis, Properties and Clinical Applications of Electrospun Nanomaterials in Periodontics

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Abstract:
Electrospinning is a technique used to fabricate polymeric fibres of nanometre dimensions by applying high voltage difference to a syringe loaded with polymeric solution. This technique has enabled production of high-quality tissue engineering scaffolds for application in periodontal regeneration and other biomedical applications. Technique depends on various parameters like voltage difference, jet speed, distance between the collector plate etc. The electro spun nanofibers possess superior physical, chemical, biological and mechanical properties which are noteworthy. The clinical application of electro spun nanofibers span across all fields of biomedical science which includes tissue engineering and regenerative medicine, diagnostics, drug delivery and wound healing. Of these specific interest lies in the field of periodontal regeneration.
The aim of this review is to familiarize the concept of electrospinning and its vast applications in the field of periodontics for its better clinical use in dentistry.
Key Word*: Electrospinning, Nanofibers, Periodontics, Regeneration, Tissue Engineering*

Date of Submission: 25-08-2021 Date of Acceptance: 09-09-2021

I. Introduction

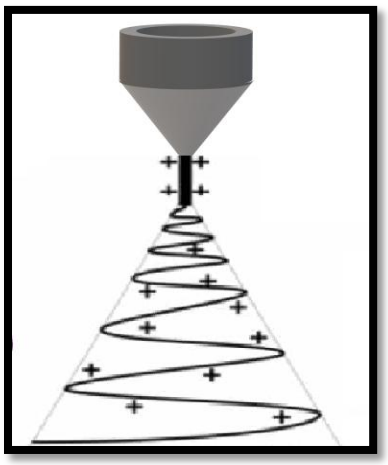
Periodontitis is an inflammatory polymicrobial disease affecting the periodontium of the teeth. Its uncontrolled progression can subsequently result in the destruction of gingival tissue, alveolar bone resorption, migration of junctional epithelium and periodontal pocket formation. Currently, the treatment of periodontitis focuses on plaque removal and local inflammation control, such as scaling and root planing and surgical treatment which attempt to minimize symptoms and prevent disease progression, but cannot achieve periodontal tissue regeneration.[1]Even though some regenerative approaches such as guided tissue regeneration and bone grafts were developed to achieve periodontal regeneration, their clinical outcomes are variable and unpredictable.[2] Over the past 10 years, a number of new biomaterials, approaches and technologies have been developed for regenerative periodontal treatment.

Electrospinning is a technique used to generate polymeric fibres in ultrafine dimensions in the nanometre scale by applying high voltage to a syringe loaded with polymeric solution or melt. It is derived from the basic concept of electrostatic spinning first described in 1897 by Rayleigh.[3] Although this is an age old concept, its application in dentistry has taken a new horizon in the past decade mainly in the field of tissue engineering(TE) and regeneration of oral and dental tissues.[4–6] Nano fibres generated through electrospinning exhibit higher material strength owing to their fibre alignment and orientation , consequently increasing packing volume.[7] Different techniques are currently in place for their fabrication, of which electrospinning is a promising candidate as it is simple, versatile, resourceful and cost effective in producing ultrafine nanofibers of superior properties.[8-12]. Electrospinning has enabled production of TE scaffolds to support specific cell line adhesion, proliferation and differentiation to resolve periodontal disease and aid in speedy recovery.[13-16] Nanotechnology based nano biomaterials are the current favourite of researchers in periodontitis management due to its superior regenerative and antimicrobial properties.

II. Concept Of Electrospinning

Electrospinning techniques is a electrohydrodynamic process in which a liquid droplet is electrified to form a jet followed by stretching and elongation to generate fibres.[17] As the repulsive surface charge from the electric source overcomes the effect of surface tension, an elongated jet stream of polymer called the Taylor cone is created .[3](Figure 1) Finally as the solvent evaporates it leaves behind dry nanofibers on the collector.[18] This enables formation of uniform fibrous structure through optimised parameters provided during electrospinning.

