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Research Paper

Characterization of Coaxially Electrospun Poly (L-Lactic) Acid/Chitosan with Heparin Modification as Patch Angioplasty Candidate

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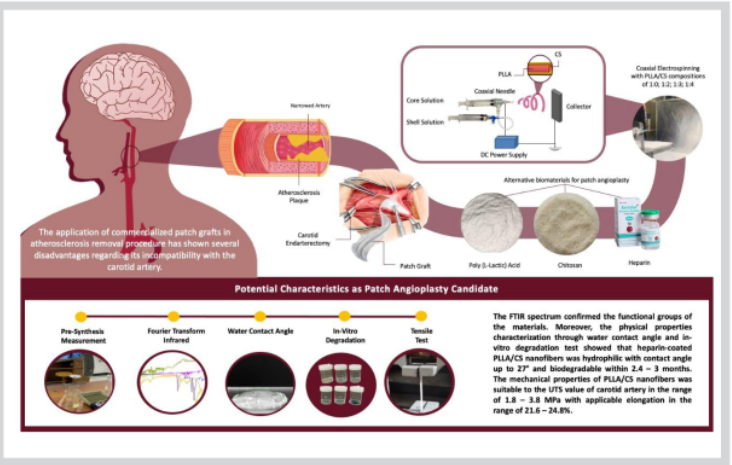
Highlights

- Nanofiber synthesis with coaxial electrospinning
- Nano-fiber crosslinking with genipin to increase mechanical properties
- Heparin coating in nanofibers to enhance hemocompatibility of the scaffold
- Suitable UTS value of PLLA/CS nanofiber with carotid artery
- Enhanced hydrophilicity and biodegradability of PLLA/CS nanofiber with heparin modification
- Nanofibers with heparin coating owed the highest cell viability

Graphical abstract



Abstract

Atherosclerosis in the carotid artery is the leading cause of ischemic stroke. Carotid Endarterectomy (CEA) is a procedure of atherosclerosis plaque removal to prevent stenosis, which significantly reduces the risk of transient ischemic attack. Currently, the application of commercialized patch grafts in CEA has shown several disadvantages regarding its incompatibility with the carotid artery. Poly (L-Lactic) Acid (PLLA)/Chitosan (CS) electrospun fibers with heparin modification were fabricated as biocompatible patch graft through coaxial electrospinning with composition variations of 1:0; 1:2; 1:3; 1:4. Pre-synthesis measurement of viscosity and surface tension was conducted to optimize the electrospinnability of PLLA 10% and CS 3% (w/v). FTIR results confirmed the existence of each material's functional group. Physical and mechanical properties were enhanced along with the increased PLLA/CS ratio. The hydrophilicity was optimized by the 1:4 electrospun fibers, which reduced the contact angle to 27°. The 1:4 electrospun fibers also resulted in a suitable degradation rate within 72 days and desirable tensile strength at 3.864 with 24.8% elongation. According to the results, Poly (L-Lactic) Acid/Chitosan electrospun fibers have a promising potential as a patch angioplasty candidate.

1. Introduction

High intake of low-density lipoprotein cholesterol (LDL) is the underlying cause of arterial blockage that leads to atherosclerosis or cardiovascular diseases (CVD) such as heart attack and stroke [1]. According to the World Health Organization (WHO) report in 2018 [2], around 85% of 17.9 million total deaths were caused by heart attack and stroke, whereas 85% of strokes happen because of the ischemic on a carotid artery [3]. In order to prevent the risk of ischemic stroke, atherosclerosis plaque removal is commonly performed through Carotid Endarterectomy Procedure (CEA). The implementation of patch graft in patch angioplasty for arteriotomy closure has shown more advantageous clinical results, including an increase in vessel diameter that could prevent reocclusion [4]. However, the biocompatibility of commercialized patch graft materials (i.e. Dacron and PTFE) is insufficient. Several infections, thrombosis, aneurysms, and venous disorders have been reported after CEA, which were caused by the discrepancy between patch graft and carotid artery characteristics [5]. Therefore, an approach to develop an ideal patch graft is required to overcome these drawbacks.

