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TECHNIQUE FOR REDUCING THE SURGICAL POROSITY OF SMALL-DIAMETER VASCULAR GRAFTS

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High surgical porosity (SP) is one of the causes of significant blood loss, as well as hematoma formation. So, reducing the SP of small-diameter vascular grafts (VGs) is a crucial task. The **objective** of this work was to develop a technology for the formation of polycaprolactone (PCL)-based small-diameter VGs with a bioactive coating with reduced SP. **Materials and methods.** Porous VGs with an inner diameter of 3 mm were fabricated by electrospinning from 5% PCL solution with addition of 5–30% gelatin (PCL/G) on an NANON-01A unit (MECC C^O, Japan). Bioactive coating was applied by sequential incubation of VGs in solutions of bovine serum albumin, heparin and platelet lysate with fixation in a glutaric aldehyde solution. The surface structure and mechanical properties of the samples were investigated. Functional properties of the bioactive VGs were evaluated in relation to their interaction with cell cultures *in vitro*. **Results.** It was found that introduction of gelatin into the working solution reduces SP from 30.4 ± 1.5 mL/(cm^2·min) to 2.8 ± 0.5 ml/(cm^2·min). It was shown that at a PCL/gelatin ratio of 9 : 1, the outer and inner sides of the bioactive VGs samples are characterized by surface uniformity (no defects), mechanical properties close to blood vessels of the same diameter (Young's modulus 6.7 ± 2.1 MPa, tensile strength 26.7 ± 4.9 N and elongation to break 423 ± 80%) and ability to support adhesion and proliferation of human umbilical vein endothelial cell line, EA.hy926. **Conclusion.** Introduction of 10% gelatin content (by the polymer weight) into PCL solution reduces the SP of small-diameter VGs, leads to uniformity in their inner and outer surface, improvement in their mechanical properties without reducing their ability to support adhesion and proliferation of vascular endothelial cells.

Keywords: small-diameter vascular grafts, polycaprolactone, gelatin, surgical porosity, mechanical properties, endothelial cells.

Surgical porosity (SP) is one of the most important characteristics of vascular grafts (VGs). GOST 31514-2012 [1] defines it as water permeability, the amount of water going through 1 cm^2 of VG wall area during 1 minute at 120 mm Hg pressure. High permeability of the implant promotes the formation of hematomas, which, when organized, cause fibrosis and reduced prosthesis lumen [2, 3]. Water permeability >50 mL/(cm^{-2}·min^{-1}) is a criterion that determines the need for additional efforts to reduce SP [4, 5].

A study of textile VGs made of polyethylene terephthalate showed that for the pore size (20 to 100 μm), there is a positive correlation ($R^2 > 0.9$) between water permeability and blood loss, but blood loss is about 10 times less than water permeability [6]. This is down to the higher viscosity of blood plasma and the presence of formed elements in it.

The simplest method to reduce surgical porosity is to impregnate the finished vascular graft with a natural sealant. Whole blood is most often used as a sealant [1]. The method is called "preclotting" (from the word clot, a blood clot). Immediately before implantation, the implant is impregnated with fresh autologous blood containing no anticoagulants and incubated at 37 °C for a time interval sufficient to ensure fibrin formation [7]. This method exists up to the present, including for electrospinning-derived VGs [8]. In addition, fibrin glue [9], cross-linked hydrogels based on proteins (albumin, collagen, gelatin, etc. [10–13]), chondroitin sulfate [14], silk fibroin [15], sodium alginate [16], dextran derivatives [17], and chitosan [18], are used as a fibrin source to reduce the SP of high-porosity VGs.

One of the significant problems of hydrogel coatings for reducing VG porosity is their rather high resorption

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rate, which leads to the need for additional crosslinking [19–22]. Crosslinking agents (dialdehydes, polyepoxy compounds, isocyanates, etc.) are toxic substances that are difficult to completely remove from the coating volume. Besides, additional neutralization of unreacted reactive groups and potentially toxic derivatives formed by the interaction of crosslinking agents with proteins is required.

