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DEVELOPMENT OF THE METHOD FOR ESTIMATING COMPLEX FORMATION USING THE ELECTROCHEMICAL IMPEDANCE SPECTROSCOPY ON THE EXAMPLE OF THE DOXYCYCLINE AND IRON (III) INTERACTION

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The aim. To develop an EIS method for study the interaction between medicinal products and metal salts on the example of the Doxycycline and iron (III) interaction.

Materials and methods. Measurements of the total impedance of the studied solutions have been performed using a vector circuit analyzer ZNB40 (Rohde & Schwarz, Germany). The calculations of electrical models were performed using the software package EC-Lab V10.40. Measurement cell was made of Teflon, 1 ml of volume, had 2 parallel nickel plated steel electrodes with diameter 6 mm, distance between electrodes is 9 mm. Basic electrical elements of model circuit were calculated according to type of electrochemical process that were described by Nyquist plot (R_{Ω} , R_{ct} , R_s , C_{dl} , C_s etc.). Solutions were prepared immediately before the measurement. Measurements were performed at a temperature of 296 ± 3 K. 6 control solutions of doxycycline and 6 control solutions of iron (III) chloride were prepared and measured. 11 study solutions at a molar ratio 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1 were prepared and measured. Concentration of the solutions was $X \cdot 10^{-3}$ mol/L respectively.

Results. EIS analysis of Nyquist curves of study solutions in the range of molar ratios 1: 6, 1: 5, 1: 4, 1: 3, 1: 2, 1: 1, 2: 1, 3: 1, 4: 1, 5: 1, 6: 1 showed a change in the dynamics of electrical resistance at a ratio of 1:1. In the aqueous solution at $T=296 \pm 3$ K the constant formation of the solution of doxycycline hyclate and iron (III) chloride is 2.9. This value of the complexation constant indicates that doxycycline hyclate forms a stable metal-ligand complex with iron (III) ions.

Conclusions. EIS method can be applied to study the interaction of medicinal products. Model of this study was created on the example of doxycycline hyclate and iron (III) chloride. Metal-ion complexation of these two molecules was once again confirmed by using the EIS method

Keywords: electrochemical impedance spectroscopy, complexation, antibiotics, drug interaction, doxycycline hyclate

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1. Introduction

With the constant growth of the number of medicinal products on the market, the threat of polypharmacy is growing. Drug-drug interactions can lead to medicines ineffectiveness, cause adverse reactions or side effects [1, 2]. According to the data obtained in the longitudinal studies the prevalence of clinically significant drug interactions is about 6 % in patients taking 2–4 drugs, 50 % in those taking 5, and almost 100 % in those taking 10 drugs [1, 2].

Therefore, the drug-drug interaction studies are highly important. They can be performed by both *in vivo* and *in vitro* studies. On the other hand, results of chemical, physicochemical experiments (*in vitro*) are important for estimating when *in vivo* studies may be necessary to fully define the drug interaction profile, and when they can be waived [3].

In vitro drug interactions studies can be performed by using different chemical and physicochemical methods. In our previous research we intended study the interaction between antibiotics and metal salts presented in the soft drinks and mineral water by UV-spectrophotometry and *in vitro* biowaiver test, but unfortunately these methods could not help us to establish the ratio of complexation [4, 5].

Electrochemical impedance spectroscopy (EIS) is an electrochemical technique that presents the signal as a function of frequency at a constant potential [6, 7]. Although EIS is not a pharmacopoeial method, but it started to be used in the pharmaceutical and biomedical studies. New devices based on this method were created and used or rapid analysis of biological samples and optimization of many technological processes in the food and chemical industries [8]. Usage of EIS to study complexes of different transit metals like cobalt (II), nickel (II) and copper with several antibiotics and Schiff bases was reported [9, 10].

Tetracycline antibiotics are widely recognized as organic ligands that can interact with metal cations and form chelate complexes [11]. Although in the literature sources there is an information, that properties for complexation may differ within the group [12, 13].

Considering mentioned above for the study it was decided to use doxycycline as a study object to model the interaction of doxycycline (Fig. 1) and the iron (III) in the aqueous solution and to study it by using the EIS method. Consequently, the results of the doxycycline and Fe^{3+} interaction study obtained by EIS and electrochemical modeling can be compared with estimates reported

before and provide an appropriate chemical interpretation of the processes that take place.

