BIOCOMPATIBLE ANTIMICROBIAL ZnO COATINGS ON Ti13Nb13Zr ALLOY FOR ORTHOPAEDIC APPLICATIONS

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Abstract

Biocompatibility is one of the requirements that every medical device must meet. The biological assessment of an implant or other medical device is performed according to the requirements of the EN ISO 10933 standard. Despite research on the biocompatibility of medical devices, the risk of bacterial, peri-implant, or hospital-acquired infections still exists, which prolongs healing processes and may cause issues with the proper acceptance of the implant by the body. To mitigate these infections, various solutions have been proposed to enhance antibacterial properties. The work attempts to develop and assess the suitability of the ZnO antibacterial coating to improve the physical and chemical properties of the Ti13Nb13Zr titanium alloy used for implants in bone surgery. The scope of the research included surface wettability tests, scanning electron microscope observations, surface roughness measurements, tribological tests, tests of coating adhesion to the surface, evaluation of electrochemical properties, and cytotoxicity tests. Based on the results, it was found that the applied ZnO coating showed the hydrophilic character of the surface and also improved the electrochemical properties of the surface, so it can be effectively used in biomedical applications simultaneously improving resistance to hydrophobic strains of bacteria.

Keywords: *ALD - atomic layer deposition, antimicrobial coatings, ZnO coating, biocompatibility, orthopaedics*

Introduction

Biocompatibility is one of the requirements that every medical device must meet. Despite research on the biocompatibility of medical devices, there is still a risk of bacterial infections that prolong healing processes and may cause undesirable reactions of the body to the implanted device [1,2]. The effects of nosocomial infections are compounded by infections with bacteria that are resistant to antimicrobials. These infections can lead to complications, prolonged hospital stay, or death [3], also, the excessive and unjustified use of antibiotics makes it impossible to effectively reduce the incidence of HAIs (healthcare-associated infections) caused by antimicrobial-resistant infections. Antimicrobial resistance is a growing threat to human health [3]. In the skeletal system, fractures, joint damage, or diseases related to individual bones are most often treated. To restore proper function of joints, bones, or the entire system, the use of implants is inevitable.

Currently, in addition to work on improving the physicochemical properties of biomaterials used for implants in surgery, as in the case of implants in contact with blood, work is being done on modifying the surface layer. The ability to modify and control surface properties at the nano and micro levels is one of the most important breakthroughs because it opens a completely new range of strategies to find the desired interaction of the implant with the biological environment [4]. The main direction of the current work related to surface functionalization is to reduce the risk of implant-related infections.

Due to the need to improve the antibacterial properties of biomaterials for contact with blood or bone tissue, new methods of surface modification are still being sought, and modification of the surface layer by applying a ZnO coating is one such solution [5-7]. The main function of zinc (Zn) is to support bone growth, formation, and mineralization. Its broad antimicrobial effect against both Gram-positive and Gram-negative bacteria has been proven. This element shows a very high degree of biocompatibility and biological stability, with low toxicity [8]. It has been proven that the zinc ferrite ($ZnFe_2O_4$) exhibits greater biocompatibility and lower toxicity than other metal ferrites; it also exhibits antimicrobial activity against, among others, *E. coli* and *S. aureus* [9]. Zinc oxide nanoparticles can also be used successfully in biological sensors for drug detection. Because of their unique properties, ZnO nanoparticles are ideal for enhancing the sensitivity and selectivity of biosensors. These nanoparticles facilitate efficient electron transfer and improve signal transduction, making them highly effective in detecting trace amounts of pharmaceutical compounds [10,11]. ZnO nanoparticles could provide new developments in drug delivery, especially for diagnosis, imaging, and therapy [12]. Zinc ions are also widely used in surface modifications of metal implants as an antimicrobial agent. Additionally, coatings based on ZnO nanoparticles can promote osteoblast proliferation and differentiation, which is beneficial for coatings on orthopaedic implants [13-15]. It is worth pointing out that ZnO can also be a flexible coating agent to modify the release and intracellular uptake of other polymeric or inorganic nanoparticles [12].

Due to the issue of hospital-acquired infections and implantation-related infections, antibacterial solutions are increasingly being implemented, which help reduce or eliminate infections through antimicrobial and disinfecting properties. For this reason, this work will present tests to assess the suitability of an antibacterial biocompatible coating, which may become a solution as a coating for the surface of implants.

The aim of this research was to evaluate the effectiveness of using an antibacterial ZnO coating to enhance the physicochemical properties of the Ti13Nb13Zr alloy, which is used to manufacture implants for bone surgery. To achieve this objective, the following research scope was proposed: surface wettability tests, observations using a scanning electron microscope, surface roughness measurements, tribological tests, evaluation of coatings adhesion to the surface, assessment of electrochemical properties, and cytotoxicity tests.

