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STUDY OF ELECTROSPUN FIBROUS SCAFFOLDS FOR VASCULAR GRAFTS

Summary

This paper focuses on the study of the mechanical, hydrophilic, and porous properties of vascular scaffolds obtained by electrospinning. Hybrid vascular scaffolds are made of a synthetic polymer, polycapralactone (PCL), and a natural polymer, type I collagen. The purpose of this work is to determine the effect of the collagen content and the concentration of PCL in solution on the mechanical properties of the vascular scaffolds. Using electrospinning technology, three different nanofibers were prepared with a base solution of PCL in chloroform solvent, at different concentrations (10%, 12% and 15%) and different amounts of collagen (2 ml, 3 ml and 5 ml). The resulting nanofibers were subjected to bench tensile tests and morphological structure analysis. The contact angle of the electrospun nanofibers was monitored. The porosity of the scaffolds was evaluated using the liquid penetration method. The results of the study show that the mechanical properties differ depending on the concentration of the solution and the amount of collagen in the solution.

Key words: *electrospinning, blood vessels, scaffolds, polycapralactone, mechanical properties*

1. Introduction

According to the World Health Organization, cardiovascular diseases (CVD) are the main cause of death in the world, with 17.9 million people dying from them every year [1]. Almost 85% of CVD-related deaths are caused by heart attack and stroke, and one-third of these deaths are in people under 70 years of age. Atherosclerosis is the main cause of CVD.

Due to the prevalence of cardiovascular disease, there is a great need for small diameter vascular grafts. Autologous vascular grafts are considered the gold standard for bypass and revascularisation surgeries. The great saphenous vein in the legs is used for this purpose. However, 20-40% of patients lack suitable vein grafts due to their disease, excessive diameter, and other reasons [2]. Therefore, an alternative to autologous vascular grafts is needed. Medium and large diameter synthetic blood vessels made of polyethylene terephthalate (Dacron) are used in medicine [3]. However, these synthetic grafts are not suitable for small-diameter vessels

(<6 mm in diameter) due to rapid occlusion and acute thrombogenicity. Due to the unique dynamic environment that exists in small vessels, suitable small diameter vascular grafts have not been developed. To achieve long-term patency, a successful vascular graft should closely match the mechanical properties of the local tissue, be non-thrombotic and non-immunogenic, and induce an appropriate healing response.

In recent years, regenerative medicine, tissue engineering, and new material development have become key areas of focus in this field, and electrospinning technology to prepare nanofibrous materials for cardiovascular disease treatment has attracted wide attention. Electrospinning is a promising approach to creating suitable vascular grafts.

Electrospinning is a method that allows the formation of continuous ultrafine membranes composed of polymer fibres. The process consists of applying a high voltage to induce evaporation of the solvent in the polymer solution, resulting in the formation of micro- and nanometre fibres on a metal surface called a collector [4]. In this technique, a high-potential electric field (about 10-30 kV) is applied between a metal syringe needle through which a polymer solution exits with a controlled flow and a metal grounded collector. Vascular tissue engineering typically uses a rotating collector to produce a tube-shaped graft. As the electrospinning current moves toward the collector, the nanofibers wrap around the perimeter of the rotating collector. A uniform fibre sheet can be produced by using different length-to-diameter ratios at different rotational speeds.

More than 40 synthetic and natural polymers are suitable for electrospinning and some have been successfully applied in vascular tissue engineering, one of which is polycaprolactone PCL [5, 6]. PCL is a biocompatible, bioresorbable polymer, an aliphatic polyester that belongs to the poly-α-hydroxy acid group, in the same chemical group as polylactide (PLA) and polyglycolic acids (PGA). PCL is a semicrystalline hydrophobic polymer with a glass transition temperature of -60°C and a low melting point ranging from 59°C to 64°C. It also exhibits better viscoelastic properties than other biodegradable polymers, making it easy to fabricate and manipulate, allowing for a wide range of structures (microspheres, fibres, films, nanofibers, etc.) [7].

