doi: 10.21823/2311-2905-2020-26-2-109-119

Micro-Arc Zn- and Ag-Containing Coatings for Implants with Complex Porous Architecture Obtained by 3D Printing Method from Titanium Alloy

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Abstract

Background. The creation of porous three-dimensional materials for bone defects compensation and its subsequent regeneration is an important direction of medical materials science. The key issue in the interaction of an implant and bone tissue is the surface properties of the implant. ***The purpose of the study*** is to evaluate the physicochemical properties and compatibility of tissues of a living organism and porous implants with calcium phosphate Zn- and Ag-containing formed by microarc oxidation. ***Materials and Methods.*** Implants with various types of porous structure were made by direct laser sintering of titanium alloy Ti-6Al-4V powders. The calcium phosphate coatings, including Zn- and Ag-containing, were formed on the implants surface by microarc oxidation. ***Results.*** Coatings, deposited in electrolytes of various compositions, were uniformly distributed over the implants mesh structure. The phase composition of Zn-containing coatings, deposited in the acidic electrolyte, was represented by amorphous calcium phosphates. Ag-containing coatings, deposited in the alkaline electrolyte, had an amorphous-crystalline structure, the crystalline phase of which was identified as tricalcium phosphate in the α and β modifications. The samples of extracts of calcium phosphate Zn and Ag-containing coatings were co-cultured with pFb line of the human postnatal fibroblasts for 48 hours at 37°C in 5% CO_2 atmosphere. The MTT test revealed a high metabolic activity of the co-cultured fibroblasts in comparison with the fibroblasts of control. ***Conclusion.*** The pFb line of the human postnatal fibroblasts retained their viability for 48 hours of co-culturing with calcium-phosphate Zn- and Ag-containing coatings. The tested product and its components did not negatively affect the cellular respiration. However, further studies are needed to determine the rate of bioresorption and the degree of antibacterial activity of calcium-phosphate Zn- and Ag-containing coatings.

Keywords: additive technologies, three-dimensional framework, porous structure, microarc oxidation method, antibacterial biocoating.

Cite as: Sharkeev Yu.P., Sedelnikova M.B., Tolkacheva T.V., Shcheglova N.A., Panchenko A.A., Krasovsky I.B., Solomatina M.V., Efimenko M.V., Pavlov V.V., Cherdantseva L.A., Kirilova I.A. [Micro-Arc Zn- and Ag-Containing Coatings for Implants with Complex Porous Architecture Obtained by 3D Printing Method from Titanium Alloy]. *Travmatologiya i ortopediya Rossii* [Traumatology and Orthopedics of Russia]. 2020;26(2):109-119. (In Russian). doi: 10.21823/2311-2905-2020-26-2-109-119.

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Received: 27.02.2020. Accepted for publication: 05.06.2020.

Introduction

The creation of new composite materials and coatings with desired properties is one of the main directions of modern science and technology. The contemporary research is aimed at creating biocompatible, osteoconductive and biostable scaffolds [1, 2] for tissue engineering, with the required mechanical strength to perform the necessary supporting functions [3, 4]. To improve osseointegration, scaffolds for tissue engineering are made porous to be close in structure to bone tissue [2]. Porous three-dimensional material provides the necessary conditions for cell growth and division, while architectonics determines the final structure of the newly formed bone [3].

Additive technologies are an important and rapidly developing area of production technology in the field of mechanical engineering, aircraft industry, and biomedical engineering [5]. The direct metal laser sintering (DMLS) has several advantages over traditional manufacturing technologies. The main one is the ability to quickly produce geometrically complex parts without the need for their machining. DMLS technology makes it possible to simultaneously create several models, the number of which is limited only by the size of the working chamber, as well as to create individual implants of complex shape for reconstructive interventions.