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An ideal patch graft should possess adequate mechanical properties and biocompatible and hemocompatible features to provide cell attachment and revascularization [6]. Considering the impressive mechanical traits, biodegradable synthetic polymers such as Poly (Lactic Acid) (PLA), its isomer Poly (L-Lactic Acid) (PLLA), and other copolymer appear to correspond as a scaffold for vascular tissue engineering. Nevertheless, their lack of hydrophilicity will cause a deficiency in blood compatibility [7]. Combination with a natural polysaccharide such as Chitosan (CS) would lead to the desirable characteristic related to its high cellular affinity and superior hydrophilic nature. However, the polycationic structure of CS can cause unwanted interaction with platelets that triggers blood coagulation [8]. Heparin is known as a polyanionic natural polysaccharide with a remarkable anticoagulation profile. Heparin is widely used in various clinical applications and medical devices to prevent thrombosis [9]. An earlier study showed a successful attempt to incorporate PLLA/CS with heparin for vascular gasket [10].

Hence, these materials were chosen to optimize the characteristics of electrospun fibers for patch angioplasty in the present study. PLLA/CS was fabricated with various compositions through coaxial electrospinning to obtain an electrospun fiber with a similar structure to the extracellular matrix (ECM) [11]. Heparin modification was carried out after genipin crosslinking to enhance its attachment and mechanical properties of the electrospun fibers. Genipin is known as a non-toxic natural cross-linker that is highly biocompatible compared to glutaraldehyde [12]. The chemical structure and tensile strength were studied to determine the impact of PLLA/CS composition on electrospun fiber characteristics.

2. Materials and Methods

2.1 Materials

Poly-L-lactic acid (PLLA) (Mn = 100,000-125,000 Da) was purchased from PolySciTech Akina, Inc. Chitosan ~85% deacetylated (Mw = 200 kDa) was provided by Sigma Aldrich and *Genipin Powder* ≥ 98% (HPLC) was obtained from Tokyo Chemical Industry. Heparin inviolate from a bovine source (5000 IU/mg) was used for coating. *Reagent-grade acetic acid* (CH_3COOH) (SAP Chemical), *chloroform* analysis (Merck), and ethanol 96% were used as a solvent. Aquades, *Phosphate Buffer Saline* (PBS) pH 7.4, human blood sample, cryoprecipitate from human plasma, and BHK-21 cells were also used as supporting materials for in-vitro study and characterization.

2.2 Preparation of Electrospinning Solution

PLLA powder was dissolved in chloroform to attain 10% PLLA (w/v), while 3% CS (w/v) was acquired with dilution in 70% acetic acid. Each solution was stirred at 500 rpm for 6 hours a room temperature to ensure homogeneity. The solutions were then prepared to measure viscosity and surface tension before the electrospinning process to ensure the formation of the electrospun fibers.

2.3 Viscosity and Surface Tension Measurement

The value of viscosity and surface tension was used as a parameter to determine the electropinnability of the solutions. Viscotester VT-04F Rion Co. Ltd was used to measure the viscosity in dPa.s of 50 ml of PLLA 10% (w/v) and CS 3% (w/v) solution, respectively. While the surface tension was measured in N/m with the same solutions using the Wilhelmy Plate Method and calculated using the Wilhelmy equation.

$$\gamma = \frac{F}{2(p+t)} \quad (1)$$

2.4 Synthesis of PLLA/CS using Coaxial Electrospinning

Coaxial electrospinning was used to fabricate fibers with a core-shell configuration comprising PLLA 10% (w/v) as the core solution and CS 3% (w/v) as the shell solution. The PLLA and chitosan solutions were pumped into the syringe pumps (10 ml) separately according to the composition variations of PLLA: Chitosan, which is 1:0 (K0); 1:2 (K1); 1:3 (K2); 1:4 (K3). The coaxial needle in this process was obtained handmade according to the scheme [13]. The coaxial electrospinning process was performed for 4 hours within a control on the process indicators including the input voltage between 10-15kV from the DC power supply, the spinning speed for both solutions within 5ml/hour, 12 cm distance of the collector and needle with a relative humidity of 40% at 25°C [10,14,15]. A collector plate covered with aluminum foil was used to collect core-shell electrospun fibers. Then it was dried for 15 minutes in an oven and stored at room temperature.