Today, composite materials are preferred and have started to replace traditional materials in many industries [8, 9, 10]. Synthetic copolymers (e.g. PCL, PLA, and PGA) and natural polymers (e.g. collagen) have been applied as biomaterials for vascular grafts because of their good elastic and biodegradable properties. Collagen as a natural hydrophilic polymer has received a great deal of attention in biomedicine due to its biological activity, degradability, and biocompatibility [11]. Very few electrospun grafts have been produced using a single pure polymer without modifications. Synthetic polymers typically exhibit excellent, tunable mechanical properties, including stiffness and elasticity, but are generally hydrophobic and lack a suitable interface for cell adhesion, spreading, and proliferation. However, although natural polymers have high biocompatibility and cell affinity, they lack the mechanical strength required for the dynamic environment inherent in the arteries. Therefore, most of the research today is focused on combinations of synthetic and natural polymers.

Venugopal et al. [12] conducted a comparative study of collagen and PCL nanotubes on the proliferation of human coronary artery smooth muscle cells. They found that collagen-coated PCL and collagen scaffolds showed better properties than PCL scaffolds. Given the high intraluminal physiological pressure, it is likely that pure collagen scaffolds will be susceptible to mechanical degradation. They found that the maximum pressure of the collagen graft was approximately 225 mmHg, supporting the use of collagen-coated PCL scaffolds or alternative composite scaffolds for vascular grafts.

Ma et al. [13] investigated the benefits of adding collagen to a PCL/heparin construct. Their electrospun collagen/PCL/heparin composite tissue-engineered vascular grafts exhibited

not only mechanical properties similar to native blood vessels, but also cell compatibility due to the biocompatibility of collagen and the ability to avoid structural deformations during stretching. Additionally, the presence of collagen allowed the release of heparin to be controlled, which promoted tissue regeneration. Sharif et al. [14] produced PCL- and collagen-grafted nanofibrous membranes treated with plasma and EDC/NHS chemistry. On the basis of contact angle measurements, they found that collagen provides greater hydrophilicity and a better surface for cells to attach and spread. They also found that collagen-coated PCL scaffolds had better mechanical properties than PCL scaffolds [14]. Awad et al. [15] discussed and analysed the mechanical properties of native blood vessels and observed that different evaluation and fabrication methods lead to differences in data between the mechanical properties of the same tissues. Ideally, synthetic blood vessels should mimic native blood vessels in their structure and functions, be biocompatible and biologically active, and have good mechanical properties.

The concept of a tissue-engineered vascular graft involves creating an alternative vascular graft that integrates with the patient's tissues and behaves like a native blood vessel, including self-regenerative and growth functions [16]. The vascular graft should be biologically noncytotoxic, nonimmunogenic, nonthrombogenic, and hemocompatible. In addition, it should provide conditions for cell attachment. Hydrophilicity promotes cell adhesion and proliferation in the material, which facilitates the necessary vascular regeneration [17]. In addition, vascular grafts must be resistant to physiological hemodynamic forces. From a mechanical point of view, it is very important that the artificial blood vessel withstands blood pressure and is not damaged or irreversibly deformed. Another factor to consider is graft porosity, as maintaining patency, especially in small-diameter vascular grafts, is still a challenge in vascular tissue engineering. Porosity is essential for cell nutrition, proliferation and migration, tissue vascularisation, and new tissue formation [18].