Among other factors, the effectiveness of the implant interaction with living tissues is determined by the surface properties of the interacting structures [6, 7, 8, 9, 10]. To make a biologically inert metal biologically active and minimize connective tissue formation in the implantation zone, the implants surface is coated with calcium phosphate by various methods [6, 8]. The method of microarc oxidation (MAO) has many advantages over others, since it allows the formation of protective, corrosion-resistant, hardening, and biologically active coatings on the surface of valve metals [11, 12]. Using the MAO method, it is possible to precipitate calcium phosphate (CaP) compounds on complex metal substrates and, thus, to modify and functionalize the surface of various implants [13, 14, 15, 16, 17]. For coating materials, the compounds that are closest in composition and properties to the components of human bone tissue are mainly used, namely hydroxyapatite (HA), tricalcium phosphate (TCP), octacalcium phosphate [12, 13, 14, 15], acidic calcium phosphates (brushite, monetite) [16, 17]. A serious problem in the field of reconstructive biomedicine is an implant-associated infection, which may be the causes of severe inflammation in the implantation zone and is accompanied not only by pain, but also by the development of purulent-destructive tissue changes with the development of septic loosening of implants [18, 19].

The study purpose — to evaluate the physicochemical properties and compatibility of living organism tissues and porous implants with CaP+Zn- and +Ag-containing formed by MAO.

Materials and Methods

The porous implants were made of titanium alloy powders EOS Titanium Ti64ELI (Ti-6Al-4V) by DMLS. The chemical composition of the powder was corresponded to ASTM F136 and ASTM F3001. The preparatory process included the creation of a three-dimensional computer model of the implant sample with a variable porous structure based on multi-slice computed tomography, geometry modeling and desired implant structure. The resulting computer three-dimensional model of the implant was exported to specialized EOSM290 3D printer software. The 3D printing of the implant was performed by DMLS of finely dispersed titanium powder. After cooling, the implant was removed from the working chamber and subjected to heat treatment to relieve internal stresses and increase the ductility of titanium. During the heat treatment, the prod-

uct is gradually heated in a vacuum medium or in argon medium to 500–1000°C, held for 1 to 6 hours at the required temperature, and gradually cooled to room temperature. Then the implant was washed in an ultrasonic bath with solutions of alkali, inorganic acid or a mixture of acids. The process was completed by repeated washing of the implant in an ultrasonic bath with distilled water for 30–60 minutes to remove solvents. Before coating, the implant was subjected to the standard procedure of disinfection and sterilization by autoclaving in a way that guaranteed sterility of the products, followed by placement in a sterile sealed package.

The coatings were applied by the MAO with MicroArc-3.0. The method includes: a switching power supply, a computer for setting parameters and controlling the coating process, a galvanic cooled bath and a set of electrodes. Two types of electrolytes were employed.

No 1, the acidic electrolyte, (pH = 1–2), included H_3PO_4 (30% solution), $CaCO_3$ (50–75 g/L) and HA nanopowder of two different compositions (40–60 g/L): a) stoichiometric HA $Ca_{10}(PO_4)_6(OH)_2$ and b) Zn-substituted HA $Ca_{9.5}Zn_{0.5}(PO_4)_6(OH)_2$. With an acidic electrolyte, two types of coatings were obtained: CaP coating without additives (CaP-acid) and CaP with Zn (Zn-CaP).

No 2, the alkaline electrolyte, (pH = 10–11), contained Na_2HPO_4 (30–40 g/L), NaOH (3–5 g/L), β-tricalcium phosphate (β-TCP) powder with chemical formula β-$Ca_3(PO_4)_2$, 60–90 g/L). The β-TCP particle size was 1.5–5.0 μm. In this electrolyte, CaP containing no trace elements (CaP-alk) coatings were formed. After $AgNO_3$ (0.3–1.0 g/L) was added to electrolyte No. 2, Ag-containing CaP (Ag-CaP) coatings were also made.

The coating was carried out by MAO discharges migrating over the surface of the processed material immersed in the electrolyte. The process parameters were as follows: pulse duration — 100 μs, pulse repetition rate — 50 Hz, pulse voltage value — 200–500 V, process duration — 10–20 min. To study the surface morphology of the coatings, we used the LEO EVO 50 scanning electron microscope (SEM), Carl Zeiss, Germany, equipped with energy dispersive microanalysis equipment of Collective use center "Nanotech", Tomsk, Russia (Nanotech). The coatings thickness was measured by the MK-25 micrometer. The coating phase composition was determined by the method of X-ray phase analysis using CoKα radiation ("Nanotech"). The crystalline phases were identified using the standard Joint Committee on Powder Diffraction Standards (JCPDS) card index.