2.5 Genipin Cross-linking and Heparin Modification

The cross-linking process of PLLA/CS electrospun fibers was carried out by immersing electrospun fibers (1x1 cm) in a genipin 0.5% (w/v) solution for 24 hours. Genipin solution was prepared by dissolving genipin in ethanol 96%. Successful cross-linking was indicated by the presence of blue pigment caused by the polymerization reaction with oxygen. The electrospun fibers were then immersed in a heparin solution for coating within 15 minutes. After that, it was rinsed with deionized water to cleanse the impurities, then dried at 45°C for 24 hours.

2.6 Characterization

2.6.1 Fourier-Transform Infrared Spectroscopy (FTIR)

The FTIR was conducted using *Fourier-transform infrared spectroscopy* (FTIR) from Bruker® Tensor™ 27, Germany to identify functional groups and chemical reactions on electrospun fibers, based on the absorption of infrared radiation within a wavelength range in 4000–400 cm^{-1}.

2.6.2 Water Contact Angle Assay

The hydrophilicity of electrospun fibers was examined by measuring the angle (θ) between the drops of water with the material surface on a horizontal plane. The water contact angle test was carried out by dripping 20 µL of equates into the surface of electrospun fibers on a microscope slide. The contact angle was measured and analyzed using a drop analysis essay on ImageJ software in a particular area within 5s.

2.6.3 In-Vitro Degradation Test

The degradation test was used to analyze the degradation ability of the electrospun fibers (1x1cm) through immersion in a Phosphate Buffer Saline (PBS) solution for 7, 14, and 21 days. First of all, the initial weight of the electrospun fibers (Wo) was measured. Then it was put into 10 mL of PBS solution at 37 °C. After that, the electrospun fibers were dried and the final weight was measured as (Wt).

$$\Delta W = \frac{(W_0 - W_t)}{W_0} \times 100 \quad (2)$$

2.6.4 Tensile Strength Test

Shimadzu AGS-X was used for the tensile test with 25.9°C temperature and 61% humidity. The tensile test was done using a dog bone-shaped sample gained by cutting a large sheet of electrospun fibers into 15x150x0.1 mm for each variation ($n=3$), corresponding with the standard for the tensile test specimen. The load cell used in this test was 5 kN with a 5 mm/min clamping speed.

2.6.5 MTT Assay

The viability and proliferation of the cells were determined to analyze the cytotoxicity of the electrospun fibers through MTT Assay. The sterilized electrospun fibers were put into a 96-micro-well plate and then the cultured BHK-21 cells were added to the plate. The plate was incubated for 4 hours at 37°C. After the removal of the electrospun fibers, the optical density was measured to calculate the percentage of cell viability.

3. Results and Discussion

Failure of revascularization and carotid restenosis are the major problems of commercial patch grafts (i.e. Dacron and PTFE) application in CEA procedure. Therefore, composite electrospun fibers were developed from PLLA, chitosan, and heparin to get an ideal patch angioplasty candidate. Superior mechanical characteristics and biodegradable properties of PLLA were combined with the hydrophilic properties and high cellular affinity of chitosan [8,16]. Meanwhile, heparin was used to coat the electrospun fibers due to its anticoagulant properties to improve the hemocompatibility of the materials that were intended for vascular tissue engineering [9].

3.1 Coaxial Electrospinning of PLLA/CS Electrospun Fibers

Coaxial electrospinning was utilized to synthesize electrospun fibers with a core-shell structure from materials with different functional properties for particular applications [17]. In this study, coaxial electrospinning was chosen to overcome the difficulty of solution blending due to the differences in hydrophilicity between PLLA and chitosan. Conventional electrospinning of this mixture would hinder the formation of electrospun fiber and cause a peculiar structure and morphology compared to the coaxial spun fibers.

PLLA solution was used as a core solution due to its remarkable mechanical properties, while chitosan was used as a shell solution to increase the biocompatibility of the electrospun fibers [10]. Before the electrospinning, surface tension and viscosity measurements were performed to optimize the solution parameters. PLLA 10% and CS 3% (w/v) fulfilled the desirable criteria as electrospinnable solutions according to the viscosity and surface tension value that is shown in Fig. 1.