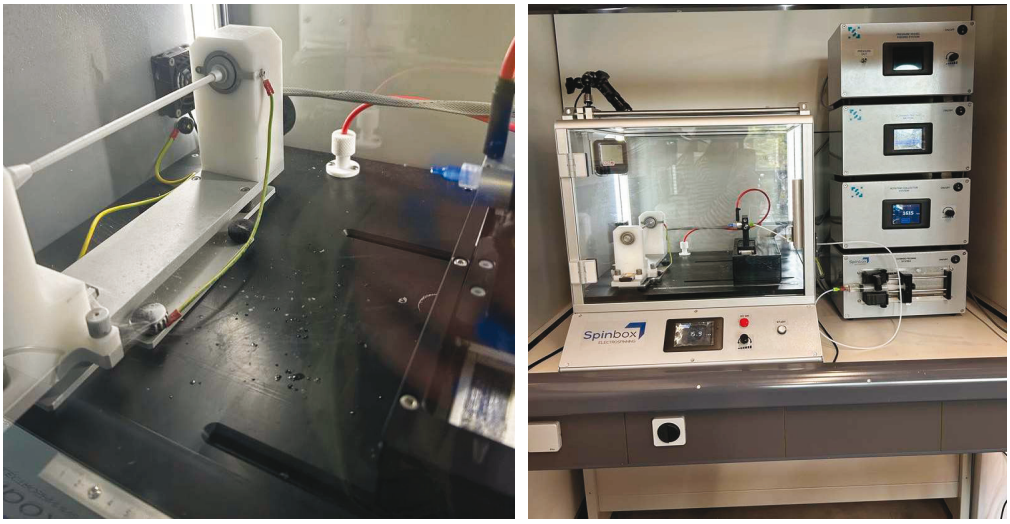
The aim of this study is to produce blood vessel grafts from a mixture of polycapralactone (PCL) and collagen using the electrospinning method and to analyse their mechanical properties, to determine the influence of the PCL and collagen concentration ratio on the mechanical properties, and to study the porosity and hydrophilicity properties of the blood vessel scaffolds.

2. Materials and methods

PCL with an average molecular weight of 80,000 (Sigma-Aldrich) was dissolved using chloroform (CF) as a solvent (Sigma Aldrich). Three different concentrations of PCL (10%, 12% and 15%) were prepared. The mixing vessel was placed on a stirrer with a heating tile that promotes the dissolution process of the PCL granules in the solvent. Electrospinning solutions were prepared by dissolving an appropriate amount of PCL granules in the solvent at 40°C with stirring for one hour to completely dissolve the PCL granules. Chloroform is a toxic solvent, so mixing was done in a fume hood. Before electrospinning, after the solutions were cooled to room temperature, different amounts of rat tail type I collagen (Sigma Aldrich) were injected into the solutions of different PCL concentrations with the help of a syringe: 5 ml of collagen was added to a 10 wt% PCL solution, 3 ml of collagen was added to a 12 wt% PCL solution, and 2 ml of collagen was added to a 15 wt% PCL solution.

Spinbox Electrospinning Equipment (Bionica S. L. Spain) was used for the production of vascular grafts. The following parameters were set in the equipment: voltage 18 kV, distance from the needle to the collector 18 cm, flow rate 4 ml/h, and number of revolutions of the collector per minute 1650 rpm. A 20 ml syringe filled with the solution was inserted into the syringe pump. The fibres were collected on a cylindrical collector (diameter 5 mm). All experiments were carried out at room temperature (18–25°C) with a relative humidity of

40–50% in a closed chamber. Spinbox's WinPumpTerm programme sets the infusion parameters such as syringe diameter (ml); infusion rate (ml/h); target volume (ml). A photograph of the cylindrical collector and Spinbox ready-to-use electric spinning equipment is shown in Fig. 1.



a) b)

Fig. 1 Cylindrical collector (a) and ready-to-use electriospinning equipment Spinbox (b)

A tensile test of the manufactured cylindrical specimens was performed using the Mecmesin MultiTest 2.5-i equipment (Fig. 2). The speed of stretching the specimen was determined according to the recommendations of BS EN ISO 7198: 2016 "Cardiovascular implants and extracorporeal systems - Vascular prostheses - Tubular vascular grafts and vascular patches", taking into account the length and width of the specimen. In this study, the dimensions of the nanofiber samples were 5 cm in length and 0.4±0.2 mm in thickness. According to the standard, a tensile speed of 10 mm/min and a breaking load of less than 5 N are recommended for this sample. The length, width, and thickness of the obtained fibre samples were measured with a micrometre with an accuracy of 0.01 mm. Before the tensile test, the obtained nanofibers were immersed in a physiological 0.9% NaCl solution for 30 min and then dried.