The biocompatibility evaluation of Zn–CaP and Ag–CaP coatings in vitro was carried out by testing the extracts [20] in the culture of human postnatal fibroblasts (HPF) pFb.

The extracts were made by incubating the test samples (average weight of one sample = 12.9 g) in Dulbecco's Modified Eagle's Medium (DMEM) with gentamicin 100 IU/ml at 37°C (2 ml/sample) in 5% CO_2 atmosphere for 72 hours.

To produce a subconfluent monolayer of the HPF culture, the latter were placed in a 96-well plate and cultured for 24 hours in DMEM culture medium supplemented with 10% fetal bovine serum and gentamicin 100 IU ml at 37°C in 5% CO_2 atmosphere. Then, the obtained extracts of the studied samples were placed into a 96-well culture plate to the subconfluent monolayer of the HPF culture and contained for 48 hours in an incubator at 37°C in 5% CO_2 atmosphere. An intact culture medium was used as a control, which was incubated for 72 hours at 37°C in 5% CO_2 atmosphere. After incubation, it was introduced simultaneously with the extracts of the studied samples into the HPF culture for 48 hours [21]. The cell viability was evaluated by the MTT test according to the standard method with the MTT Cell Proliferation Kit (Roche Diagnostics, Germany). Determination of the HPF viability was based on an assessment of the cells metabolic activity by their ability to reduce

the tetrazolium dye 3-(4,5-dimethylthiazol-2-yl) -2,5-diphenyl-tetrazolium bromide into insoluble formazan of dark violet color [21]. Absorption was measured automatically by the ELx808 photometer (BioTek Instruments Inc., USA) at a wavelength of 540 nm. For each test sample (n = 15) and for the control (n = 1), 8 independent measurements of the optical density of the solution were carried out during the MTT test.

Statistical analysis

In the statistical analysis of the obtained data the average values and standard deviations were calculated. Data processing was performed with Microsoft Office Excel 2013. The obtained data set was checked for distribution normality by the Shapiro-Wilk test with the STATISTICA 6.0 software package. The confirmation of the distribution normality made it possible to use the parametric statistics (Dunnett's test) to compare the data of the experimental groups with the data of the control.

Results

The samples of porous implants with various types of porous structure were made by DMLS from titanium alloy powders. With this technology, the print resolution averages around 20 μm. For comparison: a typical thickness layer in printers using Fused Filament Fabrication (FDM) is about 100 μm. The advantages of surgery with implants made by 3D printing technology are as follows: the exact matching with a bone defect in shape and geometry, an individual approach to complex defects repair, and the implants surface as close as possible to the bone tissue.

For the experiments, the samples of porous structures with the following dimensions were designed and made by 3D printing: 10 mm length, 10 mm width, 5 mm height. A porous structure of 4 mm high was formed on a solid metal substrate of 1 mm high. The appearance of the samples is shown in Figure 1.

The porous structure parameters (Figure 2):

Sample I. The average pore diameter of 0.8 mm; diameter of a grid core of 0.5 mm; volumetric porosity of the mesh structure 56%.

Sample II. The average pore diameter of 0.85 mm; diameter of a grid core of 0.5 mm; volumetric porosity of the mesh structure 58%.

Sample III. The average pore diameter of 0.75 mm; diameter of a grid core of 0.5 mm; volumetric porosity of the mesh structure 55%.

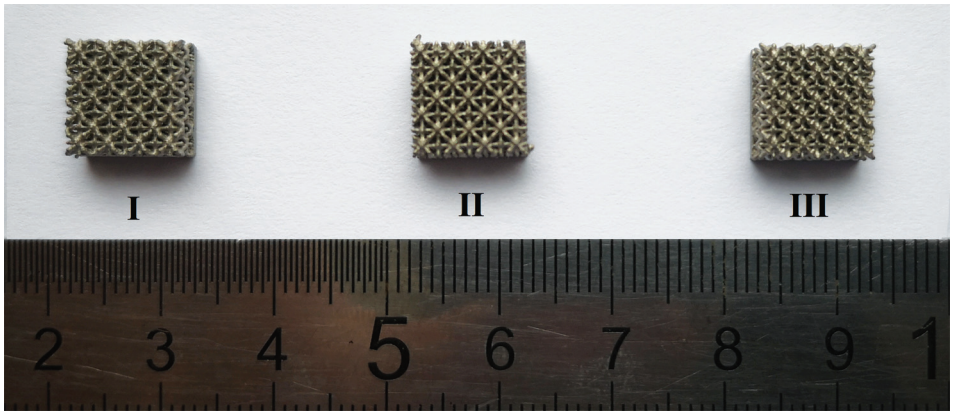

Fig 1. Samples of the porous materials made by DMLS.