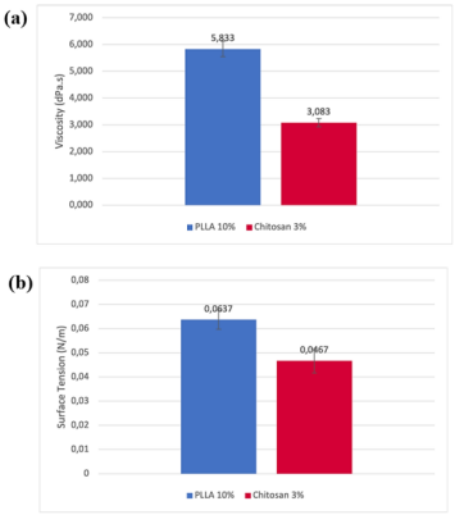

Fig. 1. (a) Viscosity and (b) Surface tension of PLLA 10% and CS 3% (w/v)

The ideal viscosity for an electrospinning solution is 1-20 dPa.s and the ideal surface tension value is between 0.033-0.055 N/m [18]. The viscosity of PLLA 10% and CS 3% (w/v) is 5.833 dPa.s and 3.083 dPa.s, respectively. Additionally, the solutions for coaxial electrospinning need to have a viscosity ratio (ηcore/ηshell) in the range of 1.22–2.82 [19]. The viscosity ratio of both solutions was 1.89, which corresponds to the ideal range. The surface tension of chitosan 3% (w/v) was 0.04467 N/m while the PLLA 10% (w/v) was 0.0637 N/m, which is slightly higher than the ideal value. Strong intermolecular force could increase the solubility, while temperature drops can cause an increase in surface tension. The solutions with higher surface tension were less electrospinnable but soluble by increasing the input voltage [20].

3.2 Genipin Cross-linking and Heparin Modification

The electrospun fibers from coaxial electrospinning were cross-linked with genipin to increase molecular bonds and enhance the mechanical characteristics of the fibers. Based on Fig. 2 (a), the blue pigment in the electrospun fibers indicated that genipin cross-linking was successful. The blue pigment was formed through the polymerization reaction of genipin with oxygen and primary amine groups from electrospun fibers [21]. The electrospun fibers were then coated with heparin, as seen in Fig. 2 (b).

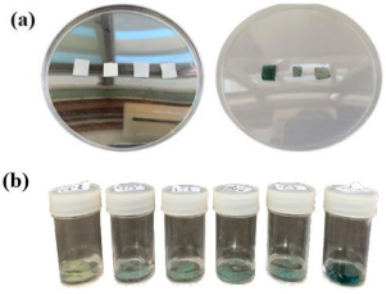

Fig. 2. (a) Cross-linked PLLA/CS electrospun fibers (b) PLLA/CS Electrospun fibers with heparin coating

3.3 Fourier Transform Infrared Spectroscopy (FTIR) Spectrum

According to Fig. 3, the FTIR spectrum showed the vibrations of ester, amide, and sulfate in the electrospun fibers that correspond to the functional groups characteristic of PLLA, Chitosan, and Heparin [8, 14]. These results indicated that the crosslinking and coating process of the electrospun fibers was successful.

The spectrum showed C=O functional group with a wavelength of 1751.3 cm^{-1} in K0 electrospun fibers. Meanwhile, in K1 and K2 electrospun fibers, the C=O functional group was shifted to 1688.75 cm^{-1}, while C=O functional group for K3 shifted to 2349.4 cm^{-1} as a result of the cross-linking process with genipin [12]. The addition of PLLA/CS compositions affected a shifting of amine (NH_2) group vibration in 3400-3250 cm^{-1} to amide (NH) group from 1569.16 cm^{-1} to 1561.4 cm^{-1} for K1, K2, and K3 electrospun fibers, which also indicates the occurrence of the cross-linking process [12]. Moreover, the vibration of the S=O group in the range 1343.48-1017.4 cm^{-1} from heparin on K1, K2, and K3 electrospun fibers indicates that heparin coating was successful [8].