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Materials and Methods

Samples of the Ti13Nb13Zr alloy with a diameter of 14 mm were used for the research. The surface preparation of the material included grinding and polishing using an automatic polisher Tegramin-30 (Struers). Grinding was carried out using SiC abrasive papers with the following grades: 500, 800, 1000, 1200, 2000, and 4000, for 2 min each. The mechanical polishing process was performed using an Al_2O_3 suspension (OPS) on MD-Nap polishing cloth for t = 7 min. After initial surface preparation, the samples were cleaned using EMAG's Emmi-MF60 ultrasonic cleaner in a 99.5% isopropanol solution. The cleaning was carried out for 15 min at a frequency of 20 kHz.

In the next stage, thin coatings were obtained using Atomic Layer Deposition (ALD) method, employing diethyl zinc ($C_4H_{10}Zn$) as the precursor and water (H_2O) on the samples. The process was carried out at T = 200°C for 500 cycles. Each cycle consisted of two precursor pulses, each lasting 100 ms, interspersed with two purge pulses, each lasting 1 s. The carrier and purge gas was nitrogen (N_2) with a purity of 5.0 and a flow rate of 200 cm^3/min (TABLE 1).

TABLE 1. Parameters of the application process.

Parameter	
Number of cycles	500
Reactor temperature [°C]	200
Precursor pulse	2 pulses, 100 ms each
Purge	2 pulses, 1 s each

Surface observations

Microscopic observations of samples in the initial state and after the application of the coating were carried out using Tescan Vega 4 scanning electron microscope equipped with a spectrometer measuring X-ray radiation energy (EDS - Oxford Instruments).

Surface wettability tests

The wettability tests of the sample surfaces were carried out using the sitting drop method at room temperature (T = 22°C). The tests were performed on samples in their initial state and with the applied coating. Three drops of water and diiodomethane with a volume of 1 mm^3 were placed on the surface of each sample. The contact angle measurement lasted for t = 60 s. Based on the obtained contact angle values with water and diiodomethane, the surface free energy (SEP) was determined by the Owens-Wendt method. Understanding the wettability of ZnO-coated surfaces helps predict their behaviour in a biological environment, which is essential for ensuring optimal cell attachment and tissue integration.

Surface roughness measurements

Surface roughness measurements were carried out in accordance with the requirements of the ISO 25178 standard, using a Leica optical profilometer with DCM8 confocal mode with Leica Map Premium 9 software at 20x magnification. Calibrations of the profilometer before measurements were carried out using a standard plate of known roughness and a standard plate of known fringe width. The following parameters were tested: Sa (average difference in height over measurement area), Sz (the sum of the largest peak height and pit depth values within the measurements area), Sp (maximum peak height over measurement area), Ra (average difference in height along the measurement trace), Rz (the sum of the largest peak height value and the largest pit depth value along the sampling length), Rp (maximum profile peak height). The analyzed parameters allow for a detailed description of surface roughness, which significantly affects the surface properties of orthopaedic implants, among others, osteointegration, osteoconductive, or bacterial adhesion properties. The evaluation of surface roughness provides insight into how coatings might influence cellular responses and mechanical stability, contributing to the overall success of the implant.

Tribological tests

The tribological wear test was performed using the pin-on-disc method using the TRB^3 tribometer (Anton Paar). A steel ball and a ceramic ball (Al_2O_3) were used as a counter-sample. The nominal force applied during the test was 0.5 N and the linear velocity was 4.13 cm/s. The analysis of the wear trace, which included the morphological assessment of the surface and the determination of the wear volume, was carried out using an optical profilometer with Leica Map Premium 9 software. Determination of abrasion resistance allows estimation of wear resulting from frictional forces in the implant-bone system. These tests measure the coefficient of friction and the wear rate of the coated surfaces. The wear index W was determined for each sample according to the following formula:

$$W = \frac{V}{F_n \cdot S}$$

W – wear rate [mm^3/Nm]
V – wear volume [mm^3]
F_n – nominal force [N]
S – total sliding distance [m]

The adhesion of the coating to the surface

Tests of the adhesion of the applied coatings to the surface were carried out using the scratch test method using an open platform from CSM equipped with a micro-combi-tester using a Rockwell diamond penetrator. The test was performed with a loading force increasing from 0.03 to 30 N, with a constant loading speed of 10 N/min, with a table travel speed of 1 mm/min, and a scratch length of ≈3 mm. The critical force value was assessed based on the recorded friction force and microscopic observations of scratching. The following parameters were determined: Lc_2 - the force causing the first crack and Lc_3 the force causing complete delamination of the coating. Testing the adhesion of coatings to the substrate makes it possible to determine their durability and resistance to mechanical damage.

