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Electrospun Poly-Lactic Acid Nanofibers as a scaffold for Regenerative Endodontics purposes: Fabrication and Characterization

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Abstract

Poly (lactic acid) (PLA), which is a polyester, undergoes hydrolytic degradation into lactic acid, a natural metabolic byproduct, making it well-suited for medical applications. PLA nanofibers have expanded the potential applications of PLA scaffolds, particularly in regenerative medicine and drug delivery. These nanofibrous scaffolds offer several advantageous features, including a high surface area, the ability to mimic the architecture of the native extracellular matrix, and tunable mechanical properties (factors that are crucial when designing scaffolds for specific organ systems). This study deals with the synthesis, characterization, and evaluation of PLA nanofibrous scaffold. For the fabrication. Polylactic acid (PLA) polymer solution at a concentration of 25 wt% was processed into Fibres. Characterization used in the current study included scanning electron microscopy (SEM), Fourier-transform infrared spectroscopy (FTIR), degradation tests. The antimicrobial properties were tested against *Porphyromonas gingivalis* (*Pg*) and *Enterococcus faecalis* (*Ef*). SEM imaging showed Fibres with submicron diameters, and FTIR spectra of nanofibers showed that PLA was evident by the presence of the characteristic peaks. Antimicrobial activity was confirmed via agar diffusion assays, showing evidence of antimicrobial activity against the tested bacteria. These findings suggest that PLA scaffolds could serve as a biologically safe system for further use in regenerative endodontics.

Keywords: Electro spinning, poly lactic acid, nanofiber, pulp regeneration, scaffold

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1. Introduction

Nanotechnology as a field of science focuses on understanding and manipulating materials at extremely small scales, ranging from 0.1 to 100 nanometers. It holds great promise for revolutionizing various sectors, contributing to advancements in both scientific knowledge and economic progress. Nanofibers, a relatively recent class of nanomaterials, offer solution to many of these challenges. Due to their unique size-dependent properties, nanofibers have garnered significant interest in the academic world over the past few decades [1]. The quality of nanofibers is determined by various factors such as diameter, shape and surface texture. These characteristics influence their performance in specific applications. For instance, a nanofiber diameter and shape, whatever hollow or core shell, provide flexibility in designing fibers for tailored properties this allow for optimizing nanofiber attributes for different uses by adjusting their structural features [2]. Nanofibers can be produced using a variety of fabrication techniques, which are categorized under distinct approaches such as top-down and bottom-up methods, as well as physical, chemical, and biological processes.

These methods are further divided into spinning and non-spinning techniques, each offering unique advantages for

creating nanofibers scaffolds with specific properties [3-4] Electro spinning is a technique to create nanofibers scaffold in pulp tissue engineering. Using this technique can result in the efficient fabrication of scaffolds with nanofibers. Characteristics of the fabricated scaffolds including surface area and aspect ratio of the scaffolds can be controlled through the change in the electro spinning parameter directly. Furthermore, the fibers' diameter can be controlled altogether the possibility of modification of scaffolds' final form with a considerable degree of flexibility [5]. Synthetic polymers such as polylactic acid (PLA), polyglycolic acid (PGA), poly-l-lactic acid (PLLA), and polylactic-glycolic acid (PLGA) have been effectively used as scaffold materials in pulp tissue engineering. These are non-toxic, biodegradable, and allow precise control over their physicochemical properties, including mechanical stiffness, degradation rate, porosity, and microstructure [6-7]. PLA was selected as supporting material because it is biodegradable, biocompatible, and can support proliferation and attachment of various cells.

The high porosity and large surface area of the nanofiber mat is expected to increase the interaction between with drugs and tissue and also modulate the cellular function to promote regeneration. Nano-fibrous scaffolds (closely resembling the native extracellular matrix) have been fully manufactured by various techniques, including electro spinning. Scaffold synthesis's common target has been the capability of boosting cell guidance through the meticulous design and maneuver of a multitude of biochemical and physical signals competent of governing and arousing specific events at the cellular and tissue levels. [8]. Hence, enhancing cell attachment, spatial organization, cell attraction, and allowing their use as effective drug delivery systems inside the root canals. This has benefit of controlling rate of drug release and delivered concentrations to favor outcomes of the treatments performed. [9-10]. In this study, we deal with fabrication and characterization of PLA nanofibrous electrospun scaffolds, using different solvents and voltage conditions. The aim is to optimize the ideal fabrication parameters for PLA nanofiber scaffolds to improve structural support during pulp regeneration process.