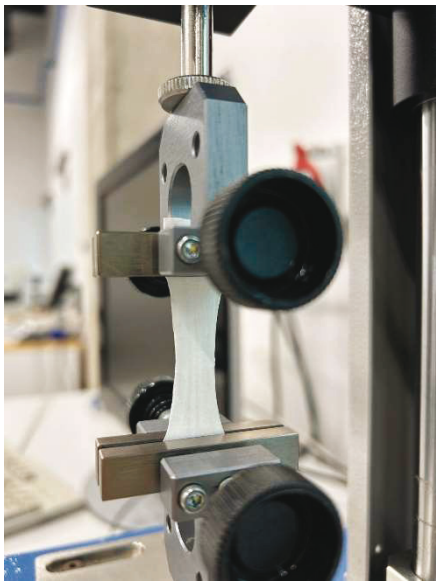


Fig. 2 Mecmesin MultiTest 2.5-i mechanical properties testing device with holder and specimen

For the validation of the experimental results, the theoretical calculation of the elastic modulus and density of the composite was used according to the rule of mixture (Voigt model) (Gibson and Ashby) [20]. The modulus of elasticity E_c of the composite is calculated according to the formula:

$$E_c = E_1V_1 + E_2\left(1-V_1\right) = E_1V_1 + E_2V_2, \tag{1}$$

where E_1 is the modulus of elasticity of the material of the first component of the composite, MPa; V_1 is the volume fraction of this material (V_I/V_c); E_2 is the modulus of elasticity of the material of the second component of the composite, MPa; V_2 is the volume fraction of the second material (V_{II}/V_c); V_c - total volume of the composite, cm^3, V_I and V_{II} are the volumes of the composite materials, cm^3. For the unit volume of the composite:

$$V_1 + V_2 = 1, \tag{2}$$

where V_1 is the volume fraction of the first component of the composite; V_2 is the volume fraction of the second component of the composite.

The density of the composite is calculated according to the formula:

$$\rho_c = \rho_1V_1 + \rho_2V_2. \tag{3}$$

The contact angle of PCL/collagen nanofibers was monitored to assess hydrophilicity [17]. Square 2×2 cm PCL/collagen samples were placed on a glass dish and water was dripped onto them. The contact angle between the water and the surface was measured using ImageJ analysis software. Depending on the angle of contact (θ) of the water droplets, the material was classified as hydrophilic (θ <90°), hydrophobic (90° <θ <150°) or superhydrophobic (θ > 150°).

The porosity of the PCL/collagen samples was evaluated using the liquid penetration method [18, 19]. This method first measured the dry weight of 20-mm-long specimens. The samples were then immersed in 98.8% ethanol for 24 h with agitation to ensure complete hydration. Ethanol was chosen because it can penetrate porous scaffolds without swelling or shrinking the material. Subsequently, they were removed from the ethanol and dehydrated to remove excess fluid. The weight of the wet samples was measured, and the volume of PCL/collagen within the sample and the volume of ethanol entrapped in the scaffold pores were calculated according to the following formulas:

$$V_{\text{PCL/collagen}} = \frac{m_{\text{dry}}}{\rho}, \tag{4}$$

where m_{dry} – dry weight of the samples, g; ρ – density of the PCL/collagen specimens, g/cm^3; $V_{\text{PCL/collagen}}$ is the volume of the PCL/collagen within the sample:

$$V_{\text{EtOH}} = \frac{m_{\text{wet}} - m_{\text{dry}}}{\rho_{\text{EtOH}}}, \tag{5}$$

where m_{wet} – wet weight of the samples, g; ρ_{EtOH} – ethanol density, 0.789 g/cm^3; V_{EtOH} is the volume of ethanol entrapped in the scaffold pores.

Porosity was estimated according to the formula:

$$\varepsilon = \frac{V_{\text{EtOH}}}{V_{\text{PCL/collagen}} + V_{\text{EtOH}}} \times 100\ \%. \tag{6}$$

A Kern balance (ABJ-NM/ABS-N model, 0.0001 accuracy) was used to weigh the specimens.

The morphology of the produced nanofibers and the diameters of the nanowires were examined with a Hitachi S-3400N scanning electron microscope (SEM).