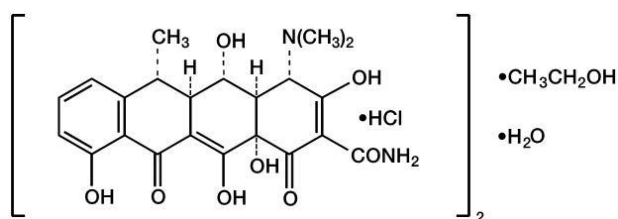


Fig. 1. Doxycycline hydrochloride

The aim of the research. To substantiate and develop approaches to the study of metals and doxycycline complexation using the EIS method. To create a model (tool) for studying the interaction by using this method, for its further use to study the interaction of other medicinal products.

2. Planning (methodology) of research

At the first stage the total impedance of six iron (III) chloride solutions, the concentration of which varied from $1 \cdot 10^{-3}$ to $6 \cdot 10^{-3}$ mol/L, was measured using EIS. The total impedance of six solutions of doxycycline hydrochloride, the concentration of which varied from $1 \cdot 10^{-3}$ to $6 \cdot 10^{-3}$ mole/L.

At the second stage, 11 aqueous solutions of doxycycline hydrochloride and iron (III) chloride were prepared in the following molar ratios: 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, and for each of them the electrochemical impedance was measured and the electroimpedance spectral characteristics were constructed in the form of Nyquist plot.

For six molar concentrations of doxycycline and iron (III) at the range $1 \cdot 10^{-3}$ - $6 \cdot 10^{-3}$ mol/L, as well as for such ratios of concentrations of Dox and the iron (III) as 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1 the frequency dependences of the real and imaginary parts of the impedance on which the Nyquist curves were constructed. Thereafter, a qualitative analysis of the Nyquist curves was performed, equivalent electrical models were constructed and their electrical elements (R_{Ω} , C_d , Z_f) were calculated.

3. Materials and methods

3.1. Reagents

Doxycycline hydrochloride substance used for preparation of the study solutions was purchased from Yangzhou Liberty Pharmaceutical Co., Ltd, China. Iron (III) chloride hexahydrate substance was from Sigma Aldrich, Germany. Grade "A" glassware were used during the study. All used reagents were of analytical grade. Purified water was used as a main solvent [14].

3.2. Preparation of samples

The following aqueous solutions were prepared (control solutions): doxycycline hydrochloride 1, 2, 3, 4, 5, 6; iron (III) chloride 1, 2, 3, 4, 5, 6 (with concentration respectively $X \cdot 10^{-3}$ mol/L). Stock aqueous solutions of doxycycline and iron (III) chloride were prepared. Study solutions were obtained from stock to receive mixed

solution of doxycycline and Fe^{3+} in the following molar ratio: 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1 (with concentration respectively $X \cdot 10^{-3}$ mol/L). Solutions were prepared immediately before the measurement. Measurements were performed at a temperature of 296 ± 3 K.

3.3. Instrumentation and method

The measuring cell, which includes electrodes, and the electrochemical processes occurring in it during measurement, can be modeled by an equivalent electrical circuit [15]. In the electrochemical cell when measuring the total impedance of the studied chemical solutions, there is a charge transfer between them and the electrodes. Thereby there are certain Faraday processes, thus the most appropriate electrical model is the equivalent Randles electrical circuit [6, 15]. Basic electrical elements of model circuit were calculated according to type of electrochemical process that were described by Nyquist plot (R_{Ω} , R_{ct} , R_s , C_d , C_s etc.) [6, 15]. Constant phase elements together with Warburg resistance characterize the features and dynamics of chemical processes in the studied solutions [16]. Thus, by building the appropriate electrical model based on the results of total impedance measurements and calculating its elements, it is possible to assess the peculiarities of chemical processes and draw conclusions about the complexation between the studied substances and metal salts.

During our research, both approaches were used – qualitative estimation by Nyquist curves and modeling by values of an electric circuit, as well as quantitative estimation of its elements and determination by their dynamics of electrochemical processes occurring in the studied solutions.

Measurements of the total impedance of the investigated solutions were performed using a vector circuit analyzer manufactured by Rohde & Schwarz ZNB40.

Measurement cell used in the study was made of Teflon, 1 ml of volume, had 2 parallel nickel plated steel electrodes with diameter 6 mm, distance between electrodes is 9 mm.

The calculation of electrical models was performed using the software package EC-Lab V10.40, which implemented randomization and simplex methods for calculating the parameters of electrical circuits for a full cycle of iterations to achieve 5000 iterations.

