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APPLICATIONS OF ELECTROSPUN NANOFIBERS IN THE TREATMENT OF PERIODONTAL DISEASES

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ABSTRACT: A periodontal disease is a group of pathological diseases, i.e., a widespread infectious disease that mainly causes tooth loss in 15% of adults worldwide. For the treatment of these periodontal diseases, localization of the drug is necessary *i.e.;* the drug has to be delivered to the periodontal pocket, which is the main area for the development of bacteria. So, researchers have made many attempts to develop the treatment of periodontal disease, including drug delivery to the infection site and regeneration approaches; they really provide a useful experimental mode for evaluating therapies for future periodontal diseases. This review mainly focuses on the pathogenesis of periodontal diseases, the process of fabrication of nanofibers using electrospinning techniques, and mainly how these electrospun nanofibers are used in the treatment of periodontal diseases. And gives an overview of how antibiotics, antimicrobial agents, and nanocomposite electrospun nanofibers are used in the treatment of periodontal diseases.

INTRODUCTION: Periodontal disease is a general term for a group or number of pathological conditions which can be characterized by inflammation and degeneration of gums (gingival), supporting bone (alveolar bone), periodontal ligament, and cementum where they have a complex etiology and high incidence rates, with one in two adults being affected [1, 3]. These periodontal diseases mainly affect the supporting tissues of the teeth [4]. American Academy of Periodontology (AAP) in 1999 classified plaque-induced inflammatory periodontal diseases into two types depending on the extent of the inflammatory infiltrate, and the absence or presence of clinical attachment loss; they are (i) gingivitis and (ii) periodontitis.

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Plaque-induced gingivitis is the most prevalent form of periodontal disease. The inflammation is limited to the gingiva with no loss of connective tissue attachment, and the junctional epithelium is still at the cementoenamel junction (CEJ). This type is reversible because the situation returns to normal once the dental plaque is removed, Gingivitis may progress to periodontitis in susceptible individuals in whom the balance between bacterial challenge in dental plaque and the host response to this challenge is disturbed [5, 7].

But whereas in periodontitis, the inflammation extends from the gingiva to involve deeper periodontal tissues causing gradual and irreversible destruction of periodontal ligament and alveolar bone with subsequent loss of connective tissue attachment and apical migration of the junctional epithelium along the root surface, which is evident clinically as periodontal pocket formation, recession or both, and may lead to tooth loss if not treated, in this the major part of tissue destruction is related to the host's inflammatory response.

Since, every individual varies in their body's inflammatory responses, there is a chance to vary in their particular nature to periodontitis [8, 9]. One of the key elements for the development of periodontal disease is the colonization of teeth and periodontal tissues by pathogenic bacteria, which release lipopolysaccharides that activate the immune system. This leads to inflammation that causes damage to the periodontal tissues due to the increased levels of cytokines and matrix metalloproteinases. The host immune response is essentially protective, but the response is not normal when a host is susceptible to various habits, such as smoking, poorly controlled diabetes, stress, or genetic factors. Hypo or hyper-responsive inflammatory pathways lead to enhanced tissue destruction and formation of periodontal pockets.

The consequences of inappropriate body response and chronic inflammation in the body lead to chronic periodontal diseases. And also, some recent studies reported new evidence that periodontal disease could be associated with systemic oxidative stress state, reduced overall antioxidant capacity, and increased biologic markers for alveolar bone degradation in saliva. These periodontal diseases are difficult to treat because it is a pathological condition which is a complex disease that may be affected due to several factors. Taking these into account, there are three different approaches for treating periodontal diseases: (i) removal of dental biofilm with brushing and additional antimicrobial therapy; (ii) modulation of host inflammatory response aiming to suppress inflammation and restore homeostasis; and (iii) regenerative periodontal therapy of a destructed periodontium [10, 12].

The currently available delivery systems for recolonization are inadequate, as they do not ensure the target probiotic's efficient recolonization of the periodontal pocket due to the need for prolonged local retention after delivery. Indeed, probiotics are incorporated into fast-release formulations (*e.g.*, tablets, mouthwash, toothpaste, solutions, gels, films, or chips.). Still, they result in a limited contact time between the probiotic cells and the oral mucosa or dental surfaces [10, 12]. There remain two key limitations for the successful treatment of periodontal disease: (i) the lack of potent probiotics isolated from the human oral microbiota and (ii) the lack of solid delivery systems for prolonged probiotic retention in the periodontal pocket [13]. So, to overcome these problems, scientists aim to develop, formulate and characterize a novel delivery system for the targeted recolonization of periodontal pockets where the dosage forms for the treatment of periodontal disease have to be specifically fit in the periodontal pockets, stay there for prolonged periods, be in tight contact with surrounding tissue, and be able to control the release of the drug. Thus, a potentially probiotic bacterial strain was initially selected from healthy volunteers, showing activity against the periodontal pathogen. This selected bacterial strain was then incorporated into novel delivery systems for its local delivery.