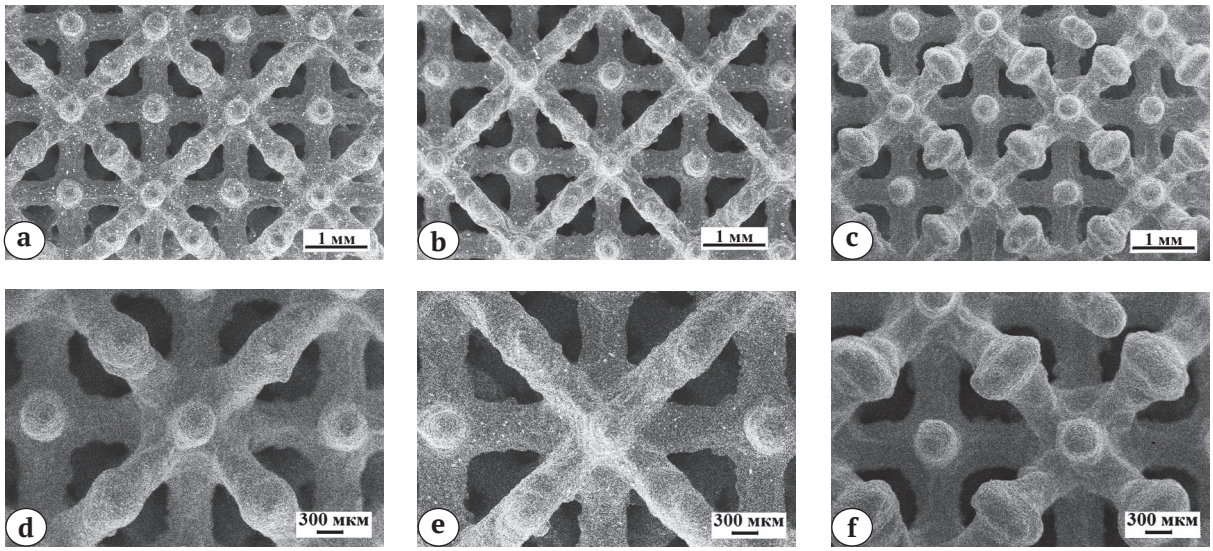

Fig. 2. SEM images of the porous implants structures made by DMLS:
types I (a, d); types II (b, e); types III (c, f). Magnification: ×50 (a, b, c), ×100 (d, e, f).

Coating CaP-acid and Zn-CaP in acidic electrolytes were formed on the surface of porous implants by the MAO, as well as CaP-alk and Ag-CaP coatings in alkaline electrolytes. By varying the MAO electrophysical parameters, the optimal duration and voltage of the process were established: 20 min and 200 V for an acidic electrolyte; 10 min and 400 V for alkaline electrolyte. Under such conditions, the coatings were most evenly distributed over the surface and internal pore space of the implants. The coating thickness varied in the range of 41–58 μm, and the roughness with respect to the parameter Ra varied in the range of 3.5–4.6 μm (Table 1).

SEM images show the relief and surface morphology of the coatings. The analysis of micrographs showed that coatings of all types, applied both in acidic and alkaline electrolytes, were uniformly distributed over the mesh structure of the implant (Fig. 3 a, d, g, j).

