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Original paper

Mechanical, biological, and microstructural properties of biodegradable models of polymeric stents made of PLLA and alginate fibers

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Due to lack of effective methods for preventing the complications associated with stent implantation, the search for new solutions is conducted, including those based on the use of biodegradable polymers. Such materials could allow us to develop a temporary implant that would ensure flow in the vessel until its regeneration, while minimising the negative effects connected with long-term implant–tissue interaction. In this study, models in the form of biodegradable stents of different materials and geometry were prepared. Due to the fact that one of the basic requirements imposed on vascular stents is the ability to resist radial loads caused by the surrounding tissue, the maximum radial forces causing destruction of prepared models were investigated. The results were compared with the values obtained for commercially used metallic implants. Models were also incubated in Eagle's medium enriched with albumin in order to assess potential adhesion capacity of proteins on their surface. Scanning electron microscope enabled monitoring of microstructural changes during incubation. The results obtained were used to evaluate the ability to obtain a functional, biodegradable vascular stent.

Key words: *power, biodegradable stent, radial strength, mechanical properties, biological properties, polymer structure*

1. Introduction

Cardiovascular diseases are currently one of the leading causes of death in the world. According to forecasts prepared by the World Health Organisation, we can expect a further increase in mortality due to these pathologies. Despite a continuous improvement in the intervention technique of balloon angioplasty and intensive use of pharmacotherapy, the outcome of the procedure can be unsatisfactory due to the risk of the occurrence of restenosis associated with elastic recoil or artery dissection [1], [2]. In order to eliminate this phenomenon, stents were implanted [3] to provide support and to reduce negative remodelling connected with physiological, elastic properties of tissues [4]. At the same time, early and late side effects of the procedure became apparent, such as recurrent stenosis (the so-called restenosis) connected with excessive proliferation of structural elements of the vessel wall and formation of blood clots [5], [6]. The factors that initiate these changes include inflammation after implantation [7], [2], allergic reaction to material [8], and electrostatic interactions between metal and blood components [9]. Despite the large variety of stents [3], [10], [11], negative side effects associated with their implantation could not be eliminated. Therefore, the search is continued for new alloys and construction materials to obtain stents. In particular, there is an increased interest in the ability to use bio-

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degradable materials, which are capable of disintegration after a specific period of time [5]. This gives hope of obtaining a structure whose radial strength is similar to the strength of the existing implants [12], providing stable and uniform support of a vessel necessary to restore the flow, with the simultaneous reduction of long-term negative side effects through implant resorption after a predefined period of time. Attempts have been made to construct a temporary vascular stent with such resorbable metallic materials as iron [13], [14] and magnesium [15]. The first reports of a fully biodegradable polymer stent date back to the 1980s [16], whereas the first clinical tests of such implant on humans were carried out by the Igaki Medical Planning team [17]. Serpentine design ensured radial stability of the vessel, but to reduce elastic recoil, implant expansion required bringing it to the softening temperature of approx. 70 °C. The procedure strained the surrounding tissues, precluding further use of that implantation method. Long-term results published by TAMAI et al. [18] showed no clear signs of polymer hydrolysis in the 12-month observation period and the appearance of restenosis. In 2001, a self-expanding stent was proposed, made of poly(L-lactide) and poly(D-lactide) copolymer [19] in the form of a double helix intended to insure implant elasticity but further research was abandoned due to the small degree of expansion and slow progression of expansion (up to 24 h), and low radial strength. LAUTO et al. [20] used chitosan in their construction of a helically wound, serpentine implant; the structure was characterised by high rigidity hindering endoscopic manipulations and adverse effect of blood flow on the process of expansion. Attempts were also made to build stent with the use of polyhydroxybutyrate with the addition of triethyl citrate as a plasticizer [21], but the results of studies of a laser-shaped implant demonstrated an unusually intense inflammatory reaction in the vessel wall. Other biodegradable implants were serpentine designs left at the prototype stage, self-expanding [22] and balloon-expandable ones [23], made of poly(L-lactide) or poly(D,L-lactide) [24]. Currently, clinical tests are underway of a BV/Abbot polymeric stent made of poly(L-lactide) [25] and of a stent by Reva Medical. At the same time it should be noted that so far none of the temporary polymeric implants has been introduced into clinical use.