Thus, finally, researchers developed a new alternative drug delivery system, the nanofibers, which can load a drug and tailor the drug release profile by modifying the composition and its morphology. Their large surface area increases the tendency to adhere to the tissue in the periodontal pocket. These nanofibers are prepared by the electrospinning technique, which can produce nonwoven fibers with high porosity that nanoscale fibres provide a large surface area that accelerates delivery rate. The release profile can be adjusted by biodegradable polymers [16]. Drug delivery using nanofibers is electrospun as an impregnated matrix of active ingredients. The most appropriate materials for the preparation of nanofibers by electrospinning technique and for the delivery of a wide variety of active ingredients are biodegradable polymers, such as chitosan, poly (ethylene oxide), poly (vinyl alcohol), poly (lactic-glycolic acid), poly(ε-caprolactone) (PCL), poly (DL-lactide-co-glycolide) [14, 15]. A different solution, selection of the solvent, a mixture of polymers and their ratios, process parameters (flow rate, high voltage), and environmental parameters influence nanofiber formation and their morphology. The erosion rate of corresponding polymers determines the release rate over treatment time based on the porosity and scale of produced nanofibers [16].

Pathogenesis of Periodontal Disease: Periodontis is referred to as a "mixed bacterial infection"– commensal and pathogenic interplay Subgingival biofilm and host-immune- inflammatory events lead to the breakdown of periodontal fibers,

Clinical attachment loss, and bone resorption. The quality and quantity of the microorganisms should be noted. In general, the inflammation, but this ideal condition is very rarely seen in microscopic tissue sections. This is because most of the human gingival tissues are, no matter how clinically healthy in appearance, slightly inflamed due to the constant presence of microbial plaque [27]. The formation of dental plaque can be briefly described in the following three states. First, salivary proteins and glycoproteins adhered on the tooth surface form a thin and non-cell associated biofilm named acquired pellicle, which can provide specific receptors for bacteria (*e.g.*, Gram-positive bacteria) and further enhance bacterial adhesion. Second, accumulated bacteria, such as Streptococcus, different types of bacteria on the acquired pellicle rapidly aggregated normal healthy gingiva is characterized by Bacillus and Actinomyces, in the oral cavity continuously colonized on the acquired pellicle [27].

Finally, its pink color and its firm consistency [28,30.] Among all these, the periodontal gingivalis is considered the primary driver of periodontal disease, utilizing various weapons, including lipopolysaccharide, fimbriae, and proteases (*e.g.*, gingipains), to damage the periodontal tissue and bring the activation of host immune responses. Also, another key factor in promoting periodontal disease is the host immune response to bacterial infection, specifically the extent and duration of inflammation [31, 32].

And also Even in a very healthy state, the gingiva has a leukocyte infiltrate that is predominantly comprised of neutrophils or polymorphonuclear leukocytes. These leukocytes are phagocytes whose primary purpose is to kill bacteria after migrating through and out of the tissues into the gingival crevicular area or the gingival pocket. A subgingival plaque sample will invariably show plaque microorganisms and neutrophils when viewed under the microscope. Neutrophils are recruited to the periodontal pocket or the gingival crevice because of attracting molecules released by the bacteria, called chemotactic peptides. Furthermore, as bacteria damage the epithelial cells, they cause epithelial cells to release molecules termed cytokines that further attract leukocytes (predominantly neutrophils) to the crevice. Cytokines play a major role in the recruitment of host immune cells by acting as chemo-attractants and stimulating the expression of intercellular adhesion molecules and vascular cell adhesion molecules, further enhancing margination and diapedesis procedures [35]. Such mechanisms can significantly increase the population of polymorph nuclear neutrophils (PMNs) in the infected area, which results in an elevation of free radical-mediated periodontal tissue damage, further increasing pro-inflammatory cytokine release [33, 34]. This effectively leads to an auto-amplification situation as greater concentrations of immune cells in the infected area enhance reactive oxygen species (ROS) production and release [33]. The neutrophils within the crevice can phagocytose and digest bacteria and, therefore, remove these bacteria from the pocket. If the neutrophil becomes overloaded with 10 bacteria, it degranulates or explodes'' [37].

This causes tissue damage from toxic enzymes that are released from the neutrophils. Therefore, neutrophils can be viewed as being both helpful and potentially harmful. The neutrophil defense may in some instances, operate well and reduce the bacterial load and can be considered important in preventing the gingivitis lesion from becoming established. If there is an overload of microbial plaque, then the neutrophils and the barrier of epithelial cells will not be sufficient to control the infection.