Table 1

Properties of the coatings formed at the MAO optimal electrophysical parameters

Indicators	Type of electrolyte		
	No 1 (pH = 1–2)		No 2 (pH = 10–11)
Type of coating	CaP-acid	Zn-CaP	CaP-alk
MAO voltage, V	200		400
MAO duration, min	20		10
Thickness, μm	58±2	50±3	41±3
Roughness, Ra, μm	3.7±0.1	3.5±0.2	3.6±0.4

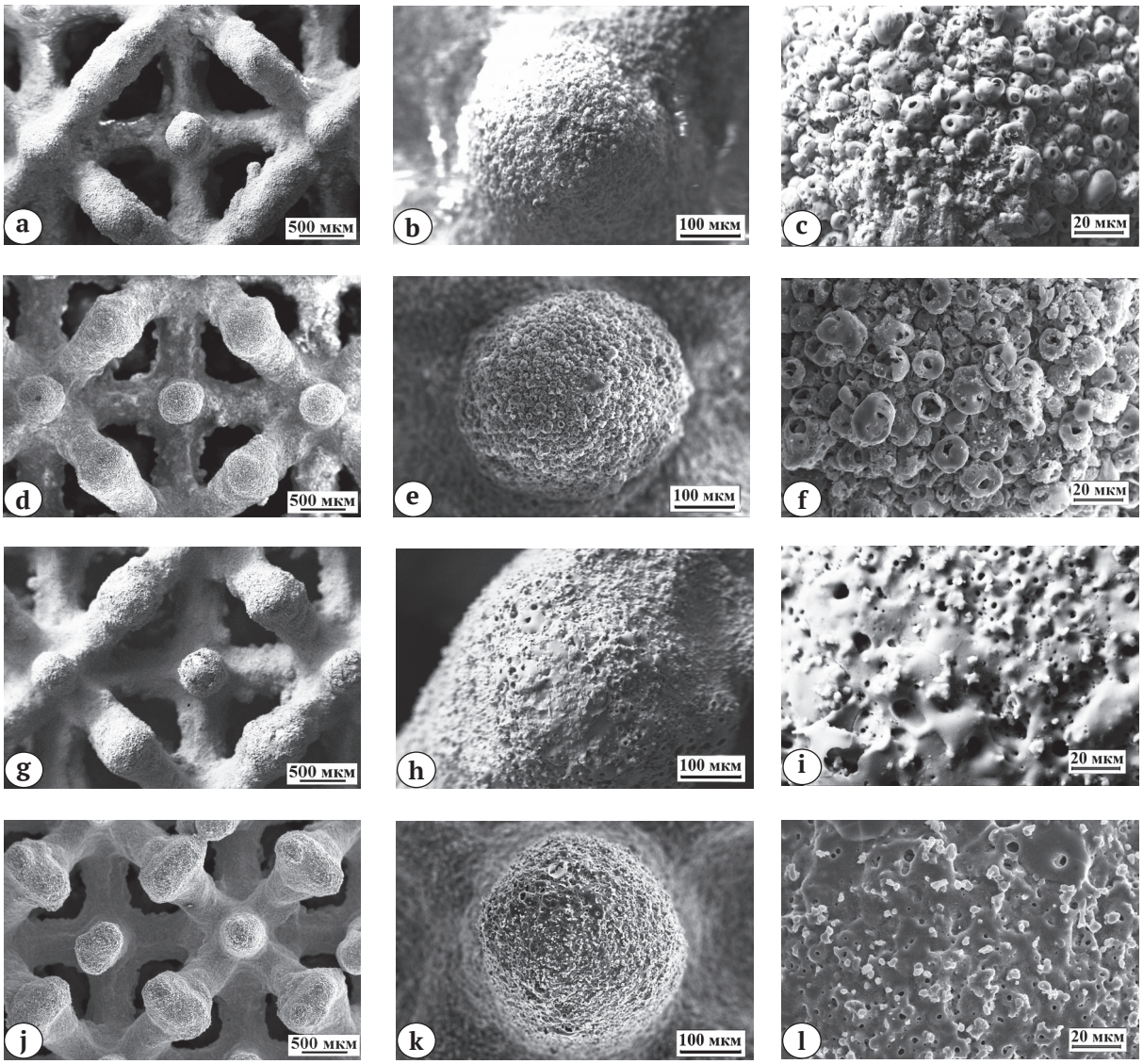

Fig. 3. SEM images of the porous implants coatings:
CaP-acid (a, b, c), Zn-CaP (d, e, f), CaP-alk (g, h, i) and Ag-CaP (j, k, l).
Magnification ×100 (a, d, g, j), ×500 (b, e, h, k), ×2000 (c, f, i, l).