A distinctive feature of the electrospinning method is the possibility to obtain highly porous materials from fibers with diameters varying in a wide range from hundreds of nanometers to tens of micrometers. By varying the formation parameters (polymer solution concentration, nature of solvent, voltage between electrodes, humidity, temperature, etc.), it is possible to obtain highly porous materials with different fiber structure, pore size and surface morphology [22–25].

Previously obtained VGs, made of pure polycaprolactone, had a SP close to the maximum permissible value [26]. The objective of this study was to optimize the VG formation technology in the form of 3 mm diameter tubes with reduced water permeability.

MATERIALS AND METHODS

Fabrication of vascular grafts

Tubular VG specimens with an inner diameter of 3 mm were made by electrospinning from 5% (w/w) solution of polycaprolactone (PCL, MM 80000, Sigma-Aldrich, USA), as well as from PCL with gelatin addition (Sigma-Aldrich, USA) at a concentration of 5–30% (by the polymer weight) in hexafluoroisopropanol (PIM-INVEST, Russia), on electrospinning unit NANON-01A (MECC C^{O}, Japan) at a 25 kV voltage between the electrodes, 4 mL/h solution feed rate, 100 mm distance to the collector, 1000 rpm rotation speed of the substrate rod, using a 18 G needle. After the end of the solution application process, the obtained samples were dried in a thermostat at 37 °C for 2 hours, followed by vacuuming to remove traces of the solvent at 10–20 mmHg residual pressure and 37 °C for 24 hours.

Application of bioactive coating on the vascular graft surface

To form a bioactive coating, the VGs were incubated in 1 mg/mL bovine serum albumin solution (SPE PanEco, Russia) for 1.5–2 hours at 37 °C, then treated with aqueous 1 mg/mL heparin solution (Sigma-Aldrich, USA) for 1.5–2 hours at 37 °C. The coating was fixed with 1% glutaraldehyde solution for 18 hours at room temperature, then re-treated with 1 mg/mL heparin solution for 1.5–2 hours at 37 °C. Between the stages and at the end of the modification procedure, the vascular graft was washed three times in 100 mL of distilled water. The obtained heparinized sample was dried at 37 °C with subsequent vacuuming at room temperature and 10–20 mm Hg residual pressure, and sterilized by gamma radiation at a 1.5 Mrad dose.

The required volume of human platelet lysate solution (hPL, Renam, Russia) was obtained by diluting it in a 1 : 9 ratio with Hanks' Balanced Salt Solution containing no Ca^{2+} and Mg^{2+} ions (HBSS, Gibco® by Life Technologies™). The hPL solution was sterilized by filtration through a membrane filter with a pore diameter of 0.22 μm. Sterile heparinized VG samples were treated with hPL solution under aseptic conditions for 1 hour at 37 °C immediately before the experiment.

Surface morphology of vascular grafts

The surface structure of the VG samples was analyzed on a scanning electron microscope (SEM) JSM-6360LA (JEOL, Japan) at an accelerating voltage of 5 kV and magnifications ×100 and ×500. To create a conductive coating, gold was sputtered on a JFC-1600 (JEOL, Japan) for 40 seconds at a 5–7 mA constant current.

Stress-strain behavior of vascular grafts

Mechanical tests of VG samples were conducted on tensile tester Shimadzu EZ Test EZ-SX (Shimadzu Corporation, Japan) with TrapeziumX software, version 1.2.6, at a tensile speed of 5 mm/min.

The following stress-strain properties of the samples were recorded in both longitudinal and transverse directions: elongation at break expressed as a percentage of the original sample size, tensile strength expressed in N, and Young's modulus expressed in MPa characterizing the ability of the test sample to stretch and compress.