In such instances, the gingival tissue will become very inflamed, which is clinically seen as gingivitis. Most individuals develop clinical signs of gingivitis after 10–20 days of plaque accumulation [36]. Gingivitis appears as redness, swelling, and an increased tendency of the gingiva to bleed on gentle probing. These destructive processes are initiated by bacteria but are propagated by host cells. Thus, it is the host response that results in tissue destruction. The host produces enzymes that break down tissue. This is a necessary process initiated and controlled by the host to allow the tissues to retreat from the destructive lesions initiated by bacteria [37]. The pathogenic processes in periodontal disease can be likened to a situation where the host strategy is to eventually expel the tooth so that the inflammation will be stopped. Once the tooth has been expelled,

the lesions are finally defused. This is because there is no further tooth site for the plaque to build upon, and simplistically, there is no periodontium left to be infected. Thus, the exfoliation of teeth during periodontal disease might be considered a host preventive strategy to protect against deeper infection[34, 37].

Electrospinning Technology for the Formation of Electro Spunnanofibers: Electrospinning has become a more powerful tool for fabricating nanoscalenanofibers. And it is an inexpensive method that creates Polymeric nanofibers of different diameters, which are a relatively new nanostructured material with several remarkable features, like fiber diameter, a high surface-to-volume ratio, a porous structure, and a theoretically unlimited length, together with better mechanical performance and flexibility [17, 22, 23]. Electrospinning utilizes a polymeric solution or melts to generate nanofibers in high electrostatic fields (high voltage) [25]. The electrospinning setup requires four components: (i) a syringe pump (containing solution/melt liquid/suspension to be electro spun), (ii)a spinneret with a metallic needle (as a capillary), (iii) a high-voltage power supply (for generation of high electrical voltage) and (iv) a grounded conducting collector (static plate or rotatable drum) [17, 20] as shown in **Fig. 1.**

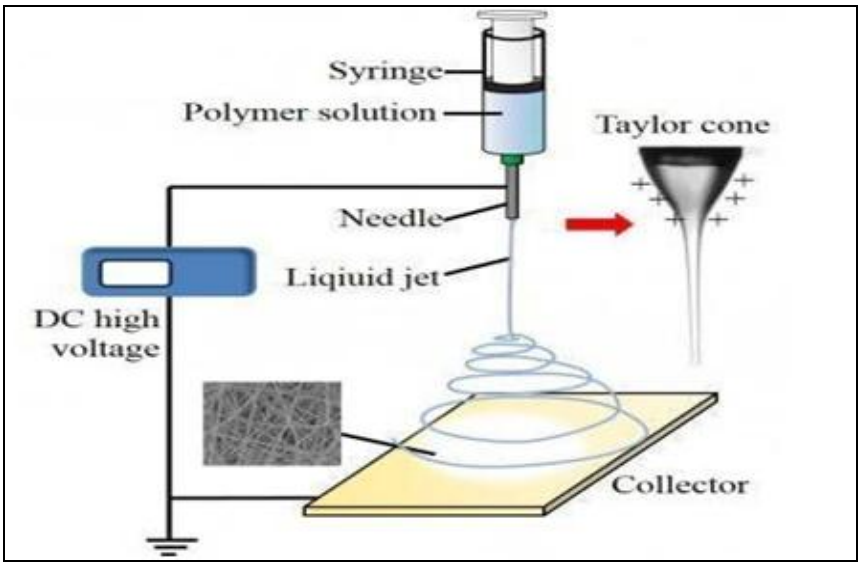

FIG. 1: ELECTROSPINNING APPARATUS SHOWING THE FIBER FABRICATION

In the electrospinning process, a high voltage is used to form a nanofiber; the application of high voltage results in an electrically charged jet of polymeric solution ejecting from a needle with an inner diameter of 0.5–1.5 mm (lies in between these mm) i.e., When an electrical force is applied to an ejected polymer solution, pendant droplet at the tip of the needle is formed.

Due to the application of the electrical charge on the drop's surface, the droplet changes its shape from hemispherical to conical. The conical shape of the ejected solution is typically referred to as Taylor cone [21]. When the droplet is subjected to an external electric field, the conical surface is formed with an angle of 49.3°. When the intensity of the electric field (V) attains the critical value (VC), the electrostatic forces overcome the surface tension of the polymer solution and force the ejection of the liquid jet (cone-jet) from the tip of the Taylor cone [21]. The highest charge density is present at the tip of the cone from where the jet is initiated.

As the jet dries in flight, the mode of current flow changes from ohms to convective form so that the charge gets migrated to the surface of the fiber, then the jet is elongated by a whipping process as shown in **Fig. 2,** which is caused by electrostatic repulsion force which is then initiated at small bends in the fiber, until it is finally deposited on the grounded collector. The elongation and thinning of the fiber due to electrostatic repulsive force results in the formation of uniform fibers with nano-sized diameters [24]. Thus, the electrospinning technique forms nanofibers using high voltage.