Due to the specific, dynamically changing operating environment of a vascular stent and strict biocompatibility criteria, the development of a polymeric vascular stent is a very complex issue. In order to fulfil its main function, i.e., to ensure vessel patency, stent design should maintain radial stability and load-bearing function under loads exerted by the surrounding tissues. This is particularly important considering the structures made of polymeric materials, whose properties differ significantly from the properties of steel, which is currently the most widely used construction material for vascular implants. It should also be remembered that the structure of the material undergoes changes during the process of degradation, which affects the mechanical properties of an implant. Due to the nature of work and continuous contact of a stent with blood environment, the material used for construction of a biodegradable vascular implant should meet specific requirements of its interaction with the biological environment, inter alia, it should not cause inflammatory reactions or stimulate formation of blood clots. We can, therefore, conclude that the primary parameters characterising a vascular stent are its radial force responsible for the maintenance of load-bearing function and surface microstructure and reactivity, stimulating cellular response of the body to the implanted material.

The aim of the study was to develop the models of biodegradable vascular stents and to assess their mechanical, structural, and biological properties and degradation dynamics. The dimensions of the design were selected with a view to its use in vascular, peripheral, and urological stents. The models were subjected to uniaxial compression tests in order to determine the values of radial forces causing destruction of the structure. The results obtained were compared with the parameters characterising commercially used implants. The prototypes developed were subjected to tests in order to monitor the degree of implant resorption based on microstructural changes during the degradation. The reactivity of stent surfaces was also assessed in a simulated biological environment. The studies conducted allowed us to assess the usefulness of selected materials and developed models for preparing vascular and urological stent structures.

2. Materials and methods

The study involved the following commercial biodegradable polymers based on polylactic acid:

a) poly(L-lactide) (RESOMER L210: 3.4 dl/g, Boehringer Ingelheim, Germany) (PLLA),

b) poly(L-lactide/D, L-lactide) (PURASORB PLDL 8038: 3.8 dl/g, 80/20 L-lactide/DL-lactide) (PLDLA).

Modified fibres made of sodium alginate (NaAlg) were produced by the wet method from alcohol solution at the Department of Man-Made Fibres in the

Faculty of Textile Engineering and Marketing of the Technical University of Łódź.

Stents were prepared of various sizes and shapes, corresponding to the designs used in different parts of the vascular and urological systems (figure 1):

a) Helical design made by solution casting method (n = 7): PLLA and PLDLA in a ratio of 1:16 were dissolved in methylene chloride, thickness of polymer films after solvent evaporation was 0.12 mm and 0.19 mm, respectively. The layers obtained were cut into 3-mm wide strips, then wound onto glass mandrels with a diameter of 3.4 mm and subjected to a temperature of 60 °C to fix the shape.

b) Helical design (n = 7): layers from PLLA with a thickness of 0.5 mm and 1 mm were made by hot-press molding. The layers obtained were cut into 0.5-mm wide strips, then wound onto glass mandrels with a diameter of 3.4 mm and subjected to a temperature of 60 °C to fix the shape.

c) Coil design (n = 7): extruded polymer fibres with diameters of 1.3 mm and 1.9 mm were made of PLLA and wound to obtain spirals with the inside diameter of 5.8 mm.

d) Tubular design (n = 7): in order to obtain composite models, NaAlg fibres were unidirectionally wound onto mandrels with a diameter of 5.8 mm and then immersed in CH_2Cl_2 (POCH) solution of PLA polymer to obtain a stent with a wall thickness of 0.25 mm.

The tests of radial strength were conducted on an MTS Synergie 100 strength machine at a speed of 0.5 mm/min. The study established the values of force at which there was a 50% reduction in the initial stent diameter; percentage changes in diameter values after unloading were also measured.

ally wound NaAlg fibres, and had a diameter of 1.5 mm and the wall thickness of 0.1 mm. The models (n = 7) were incubated in distilled water and Ringer's solution at a temperature of 37 ± 1 °C for a period of six weeks (volume ratio of solution to sample was 100:1). Each week of incubation, the changes in the pH value and the conductivity of the incubation solution were measured.