Cultivation of human umbilical vein endothelial cell line, EA.hy926, on the vascular graft surface

The functional properties of the VG samples were evaluated by interaction with human umbilical vein endothelial cell line, EA.hy926 (endothelial cells), from the American Type Culture Collection (ATCC). All studies were performed under aseptic conditions. Before use, the endothelial cells were stored in liquid nitrogen at –196 °C. After thawing, the cells were seeded into 25 cm^2 or 75 cm^2 standard culture vials (CELLSTAR® Greiner Bio-One, Germany) and cultured in complete growth medium DMEM with high glucose content (4.5 g/L, DMEM high glucose with HEPES, PanEco, Russia) supplemented with 10% fetal bovine serum (ETS, HyClone,

USA), antibiotic and antimycotic Anti-Anti (Gibco®, Life Technologies Corporation, USA) and 2 mM glutamine (PanEco, Russia) in a CO_2 incubator under standard conditions: 37 °C, in a humidified atmosphere containing (5 ± 1)% CO_2. Before the experiment, cells were removed from the surface of culture plastic using dissociation reagent TrypLE™ Express Enzyme (Gibco®, Life Technologies Corporation, USA) and a suspension with the required cell concentration was prepared. The initial endothelial cell count in the suspension was determined using an automated cell counter (TC20™ Automated Cell Counter, BIORAD, Singapore) with simultaneous determination of viability by trypan blue dye exclusion (BIORAD, #145-0013, Singapore).

The studied sterile samples of unmodified and modified VGs were pre-cut lengthwise, straightened, placed on the bottom of a flat-bottomed 24-well culture plate (CELLSTAR® Greiner Bio-One, Germany) with the inner side up and fixed with sterile silicone rings and seeded under aseptic conditions. The initial seeding density of the endothelial cells on the tested samples was 5×10^4 cells/cm^2. After seeding, the plates with samples were cultured in a CO_2 incubator under standard conditions for a specified time interval.

Assessment of metabolic activity and cell count

The metabolic activity of endothelial cells was recorded using PrestoBlue™ HS Cell Viability Reagent (Invitrogen™, Thermo Fisher Scientific, USA) according to the protocol recommended by the manufacturer. 10% PrestoBlue™ HS Cell Viability Reagent was added to wells containing the test samples and a cell-free control sample (cell-free complete growth medium), after which the plate was incubated for 4 hours at 37 °C in a humidified atmosphere containing (5 ± 1)% CO_2. Changes in absorbance of the medium were recorded using a Spark 10M microplate reader (Tecan, Austria) with Spark Control™ Magellan V1.2.20 software at 570 nm and 600 nm wavelengths. The percentage of reduced PrestoBlue™ characterizing the metabolic activity of the cells was then calculated according to formula (1):

$$\frac{117.216 \cdot A_{570\ Samp} - 80.586 \cdot A_{600\ Samp}}{117.216 \cdot A^0_{570} - 80.586 \cdot A^0_{600}} \times 100\%, \quad (1)$$

where: 117.216 and 80.586 are the molar extinction coefficients for the oxidized form of PrestoBlue™ Vital Reagent at 600 nm and 570 nm wavelengths, respectively; 155.677 and 14.652 are the molar extinction coefficients for the reduced form of PrestoBlue™ Vital Reagent at 570 nm and 600 nm wavelengths, respectively; $A_{570\ Samp}$ and $A_{600\ Samp}$ are the absorbance of the test sample at 570 nm and 600 nm wavelengths, respectively; A'_{570} and A'_{600} are the absorbance of the cell-free control sample at 570 nm and 600 nm wavelengths, respectively.

The number of the EA.hy926 endothelial cell line on the VG surface was estimated using calibration curves linear in semi-logarithmic coordinates up to a cell concentration of 0.8×10^5. To construct the calibration curve, cells were seeded into flat-bottomed 24-well culture plates (CELLSTAR® Greiner Bio-One, Germany) at a seeding density of 1–20 × 10^4 cells/cm^2. After 24 hours, PrestoBlue™ Vital Reagent was added to wells containing the required number of cells and a cell-free control sample, the plate was incubated for 3 hours at 37 °C in a humidified atmosphere containing (5 ± 1)% CO_2 and the change in media uptake was recorded. The percentage of recovered PrestoBlue™ determined by formula (1) was plotted on the graph on the y-axis, and the corresponding number of cells was plotted on the x-axis.