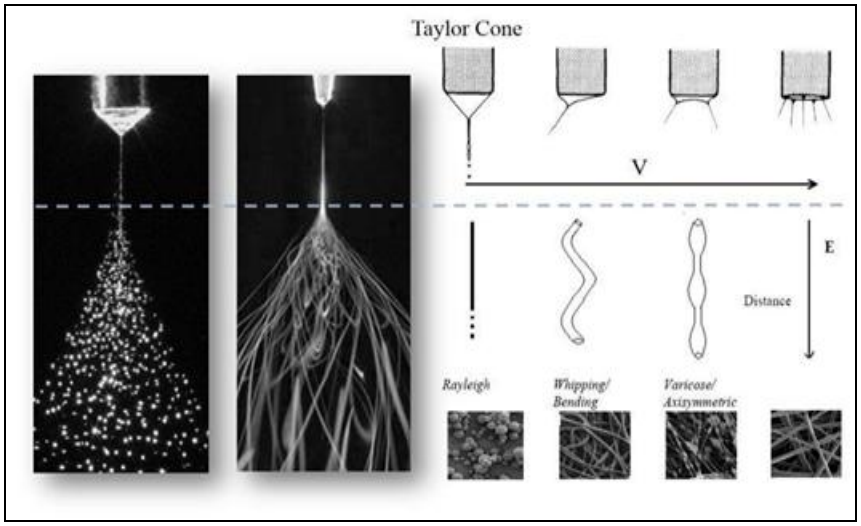

FIG. 2: DIAGRAM SHOWING THE FIBERS FORMATION FROM THE TAYLOR CONE

TABLE 1: PARAMETERS AFFECTING ELECTRO SPUNNANOFIBERFORMATION

Solution parameters	Process parameters	Ambient parameters
viscosity	Flow rate	Temperature
Conductivity of the polymer, and solvent solution	Distance b/w capillary and collector	Air velocity in the chamber
Surface tension	Shape of collector	Humidity
Elasticity	Tip of collector	
Solution temperature	Geometry of spinneret	
Added salts to solution	Applied voltage	
Vapour pressure		

These are the parameters that affect the formation of electro-spunnanofibers. So, all these parameters need to be maintained to get uniform size nanofibers [26].

Nanofibers in Periodontal Therapy: Nanofibers are a kind of biomaterial used for the periodontal Drug Delivery System, which is composed of one or more of components that contain drugs, proteins, and peptides with a polymeric carrier in the form of homo, bi, or multicomponent fibers. Such fibers are placed individually in packed form, tablet, or capsules. Nanofiber Drug Delivery System works as a reservoir filled with therapeutic agents released simply by a diffusion process [38, 39]. Nanofiber for the treatment of periodontal disease was found more effective because they are designed to enable local or systemic drug administration, prolonged retention in the periodontal pockets, and controlled release of antibacterial or anti-inflammatory agents or any other active substance incorporated, which may support tissue regeneration. Natural and synthetic polymers, including collagen, alginate, chitosan, polyurethane, polypropylene, and cellulose acetate propionate, have been investigated as fiber matrices for drug delivery to the periodontal pockets. Polymeric nanofibers show a promising treatment for periodontal disease due to their special structure, which can deliver the drug in a controlled manner and mimics the extracellular matrix. Bio mimeticnanofibers in the form of porous membrane can increase cell adhesion and proliferation and thus improve the regeneration of the degraded periodontium [53]. These nanofiber systems are designed to fit the drug in the periodontal, and the periodontal pocket holds the drug and regulates the release pattern of the drug for a required amount of time.

In the literature, many comprehensive articles are available on the production [40] drug loading [44, 46] characterizations [47, 49] and therapeutic application [46, 50, 52] of nanomedicine nanofibers. Some of the advantages of the nanofiber-based drug delivery in the periodontal treatment were mentioned in **Table 2.**

In recent years, fibers have gained much attention due to their suitability and adaptability in the process [55]. Various techniques are used to fabricate fibers, known as phase separation, melt fibrillation, electrospinning, a gas jet, an island in the sea, nanolithography, self-blowing, melt blowing, *etc*., but in these recent years, some researchers have

successfully encapsulated drugs within fibers by mixing the drugs in the polymer solution that could go through the process of electrospinning. Different solutions containing low molecular weight drugs have been electro spun, including Metronidazole, tetracycline, meloxicam and MIN. Drugs released through a diffusion process from fibers directly act on the target site to control the infections. The drug release behaviour from such systems mainly depends on the polymer type, polymer concentration, nature of the drug, and the manufacturing process equipment type [55].

Out of all these, the nanofibers should possess some important properties for their design and *in-vivo* performance; they are (i) physical and chemical properties, (ii) technological aspects, (iii) biopharmaceutical, and pharmacokinetic benefits [56,] their properties are given in the following **Table 3.**

TABLE 2: ADVANTAGES OF NANOFIBERS IN PERIODONTAL TREATMENT

1.	Improved drug loading capacity
2.	Tunable mechanical properties
3.	Better targeting
4.	Better adsorption
5.	Ease of fabrication
6.	Easily applied to the target site