2. Materials and Methods

2.1. Materials

Polylactic acid (PLA, L207S) was purchased from Evonik, Germany. PBS (pH=7.4: Disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride and sodium chloride, were purchased from El-Nasr Chemical Co., Cairo, Egypt). Chloroform was purchased from Sigma-Aldrich, Steinheim, Germany. All other chemicals and solvents were of excellent grade and utilized as purchased.

2.2. Fabrication of PLA nanofibers scaffold

Firstly, PLA (10 % w/v) was dissolved in a mixture of different solvents at constant ratio (70:30 v/v); using magnetic stirring for 30 min at 700 rpm at room temperature, in a closed vessel till a homogenous system obtained. The obtained solution was then subjected to electrospinning [7-12]. The electrospinning was performed using NANON-01A Electrospinner (MECC Co., LTD., Japan). Different potential voltage differential was used, ranged from 16 kV to 20 kV, and the needle-collector was constant held at 80 cm. A syringe pump supplied rates of 0.5 mL / h. Every experiment was carried out at 25°C ± 0.2 temperatures and (36 – 42 %) relative humidity. The fibers were collected on an aluminum-foil-covered rotating mandrel. After that, the electrospun scaffolds were dried in a desiccator for 48 h under vacuum to remove any remaining solvent and stored at 4°C [13].

2.3. Characterization of PLA nanofibers scaffold

2.3.1. Scanning electron microscopy (SEM)

The average fiber diameter and fiber distribution were determined by SEM imaging. The morphology of the prepared electro spun was detected using SEM [14]. Sample preparation for SEM imaging included: samples fixation on aluminum foil, followed by gold coating for 45s under argon atmosphere using a coating system (MED020, Bal-Tech, USA). The measurements were performed using an acceleration voltage of 20 kV and a working distance of 10 mm [15-16].

2.3.2. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectrophotometer (Thermo Nicolet AVATAR 330, Madison, WI, USA) was used to analyze prepared PLA electro spun nanofibers [15-17]. The instrument was outfitted with a single reflection detector (Jasco ATR PRO470-H). The measurements were recorded in absorbance mode, and a background was obtained before each measurement. At room temperature, 100 scans were acquired for each spectrum between 400 and 4000 cm^{-1}, at a resolution of 4 cm^{-1}. For data acquisition, the Spectra Manager-II software (Jasco, Easton, MD, USA) was utilized [17].

2.3.3. X-ray Diffraction Calorimetry (XRD)

XRD (Shimadzu XRD-6000 diffractometer, Japan) was performed to examine the crystallinity of the prepared electrospun PLA nanofibers. The XRD was run at 40 kV and 40 mA utilizing Cu-K radiation in the range of (2Θ) 5°- 60° with a scanning rate of 0.05°/s at ambient temperature. The area integration approach was used to determine the crystallinity level [18].

2.3.4. Degradation test

In an attempt to predict the degradation time of the prepared nanofibers in-vivo, this test was carried out. Strips of the prepared PLA nanofibers (2 × 2 cm) were placed in a closed containers filled with 20 mL of PBS (pH=7.4). Samples were then transferred to the mini-incubator (Mini ICT 5.4, Falc Instruments, Italy) and kept at 37°C ± 0.5° C (pH = 7.4), for 4 weeks. Samples were then removed from the incubator and left for drying in a desiccator at room temperature, for one week. At the end of the experiment, dried materials were analyzed by SEM [17].

2.3.5. Agar Diffusion Test

Aliquots from the prepared PLA nanofiber scaffolds buffering solutions were prepared. Rectangular-shaped scaffolds (group (n=3), 4.0 ± 0.2 mg) were cut and disinfected by UV light (1 min each side) and rinsed twice with sterile PBS. *Enterococcus faecalis* (*Ef*) (ATCC 29212) was cultured aerobically in tryptic soy broth for 24 h in 5% CO2 at 37°C. Meanwhile, *Porphyromonas gingivalis* (*Pg*) (ATCC 33277) was cultured for 24h anaerobically in brain heart infusion broth; containing 5 g/L yeast extract ultrafiltered in an anaerobic Gaspak Jar [11]. Then, 100µL of each bacterial suspension was swabbed onto brain heart infusion agar plates (Oxoid, USA) to create a lawn of bacteria. Each Agar plate

was divided into zones containing a plain PLA nanofiber scaffold. Plates were incubated following the bacterial strain they carry (aerobic or anaerobic). After 24h of incubation, the diameters (in mm) of the clear zones of growth inhibition were recorded [19].

