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THE EFFECT OF POLYMER TYPE AND FIBER ORIENTATION ON THE COMPLIANCE PROPERTIES OF ELECTROSPUN VASCULAR GRAFTS

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ABSTRACT

Vascular diseases are a major source of fatalities globally. However, the lack of accessibility of autologous vessels and the poor efficacy of commercial small-diameter vascular grafts limit surgical alternatives. Researchers therefore aimed to develop vascular prostheses that meet all requirements. Apart from the benefits of tissue-engineered grafts, significant obstacles that still hinder successful grafting include compliance mismatch, dilatation, thrombus development, and the absence of elastin. Among these issues, compliance mismatch between native vessel and artificial vascular scaffold has been mentioned in the literature as a possible cause of intimal hyperplasia, suture site rupture and endothelial and platelet cell damage. As a result, the usage of suitable materials and optimized fabrication techniques are required to achieve better control over the characteristics and functionality of the grafts. In particular, in the case of electrospun vascular grafts, the compliance can be adjusted throughout a broad range of values by adjusting the electrospinning parameters such as material selection, fiber orientation, porosity, and wall thickness. In this study, the electrospun vascular grafts consisting of pure PCL, PLA, and their blends were produced by using two different rotation speeds to achieve the oriented and non-oriented scaffolds. The impact of polymer type and fiber orientation on the compliance properties was evaluated. The results revealed that both material selection and fiber alignment have a significant effect on the compliance levels. PCL100_R grafts had the highest compliance value whereas the PCLPLA50_O scaffold had the lowest.

KEYWORDS

Vascular grafts; Electrospinning; Compliance mismatch; Intimal hyperplasia.

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INTRODUCTION

Cardiovascular diseases, which account for 32% of all fatalities worldwide, will continue to be the leading global cause of disability and death, according to experts' predictions for the future [1, 2]. There is an urgent and significant need in clinics for tissue engineered small-diameter (<6 mm) blood vessel substitutes due to a lack of availability of autologous vessels and effective commercial products used for bypass surgeries, such as vascular prostheses made of polyethylene terephthalate (PET) or expanded polytetrafluoroethylene (ePTFE), which have low clinical efficacy and a high failure rate after implantation [3, 4].

Tissue engineering faces a great challenge when attempting to replicate the unique design and distinctive mechanical characteristics of the vascular wall in order to fulfill the functional needs of the native tissue [5]. There are several design criteria that affect the properties of vascular grafts, including material selection and constructional parameters including fiber diameters, pore sizes, fiber orientation, wall thickness, and etc. [6]. In tissue engineering applications, the selection of biomaterials has an important role in providing the basic structure for mechanical properties, cell interactions, biocompatibility, biodegradability, anti-toxicity, and cell growth [7]. While natural biodegradable polymers are very successful in biocompatibility and cell activities, synthetic polymers stand out with their properties such as high strength and controllable degradation rate. Each biopolymer has advantages as well as drawbacks that need to be addressed, and the necessity of combining two or more polymers has been raised as a solution [8]. Polycaprolactone (PCL), which has a highly flexible structure and a long biodegradation period to allow the scaffold enough time for the formation of neo-tissue, is highly demanded for tissue engineering applications [9]. On the other hand, polylactic acid (PLA) is a biomaterial that is usually favored due to its great biocompatibility and outstanding mechanical qualities. However, PCL has lower biocompatibility than PLA, and factors like the brittleness of PLA make the combination of these

two materials appealing [10]. Surface production methods and parameters are as important as the selection of biomaterials for the applicability of scaffolds. Electrospinning method is a frequently preferred surface fabrication technique for obtaining three-dimensional structures in different constructions by the modification of various collector systems because it is a simple mechanism to adjust the fiber diameter, pore size and wall thickness of the samples, to obtain fiber orientation, and to facilitate the use of many biopolymers [11]. Thus, all the production parameters should be determined clearly to manufacture the ideal vascular graft that has sufficient characteristics that contribute to the material's performance.