In order to examine the process of protein adhesion to the stent surface, PLLA and PLLA/NaAlg stent models (n = 7) were incubated for 3 days in Eagle's medium with the addition of albumin at a temperature of 37 ± 1 °C. The materials were then studied, using an FTIR infrared spectrometer (FTS-60V, Digital Division, Bio-Rad), by the KBr pellet method. Also, surface roughness of the samples was measured with a Hommelwerke T1000 profilometer, before and after the incubation in Eagle's medium with albumin.

The microstructure of the composites was examined in a scanning electron microscope (Nova NanoSEM 200, FEI, USA). The test samples were covered with a thin layer of carbon.

3. Results

3.1. Tests of radial force

The prepared stent models are shown in figure 1. Based on the tests conducted, the curves representing the relationship between compressive force and percentage change in stent diameter (strain, %) were plot-

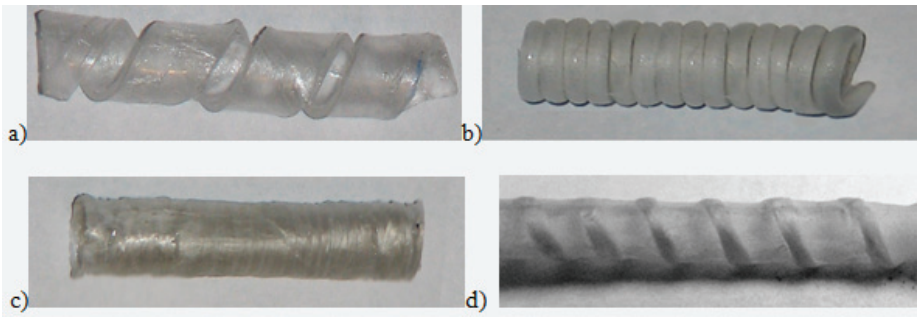

Fig. 1. The stent models: a) helical design, b) coil design, c) tubular composite design, d) tubular composite design

Due to the confirmed safety of use of poly(L-lactide) in human organism and the known degradation time of unmodified polymer [26], the studies of biological properties and the degree of resorption were only performed on the models of composite stents. The models were made with unidirectionally and bidirection-

ted for the different types of designs. Tube models with alginate fibres (figure 2c) have a wide elastic range (linear force–strain characteristic); when strain exceeds 70% of the initial diameter value there is a sudden change in the slope of the curve, which means a permanent deformation and destruction of the model.