Figure 1. Taylor cone formed by the electrified jet stream of polymer through the electrospinning procedure.



III. Technique

Electrospinning technique depends on an electrohydrodynamic principle in which a highly electrified polymer solution is forced to stretch and elongate into fibres. Various biomaterials are electro spun due to its countless applications accounting to their unique properties like greater surface area for cellular interaction, protein adsorption and binding sites to cellular receptors. Few other techniques are also currently in place for fabrication of nano fibres which includes phase separation[8], nano fibre seeding[9], template synthesis[10], self assembly[11] and electrospinning[12].

The apparatus for electrospinning includes a high-voltage power supply to initiate a polymer jet, a syringe pump to eject the polymer solution, a hypodermic needle with blunt tip, and finally a conductive collector. The power source for the apparatus can be either direct current (DC) or alternating current (AC).[19]Initially a selected polymer is dissolved in the appropriate solvent and loaded into a syringe. A high voltage electric field is created between the needle and the collecting screen through electrodes and a power supply, subsequently the polymer solution is ejected slowly by a syringe pump giving rise to a semi spherical polymer solution droplet at the tip of the needle. As the voltage increases the droplet elongates to form a conical shape termed a Taylor cone, causing the surface charge to increase with time.[20] As the surface charge overcomes the surface tension of the droplet, a polymer jet is initiated which evaporates during travel to the collecting screen increasing the surface charge on the jet.[21]The increased surface charge causes instability in the polymer jet which is overcome by dividing into multiple jets geometrically. Nano fibres are created by the action of the spinning forces provided by the electrostatic forces on the continuously splitting polymer droplets. They are deposited layer by layer on the target plate forming a nonwoven nanofibrous mat.

As a whole, the electrospinning process can be divided into four consecutive steps: (i) charging of the liquid droplet to form a Taylor cone or cone-shaped jet; (ii) extension of the charged jet along a straight line; (iii) thinning of the polymer jet due to the voltage difference and growth of electrical bending instability (also known as whipping instability); and (iv) solidification and collection of the jet as solid fibre on a grounded collector.[22,23]

IV. Variables Influencing Electrospinning Technique

Various factors govern the structure and properties of nanofibers which includes process, systemic, solution and physical parameters.

Process parameters

This includes the applied voltage, flow rate, design of the collector, needle gauge and needle to collector distance. Increased voltage and flow rate can result in beaded nanofibers with increased diameter while increase in needle to collector distance decreases the fibre diameter and increases solvent evaporation.[17,24,25].Geometry of the nanofiber can be controlled by the design of the collector plate. Li et al. used parallel bars with a gap between the two to produce aligned fibre bundles which were suspended across the non-metallic part which stay parallel due to the repulsion between the electro spun and new nanofibres.[26,27]

Systemic Parameters

Systemic parameters include the polymer type and solvent characteristics. Boiling point and solubility of the solvent governs the microscopic features of electro spun fibres including porosity, shape and size.[28]The

solvent should allow for complete polymer dissolution and reasonable boiling point in order to favour evaporation of the polymer to form jet of nanofibers.[29]

Solution Parameters

Solution parameters include molecular weight, viscosity, concentration, conductivity, dielectric constant, surface tension and charge of jet. Molecular weight decides the polymer chain length and entanglements, viscosity promotes chain entanglement, concentration affects the shape and entanglement, higher conductivity promotes Taylor cone formation. Entanglements prevents the jet from premature splitting.[29–32]

Physical Parameters

Includes humidity, temperature and air velocity which governs the diameter of the fibre and evaporation rate of the solvent.[33]

V. Properties of electrospun materials

Electro spun materials have excellent properties which render them as a unique substitute in various biomedical applications.