Electrochemical properties

Pitting corrosion resistance tests were carried out using the potentiodynamic method, recording the anodic polarization curve on samples in the initial state and samples with the applied coating. An AutoLab PGSTAT 302N potentiostat from MetroOhm with Nova 2.1 software was used for the tests. The tests were carried out in a three-electrode system with a working electrode - the test sample, and a reference electrode - Ag|AgCl(s)|KCl. The auxiliary electrode was a platinum wire. The tests were carried out on the Fisher Bioreagents PBS solution with a composition of 1.37 M NaCl, 0.027 M KCl, and 0.119 M phosphates per 1 dm^3 of solution. The study began with the determination of the open circuit potential (E_{ocp}) measured for 15 min.

Potentiodynamic curves were recorded from an initial potential of $E_{init} = E_{ocp}$ - 100 mV. The scan rate was 3 mV/s. The direction of polarization was changed when the anodic current density reached 1 mA/cm^2 or a potential of 2 V. From the obtained curves, the values of the corrosion potential E_{corr} and the polarization resistance Rp were determined using the Stern method. Assessing corrosion resistance ensures that ZnO coatings can protect the underlying alloy from degradation, thereby extending the life of the implant and maintaining its integrity in the body.

Cytotoxicity tests

The cytotoxicity of the samples was assessed based on indirect contact tests. Before testing, the samples were sterilized with ethylene oxide. The test samples were placed in the extraction medium, which was a complete culture medium. 10 ml of extraction medium was used per 1 g of sample. Extraction was carried out at 37°C for 24 hours, under constant shaking. Cytotoxicity tests were performed according to ISO 10993-5. The fibroblast line, clone L 929 - American Type Culture Collection (ATCC), was used for the study. Cells were cultured under standard conditions in Medium 199 supplemented with 10% FBS for 72 h. After incubation, fresh medium was added to all cultures, which was supplemented with extraction medium by adding 1 ml of extraction medium to 9 ml of culture medium. The cells were incubated under these conditions for 24 hours. In vitro cytotoxicity assays were chosen, utilizing relevant cell lines such as osteoblasts or fibroblasts. These assays are standard in biomaterial research for evaluating the interaction between cells and the coating material.

Statistical analysis

The results presented in this paper are presented as averages accompanied by standard deviation. To determine the significance of differences at $p < 0.05$, a one-way analysis of variance (ANOVA) was conducted.

Results and Discussions

Scanning electron microscopic observations

The surface morphology of the Ti13Nb13Zr alloy in the initial state and with the applied coating is presented in FIG. 1.

The assessment of the surface morphology, performed during observation with a scanning electron microscope, indicated that the surface is homogeneous, which is characteristic of the samples after the mechanical polishing process. No significant differences were observed between the initial state and after application of the coating. No microcracks, scratches, or discontinuity of the surface layer were found. The application of the coating did not alter the topography, and the surface of the entire sample remained homogeneous.