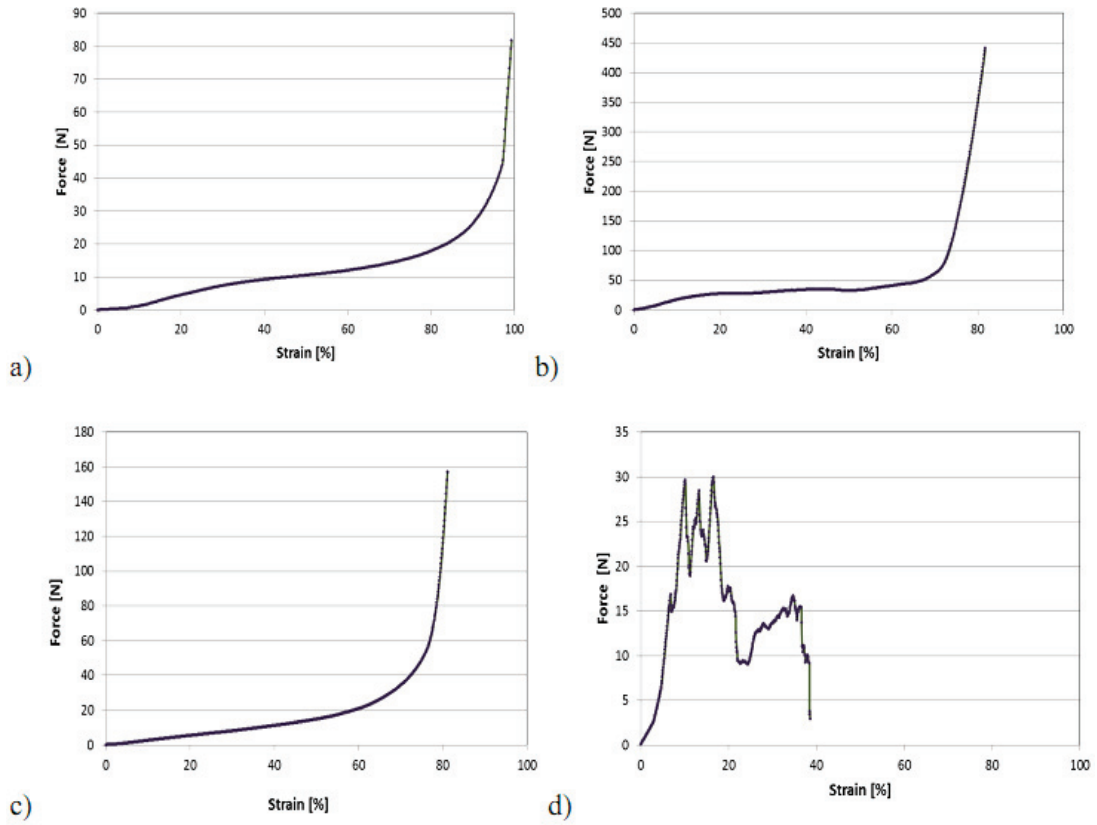

Fig. 2. The examples force–strain curves representing the following design types:
a) helical, solution casting, b) helical, melting, c) tubular, d) coil

For helical designs (figure 2a, b), plastic deformation is present at approx. 20% reduction in the diameter. The materials used in coil models show brittleness. At 10% of the strain value, the implant struts fracture (figure 2d). In a later stage, some of the loads are taken over by undamaged coils, but the total amount of strains before the implant destruction does not exceed 30% (figure 2d).

Table 1. Maximum radial forces for the models tested

Stent (wall thickness (mm))	Radial force (N)	Strains after unloading (%)
PLDLA(0.12)	1.05 ± 0.22	12 ± 4.3
PLA(0.12)	1.53 ± 0.45	17 ± 1.8
PLDLA(0.19)	7.6 ± 1.7	30 ± 7.1
PLA(0.19)	10.3 ± 0.3	36 ± 8
PLA(0.5)	24.37 ± 4.87	39 ± 7.8
PLA(1)	194.8 ± 38.9	42 ± 8.4
PLA(1.3)	16.36 ± 3.27	–
PLA(1.9)	82.80 ± 16.56	–
PLA + NaAlg(0.25)	3.32 ± 0.67	13 ± 2.6

The radial force values obtained in the tests of prepared models with a diameter of 3.4 mm fall within the range of 1–10 N (table 1). Those values correspond to the forces of the metallic stents used clinically in the treatment of vascular stenosis. There are not many studies on stents made of biodegradable polymers, and their mechanical properties are characterised by a large discrepancy. The results of our studies are consistent with reports in the literature involving comparable geometric dimensions (table 2).

Table 2. Maximum radial forces for metal implants in clinical use, measured in compression tests using flat-plate method

Stent (diameter, wall thickness (mm))	Radial force (N)	Strains after unloading (%)
VIP Plastic[27]	5.4	40
Palmaz Crown[27]	5.3	39
Ave Iliac Bridge[27]	5	32
Wallstent[27]	3.9	4
Instent Vascucoil[27]	2.7	1
Symphony[27]	3.4	1
Memotherm[27]	2.7	1
Poly(L-lactide)[28] (4; 0.17)	>1	–
Poly(l-lactide-co-glycolide[29] (6.3;1.2)	200	–

3.2. Degradation dynamics of composite stents

Figure 3 shows changes in the pH value and conductivity of water extracts during incubation of PLDLA/NaAlg tubular stents in distilled water. Their degradation do not cause rapid fluctuations in the pH value. Within six weeks of incubation, the pH of sample extracts increases by approx. 20%, but it still shows neutral reaction. The increase in pH is connected with hydrolysis of fibres made of sodium alginate.

3.3. Assessment of the adhesion capacity of proteins on the stent surface

Figure 4 shows the spectra of polylactide, polylactide with alginate fibres after incubation in Eagle's medium with the addition of albumin, and polylactide after incubation in Eagle's medium with the addition of albumin.

Comparing infrared spectra of output polylactide with polylactide after incubation in albumin we can clearly see that incubation changes the polymer surface connected with the deposition of the peptide.