Physical Properties

Electro spun nanofibers can be fabricated in various diameter, morphology, pore size and surface area which facilitates cellular attachment and migration as well as its toughness.[34]

Mechanical

Mechanical properties are targeted to provide for longer durability and structural integrity.[35] They are targeted to provide for cell growth and stability. Crosslinking aids in providing the required flexural and tensile strength for the fibres. [36]

Biological

One of the crucial factors in tissue engineering is cell attachment which favours further proliferation and functionalisation.[37] Polylactic co-glycolic acid (PLGA) electro spun nanofibers provide for excellent epithelial cell attachment. Electro spun fibres containing living cells have been reported for scaffold applications.[38]They can be incorporated with antimicrobial properties to aid in periodontal regeneration. A wide range of antimicrobial drugs which includes tetracycline, metronidazole, doxycycline etc. can be incorporated to develop a material with therapeutic properties.[39]

Chemical

Chemical properties are mainly influenced by hydrophobicity and chemical composition. Biodegradation of these materials are an important factor to be considered as these products as these products can affect regeneration.[40]

Thus, they are an excellent alternative for the natural extracellular matrix. The comparable properties of the natural extracellular matrix (ECM) and the electro spun nanofibers are briefly listed out in table 1.

Table 1: Characteristics of natural extracellular matrix and electro spun nanofibers.

CHARACTERISTICS	NATURAL EXTRACELLULAR MATRIX	ELECTROSPUN FIBERS
DIAMETER OF FIBROUS COMPONENTS	50–500nm (collagen fibres)	Tens to hundreds of nanometres
POROSITY AND PORE SIZE	Highly interconnected pores Tissue-specific	Highly porous
MECHANICAL PROPERTIES	Tissue-specific	Tailorable Vary across materials selection, porosity control and fibre orientation
PHYSICAL ARCHITECTURE	Tissue-specific	Tailorable

VI. Clinical Applications

The applications of electrospinning are numerous ranging from regenerative medicine, tissue engineering, controlled drug delivery, biosensors, and cancer diagnosis. Figure 2 depict the various applications in a nutshell.

Periodontal Regeneration

Electrospinning has recently come into forefront to recreate the actual structure and functionality of damaged periodontal ligament; a natural alternative is created via electro spun nanofibers. The various aspects of Tissue engineering are depicted in Figure 3.Multi-layered scaffold of polyethylene glycol and Polycaprolactone (PCL) developed by Vaquette and Cooper in 2011 found improved quantity and quality of highly aligned collagen fibres onto the root surface. Recently additive manufacturing techniques were employed

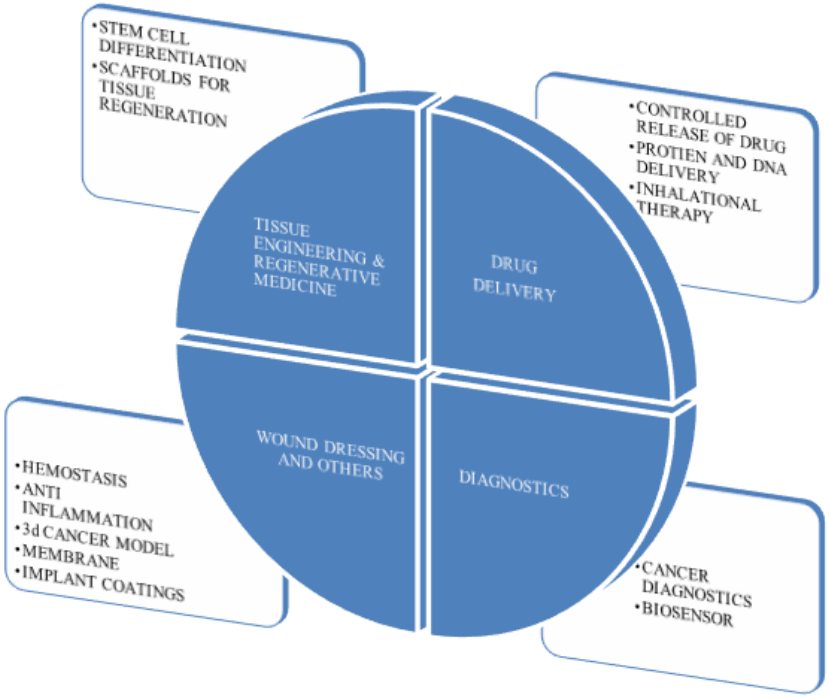
to introduce internal complexity to the electro spun membranes. Biocompatible electro spun nanofibers mimic natural ECM with controllable degradation rate and excellent mechanical properties. In addition to uniaxial electrospinning, the core structure can also be manufactured by coaxial electrospinning for drug loading. Furthermore, functionally graded membrane (FGM) with multi-functional layers can also be manufactured by sequential electrospinning.

