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Tantalum oxides as an indicating electrode for pH measurement in the human body

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The human organism is under normal circumstances a stable system. The values of traceable chemical and biochemical markers change within a known and often very narrow range. In orthopedics an inflammatory disorder after the implantation can occur. The presence of such a problem demonstrates itself, even in the initial phase, in a drop of pH. A pH sensor, which would be temporarily allocated close to the implant, could therefore instantly indicate the origin of the inflammatory process. The behaviour of tantalum as a pH indicator was studied in this work. In the tested range of pH (4.5-7.5), the potential-pH dependence of this sensor was determined to be at the approximately Nernstian level –59 mV/pH. The main drawback was the long-term initial stabilization of the signal. The only meaningful detection method that could be used in practice is the electrochemical potential-pH dependence monitoring.

INTRODUCTION

The human organism is under normal circumstances a stable system in terms of ongoing processes, and the values of traceable chemical and biochemical markers move within a known and often very narrow range. This fact is used in all areas of medicine to diagnose potential health problems (standard blood, urine, faeces etc. tests). In orthopaedics, the occurrence of inflammatory disorders in the early period after the implantation of large joint replacements can be a problem [1-4]. The solution usually starts at the moment when the inflammatory process manifests itself on a macroscopic level. The occurrence of inflammation, even in the initial phase, is connected with a drop in pH in the surgical wound. A pH sensor, which would be temporarily allocated near the implant, could instantly indicate the inflammatory process and make the intervention more effective [5-7].

An implantable pH sensor, as a medical device must meet several requirements [8]. It must be made of materials that are approved for application in the body, it must be sensitive enough within a one pH unit level change, it must be stable for several months, it must not be integrated with soft tissue and the signal should be readable through the skin [9, 10]. Postoperative infections occur in a matter of days, a period of at least 30 days is significant. It is therefore desirable for the sensor to be able to respond correctly to changes in the environment around the surgical wound ideally from the moment of surgery [9, 11, 12].

There are many articles about pH sensors for use in/on the human body (the ScienceDirect database lists about 50000 entries), but most of them are constructed for short-term contact with the body [11-15]. An important group is represented by sensors based on metal oxides [16-18]. Their sensitivity is theoretically on the level of 59 mV/pH. In the case of long-term monitoring of the pH in situ, it is necessary to use a sensor that does not have side effects on the organism, which the majority of published systems designed for short-term ex-situ measurement do not fulfil. One possible solution is to implement a sensor made of materials of the Ti, Nb, Ta group. These metals are used in the form of alloys in medicine for a long time. Their behaviour in terms of pH detection has been tested as well [10, 19-21].

Tantalum is a material that is stable in the body environment. Tantalum oxides would be in principle able to detect changes in pH. A stable tantalum/tantalum oxide surface can be one of the possibilities for the preparation of a rigid implantable sensor. Its application depends on properties – sensitivity, accuracy, long-term stability and response rate [22-24].

In the frame of this work, the properties of tantalum as a sensor of acid-base changes in a model environment were tested. The aim was to determine how an unmodified, i.e. undoped with other elements, a system based on oxides of the tantalum passive layer is able to detect pH changes. The study was also focused on the applicability of electrochemical detection techniques – open circuit potential, polarization resistance and electrochemical impedance spectroscopy.

EXPERIMENTAL

Tantalum samples (purity 99.99 %, VUK Panenské Břežany) were ground up to FEPA P2500 emery paper and degreased before measurement. In addition to this treatment, the samples were sterilized according to the standard procedure (saturated water steam 120 °C, 20 minutes) to simulate preparation for the intended application area.

The exposure environment was an aerated solution of 9 g/l sodium chloride + 5.9 g/l TES buffer, temperature 37 °C, and the pH was adjusted with diluted solutions of NaOH or HCl. The samples were transferred between individual exposure environments with a short rinse in demineralized water (37 °C) and wiped with low-lint paper (Kimwipes). Due to the possible cyclical changes of the pH in the operation wound (indicating inflammation-healing), the behaviour of the samples was also monitored under these conditions.

All measurements were carried out with a Reference 600 potentiostat (Gamry), the data were evaluated by the EchemAnalyst software (Gamry). The reference system for potential monitoring was a silver/silver chloride electrode with saturated potassium chloride solution (ACLE). Its potential was periodically checked against the laboratory standard at laboratory temperature, and the values varied within ±1 mV. The measurement sequence consisted of a combination of potential (Eocp) monitoring, polarization resistance measurement (±20 mV/Eocp, 0.125 mV/s) and possibly also impedance spectra detection (0 V/Eocp, AC 10 mV, 10 kHz – – 4 mHz).