3. Results and discussion

3.1. Development of PLA nanofibers scaffold

Electro spinning is a unique technique using electrostatic forces to yield fine fibers from polymer solution; the produced fibers were thinner diameter and large surface area compared with other spinning techniques [20]. In our efforts to develop PLA nanofibers scaffold through electro spinning technique, we used different solvents and voltage conditions. To detect which of the produced nanofiber was suitable or not; we used SEM technique as a tool to determine it. All of that was done in order to optimize the ideal fabrication parameters for PLA nanofiber scaffolds to improve structural support during pulp regeneration process. Firstly, we began by preparing a PLA solution using a solvent blend of chloroform and dimethylformamide (DMF) at 70:30 (v/v) ratio. Unfortunately, initial results were disappointing; the electro spinning process did not produce any nanofibers and instead formed cracks on collection surface (Figure 1A). This indicated that selected solvent system was ineffective for fiber formation. Further analysis revealed that boiling points of solvents significantly affected the electro spinning results. Chloroform and acetone have relatively low boiling points of 61.7 °C and 56.08 °C, respectively, which allows for rapid solvent evaporation during process. In contrast, DMF has a much higher boiling point of 153 °C, which hinders proper solvent evaporation and creates unfavorable conditions for fiber formation [21–23].

To resolve this issue, we adjusted our solvent system by dissolving PLA in a mixture of chloroform and acetone, maintaining same 70:30 (v/v) ratio. Under identical electro spinning conditions, this new formulation successfully produced nanofibers (Figure 1B). The efficient evaporation of solvents facilitated formation of fine PLA nanofibers, demonstrating the critical role of solvent selection in electro spinning [24]. After achieving successful nanofiber formation, we further optimized electro spinning parameters by varying the applied voltage between 16 kV and 25 kV. At 16 kV, voltage was too low, resulting in formation of droplets rather than well-defined fibers. In contrast, at 25 kV, while nanofibers were produced, they were excessively thin (Figure 1C). This occurred due to an increased polymer discharge rate and drawing tension at higher voltages, which reduced fiber diameter and increased variability in fiber morphology, complicating process control [25]. Ultimately, we determined that an optimal voltage of 20 kV produced well-formed, uniform nanofibers. This voltage strikes a balance b/w an adequate electro spinning rate and manageable fiber diameter variability, enhancing both process control and fiber quality. The success of this optimization highlights importance of both solvent selection and electro spinning parameters in fabrication of PLA nanofibers (Figure 2).

3.2. SEM

SEM image of PLA nanofibrous scaffolds showed the presence of nanofibrous structures with relatively homogeneous sizes in the nano-submicron range. Nanofibers were well-defined and oriented randomly. Surface morphology was smooth and uniform. Moreover, no beads signs were observed on their surface as shown in (Figure 1B). Diameters of PLA nanofibrous scaffold were in the nano-range: 336 ±162.7 nm. This held benefit because the smaller diameter creates more surface area [26-27]. This was agreeable with Zeng et.al (2005) [28] and Can Suner et.al. (2022) [29]. In addition to that, effects of several parameters on morphology of PLA fibers have been reported by some scientists. Gu and Ren in 2005 found that diameter of PLA fibers increases with increasing polymer concentration and decreases with increasing applied voltage [30].

3.3. FTIR

According to the Olefin stretching vibrations following recorded: FTIR spectra of pure PLA nanofibers were shown in Figure 3, to verify chemical composition of the formulated nanofibers [14]. At 2922.95 cm^{-1}, most prevalent PLA bands observed due to asymmetric CH_2 stretching, while those observed at 2855.36 cm^{-1} appeared to be caused by symmetric CH_2 stretching. Furthermore, peaks at 1750 cm^{-1} and 1458.38 cm^{-1} were attributed to carbonyl stretching, while those at 1182.66 cm^{-1} and 1090.55 cm^{-1} attributed to C-O, C-C, and asymmetric C-O-C stretching [15-31]. Finally, FTIR spectra of nanofibers showed that PLA was evident by presence of characteristic peaks.

