ABSTRACT

of dissertation for the Philosophy Doctor (PhD) degree on 6D072300 - "Technical Physics" specialty

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"Physical properties of a composite materials and coatings based on calcium phosphates for biomedical application"

Brief description of the work. The dissertation is dedicated to conducting experimental research on the structural and phase state of biocomposite materials and coatings based on hydroxyapatite (HA) and sodium alginate (Alg) with added silver. Additionally, their antibacterial properties and biocompatibility were investigated. Advanced experimental methods were utilized throughout the work, conducted in laboratories of research centers in Kazakhstan and in other countries.

The relevance of this study is due to the presence of a number of problems in the field of traumatology and orthopedics, related to the emergence of antibiotic resistance in bacteria as a result of the widespread use of antibacterial drugs. The development of infections after surgery can lead to serious complications, such as osteomyelitis (inflammation of the bone marrow), osteoporosis, and others. This can result in implant failure, widespread infection (sepsis), and, in some cases, the need for limb amputation. One possible solution to this problem is the use of bone fillers and implants with antibacterial coatings based on inorganic compounds, such as zinc oxide, copper oxide, and silver ions.

In addition, there is a problem of implant rejection caused by an allergic reaction to the implant material. Therefore, the development of biocomposite materials and coatings with high osteoconductive and osteoinductive properties is a priority task.

This study proposes the creation of biocomposite materials and coatings with bioactive and antibacterial properties. Bone tissue is a natural composite material consisting of an inorganic component - hydroxyapatite, and an organic matrix - collagen. To create the composite material, it is proposed to use biomimetic hydroxyapatite incorporated into a biopolymer matrix of sodium alginate, along with the addition of silver ions as an antimicrobial agent. Additionally, it is proposed to apply calcium-phosphate coatings with the addition of silver onto the medical titanium alloy Ti6Al4V ELI to enhance the osseointegration of implants and provide antibacterial properties.

However, the mechanism of silver ion influence on the structural and phase state of the inorganic component of hydroxyapatite is not yet fully understood. Therefore, an important task is the creation of composite materials and coatings based on hydroxyapatite and sodium alginate with the addition of silver ions, as well as studying the impact of silver ions on their structural and phase state and antibacterial properties.

Research object. Obtaining a silver-doped biocomposite material and the process of applying an oxide coating based on calcium phosphates onto substrates of 3D-printed titanium alloy using a microarc method.

Research subject. Morphology, structural and phase states of the biocomposite material at different concentrations of the doping additive, the influence of silver ions on the antibacterial and cytotoxic properties of the materials and coatings.

Research methods.

Modern experimental research methods were employed in this dissertation study, such as scanning electron microscopy (SEM) to examine surface morphology, infrared spectroscopy to investigate the functional composition, as well as X-ray diffraction analysis (XRD) and transmission electron microscopy (TEM) to study the structural and phase state of the obtained materials.

The substrates were manufactured from titanium alloy powder (Ti-6Al-4V) DIN EN ISO 22674 Rematitan® using the selective laser melting (SLM) method on an additive manufacturing system (Concept Laser MLab Cusing R), and the calcium-phosphate (CP) coating was applied using the microarc oxidation (MAO) method.

The antibacterial properties of the obtained biocomposite materials were investigated using the agar diffusion and d time-kill test methods. Additionally, the biocompatibility of the materials was studied on cultures of mouse osteoblast and fibroblast cells.

Research Objective. The objective of this dissertation study is to investigate the influence of silver ions on the structure, morphology, phase composition, biocompatibility, and antibacterial properties of a biocomposite material based on hydroxyapatite and sodium alginate. Additionally, the development of a method for obtaining coatings with similar physicochemical properties through microarc oxidation for medical devices.

Tasks:

1. To synthesize a biocomposite material based on hydroxyapatite and silver-ion-doped sodium alginate, and to study the influence of silver ions on the elemental and phase composition, as well as the physicochemical properties of the biocomposite materials HA-Ag and HA-ALG-Ag.
2. Develop the deposition regimes for calcium-phosphate coatings using the microarc oxidation method.
3. Investigate the elemental and phase composition of the calcium-phosphate coating. Establish the correlation between the elemental and phase composition and the parameters of microarc oxidation (MAO) for obtaining calcium-phosphate coatings on titanium alloys.
4. Study the biocompatibility of the composite materials HA-Ag and HA-ALG-Ag on NIH-3T3 fibroblast cell cultures.
5. Investigate the antibacterial properties of the obtained biocomposite materials HA-Ag and HA-ALG-Ag.

Scientific novelty of the research:

– A method has been developed for obtaining a biocomposite material with antibacterial properties based on hydroxyapatite and sodium alginate doped with silver ions.

– For the first time, a biocomposite material based on hydroxyapatite and sodium alginate with silver ions was investigated, and the effect of alginate on enhancing the penetrability of silver ions in the studied material under the influence of ultrasound and microwaves was examined.

– New experimental data on the substitution of calcium ions with silver ions in the crystalline structure of hydroxyapatite have been obtained.

– The deposition regimes for calcium-phosphate coatings using the microarc oxidation method have been optimized.

Scientific and practical significance of the work

– The possibility of obtaining a biocomposite material with antibacterial properties for biomedical applications has been demonstrated, as confirmed by the utility model patent No. 8000 (21) 2023/0082.2.