3. Results and discussion

Figure 3 shows a 15 cm long, 0.4 mm thick vessel graft made from PCL/collagen. For the tensile test, the specimen was cut (Fig. 4).

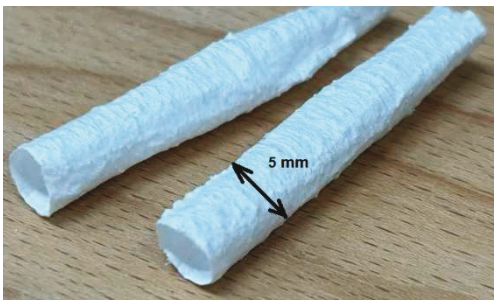


Fig. 3 Fabricated vascular grafts

Fig. 4 Tensile test specimen

After performing a uniaxial tensile test with a Mecmesin MultiTest 2.5-i mechanical parameters testing bench, initial curves were obtained showing the relationship between the load applied to the specimen and the displacement of the specimen. After the calculations, stress-strain diagrams (Fig. 5) were drawn:

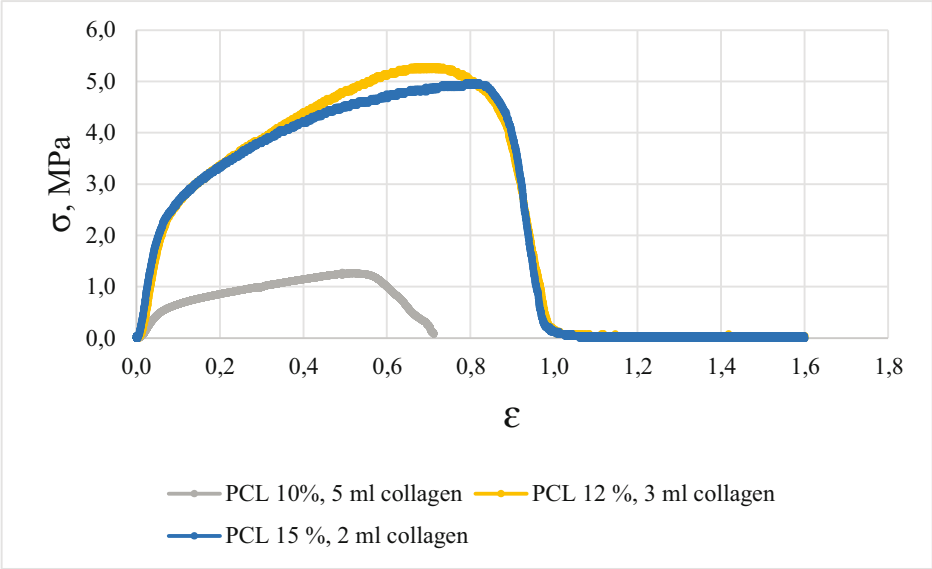


Fig. 5 Stress-strain diagrams

The calculated results for elastic modulus and ultimate strength are shown in Table 1.

Table 1 Calculated values of mechanical parameters for different nanofibers

Sample material	Modulus of elasticity, MPa	Ultimate strength, MPa
PCL 10 wt%, 5 ml collagen	64.85 ± 3.6 MPa	6.78± 0.9 MPa
PCL 12 wt%, 3 ml collagen	75.5 ± 4.9 MPa	16.9± 2.7 MPa
PCL 15 wt%, 2 ml collagen	69.6 ± 5.8 MPa	15.8± 3.6 MPa