Statistical processing

Quantitative and statistical processing of the obtained data was performed using Microsoft Excel 2019. All results are presented as mean value ± standard deviation. Differences were considered reliable at $p < 0.05$.

RESULTS AND DISCUSSION

The results of the study of the effect of the amount of applied polymer and the concentration of introduced gelatin (G) on the surgical porosity of VGs are presented in Fig. 1.

The minimum SP of gelatin-free VGs made of pure PCL is 30.4 ± 1.5 mL/(cm^2·min) and is achieved when 2 mL of 5% solution is applied [26]. As can be seen from Fig. 1, in the case of application of 2 mL of PCL/G-BASED solution, regardless of the concentration of gelatin added to the PCL solution, the surgical porosity is minimal, 1.8 ± 0.1 mL/(cm^2·min).

When the amount of applied solution is reduced to 1 mL, a similar effect is achieved only when the gelatin concentration is increased to 20% or more.

Figs. 2 and 3 illustrate the effect of gelatin concentration added to PCL on the surface structure of 3 mm diameter VGs.

As can be seen from Figs. 2 and 3, regardless of the concentration of introduced gelatin, it leads to a decrease in the diameter of fibers and an increase in the density of their packing both from the inside and outside. This is the reason for the decrease in the SP of the vascular graft. PCL/gelatin samples with 5% and 15% gelatin concentration have partially porous internal structure (Fig. 2) with inclusions of extensive areas formed by soldered filaments, and at gelatin concentration of 20%

the inner surface of VGs looks monolithic with a small number of pores on the surface.

In the case of gelatin concentration of 10% and 30% (Fig. 2), a highly porous structure formed by individual submicron-sized filaments is preserved on the inner side of PCL/G. The sample with 10% gelatin is slightly more preferable due to minimal deformations as a result of less adhesion to the surface of the electrode rods.

On the outer side (Fig. 3), PCL/G-based VGs show a more porous surface structure compared to the inner side (Fig. 2). Moreover, while at a gelatin concentration of 20%, the inner surface of VGs looks almost monolithic (Fig. 2), the outer surface shows a pronounced porous structure with many open pores. Simultaneously with the increase in porosity on the outer surface of all the examined VGs, except for the sample containing 10% gelatin, traces of pronounced mechanical deformation as a result of separation of PCL/G from the substrate are observed.

Thus, the addition of gelatin to PCL at 10% concentration (by polymer weight) is optimal in terms of formation of VGs with highly porous structure and minimal deformation of both internal and external surfaces (Fig. 4).

Table shows the experimental results characterizing the effect of gelatin concentration on the physical and mechanical characteristics of VGs of different compositions.

As can be seen from Table, addition of gelatin to PCL leads to formation of more durable VGs, which is necessary for a product functioning under constant physical stress. At the same time, the effect of gelatin addition on elongation at break is insignificant. Moreover, the presence of gelatin increases the Young's modulus,