Given that solutions of substances in water were studied, the frequency ranges in which the electrochemical impedance was measured ranged from 100 kHz to 1 GHz. Both the frequency dependences of the impedance change and its dependence on the ratio of the concentrations of the studied objects were determined. The measurement of the total impedance consisted of determining the frequency dependence of its real (Z_{Re}) and imaginary parts (Z_{Im}). Further such functional dependencies as the dependence of the total impedance modulus on the frequency – $|Z|=z(f)$; the dependence of the phase angle of the total impedance on the frequency – $\phi=\Phi(f)$ and the relationship between the real and imaginary parts of the total impedance in the form of the dependence: – $Z_{Im}=\zeta(Z_{Re})$ were determined [15].

4. Result

Fig. 2 shows the electroimpedance spectral characteristics of solutions of different concentrations of iron (III) chloride and doxycycline hyclate in the form of Nyquist curves. The diagrams in Fig. 2a show that for all concentrations of iron (III) chloride solutions the dependence has the same shape in the form of one semicircle, which begins at higher frequencies and does not have a clearly defined tail on the low frequency side. This

indicates that the kinetic processes of charge transfer predominate in the chemical system, while mass transfer due to diffusion processes is almost absent. As the concentration of iron (III) chloride increases, the size of the semicircle of the Nyquist curves decreases.

At the same time, its shape does not change and the size of the tail, which is characterized by the Warburg impedance, does not increase, and the transition between it and the semicircle remains clear.