3.4. XRD

XRD pattern the prepared PLA nanofibers was shown in Figure 4. PLA showed intensity with a broad maximum appearing at 2Ɵ angle of 16°, emphasizing that the PLA lacked polymorphic crystalline transition.

3.5. Degradation test

During experimental period (one month); it was optically observed by SEM for any change in shape of prepared PLA nanofiber scaffolds. The neat PLA fibrous scaffold deteriorates with longer incubation time. Thin, well-formed PLA fibers that put together into a thick framework showed a nearly complete degradation as shown in Figure 5A &B. During experimental period it was optically observed for any change in shape of nanofiber frame for all formulations. From day 1 to 15, it observed that nanofiber mat structure begins to undergo deformation and partial deterioration. This could be related to cleavage of chemical bonds in nanofiber polymer chains due to reaction with water molecules. During this period, fibers initially absorb water, leading to swelling and presence of water promotes hydrolysis of ester bond, breaking polymer chain into smaller fragments. Moreover, after this period from day 15 to end of experiment, surface roughness may increase, and fibers may appear more fragmented or disintegrated under microscope, fragments may dissolve or leach out, resulting in mass loss and structural integrity reduction (Figure4), displays evolution of nanofibers diameter distribution in mats during degradation. Biodegradation of PLA takes place through a mechanism that is realized through several steps including both chemical and microbial processes. Plasma cells, lymphoid cells, eosinophils, macrophages, foreign body cells, mast cells, lymphocytes, histocytes, and fibroblasts involved in in vivo degradation of PLA. After implantation, the PLA-based scaffold's surrounding tissue layer shows a decrease. Through hydrolysis of ester-bond breakage, degradation of PLA within animal or human body takes place.