In recent years, fibers have gained much attention due to their suitability and adaptability in the process [55]. Various techniques are used to fabricate fibers, known as phase separation, melt fibrillation, electrospinning, a gas jet, an island in the sea, nanolithography, self-blowing, melt blowing, etc.. Still, in these recent years, some researchers have successfully Encapsulated drugs within fibers by mixing the drugs in a polymer solution that could go through the process of electrospinning. Different solutions containing low molecular weight drugs have been electrospun, including Metronidazole, tetracycline, meloxicam, and MIN. Drugs released through a diffusion process from fibers directly act on the target site to control the infections. The drug release behaviour from such systems mainly depends on the polymer type, polymer concentration, nature of the drug, and the manufacturing process equipment type [55]. Out of all these, the nanofibers should possess some important properties for their design and *in-vivo* performance, they are (i) physical, and chemical properties, (ii) technological aspects, (iii) biopharmaceutical and pharmacokinetic benefits [56,] and their properties are given in the following **Table 3.**

TABLE 3: DIFFERENT PROPERTIES OF NANOFIBERS FOR THEIR *IN-VIVO* PERFORMANCE

Physical and Chemical properties	Technological aspects	Biopharmaceutical and Pharmacokinetic benefits
❖ Modification of surface area	❖ Drug protection against enzymatic and hydrolytic degradation	❖ Controlled release of drugs
❖ Particle size	❖ Increased physical stability	❖ Decreased dosing variation
❖ Size distribution	❖ Feasibility of large-scale production	❖ Decreased toxicity
❖ Morphology	❖ Can apply in various therapeutic areas	❖ Tissue targeting capacity of nanofibers.
❖ Zeta potential	❖ Can apply to as many drugs as possible	❖ Bacterial cell destruction in periodontal diseases.
❖ Biodegradable		❖ Mimicking extracellular matrix with nanofibers.
❖ Biocompatible		❖ Decrease in drug dose
❖ Bio Adhesiveness		❖ Solubility enhancement of the drug.
❖ Hydrophobicity		❖ Incorporation of low molecular weight of the drugs
❖ Hydrophobicity		

Antibiotics in the Treatment of Periodontal Diseases: In addition to these, different antibiotics have been incorporated into electrospun nanofibers, which are further evaluated for drug release profile efficacy of the drug, and toxicity by either *in-vitro* or *in-vivo* studies. These antibiotics include Tetracycline hydrochloride tetracycline. These are oral, broad-spectrum antibiotics that are used to treat mild-to-moderate infections caused by different microbial organisms. And it contains certain disadvantages like high doses of several forms of tetracycline given intravenously was associated with side effects like acute fatty liver that can be from severe to moderate and further result in liver failure and causes death [58] doxycyclines and doxycycline hydrochloride is a broad-spectrum antibiotic which is synthetically derived from oxytetracycline. This is a second-generation tetracycline, which exhibits lesser toxicity than the first-generation tetracycline's. It is used to treat a wide range of bacterial infections, which are indicated for the treatment of various

infections caused by gram-positive, gram-negative, aerobic, and anaerobic bacteria and also other types of bacteria [59,] Ampicillin is a penicillin beta-lactam antibiotic used to treat bacterial infections caused by gram-positive bacteria and organisms, Amoxicillin is used to treat a wide range of bacterial infections. It is a penicillin-type of antibiotic. It works by stopping the growth of bacteria. Lidocaine, also known as lignocaine, is used to numb tissue in a specific area (local anesthetic) [60] Among all the other antibiotics, Metronidazole is a front-line chemotherapeutic agent for the treatment of infections caused by anaerobic bacteria associated with periodontal diseases as it requires low minimum inhibitory concentration (MIC).

Tinidazole is an antibiotic that is used to treat certain types of parasitic and bacterial infections with a bactericidal activity [60, 61] and Metronidazole benzoate. Using any antibiotic when it is not needed can cause it to not work for future infections. All these antibiotics serve as first-line chemotherapeutic agents for treating many infections caused by anaerobic bacteria associated with periodontal disease due to their low minimum inhibitory concentration [72]. The most important feature of nanofibers that are loaded with antibiotics for treating periodontal disease is the drug release profile from nanofibers, which is controlled to maintain the local antibiotic concentration above Minimum Inhibitory Concentration (MIC) over a week or more than a week, and whereas the biodegradability and bio adhesiveness are the desired properties. Several nanofiber delivery systems for antibiotics are meant for the bactericidal drug activity for a longer period [59, 60].

In addition to these, such delivery systems are safe because neither the nanofibrousmats have the released antibiotic has been showing cytotoxic activity on human gingival fibroblasts [60]. For the past many years, scientists have developed antibiotic-loaded electrospunnanofibers for the treatment of periodontal diseases due to their improved drug loading capacity, better targeting, and can easily be applied to the site of action [40, 52]. And these antibiotic loaded nanofibers have become the most supporting drug delivery system to treat periodontal diseases due to their nature of fitting in to the periodontal pocket to treat the infection. Recent studies of some researchers describe nanofibers as a drug delivery for the treatment of periodontal diseases. And the first article describes that Kenawy *et al.* in the year 2002 fabricated electrospun nanofibers by using polymeric solutions of poly(ethylene-co-vinyl acetate) (PEVA), poly lactic acid (PLA), or a mixture of both polymers in a weight ratio of 50:50 in which tetracycline hydrochloride was loaded in the nanofibers and its release profiles were evaluated by comparing their formulation with the marketed formulation. They finally proved that the tetracycline release from the nanofibers was significantly slower than pure PLA or PEVA nanofibers over 5 days. The total tetracycline hydrochloride release from the nanofibers was very high when compared to marketed formulations [58].