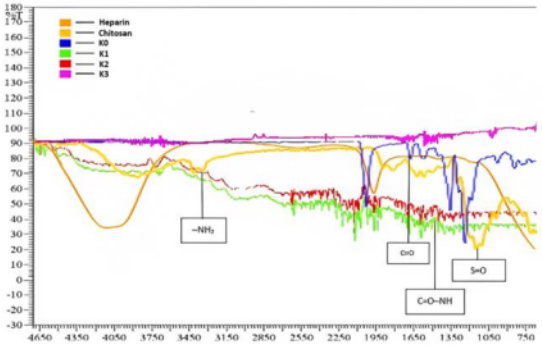

Fig. 3. *FTIR* spectrum of (a) K0, (b) K1, (c) K2, (d) K3

3.4 Hydrophilicity and Degradation Rate

Measurement of the water contact angle provides an overview of the hydrophilicity of PLLA/CS electrospun fibers. The hydrophilicity of the material will affect cell adhesion and protein adsorption which is closely related to the hemocompatibility properties of the materials [22]. The contact angle is influenced by the chemical structure and surface morphology of the materials [23]. The contact angle of K0 electrospun fibers was measured as 121.562° due to its hydrophobic chemical structure. An increase in PLLA/CS compositions was reduced the contact angle to less than 90°, which considered as hydrophilic [24]. The contact angle value for K1, K2, and K3 were 47.958°, 31.263°, and 27.363°, respectively. Therefore, electrospun fibers K3 were the most hydrophilic. The existence of hydrophilic groups such as hydroxyl, amine, carbonyl, and sulfate in chitosan and heparin on the fibers surface affected the contact angle reduction [25]. The relationship between the effects of variations in the composition of PLLA/CS is shown in Fig. 4.

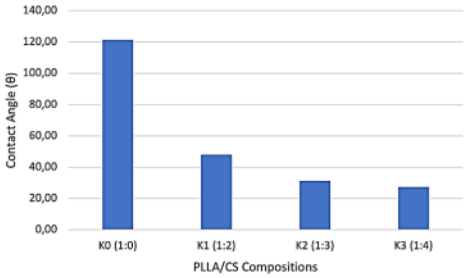

Fig. 4. Impact of PLLA/CS composition and heparin modifications in the hydrophilicity of electrospun fibers

The degradation rate of PLLA/CS electrospun fibers with heparin modification was determined through an in-vitro degradation test. Based on Fig. 5 (a), Electrospun fibers K0 has the lowest weight reduction percentage, while K3 is the highest. Weight reduction percentages for electrospun fibers K3 for days 7, 14, and 21 were 12.69%, 22.34%, dan 26.97%. Hence, the increase in PLLA/CS ratio aligns with the weight reduction. According to the weight reduction extrapolation, the estimated degradation time was increased along with the increasing composition of PLLA/CS. Fig. 5 (b) shows that the estimated degradation time of the electrospun fibers was 72 days in Electrospun fibers K3. Longer degradation time was due to the combination with CS which is easily soluble in PBS, compared to PLLA which only undergoes hydrolytic degradation [26]. Referring to Krüger-Genge *et al.* [27], the vascularization of new capillaries in occluded vascular tissue lasts for 53-75 days. Unsuitable degradation time would induce hyperplasia neointimal and postoperative failure [9].

3.5 Mechanical Properties

The scaffold's ability to maintain the shape of the lumen under blood flow was determined by an Ultimate Tensile Strength (UTS) value [14], while elongation was used to analyze an estimation of the lumen dilation due to scaffold implantation [28]. Fig. 6 shows that the mechanical properties were enhanced as the composition of PLLA/CS increased.