The morphology of the coatings surface formed in various types of electrolytes is different. On the surface of coatings CaP-acid and Zn-CaP formed in electrolyte No 1 at a voltage of 200 V, porous spheres and fragments 10–15 μm in size could be seen (see Fig. 3 c, f). The coatings CaP-alk and Ag-CaP synthesized in electrolyte No 2 at a voltage of 400 V have a porous structure and contain isometric particles 3–5 μm in size (see Fig. 3 i, l). These isometric particles are β-TCP particles transported from the electrolyte into the coating at the final stage of the MAO, when the intensity of microarc discharges becomes minimal, as shown in previous studies [22].

Analysis of the coatings elemental composition, determined by the method of energy dispersive microanalysis, showed a high content of the main elements, such as phosphorus, calcium, oxygen, titanium, in the coatings (Table 2).

Table 2

The content of elements in coatings, atomic percent

Elements	Type of coating			
	CaP-acid	Zn-CaP	CaP-alk	Ag-CaP
O	60.7±1.0	68.7±0.2	59.4±1.2	68.4±0.2
Al	1.0±0.03	0.7±0.05	1.4±0.3	0.8±0.07
P	20.8±0.4	15.9±0.2	14.9±0.6	10.6±0.3
Ca	5.7±0.4	5.0±0.4	10.0±1.0	8.5±0.8
Ti	11.3±0.4	9.3±0.5	13.8±1.1	12.0±0.8
V	0.5±0.03	0.5±0.03	0.6±0.06	0.4±0.03
Zn		0.06±0.03		
Ag				0.04±0.02
Ca/P ratio	0.3	0.3	0.7	0.8

The remaining elements, aluminum and vanadium, brought into the coating during the electrolyte interaction with a metal matrix, were contained in a small amount. The same can be said about the trace elements introduced into the coatings to give them special antibacterial properties — zinc and silver. Their content in the coatings does not exceed 0.1 atomic percent. Calcium to phosphorus ratio for the coatings formed in an acidic electrolyte is 0.3, and for coatings deposited in an alkaline electrolyte, the maximum — 0.8.

On the distribution maps of the elements, it can be observed that for the Zn-CaP coating, both the main elements and microelements are distributed uniformly over the surface (Fig. 4).

A different picture is observed for Ag-CaP coating. Phosphorus and calcium are concentrated mainly in β-TCP particles forming the surface relief of the coating (Fig. 5).

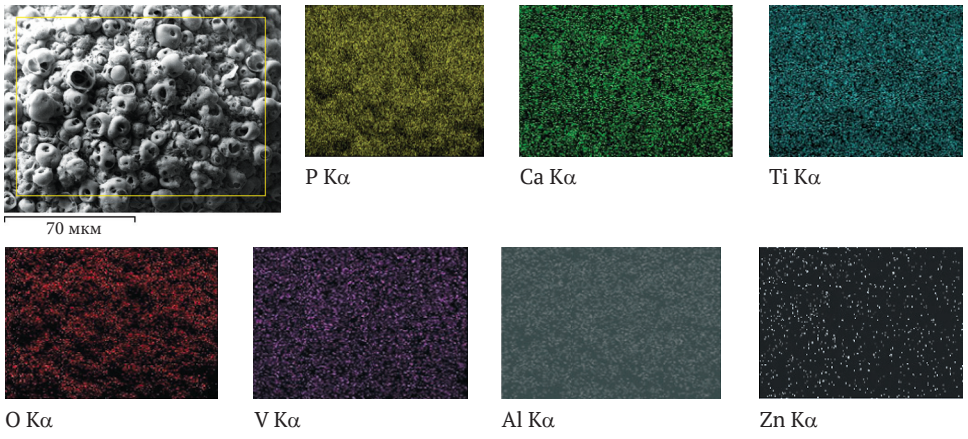

Fig. 4. SEM images and the elements distribution maps in the acidic calcium phosphate coating with Zn.