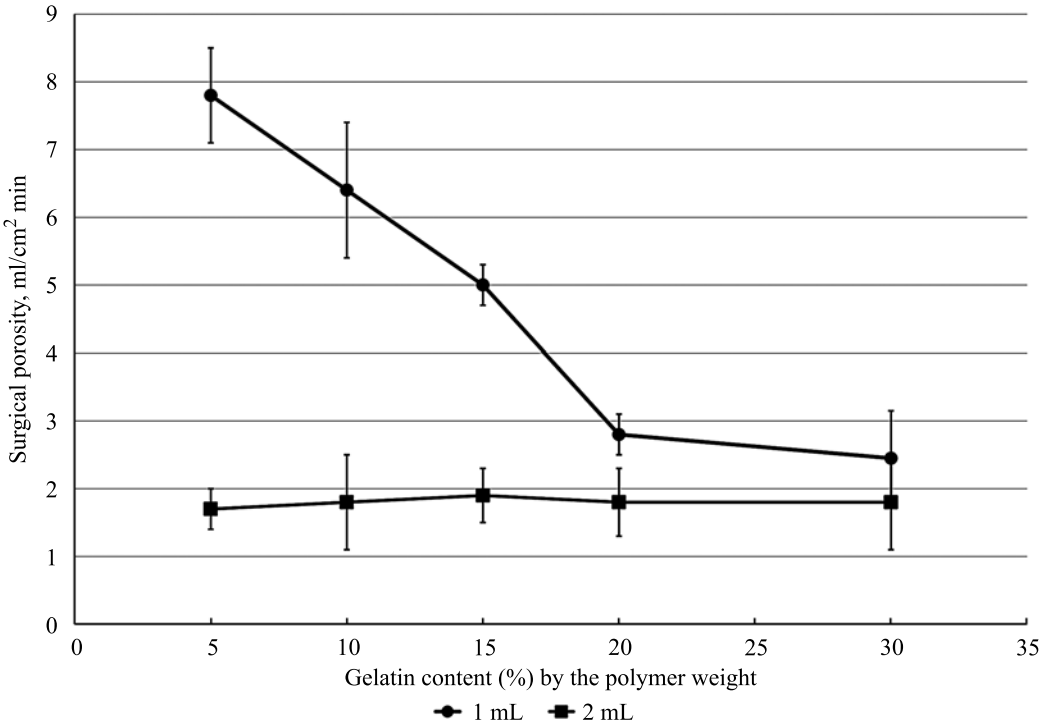


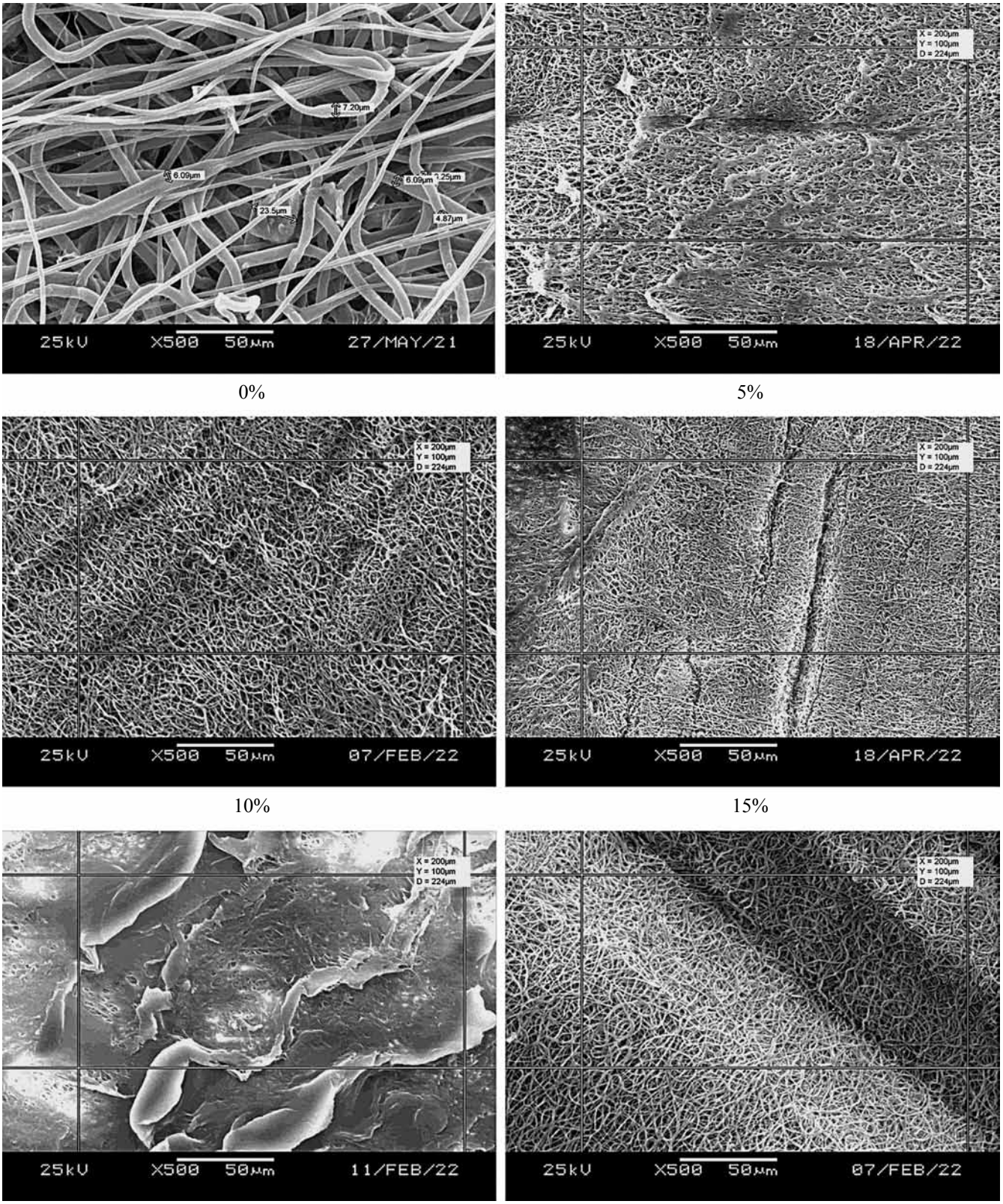
Fig. 1. Effect of the content of gelatin added to PCL and volume of the solution used on the surgical porosity of PCL/G-based VGs. Diameter 3 mm, solution flow rate 4 mL/hour