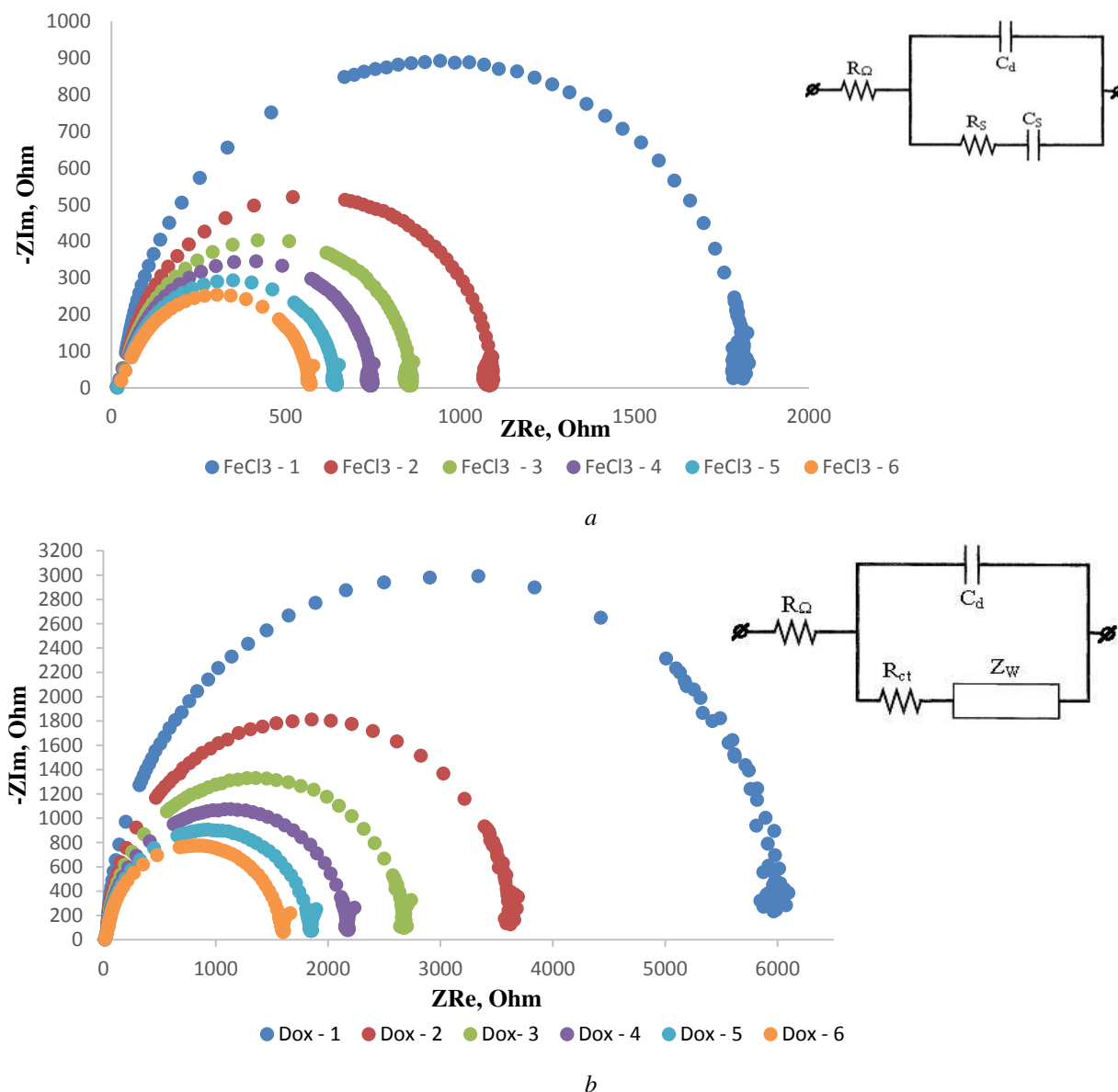


Fig. 2. Nyquist curves with inset of equivalent electrical circuit of the measuring cell for 6 molar concentrations of solutions of *a* – FeCl₃; *b* – doxycycline hyclate

As shown by the first stage of the experiment, an increase in the concentration of iron (III) chloride leads to a decrease in the resistance of the electrochemical system and, accordingly, to an increase in conductivity due to an increase in iron ions in solution. At the same time, the decrease in the concentration of iron (III) chloride does not lead to the replacement of the dominant kinetic processes of charge transfer by mass transfer processes. In general, we can conclude that in an electro-

chemical cell with a solution of iron (III) chloride Faraday processes take place. To model them, an equivalent electrochemical circuit with a series connection of a resistor R_{Ω} (which simulates the resistance of the solution in the measuring cell), and a parallel connection created by the measuring electrodes of the capacitance C_d with electrical resistance of R_S and pseudocapacitance C_S (which determine electrochemical processes occurring in the studied solutions can be chosen) (Fig. 2, a).

The values of calculated equivalent electrical elements for the electrochemical impedance model of FeCl₃ solution are given in Table 1.

They confirm that with increasing concentration of iron (III) chloride there is a decrease in the value of the electrical resistance of charge transfer R_S three times, from 1763 Ohms (C₁=1·10⁻³ mol/L) to 524 Ohms (C₆=6·10⁻³ mol/L).

The value of the pseudocapacitance of C_S is doubled from 25.65 pF to 56.91 pF with increasing concentration of iron (III) chloride from 1·10⁻³ mole/L to 6·10⁻³ mole/L. Thus, the total conductivity of the electrochemical system of FeCl₃ solution increases with increasing concentration, because of the dominance of the charge transfer process due to the increase in the concentration of Fe³⁺ and Cl⁻ ions.

Table 1

Parameters of electrochemical impedance for the iron (III) and doxycycline hyclate solutions of different concentrations

Concentration of the solution, 10 ⁻³ mole/L	R _Ω , Ohm	C _d , 10 ⁻¹² F	R _S , 10 ³ Ohm	C _S , 10 ⁻⁹ F	Q ₂ , 10 ⁻⁹ F·s ^(a₂-1)	a ₂	σ ₂ , Ohm·s ^{-1/2}
Iron (III) chloride solution							
1	21.71	6.086	1.763	25.65	–	–	–
2	23.20	6.409	1.047	34.07	–	–	–
3	24.88	6.517	0.819	43.16	–	–	–
4	25.91	6.635	0.706	46.06	–	–	–
5	27.14	6.766	0.605	50.78	–	–	–
6	28.72	5.839	0.524	56.91	–	–	–
Doxycycline hyclate solution							
1	18.74	5.813	5.966	–	6.25	1	1541
2	19.49	5.947	3.575	–	7.79	0.997	17339
3	20.20	6.021	2.630	–	8.37	0.994	45873
4	20.68	6.102	2.129	–	11.36	0.985	55426
5	21.12	6.169	1.802	–	22.47	0.936	62711
6	21.71	6.218	1.554	–	43.65	0.883	67106