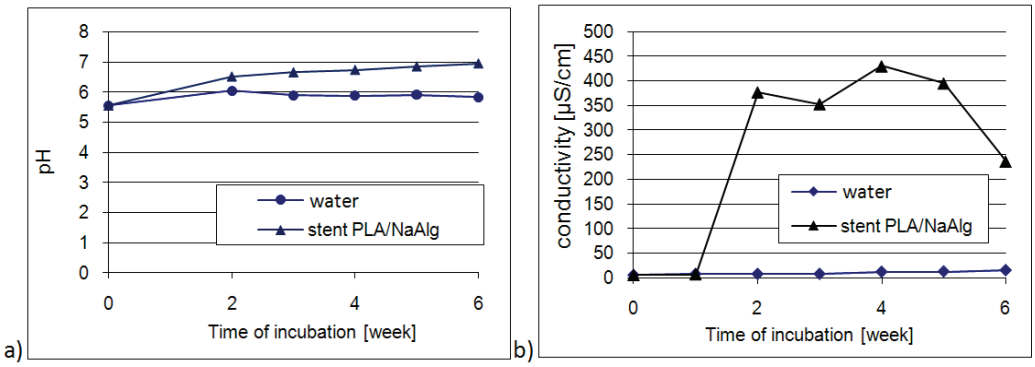

Fig. 3. Changes of: a) pH, b) conductivity of water extracts during incubation of PLDLA/NaAlg stents

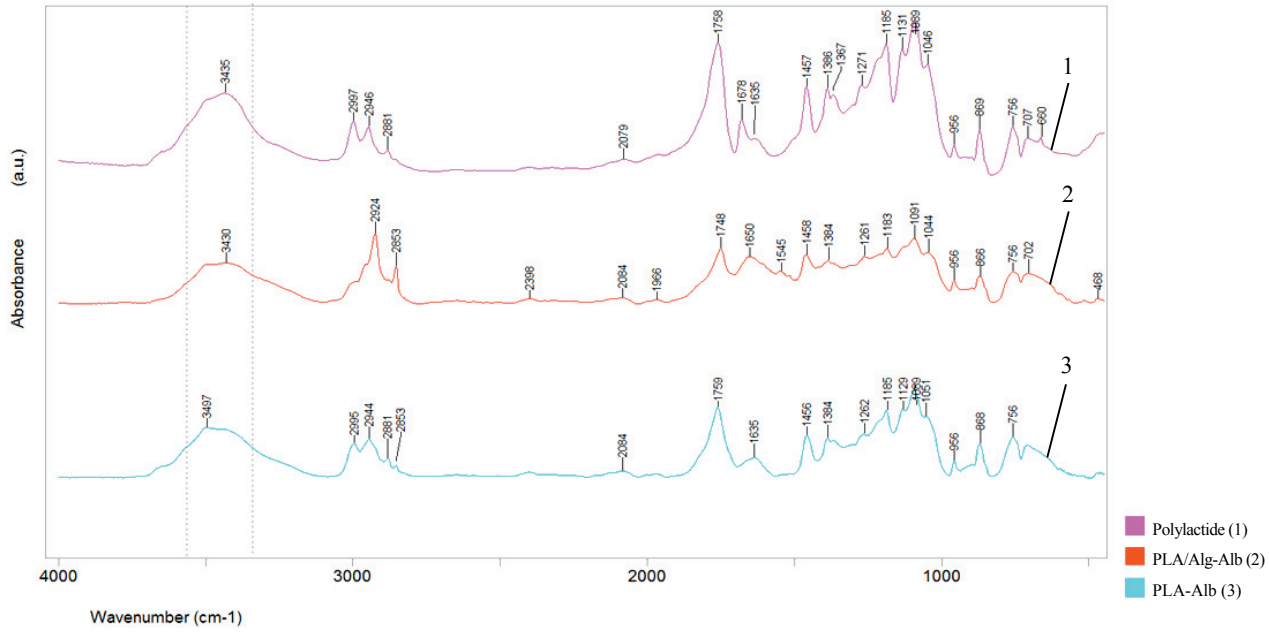

Fig. 4. FTIR spectrum of the test samples: polylactide, polylactide with alginate fibres after incubation, polylactide after incubation in Eagle's medium with the addition of albumin

After the first week of incubation the value of conductivity (figure 3b) rises which is caused by polymer and alginate fiber degradation, and thus the release of ions to the extract.