Table

Effect of the content of gelatin on the physical and mechanical characteristics of PCL/G-based VGs. Diameter 3 mm, volume 2 mL, solution flow rate 4 mL/hour

Gelatin content (%)	Young's modulus (MPa)	Tensile strength (N)	Elongation at break (%)
0	5.5 ± 1.1	10.9 ± 1.6	477 ± 38
5	11.3 ± 2.1	22.0 ± 4.7	441 ± 48
10	6.7 ± 0.7	26.7 ± 4.9	423 ± 80
15	10.7 ± 3.8	27.7 ± 3.4	432 ± 57
20	10.1 ± 4.7	26.7 ± 7.5	440 ± 129
30	11.7 ± 3.1	23.3 ± 2.9	448 ± 34

which is not desirable since the obtained values exceed those typical for natural human arterial blood vessels of the same diameter [27]. Among VGs with reduced SP due to the presence of gelatin, the variant with 10% gelatin (PCL/G10) is the most promising from the point of view of forming tissue-engineered constructs of small-diameter blood vessels, since it demonstrates increased strength and minimum Young's modulus that differ only



0% 5%

10% 15%

20% 30%

Fig. 2. Effect of gelatin content on the microstructure of the inner surface of PCL/G-based VGs. Diameter 3 mm, volume 2 mL, solution flow rate 4 mL/hour

slightly from those obtained in the case of VGs obtained from pure PCL.

The study of interaction of PCL/G10-based VGs, modified with bioactive coating with the culture of human umbilical vein endothelial cell line, EA.hy926, showed (Fig. 5) that the cells actively adhere to the tested surface (point 24 hour), and that they almost double in number after 168 hours of cultivation.