For a solution of doxycycline hyclate, the spectral curves of Nyquist have the shape of a semicircle, the size of which decreases with increasing concentration of the substance (Fig. 2, b). It means that kinetic charge transfer processes prevails in this chemical system, as well as for a solution of iron (III) chloride. However, in contrast to iron (III) chloride, the electrochemical impedance curves for doxycycline hyclate have a more pronounced Warburg impedance, which increases with increasing concentration of the substance (Fig. 2, b). The appearance of the Warburg impedance in this electrochemical system can be explained by the fact that the molecule of doxycycline hyclate has a more complex structure. In a medium of purified water (pH 5.5–7.0), i.e. at neutral pH, the molecule of doxycycline has structure of zwitterion [13]. The dimethylamino group is responsible for the basic properties, while the acidic properties are manifested due to phenolic hydroxyl in the ring D and enol groups. This structure of the molecule explains the fact that when measuring the electrochemical impedance at low frequencies under the action of an electric field, the diffusion of matter occurs due to the processes of electrooxidation and electroreduction. This leads to the appearance of the Warburg impedance on the spectral curves of Nyquist (Fig. 2, b). Considering this, to calculate the electrochemical impedance system of the doxycycline hyclate solution, we used an equivalent electrical circuit R_Ω+C_d/(R_{ct}+C₃/(R₃+W₃)) (Fig. 3, b). In the Table 1 the values of equivalent electrical elements for the above

electrochemical model of the impedance of a solution of doxycycline hyclate are given.

With increasing concentration of doxycycline hyclate there is a decrease in the value of electrical resistance R_S in four times, from 5966 Ohm (C₁=1·10⁻³ mole/L) to 1554 Ohm (C₆=6·10⁻³ mole/L), while significantly increasing the mass transfer coefficient (σ₂), which characterizes the sum of process contributions oxidation and reduction in this electrochemical system.

The dynamics of the constant phase element – Q₂ and a₂ – the deviation of the model parameters characterizes that when the concentration of doxycycline hyclate increases, the parameters of the electric model deviate from the pseudocapacitance and the influence of the Warburg impedance increases (Table 1). This can be explained by the fact that water molecules are partially replaced by zwitterionic ions of doxycycline, the number of these ions increases and the total conductivity of the solution of doxycycline hyclate. Moreover, the pH of the doxycycline hyclate solution decreases, so the number of negatively charged ions increases due to phenolic hydroxyl in the ring D and enol groups, and due to their mass transfer increases.

As it can be seen from the Nyquist diagrams (Fig. 3), the addition of iron (III) chloride to doxycycline hyclate lead to a change in electroimpedance spectral characteristics either in shape (the diameter of the impedance semicircle decreased compared to the corresponding diagrams for pure doxycycline hyclate solution (Fig. 2, b), or the clear appearance of the Warburg im-

pedance. This occurs even at the lowest concentration of doxycycline hyclate – $1 \cdot 10^{-3}$ mole/L.

It is also important to note that as the concentration of iron (III) chloride increases, the diameter of the electroimpedance semicircle decreases (Fig. 3, *a*). This qualitatively indicates a decrease in the value of the electrical resistance R_s of this electrochemical system and, accordingly, an increase in the electrochemical conductivity with increasing concentration of iron (III) chloride. The maximum electrical resistance is observed at a ratio of concentrations of solutions of doxycycline hyclate and

iron (III) chloride – 1:1, and the minimum at 1:6. The study of solutions for which the concentration of doxycycline hyclate increased showed that with increasing concentration of doxycycline hyclate relative to iron (III) chloride there is also a decrease in the electrical resistance R_s of this electrochemical system and, accordingly, an increase in conductivity (Fig. 3b).

The maximum electrical resistance is observed at a ratio of concentrations of solutions of doxycycline hyclate and iron (III) chloride – 1:1, and the minimum at 6:1.