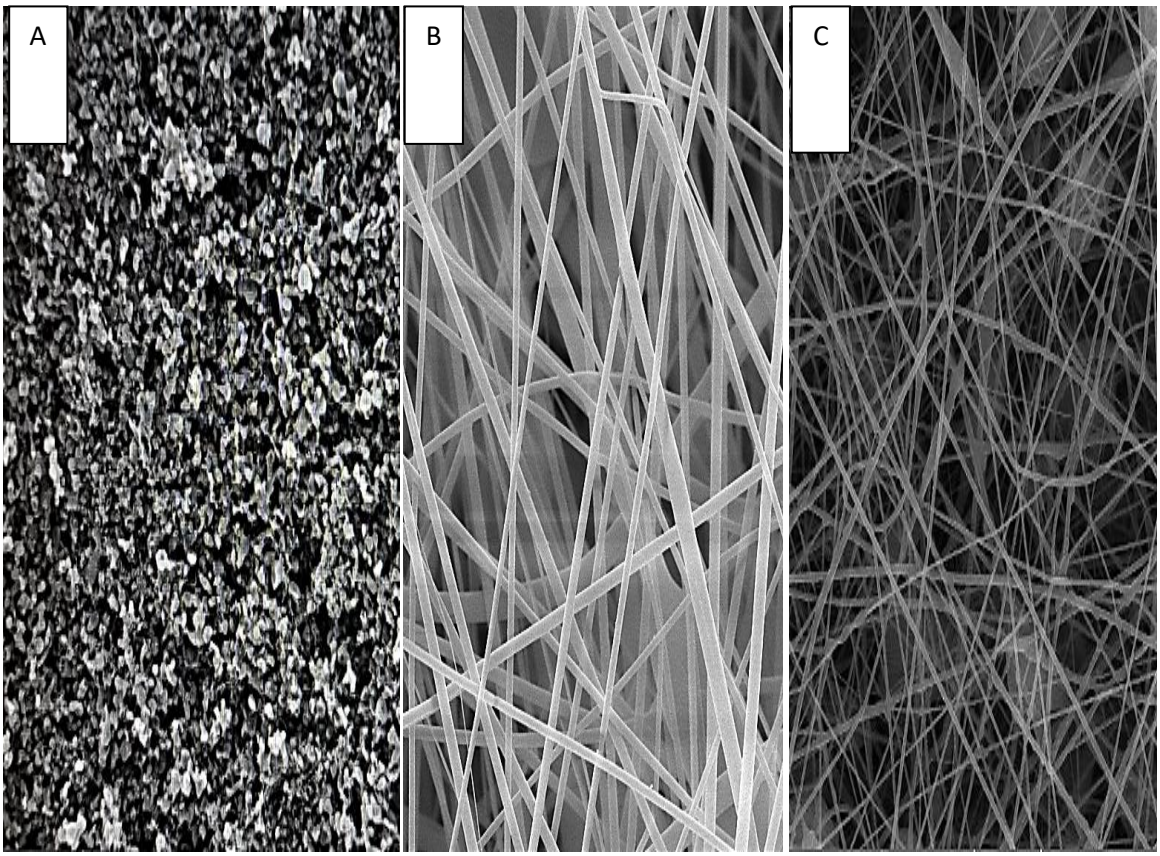

Figure 1: SEM images (A) free nanofiber using Chloroform: DMF (70:30 V/V) at 20 kV, (B) free nanofiber using Chloroform: Acetone (70:30 V/V) at 20 kV, (C) free