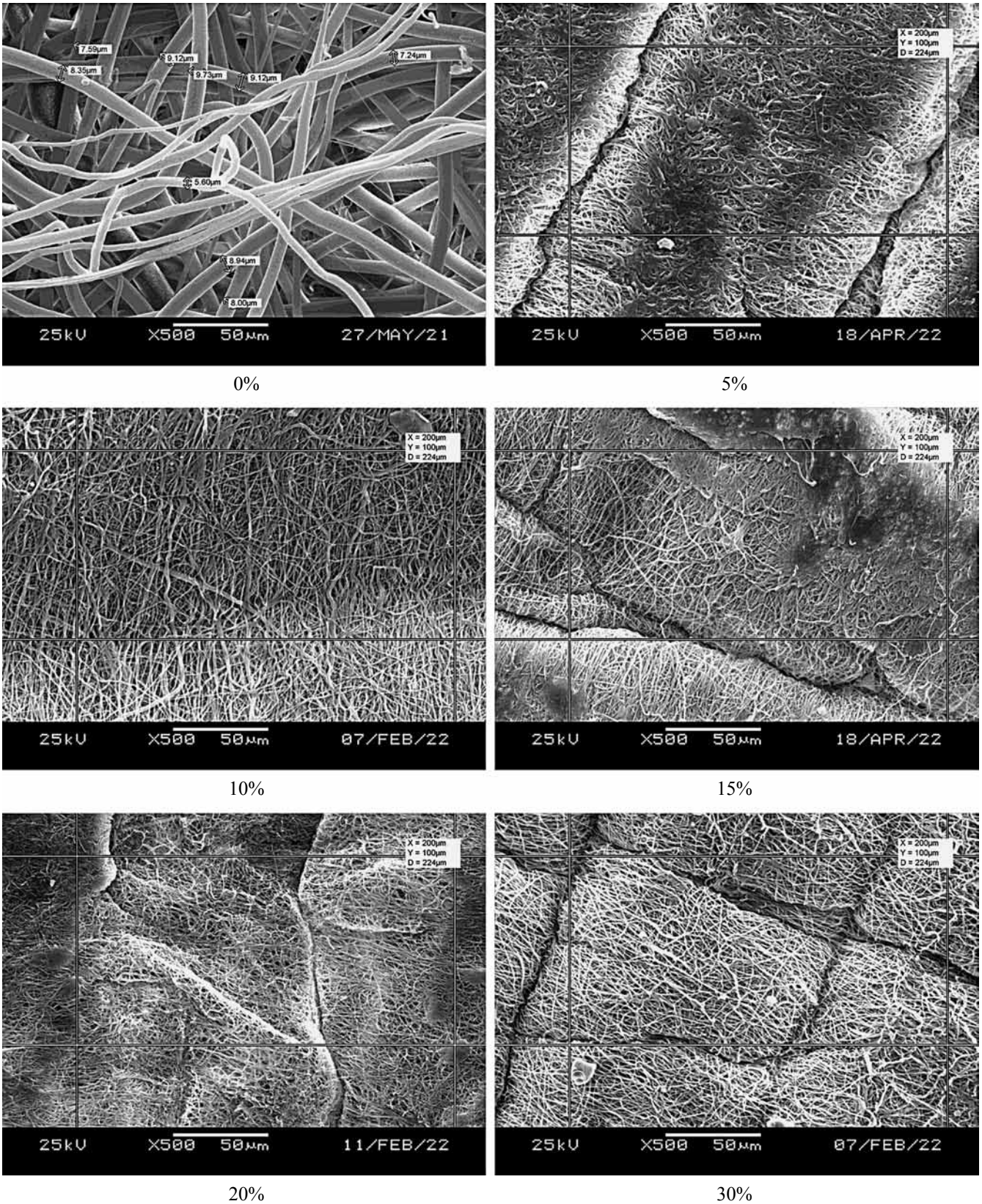
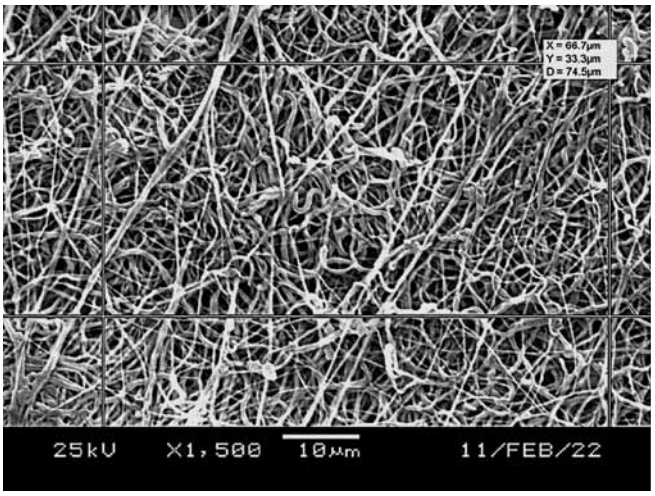
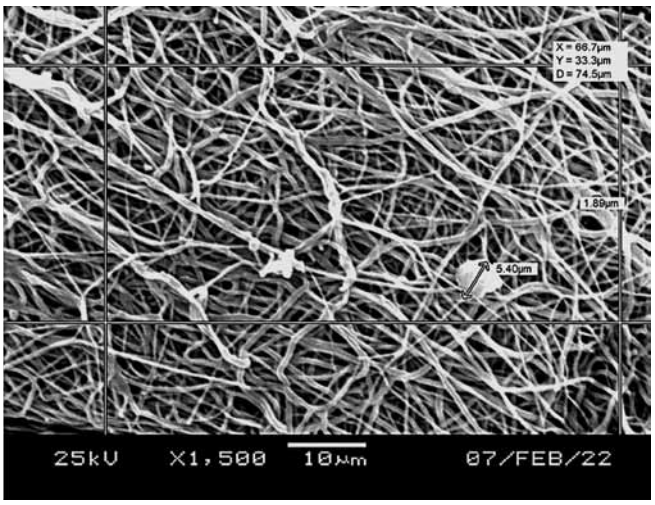