After calculating the parameters of the mechanical properties of nanofibers with different concentrations, we can see that the highest elastic modulus of 75.5 ± 4.9 MPa is the PCL 12 wt%, 3 ml collagen sample. The weakest nanofiber is the PCL 10 wt%, 5 ml collagen sample, which has the lowest elastic modulus and ultimate strength compared to the other nanofibers. This phenomenon can be explained by the collagen content and its structural interaction. At lower collagen contents (2 ml and 3 ml), the collagen fibrils are sufficiently spaced and form a network effectively, improving the mechanical properties. When the collagen content increases from 2 ml to 3 ml, the mechanical properties of the material do not change, as the additional collagen (1 ml more) still fills the existing structure well without compromising the integrity. With 5 ml of collagen, the material reaches a point where excessive collagen content causes structural overcrowding, preventing effective crosslinking or the formation of a continuous network. Thus, at higher collagen content, the electrospun material can structurally rearrange, creating a looser matrix, and this structural change explains the difference in mechanical properties. The similar mechanical properties of the samples with 2 ml and 3 ml of collagen indicate that the collagen network is the best option. In contrast, increasing the collagen content to 5 ml disrupts the structure of the material and reduces the mechanical properties.

According to various sources in the literature, the elastic modulus of natural human blood vessels can be from 4 to 130 MPa, and the gold standard for arterial bypass grafting, the limit of tensile strength of the great saphenous vein, is 13 MPa [14]. The values of the electrospun specimens are similar to those of these biological tissues and are expected to have adequate load resistance when implanted. When comparing these results with similar studies, different evaluation and fabrication methods must be taken into account, precisely because of the differences in data between the mechanical properties of the same fabrics. The concentration of the electrospun nanofiber solution had the greatest influence on the results obtained. The higher the concentration of the solution, the higher the mechanical strength of the scaffolds. After comparing the calculated mechanical properties of the nanofibers with the local mechanical properties of human blood vessels, it was observed that all the nanofibers obtained were close to the mechanical properties of the subcutaneous vein (elastic modulus from 23.7 to 130 MPa, strength limit from 6.3 to 13 MPa) [14].

To verify the experimental results, the properties of the composite scaffold were calculated according to the rule of mixture. To make the scaffold, 10 g of the polymer PCL was mixed with 5 ml of collagen. The density of the PCL and collagen was taken from the data sheet of the polymers used in the study. The PCL modulus of elasticity is 330 MPa and the density 1.145 g/cm^3. The mass concentration of the collagen used was 4 mg/ml. So, taking 5 ml of the collagen solution, there was 0.02 g of collagen. The density of Type I collagen in its dry form is 1.3 g/cm^3. The elastic modulus of collagen is 300 MPa. The volume of PCL and collagen materials was calculated using the formula: $V = m/\rho$. Next, the volume fraction of the PCL in the scaffold was determined compared to the total volume:

$$\frac{V_{\text{PCL}}}{V_{\text{c}}} = \frac{8.73}{(8.73 + 0.015)} = 0.99 .$$

Then, according to formula 2, the relative volume of collagen in the scaffold will be 0.01.

We calculated the theoretical elastic modulus and density of the scaffold without considering the porosity according to formulas 1 and 3:

$$E_{\text{c}} = 330 \cdot 0.99 + 300 \cdot 0.01 = 329.7 \text{ MPa},$$

$$\rho_{\text{c}} = 1.145 \cdot 0.99 + 1.3 \cdot 0.01 = 1.146 \text{ g/cm}^3.$$

This would be the elastic modulus and density of the scaffolds if there were no pores. The porosity of the PCL/collagen scaffolds was evaluated using the liquid penetration method according to formulas 4, 5 and 6:

$$V_{\text{PCL/collagen}} = \frac{0.074}{1.146} = 0.064 \text{ cm}^3,$$

where 0.074 g is the dry weight of the samples (Table 2);

$$V_{\text{EtOH}} = \frac{0,11 - 0,074}{0,789} = 0,045 \text{ cm}^3,$$

where 0.11 g is the wet weight of the samples.

After inserting the obtained values $V_{PCL/collagen}$ and V_{EtOH}, we gain the following porosity:

$$\varepsilon = \frac{0.045}{0.064 + 0.045} \times 100 \approx 41.3\,\%.$$

The measured wet and dry sample weights and the calculated porosity of all three material combinations are presented in Table 2.