Zamani *et al.* in the year 2010 incorporated 5-15% w/w of metronidazole benzoate by using PCL polymer, and they got very thin nanofibers of 363-999 nm diameter, depending upon the solvent ratio, and they mainly observed that the drug release rate was affected by both the solvent ratio and also by the drug concentration, also the nanofibers show the sustained release for about 19 days which is ideal treatment period for periodontal diseases. Also, they observed the low burst release effect, and these electrospun nanofibers have shown that they remain smooth and flexible without shrinking during treatment, i.e., up to 19 days.

Reise M *et al.* incorporated 0.1-40% w/w of Metronidazole by using PLA polymer in different ratios; as a result of this, they obtained the nanofibers of different nm in the range of 640-1200 nm diameters, and they observed sustained release for 7 days and the release rate dependent on drug loading, it inhibits the growth of three pathogenic bacteria (bacteria present on the tooth surface and in periodontal pockets), and there is no cytotoxicity [87]. Bottino MC *et al.* they in the year 2012 they have incorporated Metronidazole or ciprofloxacin (studies are conducted by incorporating both drugs) by using polydioxanone polymer. They obtained a nanofibers ranging in between 765-1158 nm in diameter for these in-vitro and in-vivo studies have shown that both the drugs loaded in nanofibers have shown the low burst release effect. Sustained release for 7 days, but the nanofibers loaded with

ciprofloxacin have a good antibacterial activity i.e., these ciprofloxacin-loaded-nanofibers inhibit pathogenic bacteria without affecting the growth of periodontally beneficial bacteria [63]. Chen DW *et al.* have incorporated different drugs like Amoxicillin, Metronidazole, and Lidocaine into PLGA/collagen polymer ratio in the ratio of 2:1, w/w. They get a nanofiber in different diameters ranging from 45-280 nm. The results have shown that the multidrug-loaded biodegradable nanofibers, by an *in-vivo* study on rabbits, have shown a sustained release approximately for about 1 month, and also there is no cytotoxic effect [53, 60].

Markus Reise in the year 2011 they have fabricated electrospun nanofibers with the 0.1–40% (w/w) of Metronidazole by using poly(l-lactide-co-d/l-lactide) polymer and *in-vivo* and *in-vitro* studies reveals that the metronidazole concentration influences the fiber diameters and surface areas diameter being minimal and area maximal at 20% of Metronidazole. HPLC studies showed that these 20% metronidazole fibers initially had the drug release rate faster. Then From the third day, the metronidazole release was slower and nearly linear concerning time. All the fiber mats released 32–48% of the total drug content within the first 7 days. The antibacterial activity results show the Aliquots of media taken from the fiber mats can inhibit the growth of all three bacterial strains present on the surface of the tooth and in the periodontal pockets.

Metronidazole is released up to the 28th day from fiber mats containing 40% metronidazole drug. All of the investigated fibers and aliquots showed excellent cytocompatibility [87]. Thus, the electrospun Nanofibers have many advantages compared to other drug delivery systems for local application due to their special structure and large surface area, which resembles the extracellular matrix. Therefore, researchers have focused on nanofibers with a dual role, that is, (i) delivery systems for antibiotics and (ii) nanomaterials that could enhance tissue regeneration and were successful in the treatment of periodontal diseases treatment.

TABLE 4: MOSTLY USED ANTIBIOTICS, POLYMERS AND DOSAGE FORMS TYPES AS ELECTROSPUN NANOFIBERS IN THE TREATMENT OF PERIODONTAL DISEASES

Antibiotics	Polymers used	Dosage form type
Tetracycline	PLA	Nanofibers
Tetracycline Hcl	PLGA	Biodegradablenanofibers.
Metronidazole	PEO	Biocompatiblenanofibers.
. Metronidazole benzoate	CHITOSAN	Polymeric nanoparticles with
Doxycycline hyclate	PCL	nanofibers
Ofloxacin	PVA	
Clindamycin	CHITOSAN	
Minocycline	Combination of these polymers were also used to produce	
Ciprofloxacin	the electrospunnanofibers. (i.e., difference in the ratios and	
Amoxicillin	different combinations of polymers)	
Lidocaine		

Moreover, such delivery systems are safe, because neither the nanofibrous mats nor the released antibiotic have shown cytotoxic activity on human gingival fibroblasts [60, 62].