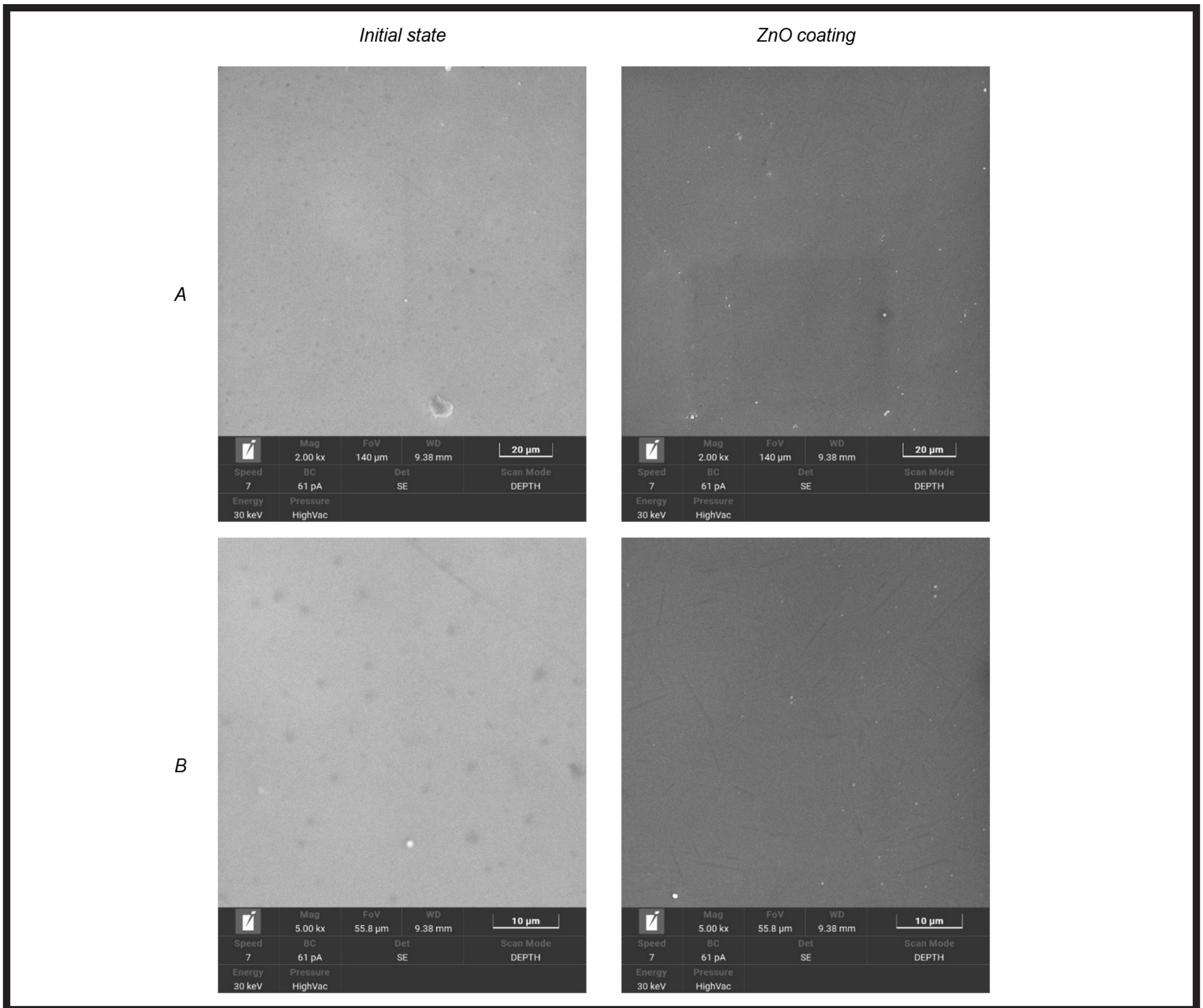

FIG. 1. Microscopic observations of the tested samples, A – 2000x, B – 5000x.

TABLE 2. Results of the surface wettability tests.

Sample	The contact angle [°]		Polar component [mJ/m²]	Nonpolar component [mJ/m²]	Surface Free Energy (SEP) [mJ/m²]
	H_2O	Diiodomethane CH_2I_2			
Initial state	81.84 ± 2.8	44.36 ± 1.57	4.17	33.41	37.58
ZnO	52.95 ± 1.12	42.76 ± 2.44	26.43	21.43	47.86

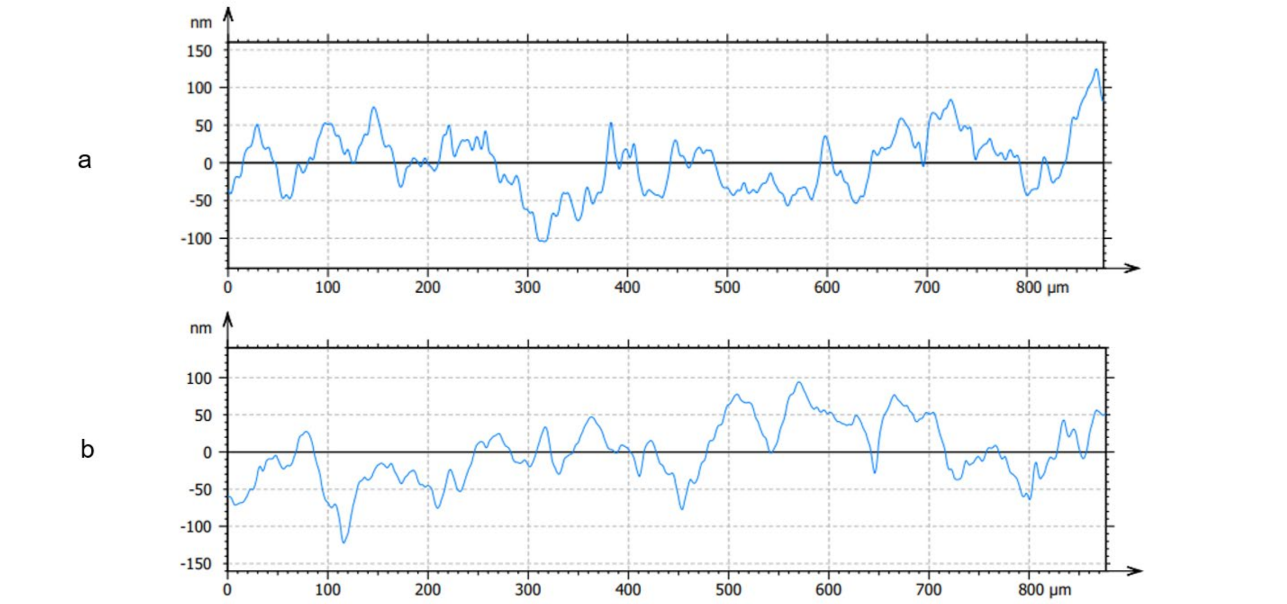

FIG. 2. An example of a roughness profile: a – sample in its initial state, b – sample with a coating.