The state of the native tantalum surface after standard sample preparation (grinding to FEPA P2500, degreasing) was determined by photoelectron spectroscopy (Escaprobe P, Omicron).

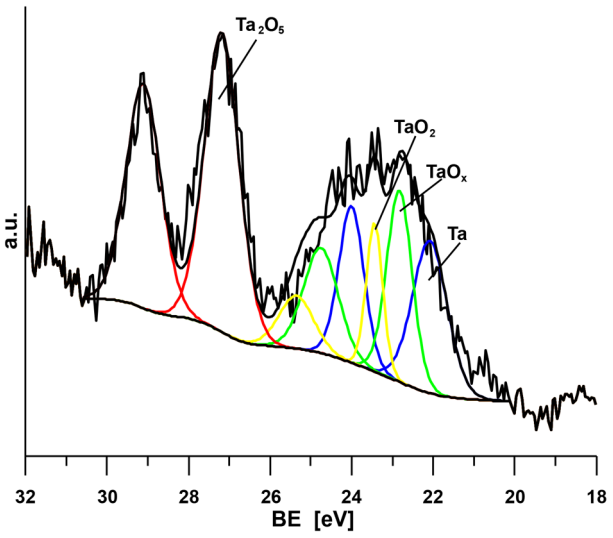

Fig. 1. XPS spectrum of the native tantalum surface

RESULTS AND DISCUSSION

Surface analysis

Analysis of the surface by photoelectron spectroscopy proved the existence of a complex oxide system on the surface (Fig. 1). The presence of the oxide in the highest oxidation state is evident but not entirely dominating.

Detection of pH changes

In the initial phase, the work was focused on the basic determination of the behaviour of tantalum samples in environments with changing pH. A relatively broad selection of pH between 4.5 and 7.4 was therefore chosen (measurement sequence 4.5; 7.0; 4.5; 6.4; 7.4; 6.0). The results are summarized in Fig. 2-4. In the given phase, only the time dependencies of the potential were measured as a logical, unambiguous, primary criterion.

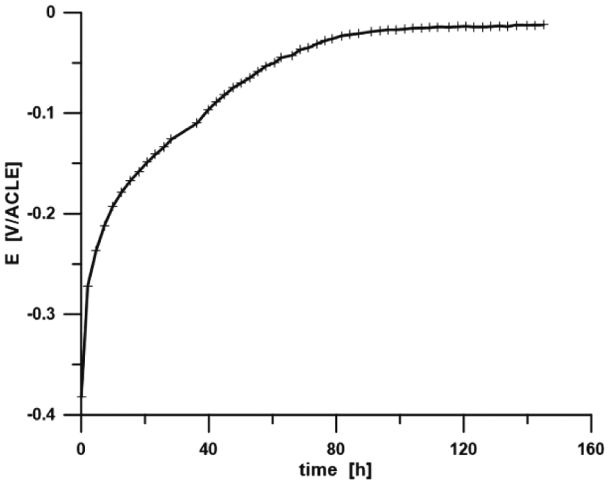

Fig. 2. Primary potential stabilization at pH = 4.5

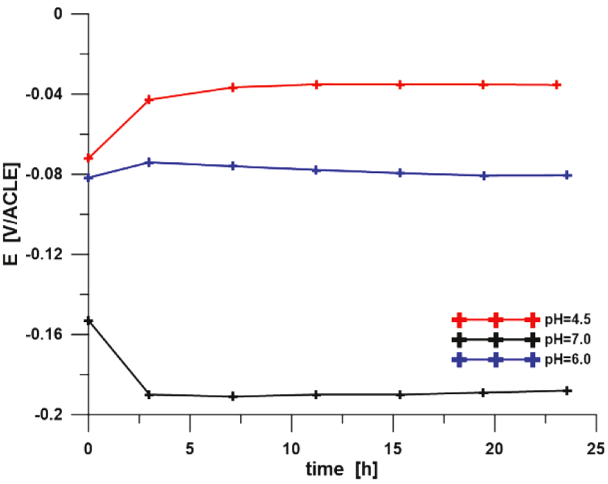

Fig. 3. Potential-time dependencies of the primary stabilized sample after pH change