This may be evidenced by changes in the relation of bands in the 3,450–3,550 cm^{-1} range, probably derived from polymer hydroxyl groups (3,450 cm^{-1}) and from the emerging amino group (3,550 cm^{-1}) derived

from albumin. Additionally, changes also occur in the intensity of bands characteristic of stretching vibrations of CH_2 and CH_3 (2,950 and 2,995 cm^{-1}). Another confirmation of protein deposition on the polymer surface are changes in the intensity of vibrations of the carbonyl group 1,635 cm^{-1}. In the case of polylactide modified with alginate, the spectrum is complex as a result of overlap of rich spectra of PLA, alginate, and albumin. However, the analysis of the FTIR spectrum of that composite shows fundamental differences with regard to the spectrum of pure polymer in the range of stretching vibrations of CH and CH_3. The strengthening of the intensity of those vibrations is probably connected with the presence of the alginate phase. It is difficult to unequivocally detect the presence of albumin on the surface of that material due to the significantly worse signal that may be a result of low material concentration in KBr and difficulties with its distribution in the reference.

4. Discussion

There is no definite answer to the question of the appropriate minimal radial strength of the stent. On the basis of the results available for metal stents in clinical use [27]–[29], we can conclude that the values of radial forces at which there is a 50% reduction in the diameter of the stent design amount to 2–6 N for the individual models of metallic implants (table 1). The analysis conducted allows us to conclude that it is possible to develop biodegradable stent models whose strength is comparable to the strength of the currently used metal stents (table 2). However, dimensional parameters should be taken into account because implant strength depends on the geometric features such as implant wall thickness, which in the case of a polymer model is significantly greater than the thickness of clinically used metal stents. In addition, its increase significantly reduces the elasticity of the design, which is connected with the properties of the polymers used, whose strain curve is typical of a brittle material. For this reason, the search for materials that can improve elastic properties of implants is more important than the improvement of their stability and radial strength. It seems advantageous to use composite material – in the studies conducted, such implants ensured sufficient resistance to the acting forces.

The process of degradation of the prepared stent models was observed on the basis of two parameters: changes in the pH and conductivity of the incubation fluid. The results of the tests conducted indicate that the process of degradation is not rapid; the pH values of immersion fluid throughout the incubation of the samples are in the range of 5–7.5 (figure 3a). This means that the release of degradation products such as lactic acid is not intensive, whereas the whole degradation time of implant exceeds 6 weeks, which according to the data in the literature [30] is the time sufficient to reendothelialise vessel wall. The rate of release of degradation products is important because literature reports suggest that acidification of the environment may cause inflammatory reactions [31] around the graft.

Table 3. Changes in the roughness parameters of the surface

Sample	Parameter (μm)	Non-incubated sample	Standard deviation	Sample incubated in albumin	Standard deviation
PLA	*Ra*	0.07	0.02 (n = 7)	0.17	0.08 (n = 7)
	Rt	0.40	0.15 (n = 7)	1.25	1.00 (n = 7)
	Rz	0.25	0.08 (n = 7)	0.59	0.35 (n = 7)

Table 3 shows *Ra*, *Rt*, and *Rz* parameters characterising the roughness of the polymer surface before and after incubation. The values of *Ra*, *Rt*, and *Rz* increase after incubation of a polymer sample in albumin, which may confirm the deposition of protein on the surface. Surface roughness can also be increased due to surface erosion in solution. However, surface roughness of the sample remains low.

3.4. Tests of composite microstructure

On the basis of microscopic examination (figures 5 and 6) we can conclude that alginate fibers perfectly adhere to PLDLA both before incubation and after 6 weeks of immersion. During that period the prepared models do not change their shape or dimensions; figures 5 and 6 show that only their surfaces change under the influence of the water environment. This is particularly apparent in the case of the external surface, which becomes porous (figure 6).