Surface wettability tests

The measurement results of the wettability of the sample surfaces, including the contact angle and the components of surface free energy, are presented in TABLE 2. The measurements were carried out for samples in the initial state and samples with the applied coating.

Based on the results of surface wettability tests, it can be concluded that the application of the ZnO coating significantly affects the contact angle values compared to the samples in their initial state. There were differences between the average contact angle of water on the surface of the samples in their initial state and those with the ZnO-applied coating (TABLE 2). The samples in the initial state exhibited a contact angle of H_2O θ = 81.84° ± 2.8, while the ZnO coating demonstrated a contact angle of θ = 52.95°±1.12, which indicates the hydrophilic nature of the surface. The average diiodomethane contact angles for both samples were similar, measuring θ = 44.36° ± 1.57 and θ = 42.76° ± 2.44, respectively. The application of the ZnO coating resulted in a decrease in the contact angle, suggesting that the coated surface is more hydrophilic than that of the samples in their initial state. The greatest differences in the surface free energy (SFE) components were observed in the polar component, where for the surface in the initial state it was 4.17 mJ/m², and for the surface with the ZnO coating it was 26.43 mJ/m². For both samples, the value of the non-polar component was greater than that of the polar component, which may indicate a greater affinity of the tested samples to non-polar groups. The samples with the coating exhibited a higher SFE value of 47.86 mJ/m², which further confirms the more hydrophilic nature of the ZnO surface compared to that of the initial state. In addition, the differences in contact angle values between the titanium alloy and the analyzed coating are statistically significant (p-value < 0.05).

Due to the hydrophilic nature of the surface, the coating may be effective against hydrophobic bacteria, such as the capsular forms of *S. aureus* and *S. epidermidis*, which are among the most frequently detected pathogens [16-18]. These bacteria are responsible for infections associated with orthopaedic catheters and implants [18].

Surface roughness measurements

Surface profiles of the samples in their initial state and that with a coating are presented in FIG. 2; the results of the roughness parameters are presented in TABLE 3.

Based on the results obtained from examining the surface topography (TABLE 3), it was concluded that the application of the coating does not significantly affect the surface roughness parameters of the tested samples. Although the values of the Sz and Sp parameters have increased, the Sa, Ra, Rz, and Rp parameters remain the same for both types of samples. The obtained values of roughness parameters for uncoated and coated surfaces are not statistically significant (p-value > 0.05). The lack of changes in the roughness parameter values may be attributed to the coating application method - ALD, which allows very precise mapping of the surface topography [19].

TABLE 3. Values of parameters obtained during surface roughness measurements.

Parameter	Initial state	ZnO
Sa [µm]	0.05 ± 0.002	0.05 ± 0.002
Sz [µm]	0.58 ± 0.036	0.6 ± 0.01
Sp [µm]	0.29 ± 0.018	0.31 ± 0.018
Ra [µm]	0.03 ± 0.002	0.03 ± 0.003
Rz [µm]	0.16 ± 0.035	0.16 ± 0.038
Rp [µm]	0.08 ± 0.024	0.08 ± 0.024