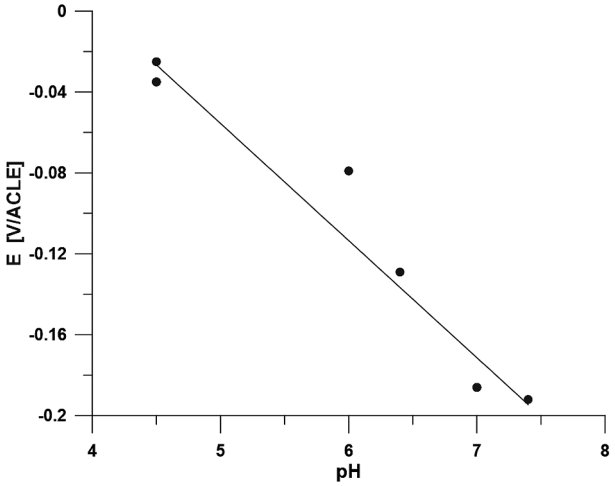

Fig. 4. E-pH dependency

The change of potential during primary stabilization was significant for approximately 3 days (80 hours of exposure). It slowed down than, the change was on the level of 65 μV/h. An important conclusion resulting from this set of data is the fact that a time in the order of tens of hours was necessary to reach a quasi-stationary state of the sensor. From the point of view of possible application, this is a long, but not entirely critical time. The E-pH dependence shown in Fig. 4 has a slope of –0.058 V/pH (correlation coefficient 0.952), which corresponds to the Nernstian behavior of the system.

Primary stabilization in a solution with physiological pH=7.4 is documented in Fig. 5 and 6. It is clear that the system, compared to the dependence shown in Fig. 2, stabilized significantly more slowly. The E-t dependence slope was 401 μV/h in the final 20 hours of exposure, which is significantly more compared to 65 μV/h in the case of stabilization in an acidic environment. This measurement was therefore, to some extent, a test if the E-pH dependence determined on a primarily not completely stabilized surface would be meaningful. The pH changes were sequence was 7.4, 6.4, 6.2, 6.6, 7.4. The stabilization of the potential during the transition between electrolytes was comparable to the previous measurement (Fig. 3), i.e. at the level of higher hours. It is clear that the system was able to provide information even under these conditions, but the data were significantly scattered. The slope of the potential-pH dependence was –0.049 mV/pH, correlation coefficient was 0.901.

The time-consuming primary stabilization, if it takes place on the original surface under standard exposure conditions, represents a significant limitation of possible practical application. If the reason for the passive layer changes during the initial exposure is the change in the ratio of oxidation states, then the electrochemical/oxidation modification could accelerate the stabilization. Several potentiostatic and potential cycling exposures (CV measurements) were tested. The results were identical in all cases – the rate of potential stabilization rather worsened.