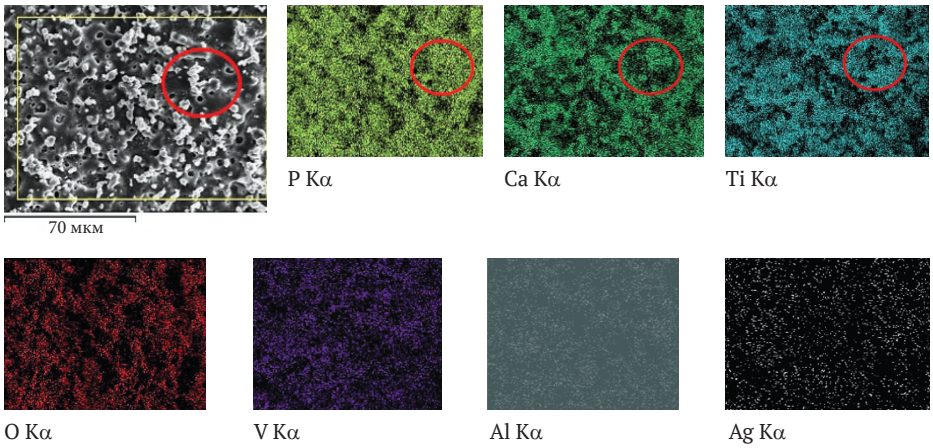

Fig 5. SEM images and the elements distribution maps in the alkaline calcium phosphate coating with Ag.

Titanium, aluminum, and vanadium are localized mainly in particle-free coating regions. Silver is evenly distributed in the coating.

The X-ray phase analysis of the coatings revealed that CaP-acid and Zn-CaP coatings had an amorphous structure, as evidenced by the halo in the range of angles 20–45° (Fig. 6 a). Single peaks taken place in the X-ray diffraction related to the base material (Ti). The CaP-alk and Ag-CaP coatings had an amorphous crystalline structure (Fig. 6 b). X-rays also showed a small halo in the region of 23–45°, which indicated the presence of an amorphous phase in the coatings.

The MTT test did not reveal any statistically significant differences in the absorption parameters of the formazan solution during incubation of HPF with extracts of the studied samples No 1 to 15 compared to the formazan solution absorbance in the intact HPF culture.

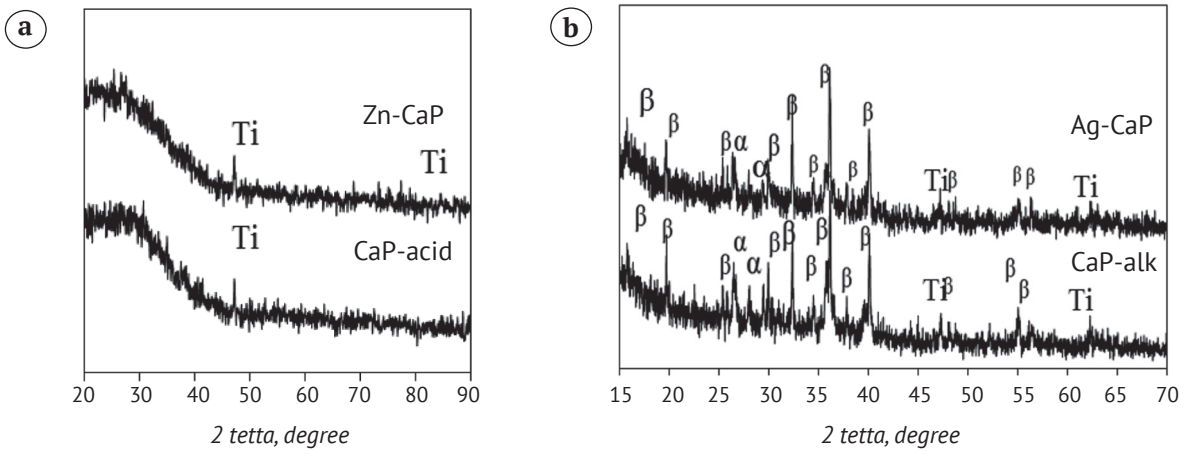

Fig. 6. X-ray coatings placed in the acidic (a) or alkaline electrolytes (b):
Ti — titanium; α — α-TCP; β — β-TCP, TCP = tricalcium phosphate.

The results of the MTT test indicated that the HPF, jointly cultivated with extracts of the samples No 1 to 7, 10, 13 to 15 of Zn-CaP and Ag-CaP coatings for 48 hours at 37° C in 5% CO_2 atmosphere, preserved their metabolic activity at the level of intact HPF culture (Fig. 7).