The functionally graded multilayer bioactive film consists of a central core layer (CL) and two bioactive surface layers (SL) containing nanoparticles of hydroxyapatite (HA) to encourage bone formation and metronidazole to inhibit bacterial colonization at the interface with epithelial tissues. The CL consists of a neat poly- D, L -lactide co- caprolactone (PLCL) layer surrounded by two layers composed of a gelatin/polymer ternary blend (PLCL:PLA:gelatin).

In order to improve electrospinning and improve mechanical properties, synthetic polymers are widely used in electro spun GBR membranes is a biocompatible polyester with excellent mechanical properties, non-toxic and easy to electro spun into nanofibers.[41] Despite the advantages described above, there are still some drawbacks. When the fibre diameter is reduced to nanoscale through the electrospinning process, hydrophobicity of PCL increases which results in reduced cell recognising sites which aids in slower degradation rate and lowered expression of alkaline phosphatase(ALP).[42] Chitosan blended with PCL provides a feasible strategy to overcome these disadvantages. The peculiarity of adding chitosan is that it can greatly improve the hydrophilic behaviour which results in improved cell attachment. Another key advantage is that due to its superior miscibility, it do not require toxic crosslinking agents for crosslinking unlike blends between PCL-gelatin and PCL-collagen (Shalumon et al., 2013; Nivedhitha et al., 2016; Masoudi et al., 2017).[43,44]

The fabrication of a novel, spatially designed and functionally graded periodontal membrane has been reported. They showed superior osteoconductive/inductive behaviour provided by nano-sized hydroxyapatite particles which was incorporated with metronidazole to combat periodontal pathogens. This electro spun FGM can be considered the future of periodontal regeneration due its superior mechanical integrity, biodegradability and cell–membrane interactions.[45]

FIGURE 2. Clinical applications of electrospinning technique.



Bone Regeneration

Over the past few years, bone tissue engineering (BTE) has been proposed as a promising alternative to classical therapies. One of the most important aspects of bone engineering is to have a suitable scaffold design that can regulate bone healing and simulate the role of ECM in bone. Zhang et al created a biomimetic nanocomposite nanofiber of hydroxyapatite/ chitosan (HAp/CTS). It was fabricated by combining the in-situ co-precipitation synthesis method with the electrospinning process. The incorporation of HAp nanoparticles into the nanofiber framework of chitosan resulted in significant bone formation compared to that of the pure electro spun CTS scaffolds.[46]

Nourmohammadi et al. in his study used a reductive alkylation process to combine chitosan with various amounts of oxidized starch. The culture of osteoblast-like cells on the scaffolds revealed that higher starch content led to an improvement in cell viability.[47]

Caries Prevention

Mucoadhesive chitosan fibres containing mangosteen extract have shown antibacterial activity against cariogenic pathogens. These mucoadhesive chitosan fibres could be prescribed for individuals who are unable to self-administer oral hygiene protocols and can be used synergistically with existing methods of oral hygiene practice to aid in caries prevention.[48]

Pulp Dentin Complex

Electro spun scaffold possess the ability to promote odontogenic differentiation and odontoblastic differentiation. Kim et al. in his study synthesised electro spun scaffolds of polyvinyl alcohol and hydroxyapatite (HA) and found that it possessed dentin regenerative properties.[40] Bottino et al. produced electro spun scaffolds of polydioxanone (PDS) in which antibiotics (metronidazole and ciprofloxacin) were incorporated in the solution, also used as root canal medicament.[6]