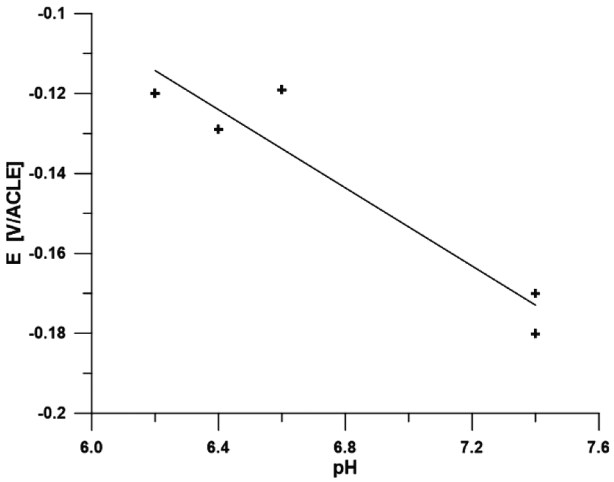

Fig. 6. E-pH dependency

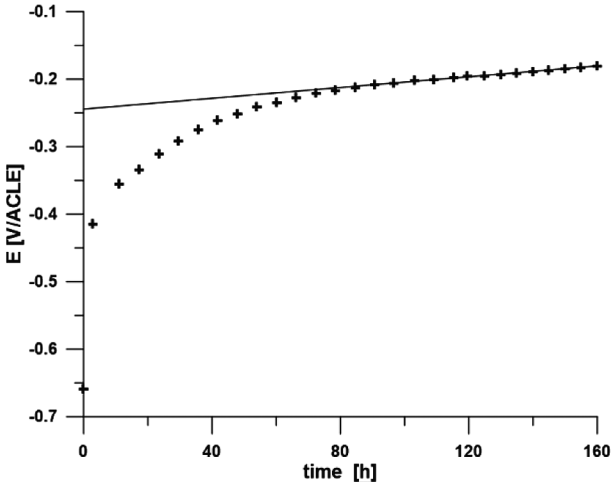

Fig. 5. Primary potential stabilization at pH = 7.4

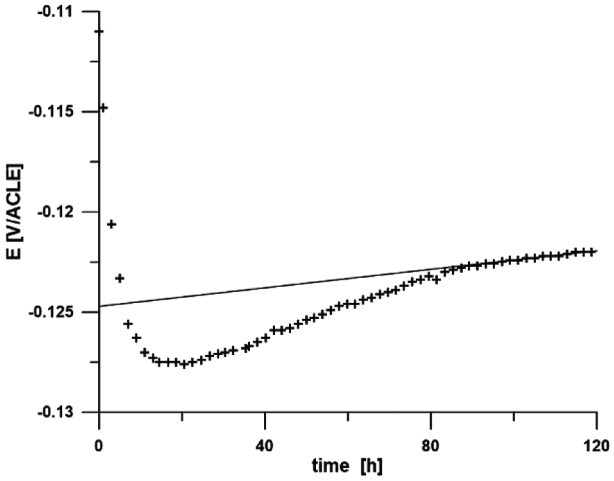

Fig. 7. Primary potential stabilization at pH = 7.4

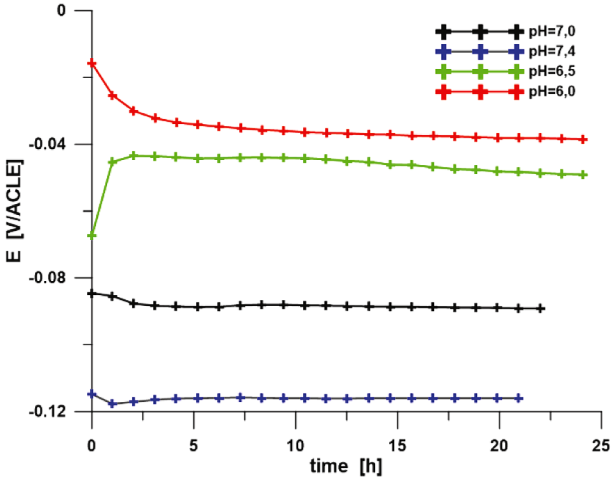

Fig. 8. Potential-time dependencies of primary stabilized sample after pH change

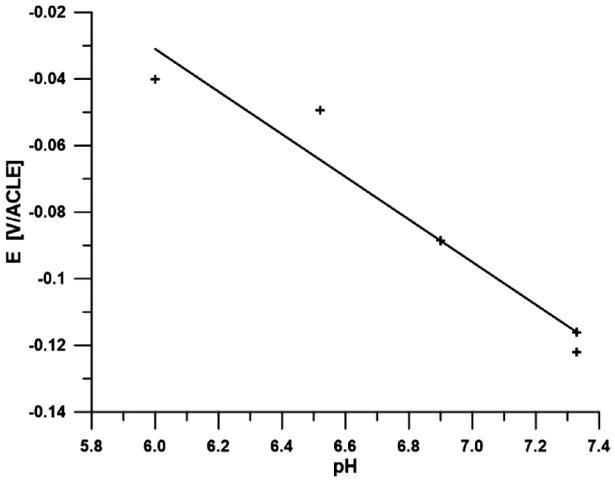

Fig. 9. E-pH dependency

On the contrary to the previous, sterilization had a positive impact. This procedure can be one of the sterilization steps before applying the medical device in practice. The increase in the potential of the sample during primary exposure in a solution with pH = 7.4 slowed down around the 80th hour, the slope of the E-t dependence was than 23 μV/h (Fig. 7). This value is roughly 3× smaller than in the case of stabilization in an acidic environment. The stated value represents, if we consider the first week after the operation as critical, an increase of potential during this time on the level of approx. 12 mV (10 mV for first 80 hours, 2 mV during subsequent 96 hours), which is important but not a critical influence on pH monitoring when the slope of the E-pH dependency is on the level of –59 mV/pH. High temperature and intensive hydration during sterilization led to a potential shift of approximately 100 mV in the positive direction. The subsequent measurement was based on pH changes sequence 7.4, 7.0, 7.4, 6.5, 6.0. The stabilization of the potential during the transition between electrolytes (Fig. 8) was comparable to the previous measurement in acidic media (Fig. 3), i.e. at the level of higher hours. The E-pH dependence (Fig. 9) had a slope of –0.061 V/pH with a correlation coefficient of 0.935.