The significant increase of the UTS in electrospun fibers K3 to 3.86 MPa was related to the cross-linking that strengthens the intermolecular bonds in the polymer chain [29]. Moreover, the hydrogen bonds were strengthened due to the combination of chitosan and heparin which resulted in the increment of elongation until 25.8% [30]. The UTS and elongation value corresponded to the Food and Drug Administration (FDA) standard for exposure vascular patches, which is 2 Mpa with an elongation of 5-50% [31]. The tensile strength was also around the carotid artery value in the range of 1.07 – 3.57 Mpa [32]. Meanwhile, the lowest UTS and elongation of electrospun fibers K0 within 1.33 MPa and 11.9% occurred due to the discontinuity of the structure of the electrospun fiber caused by the beads in electrospun fibers [26].

3.6 Cytotoxicity Test

MTT assay results in Fig. 7 showed that all variations of the electrospun fibers were non-toxic because they facilitated cell proliferation above the ISO 10993-5:2009 standard, which is more than 70% [33]. K3 electrospun fibers with heparin coating owed the highest cell viability, which was 94.13%. This indicates a positive correlation between the increase in chitosan composition and heparin modification, which affected the hydrophilicity that improves adhesion, migration, and cell proliferation [34].

4. Conclusion

PLLA/CS electrospun fibers with heparin modification showed prospective results as patch angioplasty candidates. FTIR characterization showed the presence of particular functional groups from the nanomaterials. Moreover, physical properties characterization through water contact angle and in-vitro degradation test showed that heparin-coated PLLA/CS electrospun fibers were hydrophilic with a contact angle up to 27° and biodegradable in the range of 2.4-3 months. The mechanical properties of PLLA/CS electrospun fibers were suitable to the UTS value of the carotid artery in the range of 1.8-3.8 MPa with an applicable elongation between 21.6-24.8%.

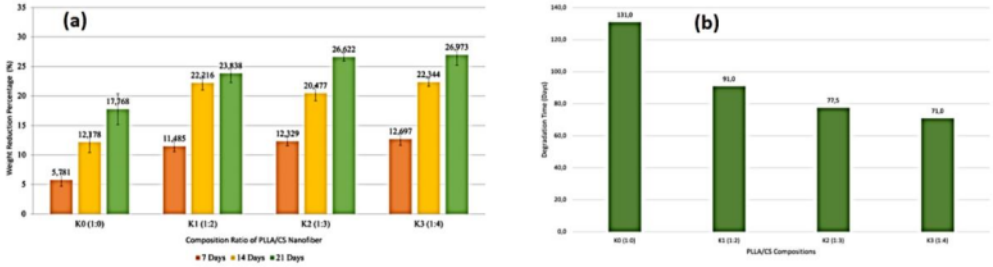

Fig. 5. (a) Weight reduction percentage of PLLA/CS electrospun fibers (b) Estimated degradation time of PLLA/CS electrospun fibers

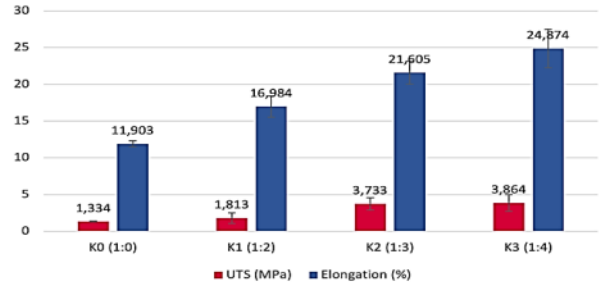

Fig. 6. PLLA/CS Electrospun fibers tensile strength test results

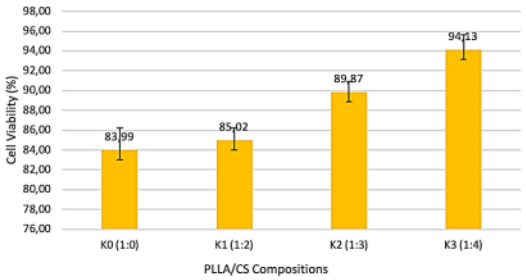

Fig. 7. Cell viability of PLLA/CS electrospun fibers

Credit authorship contribution statement

D. S. Salsabila: Conceptualization; Data curation; Roles/Writing – original draft; Formal analysis.
P. Widiyanti: Conceptualization; Investigation; Methodology; Format analysis; Validation.
E. Hernando: Validation; Visualization.
I.M. Hulu: Data curation.
T. D. P. Wibowo: Data curation.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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