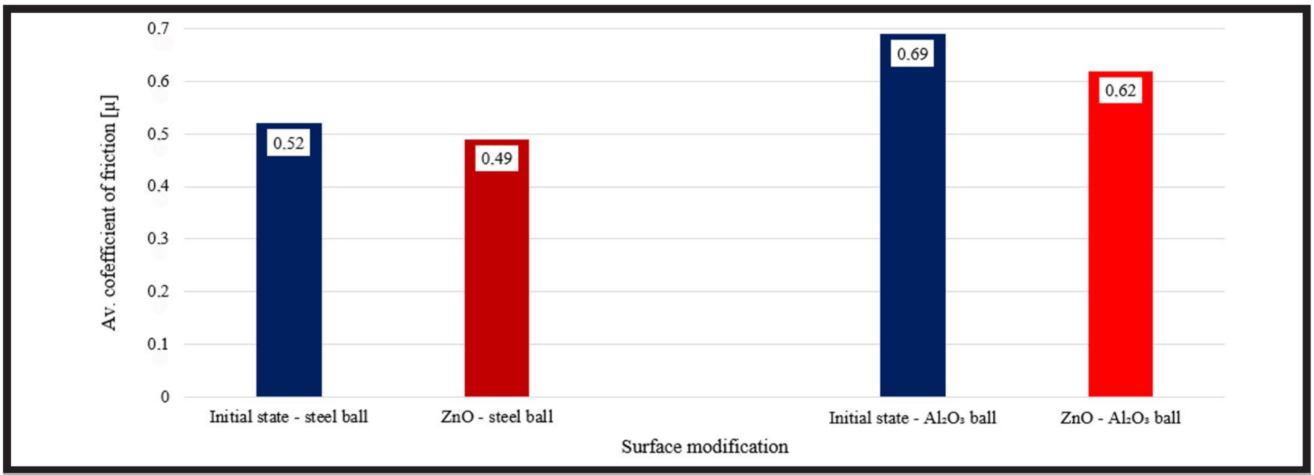

FIG. 3. Results obtained during tribological tests.

Tribological tests

The average values of the friction coefficient of the tested samples are presented in FIG. 3.

According to the results of the tribological tests, the average abrasion coefficient for the sample in its initial state was 0.52 when tested with a steel ball, and 0.69 for an Al_2O_3 ball. For the sample with the coating, the average abrasion coefficient when tested with a steel ball was 0.49, and with an Al_2O_3 ball - 0.62. The compared results show a statistically significant difference (p-value < 0.05) between the considered variants. From the results, it can be concluded that the applied coating reduces the average abrasion coefficient. Both tests with a steel ball and an Al_2O_3 ball showed that the average abrasion coefficient is lower for samples with the applied coating compared to those in the initial state. The results differ by 0.03 for the steel ball and by 0.07 for the Al_2O_3 ball.

The research indicates that applying a ZnO coating improves tribological contact by reducing the friction coefficient compared to the sample in its initial state. Based on the analyzed abrasion profiles after tribological tests, it was observed that the friction pair consisting of the ZnO coating-steel ball was characterized by a larger abrasion width of approximately 300 µm. In turn, the abrasion width obtained with the Al_2O_3 ball was around 180 µm. However, the wear volume of the steel ball was smaller ($7.2 \cdot 10^{-4}$ mm^3) compared to the ZnO-Al_2O_3 pair ($4.9 \cdot 10^{-3}$ mm^3). A similar relationship was observed in the case of the wear index value W, which was $4.7 \cdot 10^{-4}$ mm^3/Nm for the steel ball and $7.6 \cdot 10^{-3}$ mm^3/Nm for the trace produced with the Al_2O_3 ball. These values suggest that the ZnO coating exhibits greater wear resistance when in contact with a steel ball compared to a ceramic one. Given the frictional forces present in the implant-bone system, it is crucial to determine the mechanical properties of materials for clinical applications, including wear resistance. The friction coefficient results obtained for both steel and ceramic balls indicate that the use of a ZnO coating may result in reduced wear of materials in clinical applications with relation to uncoated implants.

The adhesion of the coating to the surface

TABLE 4 presents the values of the critical load Lc_2, which corresponds to the first occurrence of coating damage, and the critical load Lc_3, at which the coating is completely removed from the scratch test. FIG. 4 presents exemplary curves obtained during the scratch test.

TABLE 4. Results of testing the adhesion of the coating to the surface.

Fn [N]	
Lc_2	Lc_3
2.41 ± 0.49	5.5 ± 1.2

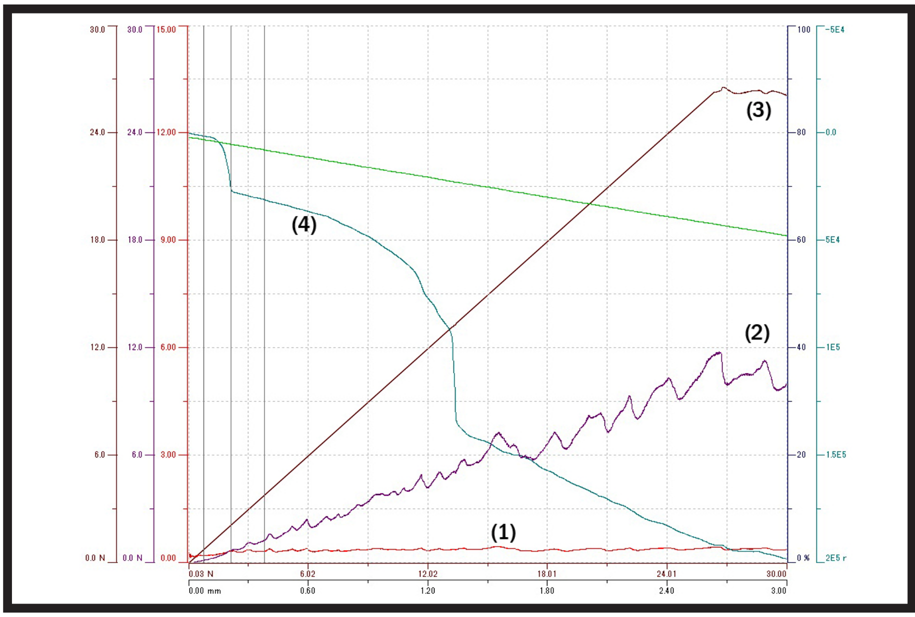

FIG. 4. Exemplary curves obtained during scratch-test:
(1) red - friction coefficient,
(2) purple - friction force,
(3) brown - normal force,
(4) blue - penetration depth.