Detection methods

In all the above cases, in addition to the open circuit potential, the polarization resistance and impedance spectra were also measured. The resulting time dependences of the polarization resistance are shown in Fig. 10-13.

It is obvious that the polarization resistance increased in all cases, and the state of the tantalum surface changed during the measurement period slowly and permanently.

The change in the acid-basic state of the environment is reflected only in the case of a sample stabilized at pH = 4.5 (Fig. 10). The increase occurs nevertheless permanently, a certain pH value cannot be assigned to a polarization resistance value. In the other two cases in a situation where the rate of increase slowed down pH value has visibly no influence on the charge transfer resistance (Fig. 11, 12). It is clear from the above results that the measurement/monitoring of polarization resistance in real conditions is not able to provide meaningful information about the pH value of the environment.

The other method which in principle could be used for sensor state monitoring is electrochemical impedance spectroscopy. An example of the typical impedance spectrum together with analysis is shown in Fig. 13. The character of the spectrum (generally all of the spectra) is distinctively capacitive. Spectra were evaluated by the equivalent circuits shown in Fig. 15a (Randless) and 15b (porous surface). Influence of porosity was important at higher frequencies nevertheless there were

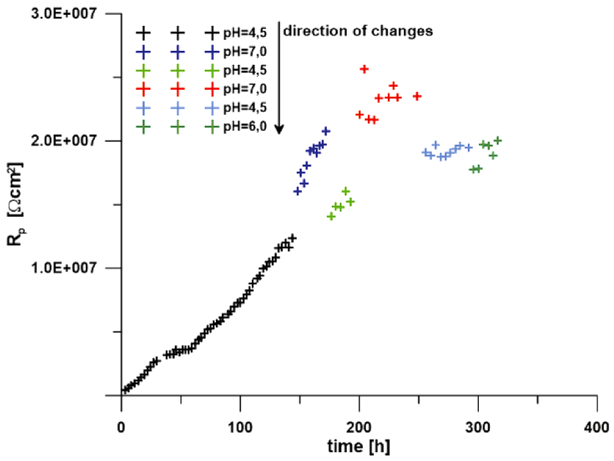

Fig. 10. Polarization resistance-time dependency (primary stabilization at pH = 4,5, Fig. 2)

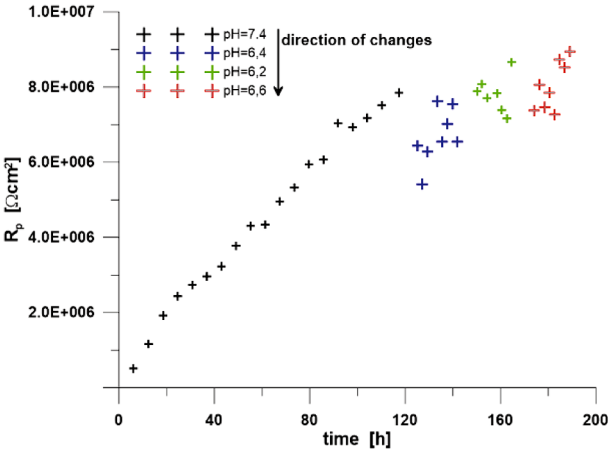

Fig. 11. Polarization resistance-time dependency (primary stabilization at pH = 7,4, Fig. 5)

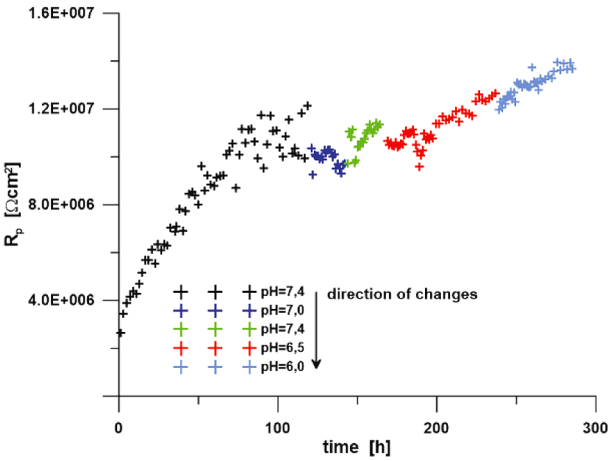

Fig. 12. Polarization resistance-time dependency (primary stabilization at pH=7,4, sterilization, Fig. 7)