In literature, morphological and biological studies are typically given top priority, whereas mechanical aspects are typically just briefly discussed. To improve the clinical efficacy of vascular grafts exposed to physiological stresses and avoid graft failure due to intimal hyperplasia, thrombosis, aneurysm, blood leakage, and occlusion, sufficient mechanical characteristics that are equivalent to native vessels must be achieved for grafts [12]. The mechanical properties of the scaffold, such as suturability, compliance, tensile strength, burst pressure, and blood permeability, are significantly influenced by the material and architecture of the scaffold [13]. In particular, one of the main reasons for graft failure over extended periods of implantation is compliance mismatch between the native artery and the inelastic artificial graft at the anastomosis sites, which produces low blood flow rates and turbulent blood flow in small-diameter vascular prostheses [14]. The blood flow fluctuations in the vascular scaffold and the stress concentration at the anastomosis regions are caused by the incompatible dimension changes of the vascular prosthesis and the native blood vessel as a reaction to pressure variations inside the lumen, which is known as compliance mismatch [15]. Low patency rates are caused by these mechanical problems, which also contribute to the scaffold material's thrombogenicity, inadequate endothelialization, luminal constriction, and trombosis, which are triggered by intimal hyperplasia [14]. It is notably difficult to create vascular prostheses that are both elastic and strong enough to resist blood pressure because burst strength and compliance are frequently inversely proportional [16]. Numerous studies in the literature demonstrate that the compliance is determined by the material selection and construction characteristics, such as wall thickness, the number of layers, and the orientation of the fibers within the layers [17-19]. Johnson et al. (2015) produced vascular grafts from various polymers and wall thicknesses. The compliance values revealed that both the polymer type and wall thickness were effective on the compliance levels. An increase in wall thickness reduced the compliance values, whereas using flexible materials improved the results [17]. Li et al. (2017) designed composite vascular graft prototypes by integrating a flexible PLA knitted fabric as an inner layer with a soft PCL matrix as an outer layer. The compliance value of all the samples was found to be below 2%/100 mmHg [20]. Also, the measured compliance values of some of the native human blood vessels are given in Table 1.

Table 1. Compliance values of native human blood vessels.

Type of Blood Vessel	Compliance	References
Saphenous vein	1.5%/100 mmHg	[21]
Coronary artery	0.0725%/mmHg	[22]
Femoral artery	3.8–6.5%/100mmHg	[23]

In this study, both the radially-oriented and randomly-distributed electrospun fibrous vascular grafts that were made of neat PCL, PLA, and their blend with a weight ratio of 50:50 were fabricated to assess the impact of the polymer selection and the fiber orientation on the compliance properties.

EXPERIMENTAL STUDY

Materials

The neat or the blended form of PCL (Mn 80,000) and PLA (Mn 230,000; Ingeo 2003 D with 4.3 mol% D-lactide content) were dissolved in a solvent system consisting of chloroform (CH)/acetic acid (AA)/ethanol (ETH) with 8/1/1 wt. at a concentration of 8% w/w. All the polymers and the solvents were supplied from the Sigma Aldrich.

Methods

Surface fabrication

The prepared neat PCL, neat PLA and PCL/PLA (50:50) solutions were stirred for 4 hours with a magnetic stirrer and immediately electrospun by using electospinning system supplied from Inovenso, Turkey (Nanospinner, Ne100^{+}). The neat and blended polymer solutions were transferred by a 10 ml plastic syringe through a distance from the needle tip which was kept at 20 cm. The mandrel with a rotational speed of 200 rpm and 10000 rpm were used for the fabrication of tubular scaffolds with randomly distributed and radially oriented fibers, respectively. Tubular scaffolds have 6mm inner diameter and the spinning time for all samples was fixed at 40 minutes. The sample codes and details are given in Table 2.

Table 2. Samples codes and details.