Analyzing the adhesion tests of the coating to the surface (TABLE 4), the critical load Lc_3 is more than twice as high as the critical load Lc_2 and is 5.5 N. The critical force values obtained for the various samples are statistically significant (p-value < 0.05). When comparing the results with those in the literature [20], it was found that the number of cycles during the deposition of the layer affects the adhesion to the surface. Analyzing the literature results, the Lc_2 parameter from our research was very similar to the findings of the authors [21], who reported a value of 2.46 N at a temperature = 200°C and 600 cycles. The obtained Lc_3 parameter is approximately 2.5 N lower.

Electrochemical properties

The values of the E_{corr} and Rp parameters obtained during pitting corrosion resistance tests for individual samples are presented in TABLE 5 and the logarithmic curves obtained during tests of electrochemical properties are presented in FIG. 5.

Based on the analysis of the results of the potentiodynamic tests (TABLE 5), it was observed that the sample with the ZnO applied coating had a higher corrosion potential value, E_{corr} = -211.5 mV, compared to the corrosion potential of the sample in its initial state without the applied coating, E_{corr} = 245.5 mV. However, the polarization resistance Rp of the samples with the applied coating was $1.8 \cdot 10^5$ Ωcm², while for the samples in the initial state, it was equal to $4.6 \cdot 10^5$ Ωcm². Comparing the obtained Rp values, it can be seen that for samples with a ZnO coating Rp values are approximately 2.5 times smaller than the values for samples without the coating. The obtained values of parameters describing the corrosion resistance of samples with and without ZnO coating show a statistically significant difference (p-value < 0.05). It can be concluded that applying a ZnO coating improves the parameters describing corrosion resistance (E_{corr}). However, in none of the considered cases was a breakdown potential recorded, indicating that pitting corrosion was not initiated. Similar results from electrochemical tests were reported by M. Staszuk et al. [20], where for samples with a ZnO coating after 500 cycles at temperature = 200ºC, the corrosion potential was -202.67 mV and Rp = $1.5 \cdot 10^5$ Ωcm². Comparing the results from P. Boryło et al. [21], a similar value of the Rp parameter was found, which for the coating deposited in 500 cycles at temp = 200ºC was $1.6 \cdot 10^5$ Ωcm². Moreover, it can be observed the similarity of the obtained values of the corrosion potential to another type of antimicrobial coating (SnO_2) also applied by the ALD method on Ti13Nb13Zr alloy substrate, reported by J. Lisoń-Kubica et al. [22]. The E_{corr} value obtained was about 211 mV; however, the SnO_2 coating had a significantly lower polarization resistance value (Rp = $0.002 \cdot 10^3$ Ωcm²) compared to the ZnO coating considered in this paper.

TABLE 5. Average values of parameters obtained during electrochemical properties tests.

Sample	Av. E_{corr} [mV]	Rp [Ωcm²]
Initial state	-245.5 ± 20.5	$4.6 \cdot 10^5$ ± 0.2
ZnO	-211.5 ± 65.5	$1.8 \cdot 10^5$ ± 0.1

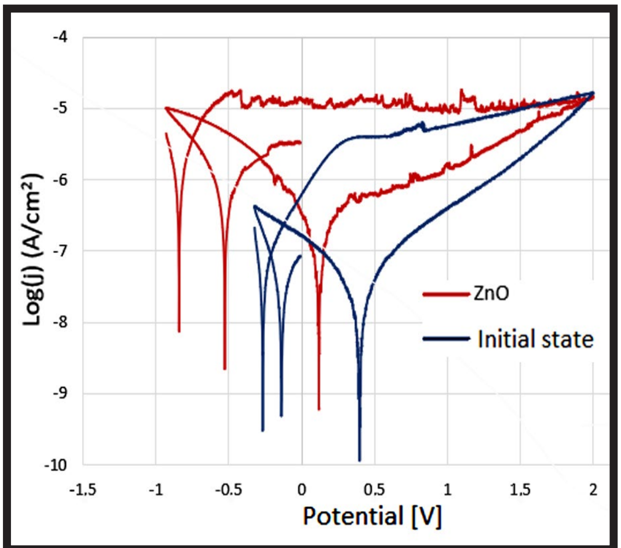

FIG. 5. Logarithmic curves obtained during tests of electrochemical properties.