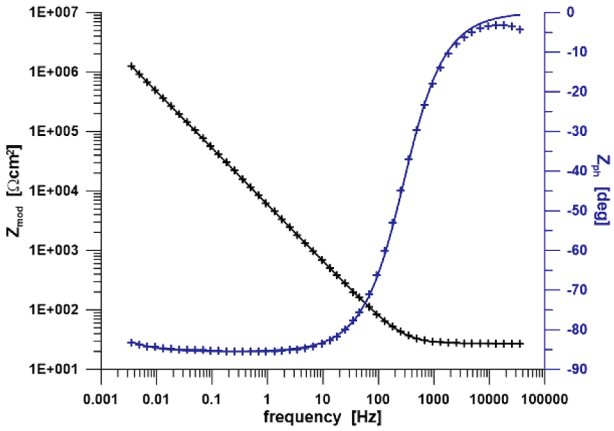

Fig. 13. Typical EIS spectrum (points) and fit (line) according to Fig. 14a (pH = 4.5, stabilized, Bode presentation)

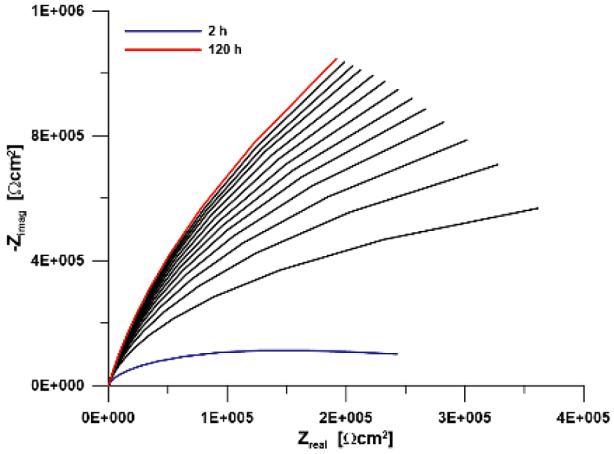

Fig. 14. Typical development of the EIS spectrum with time (Nyquist presentation)

no fundamental differences between the results of both analyses. The contribution of porosity was negligible and with increasing time of sample exposure, the model considering porosity lost its relevance. For this reason, the spectra were finally analyzed only by the simple phase boundary model shown in Fig. 15a. The quality of fits was at a very good level (goodness of fit 1.10^{-4} and better), the error of CPE determination was on the level of units of percent.

Electrochemical impedance response varied during the exposures, mainly at the very beginning, regardless of the surface conditions and pH, as illustrated in Fig. 14 (the Nyquist presentation is used, which more clearly illustrates the development of the spectrum/layer).

It resulted from the analysis of the measured dependencies, that the constant phase element value (CPEdl, Fig. 15a) continuously decreased during the entire exposure period approaching the quasi-stationary state. An example of CPE-t dependence is presented in Fig. 16. It can be assumed that at a given constant composition of the electrolyte, the only factor influencing the capacitance is the thickness of the passive layer, which visibly continuously grew during the measurement.

More detailed testing of the capacitance dependence on pH was carried out on a sample prepared by a standard procedure and long-term exposed in a pH = 7.4 solution. After reaching the polarization resistance value 1.10^7 Ωcm² pH changes were started. The value of pH was cyclically changed between 7.4 and 6.4. The results are summarized in Fig. 17.

The course of the polarization resistance corresponds to the already discussed results. From the point of view of capacitance, it is clear that the acid-basic conditions of the environment had a minimal, but measurable, effect. However, the meaningfulness of impedance spectra/capacitance measurement is for the possible real use of tantalum sensor monitoring still open to discussion.

If the polarization resistance were to be considered only as a criterion of stationary state achievement, then

from about the 350th hour of exposure, Rp oscillated. The layer capacitance, even under these conditions, nevertheless decreased. It is obvious that reaching of a real stationary state is a very time-consuming process.