In addition to these different antimycobacterial agents like Chlorhexidine, Sanguinarine, Tetracycline's, Histatins, Ofloxacin, Metronidazole, Clindamycin etc were used in the treatment of periodontal diseases. These drugs are fabricated as nanofibers and made as controlled release drug delivery systems. Their main aim of current periodontal therapy is to remove the bacterial deposits from the tooth's surface and the periodontal pocket and to shift the pathogenic microbiota to one compatible with periodontal health [90].

Nano-composite Electrospun nanofibers used in the Treatment of Periodontal Diseases: In addition to these, there are many nanocomposite electrospun nanofibers blended with polymers that are used in the treatment of periodontal therapy or regeneration [63, 71]. Different types of nanocomposite nanofibers are used in periodontal therapy.

(i) Nano-Composite Electrospun Fibers Blended with Inorganic Components: These are obtained by blending various polymers and incorporating the functional components into the polymer matrices; these nanocomposite electrospun nanofibers have a good mechanical, bioactive and biological properties when compared with a pure polymer matrices, which includes fibers blended with the following components.

(A) Ceramic Components: In this polymer is mixed with the bioceramic components, which is a complex composite made by organic collagen fibers and hydroxyapatite (HA) Bioceramic components such as hydroxyapatite nanoparticles and bioactive glasses (BG) are incorporated into the electrospunnanofiber matrices to increase bioactivity and biological, physical-chemical properties, like (i) osteoconductivity, (ii) osteoinductivity and (iii) to emulate the native inorganic bone components which are used during periodontal therapy [73, 74, 75].

Due to the incorporation of these bio ceramics in to electrospunnanofibers with natural or synthetic polymers shows the increase in osteoconductivity which helps in the periodontal treatment.

(B) Ca-P Based Components: The most thermodynamically steady synthetic calcium phosphate ceramic is Hydroxyapatite (HA), which has biocompatible, bioactive, and osteoconductive properties. In recent years a large number of researchers have worked on this, and it was proved that Hydroxyapatite was successfully incorporated into electro-spunnanofibers have the ability to improve their (i)physical-biological and mechanical properties, (ii)proliferation, and (iii)mineralization property and also, they have proved that these Ca-P based components also have a wound healing capacity[68, 76.]

(C) Ca-Si Based Components: The Ca-Si-based materials with special characteristic components have excellent osteoconductivity and osteoinductivity properties which helps in the treatment of periodontal therapy.

(D) Oxide Components: Periodontitis is a group of infections caused by different aerobic bacteria, where these bacteria release toxins; the periodontium is affected. So here, the main treatment is antibacterial therapy, but the antibiotic effect was not that effective. Then here, we need to give the components which can produce both the antibacterial effect and osteoconductive effect. The components like Zno-loaded electrospun nanofibers with PCL membrane [66] and Cao-loaded electrospun nanofibers with PCL membrane [70] have not only antibacterial activity but also it has high osteoconductive activity where these properties help in periodontal therapy.

(ii) Nano-Composite Electrospun Fibers Blended with Carbon-Based Components: The best example for Nanocomposite electrospun nanofibers blended with carbon-based components are multi-wall carbon nanotubes, which have received a great priority for their excellent mechanical properties, biocompatibility and stability of tissues these were a continuous structure and were weaved in a long fiber with 3D network structure along with a polymer. And these multi-wall carbon nanotubes were fabricated by using PLGA, hydroxyapatite, and bacterial cellulose, which gained great attention for their use in periodontal therapy [78, 79]. In Spite of these Graphene oxide (GO), a carbon compound which is derived from graphene, also has a great in periodontal therapy for its special properties like (i) mechanical strength, (ii) antibacterial property, and also for its (iii) capability to promote osteogenic differentiation. And this Graphene oxide has an increased tensile strength of fibers and well know ling used in the treatment of periodontal therapy.

(iii) Nano-Composite Electrospun Fibers Blended with Metal Components: Various metal components with different characteristics are fabricated into nanofibers to enhance membrane properties like antibacterial activity and bone regeneration activity; for example, Silver nanoparticles [80, 81] and gold nanoparticles [82, 83,] fabricated with different polymers have very least tendency to induce bacterial resistance when compared with classical antibiotics, so these Nanocomposite Electrospun nanofibers Blended With Metal Components have gained much more importance in the treatment of periodontal therapy.

(iv) Nano-Composite Electrospun Fibers Blended with Drugs, Growth Factors and Proteins: In the treatment of periodontitis, the

main approach to incorporate one or more drugs into nanofibers to promote periodontal regeneration and also to produce anti-inflammatory activity simultaneously, in which different drugs like antibiotics, antimycobacterial agents and NSAIDS drugs are used. Along with these different growth factors and proteins for bone regeneration which help in the treatment of periodontal therapy [63, 84, 86].

These are different types of nanocomposite electrospun nanofibers; due to their many advantages (used for antibacterial activity and bone regeneration), they are successfully used in the treatment of periodontitis. Some of the advantages and the directions for future development are given below in **Table 5** [63-71].