– Research conducted using experimental methods allows for a more detailed study of the morphology and physical properties of the interaction between sodium alginate and hydroxyapatite in the presence of silver ions. It also helps in better understanding the mechanisms of action of such materials on microorganisms and optimizing their properties. Conducting such research is of utmost importance as the search for and development of more effective methods for the treatment and prevention of infections, especially in the context of the growing problem of antibiotic resistance, is a priority direction in modern medicine.

– Studying the structure and phase composition of coatings allows for a better understanding of the processes occurring during microarc oxidation (MAO).

Communication of work with research projects

This dissertation was carried out at the “EKTU D. Serikbayev” within the framework of the project funded by the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan. The project titled fundamental and applied scientific research of young postdoctoral scientists under the Zhas Galym project for 2022-2024 aims to study the “Surface modification of a titanium alloy product by plasma electrolytic oxidation". Project reference number: AP14972752.

Author's personal contribution

The author's personal contribution involves conducting experimental and theoretical research, processing measurement results, and analyzing them, as well as participating in the writing of publications and discussing research results at scientific conferences and exhibitions. The analysis and interpretation of the obtained results were carried out with the active involvement of the international scientific consultant, Professor A.D. Pogrebnyak, and the domestic scientific consultant, PhD, A.Turlybekuly.

The main provisions for defense:

– Adding $AgNO_3$ to hydroxyapatite in an amount of 2 molar percent results in the substitution of calcium ions with silver ions in the structure of hydroxyapatite.

– Increasing the concentrations of silver ions in the HA-Alg-Ag composite leads to the formation of the Ag_3PO_4 phase, which is confirmed by the changes in the intensity of P-O symmetric stretching vibration (ν1) in the FTIR

spectrum, as well as the results of transmission electron microscopy and X-ray diffraction analysis.

– In the HA-Alg-Ag composite, the presence of sodium alginate weakens the electrostatic bonds between Ag and the HA matrix, facilitating the diffusion of Ag+ ions within the material. As a result, there is an observed increase in antibacterial properties by 1.5-2 times compared to the HA-Ag composite.

– Calcium phosphate coating is formed only at high pulsed voltages. Additionally, adding 0.4 g/L of silver nitrate to the electrolyte increases the thickness of the oxide coating due to the higher current density during the microarc oxidation process.

Reliability of the received results. The obtained results are reliable due to the use of reliable and well-established experimental instruments, such as the scanning electron microscope (JSM-6390LV) with energy-dispersive spectrometer (EDS), transmission electron microscope (JEOL JEM-2100), X-ray diffractometer (PanAnalytical Xpret Pro), and FTIR-801 Simex infrared spectrometer. These instruments complement each other and confirm the obtained data. The experimental results were discussed at international and regional conferences and have been published in peer-reviewed scientific journals. Open discussions and idea exchange have contributed to a deeper understanding of the research results and improvement of the methodology.

Approbation of the research results

The obtained experimental data were reported and discussed at scientific and technical conferences and seminars:

– III Congress Of Traumatologists And Orthopedists Of The Republic Of Kazakhstan October 3-4, 2019 Astana, Kazakhstan;

– At the 9th International Conference NAP-2019, "Nanomaterials: Applications & Properties," held on September 9-14 in Odessa, Ukraine;

– VI International scientific and technical conference of undergraduate, graduate students and young scientists called “Creativity of youth for the innovative development of Kazakhstan” at D. Serikbayev East Kazakhstan State Technical University, 2020, Ust-Kamenogorsk, Kazakhstan.

– IX International scientific and technical conference of undergraduate, graduate students and young scientists called “Creativity of youth for the innovative development of Kazakhstan” dedicated to the 65th anniversary of D. Serikbayev East Kazakhstan State Technical University, 2023, Ust-Kamenogorsk, Kazakhstan.

Publications. The materials of this dissertation work have been published in 9 printed papers, including 1 article in journal included in the international information resources Web of Science Core Collection (ClarivateAnalytics) and Scopus, 3 articles in scientific publications approved by the Committee for Quality Assurance in Science and Higher Education of the MOHEAS RK, and 4 in the proceedings of international and republican scientific conferences. Additionally, there is 1 patent for a utility model in the Republic of Kazakhstan.

Structure and scope of the dissertation. The dissertation consists of an introduction, 5 sections, a conclusion, and a list of references with 166 sources cited. It comprises 104 pages of main computer text, including 42 figures and 11 tables.

The introduction highlights the relevance of the research and provides an overview of the problem addressed in this work. The research objectives and tasks are formulated, and the novelty of the obtained results is described, along with their scientific and practical significance. The main propositions to be defended are presented, and the author's personal contribution, publications, and the content of the dissertation are summarized briefly.

The first section provides a literature review that examines the main materials used in modern orthopedics. It also covers information about calcium phosphates, sodium alginate, biological apatite, bone tissue, and the mechanism of silver ions' antibacterial action.

The second section analyzes the research objects and extensively discusses the principles and methods for studying the morphology, structural-phase state, and process of obtaining calcium phosphate coating on titanium alloys. The synthesis methods of biocomposite materials with silver ions, such as HA-Ag and HA-Alg-Ag, under the influence of ultrasound and microwave waves, are described.

The third section presents the results of the research on the structural-phase changes of the synthesized biocomposite materials with silver doping (HA-Ag and HA-Alg-Ag).

The fourth section describes the results of the research on the morphology and phase composition of the calcium phosphate coatings deposited by the MAO method on titanium alloy substrates.

The fifth section presents the results of the research on the antibacterial properties, cytotoxicity, and biocompatibility of the biocomposite materials with the addition of silver (HA-Ag and HA-Alg-Ag).

The conclusion summarizes and formulates the main results that have been obtained within the framework of this dissertation.