nanofiber using Chloroform: Acetone (70:30 V/V) at 25 kV.

Figure 2: Fabricated PLA nanofiber scaffold.

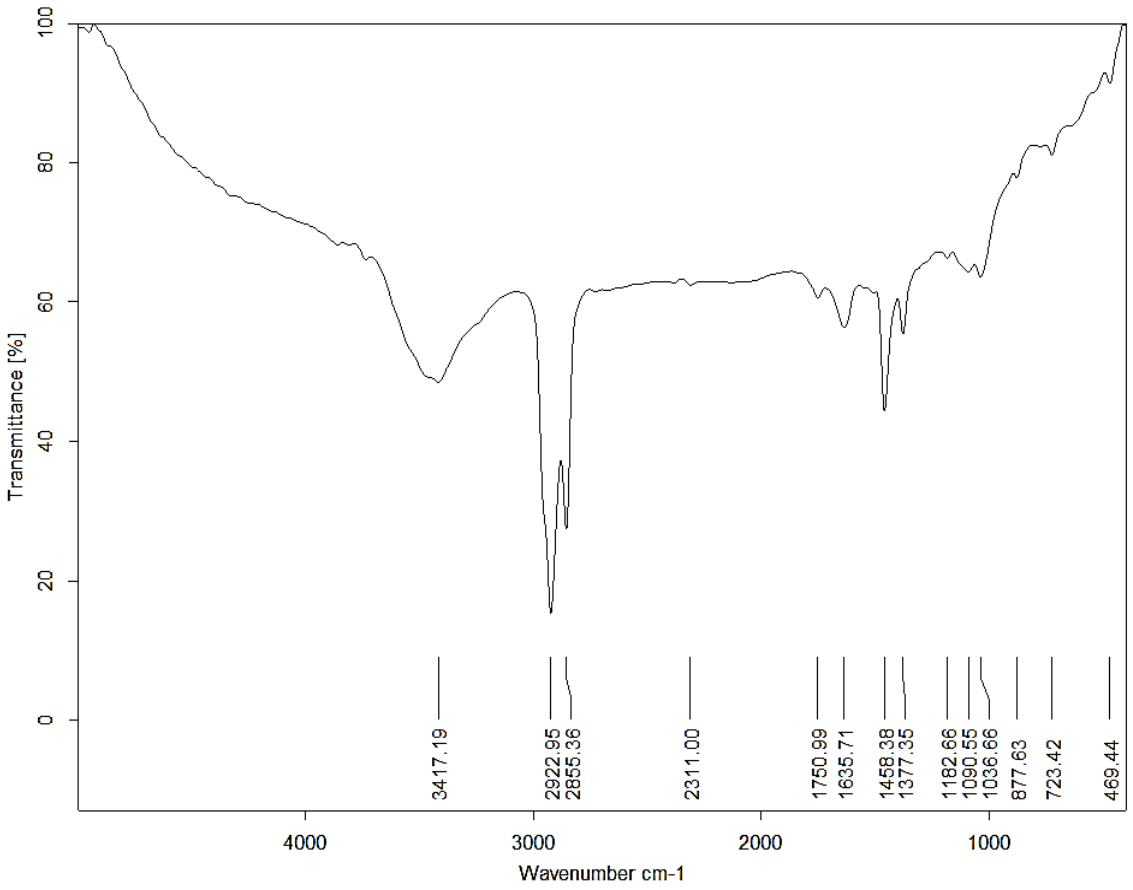

Figure 3: FTIR spectra of PLA nanofiber scaffold.