Implant Surface Modification

Electrospinning is a new alternative for implant surface biomodification to enhance osseointegration. They provide the benefit of greater surface area for fibroblast attachment. Titanium implant coated with PLGA/collagen/ nanohydroxyapatite provided superior cell attachment and improved mineralisation.[15]

Cartilage Regeneration

Electro spun PCL nanofibers were tested invitro to examine their chondrogenic potential and was found to accelerate proliferation of human chondrocyte which could be beneficial for cartilage regeneration.[49] Chitosan fibres act as scaffold for cartilage regeneration and show superior properties to foam and hydrogels.[50] Chen et al. used electrospinning for hierarchical scaffolds fabrication mimicking the zonal organization of articular cartilage.[51]The 3D multiscale fibrous scaffolds promoted chondrogenic differentiation of human mesenchymal stem cells(hMSCs) and directed tissue organization in a zone-dependent way.

Drug Delivery

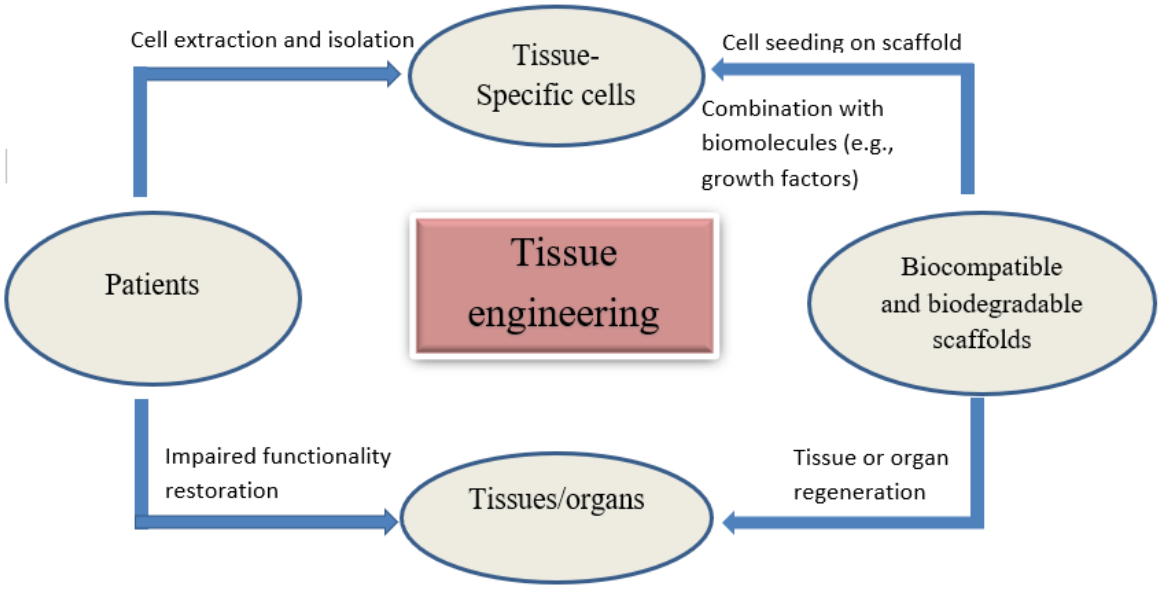
Electro spun nanofibers can be successfully used in drug delivery as they can be employed for sustained drug release due to their different drug encapsulation designs which provide for their superior bioavailability property. The usually employed drug loading strategies are the post-electrospinning modification, blend electrospinning, coaxial electrospinning, and nanoparticles encapsulation. There are various strategies to incorporate drugs as spun nanofibers. They typically include blend electrospinning and emulsion electrospinning of bioactive drugs and polymers.