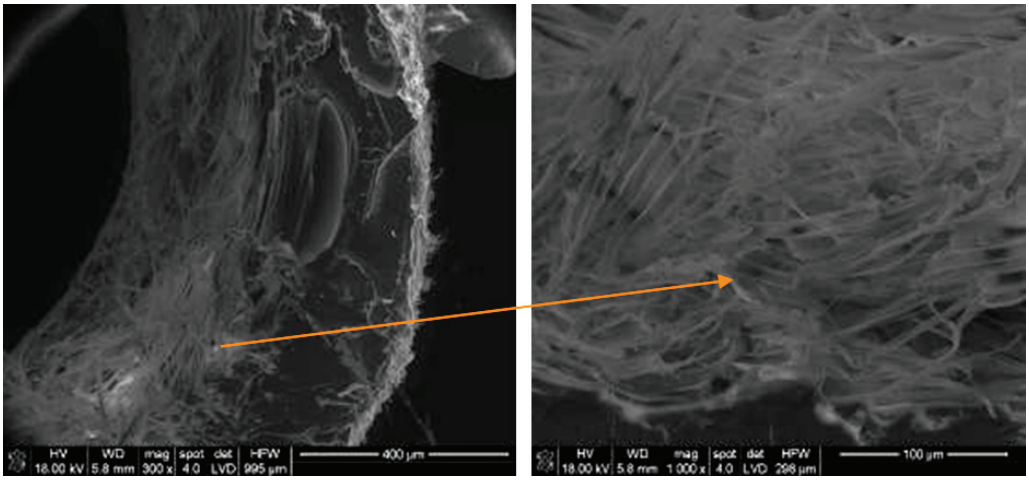

Fig. 5. SEM microphotography of the stent cross-section after a 6-week incubation in distilled water

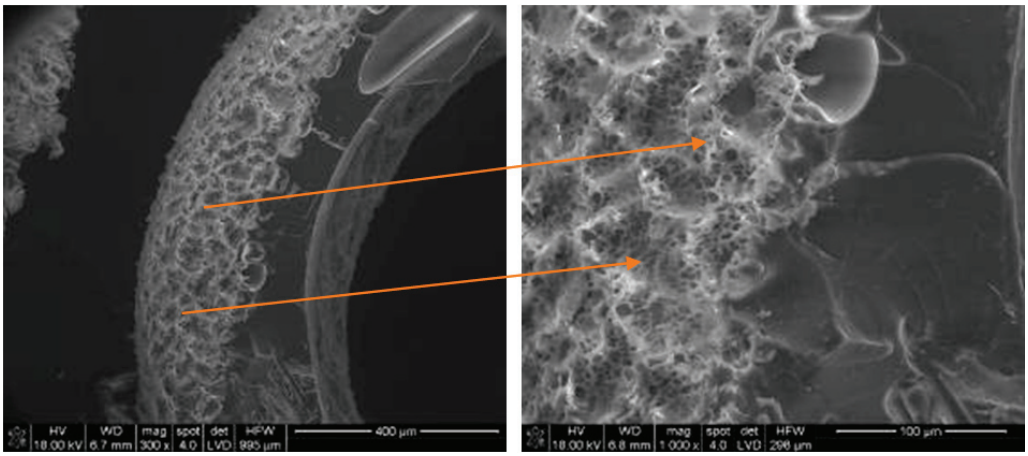

Fig. 6. SEM microphotography of the stent surface after a 6-week incubation in distilled water

The studies of the process of protein adhesion indicate that the incubation of PLLA/NaAlg stent models in Eagle's medium with albumin is followed by the deposition of peptide on the polymer surface. This is demonstrated by the results of FTIR spectroscopy as well as by an increase in roughness of the material surface. There is a concern that, due to their structure, composite stents may induce more intense tissue response than stents made of unmodified materials, whose activation is connected with the process of adhesion of plasma proteins to the stent surface. However, this claim could not be conclusively verified on the basis of the research conducted.

One very important parameter determining the functionality of a vascular implant is its structure. This is especially important in the case of composite implants, where separation of polymer-fibre phases may contribute to physical damage to the implant and to the separation of stent fragments. Their release could be a serious danger to a patient's life. At the same time, due to increased water absorption at the phase boundaries, their separation contributes to faster degradation of the material. Too rapid implant degradation, before the vessel regenerates sufficiently to be able to take over the load-bearing function, may cause the vessel to collapse. However, the microscopic examinations indicate that a good connection is obtained between the PLA coating and fibres without visible delaminations and discontinuities both before and after incubation (figure 6).

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