Table 2 Measured weights of wet and dry samples and calculated porosity

Sample material	Dry weight, g	Wet weight, g	Porosity, %
PCL 10 wt%, 5 ml collagen	0.074	0.110	41.3
PCL 12 wt%, 3 ml collagen	0.077	0.111	39.0
PCL 15 wt%, 2 ml collagen	0.075	0.110	40.3

After calculating the porosity, the theoretical modulus of elasticity of the scaffold (329.7 MPa) is corrected. For example, we obtained a porosity of 41.3%. The modulus of elasticity E of the scaffold will be 193 MPa. We obtained higher values than the results of the experimental study. This could be due to the application of different porosity determination methodologies. More precise methods, such as mercury intrusion porosimetry and gas sorption, can be used to more accurately assess the porosity of scaffolds. These methods can also provide detailed data on the pore size distribution. Micro-CT is also very effective in quantifying porosity nondestructively. However, these methods require expensive equipment. The experimentally obtained elastic modulus of a scaffold may differ from the value calculated using the rule of mixtures due to several factors related to the assumptions of the rule and the complexity of the material system, such as its heterogeneity and nonlinearity. The rule of mixtures assumes that the compound is completely homogeneous, which means that the individual phases are evenly distributed throughout the material. However, in real composites, the distribution and alignment of the fibres or phases often vary, which can affect the overall mechanical properties. The rule of mixtures assumes perfect adhesion. However, in reality, the adhesion may be weaker. This can reduce the overall elastic modulus of the composite compared to the theoretical value.

The porosity of PCL and collagen scaffolds used in vascular tissue engineering can vary depending on the specific fabrication methods and desired vascular properties. However, in general, vascular tissue engineering PCL and collagen scaffolds often have a porosity of 70-90%.

Before measuring the contact angle of the samples, their preparations for measurement were carried out. After electrospinning, the samples were air-dried to remove residual solvents. The samples were stored in a clean environment to avoid contact with potential contaminants. The surface should be as flat and even as possible to obtain reliable measurements. The contact angle measurement of the PCL 12 wt% and 3 ml of type I collagen samples is shown in Fig. 6.

Fig 6 Contact angle of PCL/collagen sample

The resulting contact angle is 110°. The contact angle is greater than 90° because the samples do not get wet and have hydrophobic properties. This means that the surface of the PCL/collagen graft needs to be modified, for example by plasma treatment, to increase wetting ability. Another way to improve the hydrophilic properties is to increase the concentration of collagen in the solution, which has hydrophilic properties.

In a study by Sukchanta et al. [17], the contact angle of electrospun polylactic acid scaffolds was monitored to determine hydrophilicity. The results showed that the contact angles are greater than 90°, the samples did not get wet, and they had hydrophobic properties. Contact angle measurements depend on surface roughness; on hydrophobic surfaces, increased roughness increases the measured contact angle. The porous structure can trap air in the pores, increasing the material's resistance to water absorption.

A variety of information about the surface morphology and structure of materials can be obtained from SEM images. Figure 7 shows SEM images of the sample with the strongest mechanical properties during the experiment (PCL 12 wt% and 3 ml of type I collagen). In SEM images, PCL is generally a homogeneous smooth material with small pores (Fig. 8).