PLGA has been approved by the Food and Drug Administration (FDA) due to its superior properties. It is nontoxic, shows reduced inflammatory reactions, and is easily biodegradable in the body.[52] A critical advantage of PLGA is that it offers the possibility of controlling the rate of drug delivery by changing the ratio between the lactic and glycolic acid monomer.[53] A study by Ranjbar-Muhammadi et al showed that by incorporation of Tetracycline into core–shell nanofibers, sustained drug release was obtained for 75 days with only 19% of burst release within the initial 2 hours.[54]

Wound Healing

Electro spun mats can be used to supply topical anaesthesia and antibiotics to surgical or traumatic wounds.[55] Electro spun fibres could also be used as dressings for oral mucosal lesions such as ulcers or surgical wounds to relieve patients discomfort .[56] Polymers such as chitin and PLGA, function as effective scaffolds for proliferation and differentiations for human mucosal cells .[57]As they superiorly mimic the physical properties of the natural extracellular matrix due to their ultrafine continuous fibre structure, high surface to volume ratio, and high porosity , it is highly recommended for effective regeneration of injured or defective skin tissue. Electro spun nanofibers are considered to be one of the most profitable and fastest growing products of technology today and display an Innumerable Potential In Wound Healing And Skin Tissue Engineering.[58]

Figure 3.Various clinical aspects of tissue engineering



Skin Repair

The electro spun ultrafine fibres can be modified as per requirement to show the desired pore distribution, high surface area–to–volume ratio, cell adhesion and proliferation. This is due to their structural resemblance to the natural extracellular matrix. Electro spun polymeric nanofibers can be successfully used as skin substitutes as they can prevent fluid and proteins loss from the wounded site, help in eliminating the exudates, exhibit antimicrobial properties, shows excellent anti–adhesion properties and guide the endogenous cells to replicate and remodel the entire area. Nanofibrous scaffolds are currently being manufactured along with growth factors and / or cells to induce factors responsible for accelerated orchestrated wound healing.[59]

VII. Limitations

Despite electrospinning being a very useful method, it does have its share of limitations. One of the major disadvantages is its inability to form fibres of larger diameter. As the diameter varies, its pore size and consequently cell infiltration capabilities decreases hampering regenerative capacity.[60] Considering its major application to be 3D scaffolds, its cumbersome to develop 3D scaffolds with precise dimension and morphology. In addition to that, the mechanical properties of these materials are also questionable as of now. They are weaker mechanically compared to cast membranes.[61] Further concern lies in the agents used for crosslinking as well as the solvents used in the process.[62] Their toxicity may influence regeneration capacity. Safety issue for the staff and sterilisation is another concern due to the high voltage involved in the process. These limitations make the clinical application difficult and further research need to be done to overcome these limitations.

VIII. Conclusion And Future Perspectives

Electrospinning is undoubtedly an excellent technology that has completely changed tissue engineering. Electrospinning allows the manipulation of material properties down to the nanoscale, which closely resembles the extracellular matrix. Instead of the traditional 2D scaffolds used in those applications, 3D scaffolds show far more resemblance to native ECM. The complete replication of cell-matrix interactions can improve regeneration. This appears to be the most promising aspect in current periodontal regeneration techniques. Therefore, the influence of nanofibers on cellular signalling mechanisms and biochemical pathways is encouraged to better the knowledge of cell-nanofiber interactions.

Drugs can be encapsulated into nanofibers through post-electrospinning modifications, which is an upcoming field in periodontal therapy. Different drug loading methods result in different drug releasing profiles to be used accordingly in different patients. As a whole, there are future opportunities for the development of multifunctional electrospinning products based on different application combinations.

There is an impending need for future prospects of such novel materials in the field of periodontal regeneration. Though there are a few hurdles in the development of such novel technology, it can be overcome with more rigorous research. Further studies in the field of bioengineering are needed to re-establish the health and function of distinct periodontal tissues lost due to periodontal disease.

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Fatima Teresa Chirayath, et. al. ‘‘Synthesis, Properties and Clinical Applications of Electrospun Nanomaterials in Periodontics.’’ *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 20(09), 2021, pp. 15-22.