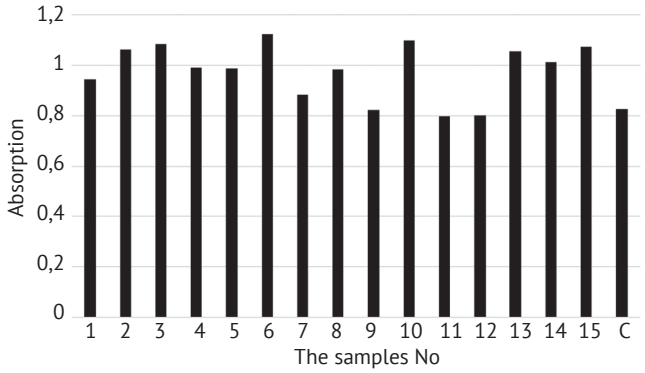

Fig. 7. The results of the MTT test. The HPFs were jointly cultivated with the extracts of the samples No 1 to 15 of Zn-CaP and Ag-CaP coatings for 48 hours at 37°C in 5% CO_2 atmosphere. The mean absorbance values M±SD, the last C — control.

These data make it possible to draw a conclusion that the extracts of the studied samples from 1 to 15 were biocompatible with HPF.

Discussion

S.M. Wallace et al. [23] showed that further prospects for developing effective protection for medical implantable devices and products were associated with the study and application of new non-specific mechanisms of action of pathogenic microorganisms control. One of the solutions to this problem may be the modification of the implant surface with coatings containing antibacterial agents, such as Ag or Zn [24]. In the present work, Zn- and Ag -containing calcium-phosphate coatings in acid and alkaline electrolytes were formed on the surface of porous implants made of titanium alloy (Ti-6Al-4V) by the MAO. Due to the different composition of electrolytes, the MAO occurred at various voltages and was characterized by various durations. M. Rizwan et al. [11] and S. Liu et al. [12] showed that MAO characterized by plasma heating in the channels of microarc discharges up to temperatures above 1100°C. As a result, the decomposition of electrolyte components and the formation of new phases occurred. In this study, in an acidic electrolyte, the amorphous structure coatings were formed. On the other hand, in an alkaline electrolyte contained TCP particles, at a temperature of 1125°C, a polymorphic transition of β-TCP to α-TCP was observed. This was also confirmed by P.V. Evdokimov et al. [25]. The product and its components did not negatively affect the cellular respiration rate. This ensured the cell viability preservation for 48 hours. Previous experimental studies demonstrated that Zn- and Ag-containing microarc coatings deposited on the surface of flat samples of titanium (VT1-0) and titanium-niobium alloy (Ti-40 wt.% Nb) revealed antibacterial activity against Staphylococcus aureus 209P [22].

Conclusion

In the process of investigation the effects of the Zn-CaP and Ag-CaP coatings of the porous surface of the implants made by DMLS from titanium alloy powders on live HPF, it was established that the cells viability was preserved. The product and its components did not negatively affect the rate of cellular respiration, which ensured the preservation of cell viability for 48 hours. This opens the possibility to employ the studied types of coatings for creation of porous titanium alloy (Ti-6Al-4V) implants with antibacterial properties.

Acknowledgements

The authors are grateful to V.V. Chebodaeva and M.A. Khimich, the Junior Research Fellows at the Institute of Strength Physics and Materials Science of the Siberian Branch of Russian Academy

of Sciences, Tomsk, Russian Federation, for their assistance in the experiments conduction.

Conflict of interest: The authors declare no conflict of interest.

Funding: This work was financially supported by the Basic Research Program of the Siberian Branch of Russian Academy of Sciences, 2013–2020, Project No III.23.23.5.

Authors' contributions

Yu.P. Sharkeev — research concept and design, literature review.

M.B. Sedelnikova — literature review, data processing, text preparation.

T.V. Tolkacheva — coatings placement, research conduction, data processing.

N.A. Shcheglova — titanium porous implants formation, research conduction, data processing, text preparation.

A.A. Panchenko — titanium porous implants formation, research conduction, data processing.

I.B. Krasovsky — research concept and design, literature review, text editing.

M.V. Solomatina — biological research conduction, data processing.

M.V. Efimenko — biological research conduction, data processing.

V.V. Pavlov — research conduction, data processing, text editing.

L.A. Cherdantseva — biological research conduction, data processing.

I.A. Kirilova — literature review, text preparation.

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