Fig. 3. Effect of gelatin content on the microstructure of the outer surface of PCL/G-based VGs. Diameter 3 mm, volume 2 mL, solution flow rate 4 mL/hour



Inner side



Outer side

Fig. 4. Structure of the surface of PCL/G-based VGs. Diameter 3 mm, gelatin content 10%, volume 2 mL, solution flow rate 4 mL/hour

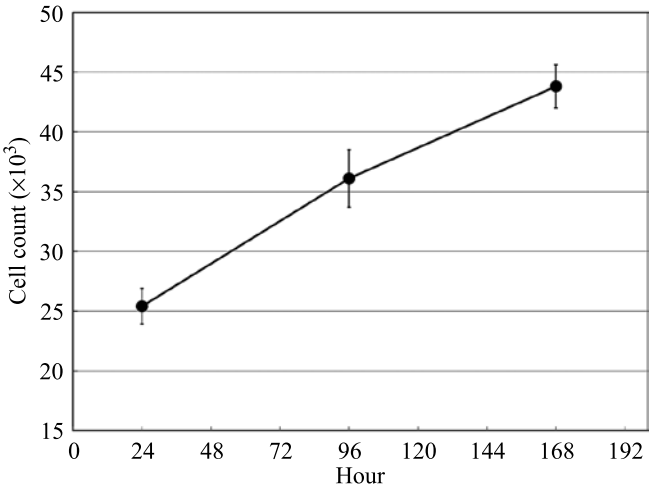


Fig. 5. Proliferation of human umbilical vein endothelial cell line, EA.hy926, on the inner surface of bioactive-coated PCL/G10-based VGs. Initial seeding density of 5×10^4 cells/cm^2

CONCLUSION

Addition of gelatin to PCL at 10% concentration (by polymer weight) is effective in terms of reducing the SP of small-diameter VGs, it provides the necessary stress-strain properties and minimal graft deformation from the inner and outer sides. The ability of bioactive coated VGs to support adhesion and proliferation of vascular endothelial cells has been confirmed. The next step is the study of the hemocompatibility and functional properties of the developed small-diameter bioactive VG sample *in vivo*.

The authors declare no conflict of interest.

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