Sample codes	Blending ratio of PCL/PLA (%)	Rotational speed of the collector (rpm)	Fiber orientation
PCL100_R	100/0	200	Randomly distributed
PCL100_O	100/0	10000	Radial orientation
PCLPLA50_R	50/50	200	Randomly distributed
PCLPLA50_O	50/50	10000	Radial orientation
PLA100_R	0/100	200	Randomly distributed
PLA100_O	0/100	10000	Radial orientation

Compliance

The custom-designed device used to test compliance provided air flow at a physiologically equivalent pressure. After the balloon was inserted through the samples, they were mounted by the sleeves to the nozzles and supplied with air from the system. The pulsatile intraluminal pressure was established at the diastolic and systolic pressures of 80 mmHg and 120 mmHg, respectively. The photos of the samples at these pressures were taken by a camera system, and the diameters at each pressure were measured by the Image J software system. After that, the compliance values were calculated by the formula below;

$$\%compliance = \frac{\frac{R_{p_2} - R_{p_1}}{R_{p_1}}}{p_2 - p_1} \times 10^4 \qquad (1)$$

R_{p1} = pressurized radii at diastolic pressure [mm]
R_{p2} = pressurized radii at systolic pressure [mm]
p1 = diastolic pressure [mmHg]
p2 = systolic pressure [mmHg]

RESULTS AND DISCUSSION

The compliance values of each sample group were given with their standard deviations in Table 3. It was clearly observed from the results that the radial fiber orientation reduced the compliance values of the scaffolds. This situation was expected as the oriented fibers are already under stress in that direction and they cannot be stretched as in the randomly oriented fibers [3]. Grasl et al. (2021) also manufactured electrospun vascular grafts made of polyurethane (PU) and PLLA with fiber orientations in different directions and measured the compliance values. It was observed that in PU samples, fiber orientation in any direction caused a reduction in compliance values, whereas PLLA showed similar compliance levels in any direction because of its stiff structure. For example, in PU scaffolds with radially oriented fibers, the compliance was 4.1 ± 0.4 mmHg %/100 mmHg whereas it was 29.7 ± 5.5 mmHg %/100 mmHg in the PU scaffolds with randomly distributed fibers. On the other hand, in PLLA samples the compliance was 1.3 ± 0.4 mmHg %/100 mmHg for the radial orientation whereas it was 1.4 ± 0.4 mmHg %/100 mmHg for the samples with no fiber orientation [24].

On the other hand, scaffolds made of PCL have the highest compliance values in all directions, whereas blended scaffolds showed the lowest compliance among all the samples. As the PCL is a flexible and pliable biopolymer with high strain values, higher compliance results were expected from the PCL100 scaffolds. In addition, PLA is a brittle and stiff material with lower elongation values, PLA100 showed lower compliance than PCL prostheses [25]. In the PCLPLA50 samples, the lowest compliance values were observed because of the mechanical failure caused by the immiscible characteristics of the polymer components. As the blending cannot be reached properly, the phase separation occurs because of the weak adhesion forces between the polymer chains in these scaffolds during the electrospinning process [26].

When the obtained compliance values were compared with the values of the native vessels, it was clear that compliance values of the samples of randomly distributed fibers were higher than those of the saphenous vein and coronary artery, with a compliance of 1.5%/100 mmHg and 0.0725%/mmHg, respectively [21,22]. Additionally, oriented samples also had higher compliance values than the coronary artery. Despite the fiber orientation lowers the compliance, it also known that it contributes to mechanical characteristics of the scaffolds such as tensile strength and burst pressure [27]. Thus, both of the structures can be utilized for different approaches in multilayer vascular graft strategies.

Table 3. Compliance values of the scaffolds at a pressure range of 80 -120 mmHg.

Sample codes	Compliance ± SD (%/100 mmHg)
PCL100_R	2,494 ± 0,791
PCL100_O	1,155 ± 0,553
PCLPLA50_R	1,542 ± 0,783
PCLPLA50_O	0,864 ± 0,350
PLA100_R	1,603 ± 1,326
PLA100_O	1,078 ± 0,353

CONCLUSIONS

In this study, PCL, PLA, and PCL/PLA blended samples were fabricated by using two rotational speeds to achieve scaffolds with randomly distributed and radially oriented fibers. The effect of the polymer type and the fiber orientation of the samples was confirmed by the compliance test results. It was seen that PCL100_R had the highest compliance value among all the samples, as it has much more elastomeric polymer and fibers without high tension. On the other hand, the PCLPLA50_O sample had the lowest compliance values because of the incompatibility of the polymer blending and stretched fibers by orientation. Although the samples with randomly oriented fibers had adequate compliance levels, combining the advantages of both structures by designing multilayered grafts should be considered to optimize the other mechanical and biological characteristics of these scaffolds.

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