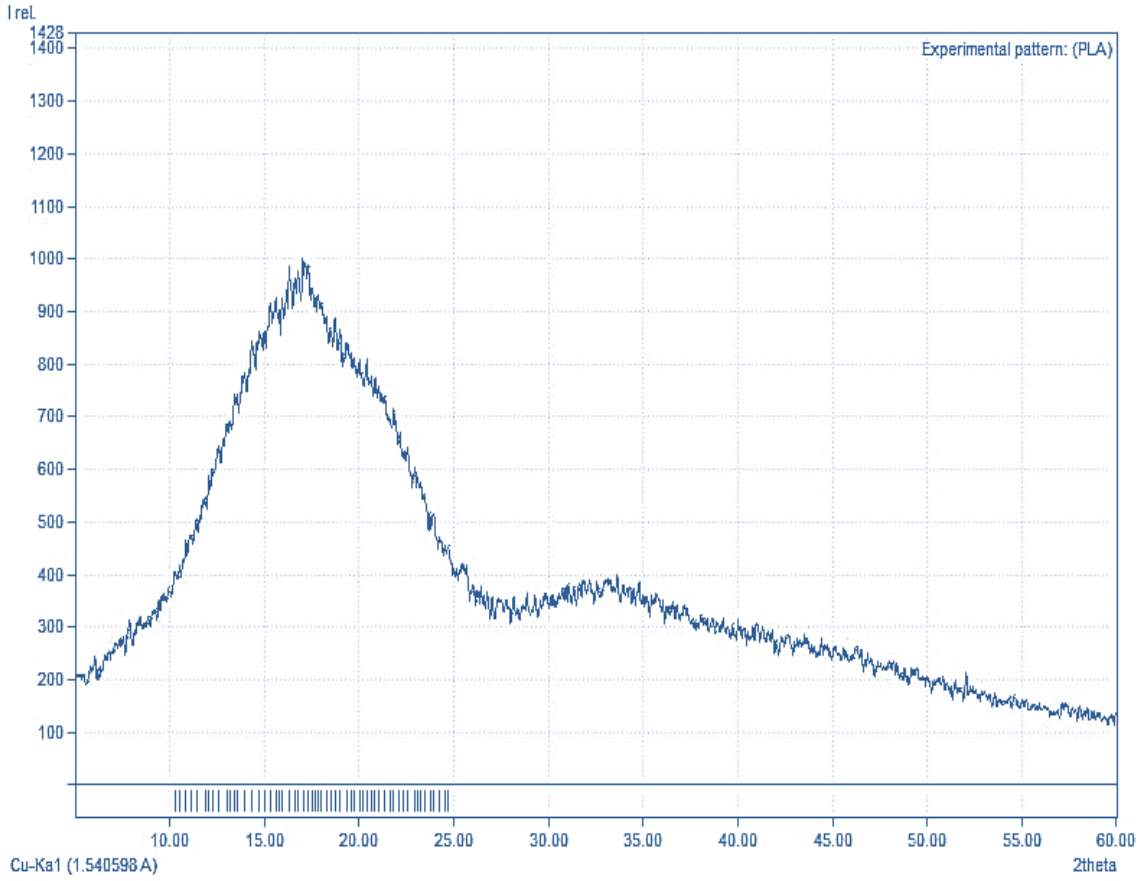

Figure 4: XRD patterns of PLA nanofibers scaffol

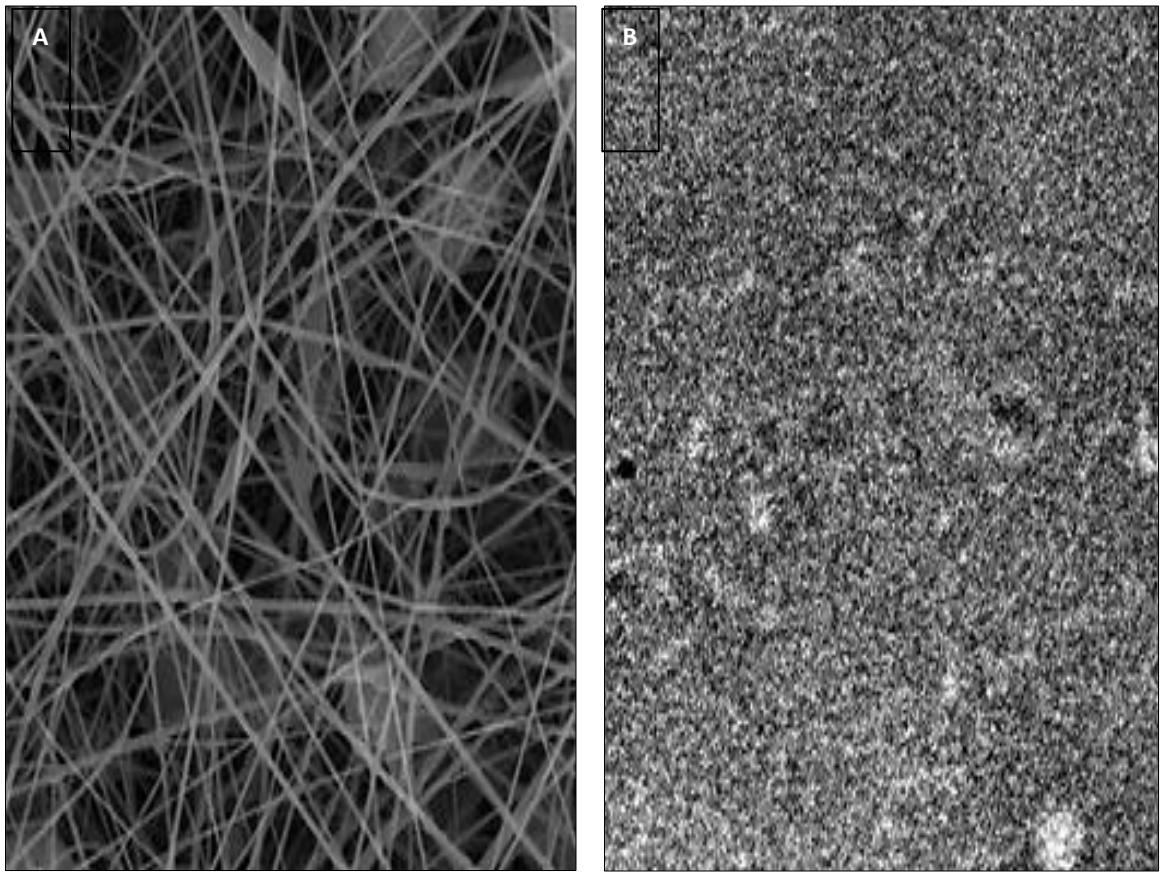

Figure 5: (A&B) showing the degradation pattern of nanofibers diameter in mats during the degradation process over the experimental period of neat PLA nanofibrous scaffold degradation pattern.