TABLE 5: ADVANTAGES AND THE DIRECTIONS FOR FUTURE DEVELOPMENT OF NANOCOMPOSITE NANOFIBERS

Nanocomposite electrospun nanofibers	Advantages	Directions for future development
Ca-P based components	Major constituent of natural bone which promotes osteogenesis	Finding proper proportion to improve mechanical properties
	Idealresorption ability	Improves diameter, porosity and contact angle
Ca-Si based components	Release silicate ions and calcium ions which are useful in osteogenesis	Enhancing the efficacy of osteogenesis activity
Oxide components	Have a good antibacterial activity	Ensuring non-toxicity and improving mechanical property
Carbon- based components	Ability to promote osteogenesis Good mechanical strength Improved toughness.	Solving non-restorability
Metal components	Excellent antibacterial activity and promotes osteogenesis Good antibacterial activity and promotes osteogenesis	Ensuring non-toxicity
Drugs	Ideal antibacterial activity Anti-inflammatory activity and also promotes osteogenesis	Further development of AuNPs incorporated nanofibers and improved the release profile
Growth factor proteins	Antibacterial activity and enhanced cell recognition	Enhancing delivery efficacy and biological activity, assurance of biological activity, and also to improve connection methods

In spite of all these Simzar Hosseinzadeh *et al.* in the year 2015 they used *Ziziphus jujuba* plant extract was prepared as nanofibers by electrospinning technique, and the plant extract release profile was studied in artificial saliva. The polymers used for fabrication include chitosan and polyethylene oxide (PEO) in different ratios, which provides the desirable hydrophilicity essential for mucoadhesive nature. The phenolic compound extracted from a plant namely *Ziziphus jujuba* was used because of its oral healing effect. Further in vitro drug release studies reveal that the Ziziphus jujuba plant extract nanofibers has a great potential to accelerate kinetic release, which is a good requirement in periodontal disease. The novel chitosan-PEO/phenolic compound nanofibers can deliver a pharmaceutical agent up to 75 min, which can facilitate the difficulties of encountering saliva conditions for local oral delivery. So finally, due to these studies they conclude that the phenolic compounds also have a role in the treatment of periodontal diseases as these compounds have an oral healing capacity, so we can localize the delivery of drug to periodontal tissue so that the drug can show its healing effect at that area [88]. And also, some researchers, like Spela Zupan in the year 2018, have introduced an innovative approach for the incorporation of newly isolated autochthonous potential probiotic bacteria into a Nano delivery system for local administration into periodontal pockets. Their main aim is to fulfill two steps in the periodontal treatment, *i.e.*, (i) inhibit the growth of gram-negative bacteria in the periodontal pockets, which is responsible for the development of periodontal disease, and (ii) and localize the Nanofibers with Incorporated Autochthonous Bacteria which can decrease the growth of bacteria and prevent the recurrence of Periodontal Disease. And they have isolated a bacterial strain from that 25.2.M was selected. It is non-pathogenic bacteria (which is harmless) and, based on its close relation to B. methylotrophicus bacteria, that have

antimicrobial substances inhibiting the growth of Gram-negative bacteria *E. coli* and Actinomycetemcomitans can grow along with the periodontal pathogen A. actinomycetemcomitans *in-vitro*, making it an autochthonous probiotic candidate. Second, the nanofibers loaded with a high number of potential probiotic spores are successfully developed (107 CFU/mg). The viability of probiotic in the Nano delivery system after 12 months of storage at room temperature was preserved, and its release could be controlled by selection of the different types of polymers (single polymer or combination of polymers were taken and combination of polymers in different ratios). And the results showed that the strain 25.2.M delivered by nanofibers showed antimicrobial activity against Actino-mycetemcomitans [89].

CONCLUSION: Periodontal disease is a chronic inflammatory disease requiring effective treatment to decrease inflammation and kill the bacteria in the periodontal pockets. So that researchers have developed a novel drug delivery system *i.e.,* electrospun nanofibers for localization of drug delivery as these nanofibers are effectively fit in the periodontal pocket and then release the drug at the site of action. But the normal effective treatment period of periodontal disease is about 2-3 weeks, so the controlled release nanofibers were developed.

To treat the inflammation and to decrease the bacteria during the treatment, different antibiotics and antimycobacterial agents like Tetracycline, Metronidazole, Doxycyclinehyclate, Ofloxacin, Clindamycin, Minocycline, Ciprofloxacin, Amoxicillin, Lidocaine, *etc.* these drugs are fabricated in the electrospun nanofibers by using different polymers (alone or in combination) and were used in periodontal therapy.

Along with these nano-composites electrospun nanofibers are used in the treatment of periodontal therapy, *i.e.,* these Nanocomposites electrospun nanofibers are mainly used in the bone regeneration property where osteoconductive polymers were used. Due to their flexibility and high mechanical strength, these fibers were used in periodontal therapy, *i.e.,* mainly for bone regeneration. Thus, these antibiotics, antimycobacterial agents, and nanocomposite electrospun nanofibers were successfully used in periodontal therapy.

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