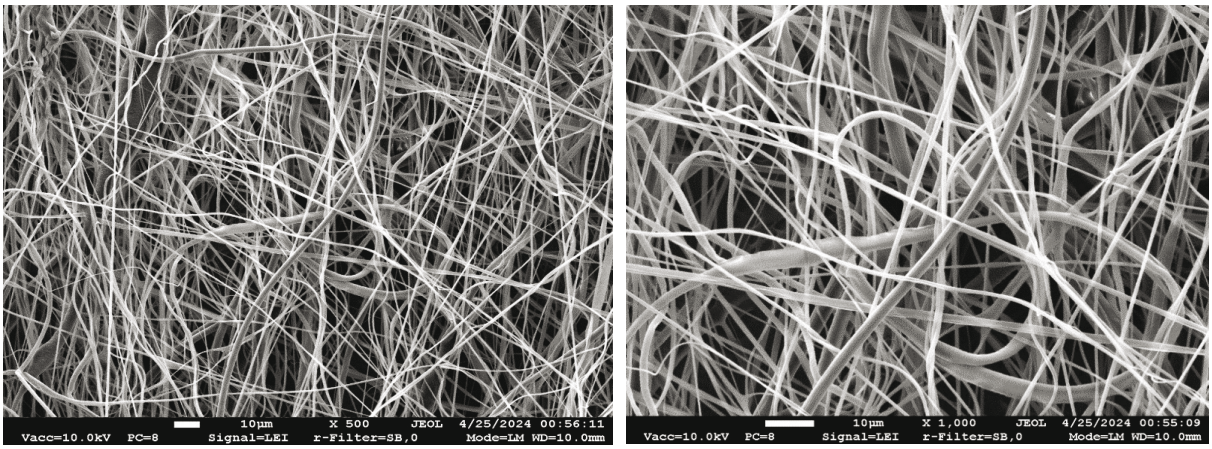


Fig. 7 SEM images of the nanofibers obtained at 500x and 1000x magnification

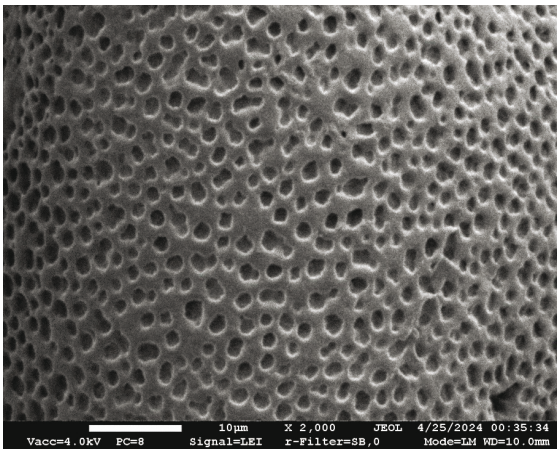


Fig. 8 Image of the outer wall of the resulting nanofiber at 2000x magnification

As we can see in Figure 7, the resulting images are fibrillar structures that form a dense interwoven mixture of fibres. The material is smooth and there are no visible structural defects, for example, cracks. The porosity of the frameworks is one of the main features visible in SEM images. Figure 7 displays a network of interconnected pores, which is very important for cell infiltration and nutrient exchange [21]. The morphology of nanofibers in SEM images depends largely on the electrospinning parameters (e.g., voltage, flow rate, and distance to the collector) and not on the molecular structure of the polymer. Parameters such as the choice of solvent and environmental conditions (temperature and humidity) also have a significant impact on fibre morphology. Although SEM provides excellent visualisation of surface morphology (e.g., fibre diameter, porosity), it does not provide information on the internal molecular structure or crystallinity of the polymer.

4. Conclusions

1. The concentration of PCL and the amount of collagen in electrospinning technology used in the production of nanofiber scaffolds affect the mechanical properties of the vascular scaffolds. PCL provides mechanical strength and durability, while collagen provides elasticity and flexibility.
2. Increasing the concentration of the solution increases the mechanical strength of the nanofiber scaffolds. The elastic modulus increases from 64.85 MPa to 75.5 MPa, and the ultimate strength increases from 6.78 MPa to 16.9 MPa. The nanofiber of the strongest sample (PCL 12 wt% and 3 ml collagen type I) is close to the mechanical properties of the subcutaneous vein.
3. A porosity percentage of about 40% was obtained for vascular scaffolds. The porosity of electrospun scaffolds can affect the mechanical properties, such as the elastic modulus. A higher porosity (70-80%) is required for a better balance between the mechanical properties, biocompatibility, biological activity, and fluid permeability.
4. For better cell compatibility and better nutrient metabolism, the scaffold should be hydrophilic. However, since the result is hydrophobic, the surface of the PCL/collagen scaffold needs to be modified, for example by plasma treatment, to increase the wetting ability or to increase the amount of collagen, which has hydrophilic properties.
5. SEM images of PCL/collagen scaffolds show that the PCL/collagen material forms a porous structure throughout the matrix, which is necessary for cell nutrition, proliferation, and migration, and for the formation of new tissues.

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