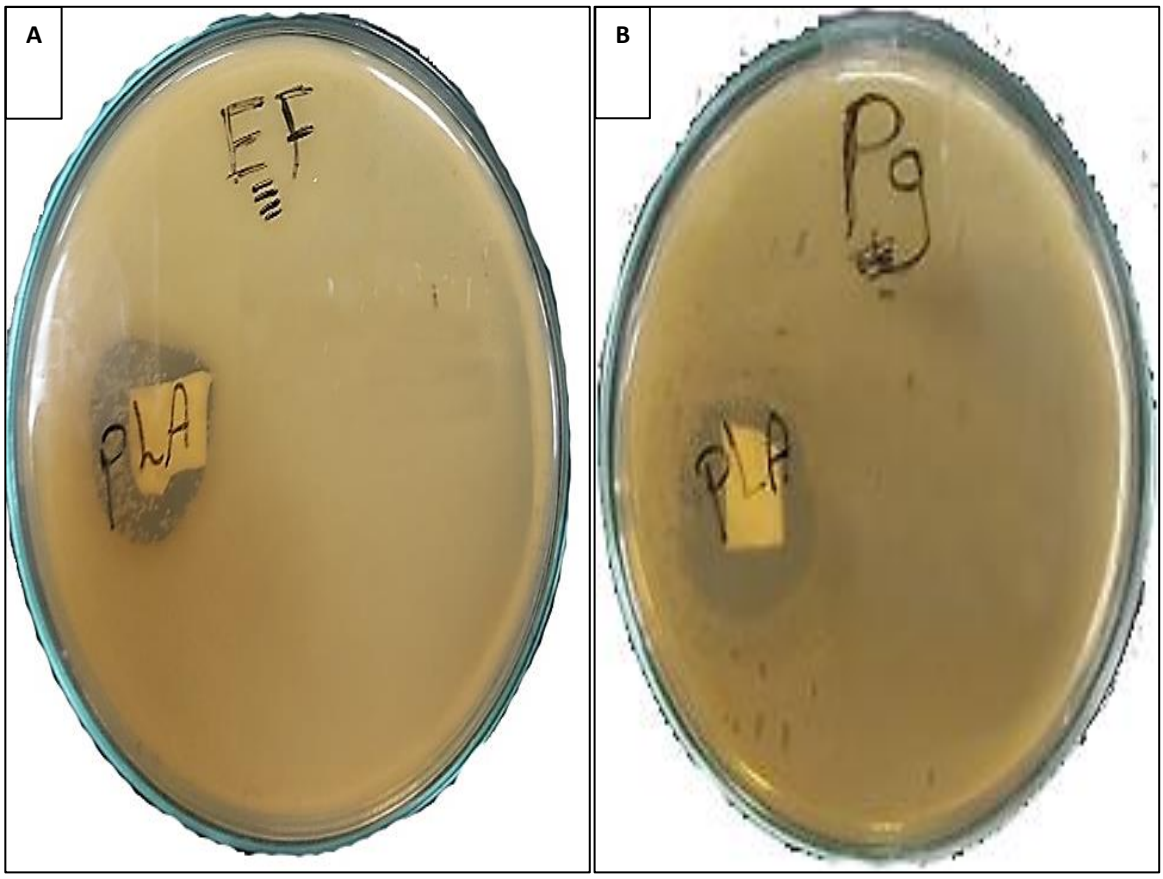

Figure 6: showing the inhibitions zones produced by different test scaffolds on both A: *E. faecalis* and, B: *P. gingivalis.*

At a late stage, degradation process may involve the tissue enzymes. Degradation process initiated due to segregation between central core and surface that consists of water absorption accompanied by molecular weight decrease and ester bond cleavage. Starting from thin surface of specimen, oligomers diffuse due to differentiation between inner core and surface of implant and allows solubilization in aqueous medium. Depending on non-reacted monomer, temperature, impurities and pH, degradation rates change. In addition to environmental factors, compounding PLA with other materials can affect its degradation. Li et al. [32] immersed PLA samples in Kirkland's bio corrosion media for 4 weeks to investigate degradation behavior of the PLA. Gradual decrease in pH observed for PLA. 1.15% mass loss in PLA sample recorded after 30 days immersion. Russias et al. [33] investigated mechanical behavior of PLA after immersion of PLA samples in salt and Hank's solution. The decrease in mechanical properties observed after immersion of PLA samples in vitro environment.

3.6. Agar Diffusion Test

In current study *E. faecalis* and *P. gingivalis* were chosen to test antimicrobial effect, due to their microbial role in root canal infection. PLA nanofibrous scaffold showed antimicrobial effect against both *E. faecalis* and *P. gingivalis.* That observed through inhibition zone for growth of both *E. faecalis* and *P. gingivalis* (Figure 6). Inhibition zones on *P. gingivalis* were smaller than those of *E. faecalis*, indicating higher antibacterial efficacy against *E. faecalis*. For PLA nanofiber scaffold this could be attributed to production of lactic acid during biodegradation, and/or possible presence of chloroform traces. Having an acidic by-product, PLA tends to have an antibacterial effect. Nevertheless, Chloroform reported to have a degree of antibacterial activity [34].

4. Conclusion

Electrospinning is a straight ward, flexible and cost-efficient technique that produce nanofibers with a high surface area to volume ratio. Adjusting electrospinning parameter is the important step that must be adjusted well to produce PLA nanofibers scaffold with an acceptable property; before using it is a tool to load any drugs for dental delivery. At 20 Kv and using a blend of chloroform and acetone (70:30) PLA nanofibers scaffold had thin diameter with biodegradable and antimicrobial properties. It can be concluded that the tested PLA nanofiber scaffolds show biocompatible traits. PLA nanofiber scaffolds have the potential to be used in the regenerative endodontics procedures as an enhancing skeleton when used as pure PLA scaffolds. Further researching this resulting scaffold for Drug Delivery and use in canines is eventually planned.

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