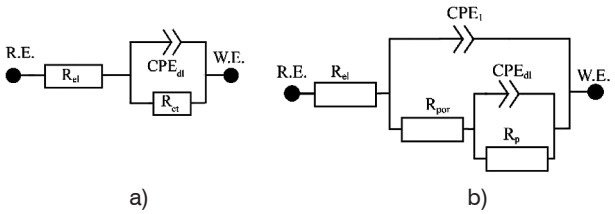

Fig. 15. Equivalent circuits: a) Randless, b) porous structure)

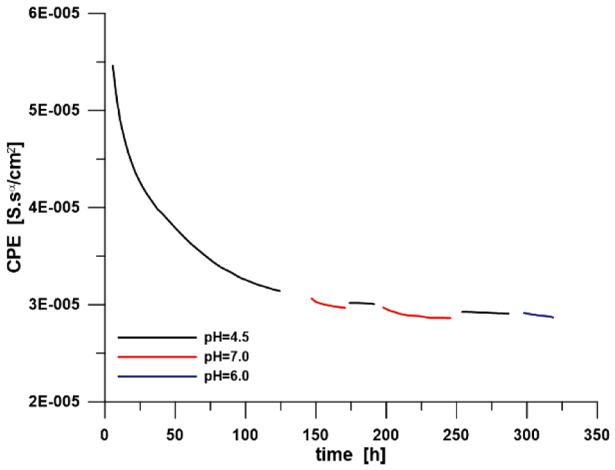

Fig. 16. Constant phase element time dependence

The measurement confirmed the previous result concerning the faster sample response in an environment with a lower pH. At pH = 7.4, the potential of the tantalum electrode was determined to be –0.188 ± 0.007 V/ACLE, at pH = 6.4 it was –0.135 ± 0.003. The value of the slope of the straight line connecting these points was –0.053 V/pH.

CONCLUSIONS

From a material point of view, the use of tantalum makes sense – it is a highly corrosion-resistant metal stable in the body's environment and approved for use in the human body. The complex and time-varying oxide layer on its surface is able to detect pH changes, and a rigid sensor based on this principle is expected to be stable for a long time. In the tested range of pH = 4.5-7.5, the potential-pH dependence was determined approx. at the Nernstian level –59 mV/pH.

A fundamental disadvantage preventing the use of this simple system as a pH sensor for the detection of postoperative inflammation, when the first weeks after surgery play a very important role, is the long-term stabilization of the surface state and sensor's signal.

The only meaningful value that could be used in practice for monitoring instrumentally simply, robustly and correctly, is the open-circuit potential.

Acknowledgement

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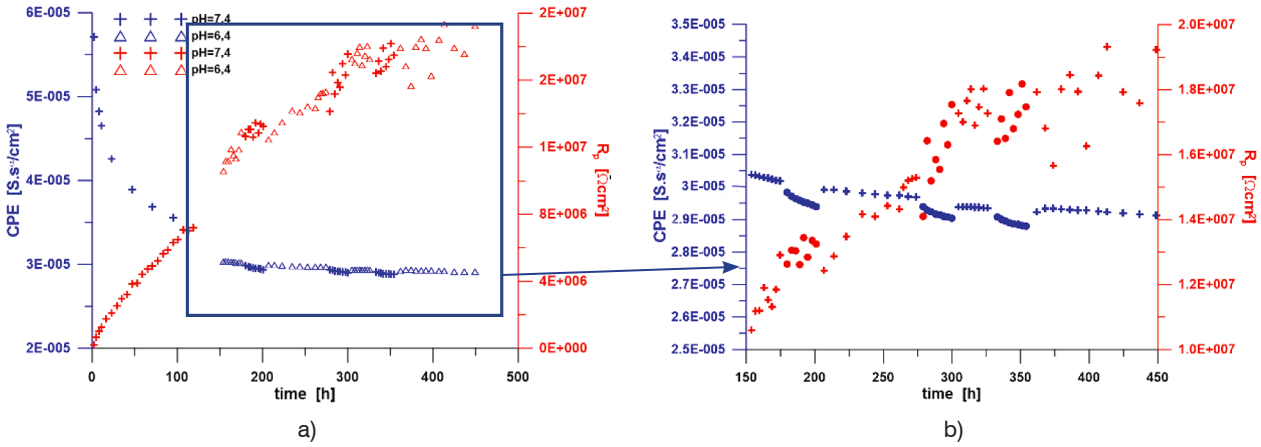

Fig. 17. Time dependence of Rp and CPE

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