TABLE 6. Cytotoxicity results.

Property	Control (C)	Initial state (R)	ZnO (B)
Viability	100%	100%	99.89%

Cytotoxicity tests

The assessment of cytotoxicity tests was carried out in accordance with the PN-EN ISO 10993-5:2009 standard: *Biological assessment of medical devices - part 5: In vitro cytotoxicity tests*. According to the standard, cell survival below 70% indicates that the tested material is cytotoxic. A quantitative and qualitative assessment was carried out (TABLE 6).

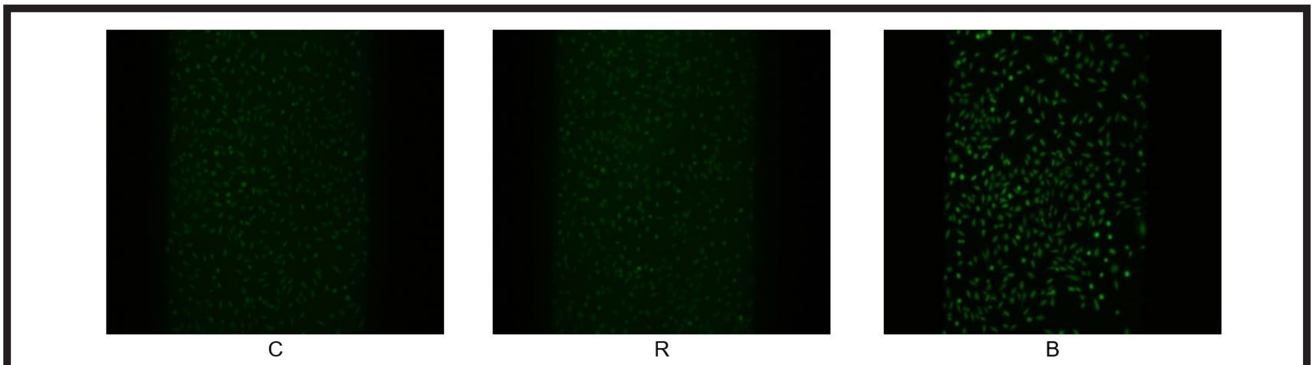

FIG. 6. Representative results - superimposed image of FDA and PI in pseudocolors; C - control, R - reference sample (initial condition), B - test sample (sample with applied coating).

Cytotoxic tests (TABLE 6, FIG. 6) proved that the cell survival rate for the polished sample and the sample with the applied coating is more than 70%, which means that the alloy used to produce the samples and the applied coating are not cytotoxic. The qualitative morphological assessment of cytotoxicity showed a grade of 0 - none, which also confirms that the material and the coating are not cytotoxic.

Conclusions

The ALD method used to apply the coating enables the production of an even coating without changing the surface topography; assessments of morphology and surface topography did not reveal any significant differences. The ZnO coating enhanced the physicochemical properties of the Ti13Nb13Zr alloy by improving its electrochemical properties by 14% and reducing the coefficient of friction by 6% with a steel ball and by 9% with Al_2O_3. The results of the adhesion test are consistent with those reported in the literature [20]. The applied coating has a more hydrophilic character face compared to the initial state, making it a potential solution against hydrophobic bacteria. Cytotoxicity tests showed that both the material and the coating are non-cytotoxic and can be used in medical applications.

The findings of this study may have significant implications for the field of orthopaedic implants. The demonstrated properties of ZnO coatings suggest that they could play a crucial role in reducing the risk of infections and improving the overall success rate of orthopaedic implants. By enhancing the surface properties of the Ti13Nb13Zr alloy, these coatings may lead to better patient outcomes and shorter recovery times. Moreover, the insights gained from this research contribute to a broader understanding of how surface modifications can enhance the performance of biomaterials used in medical applications.

While this study presents promising results regarding the use of ZnO coatings on Ti13Nb13Zr alloy for orthopaedic applications, it is important to acknowledge certain limitations. The study assumes that *in vitro* antimicrobial activity will directly translate to *in vivo* conditions, which may not always be the case due to the complex nature of the human body and potential immune responses.

Future research should focus on long-term *in vitro* studies to evaluate the clinical performance and durability of these coatings. Additionally, exploring the combination of ZnO with other antimicrobial agents could further enhance the effectiveness of the coatings. Advances in coating techniques and a deeper understanding of the interaction between the coating and the biological environment will be crucial in the development of next-generation biomaterials for orthopaedic implants. Addressing these future directions will significantly enhance the quality and impact of research in the field of biomaterials and implant technology.

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