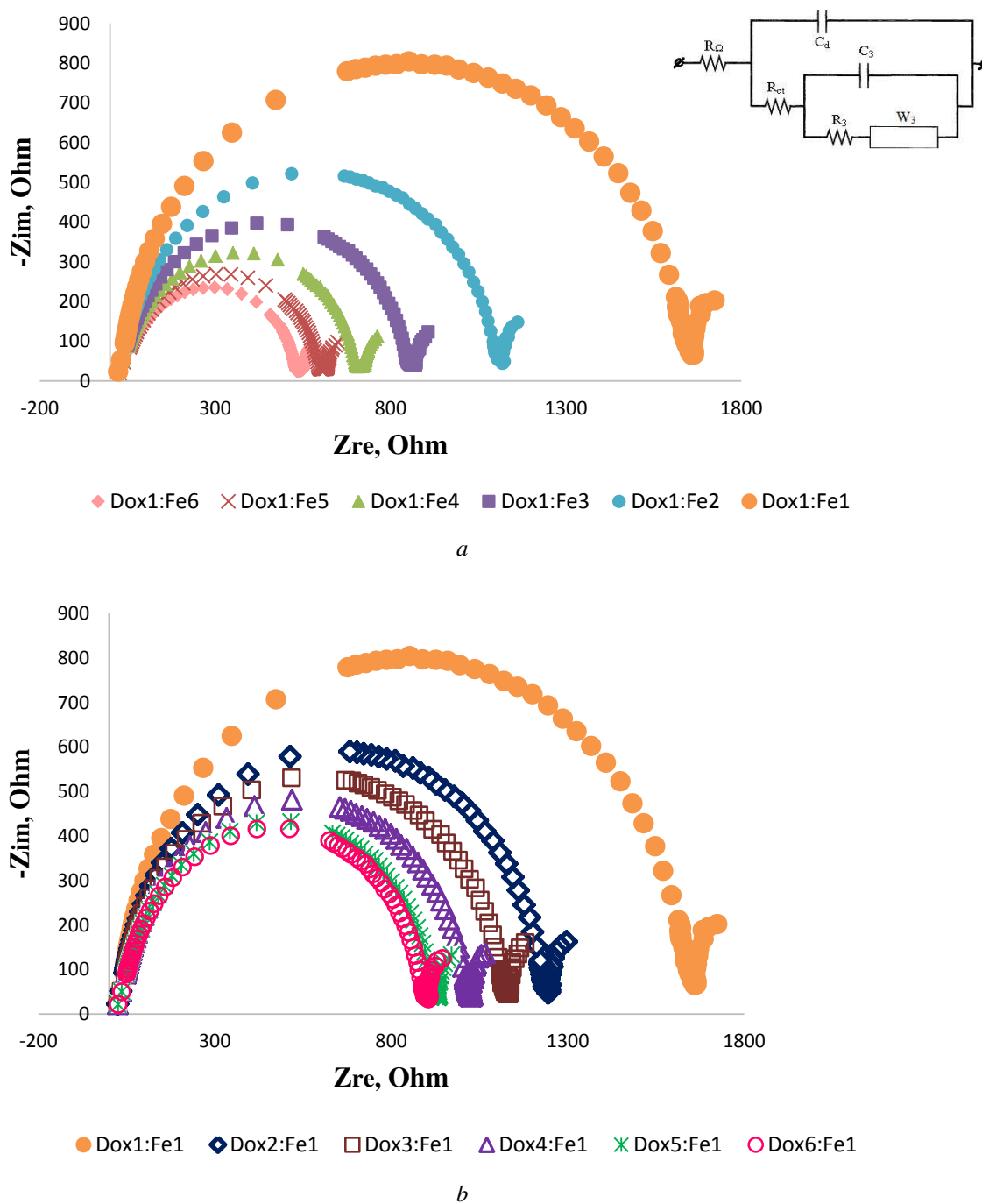


Fig. 3. Nyquist curves for doxycycline and iron (III) chloride solutions in different concentration ratios, measured at a temperature of 295 K: *a* – increase in Fe^{3+} concentration; *b* – increase in doxycycline concentration

The model parameters of the electrochemical system of aqueous solutions of doxycycline hyclate and iron (III) chloride in molar ratios of concentrations: 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1 are given in Table 2.

Analysis of the dynamics of EIS parameters showed that when the ratio of the concentration of Fe^{3+} ions to the amount of doxycycline in the studied solutions there is a slight fluctuation of the pseudocapacitance of the measuring cell C_d in the range of 4.9...5.6 pF and electrical resistance of the test solution R_Ω in the range of 39.33...31.36 Ohms. This variability can be ignored, and these indicators can be considered almost unchanged. Moreover, the EIS parameters that characterize the redox reactions and other electrochemical processes occurring in the investigated solutions significantly depend on the ratio of molar concentrations. Thus, when the concentration of Fe^{3+} ions decreases from $6 \cdot 10^{-3}$ moles/L to $1 \cdot 10^{-3}$ moles/L, there is an increase in the charge transfer resistance R_{ct} four times, which reaches a maximum value of 1.606 kOhm at a ratio of 1:1 (Table 2). Then there is a gradual decrease of almost two

times with increasing the concentration of doxycycline from $1 \cdot 10^{-3}$ moles/L to $6 \cdot 10^{-3}$ moles/L (Table 2). Herewith, the inverse dynamics is observed for the pseudocapacitance Q_2 , which characterizes the processes of mass transfer and diffusion. Thus, reducing the molar concentration of Fe^{3+} ions from $6 \cdot 10^{-3}$ moles/L to $1 \cdot 10^{-3}$ moles/L leads to a decrease in pseudocapacitance by 17 times from 1301 pF to 75.16 pF. A further increase in the concentration of doxycycline hyclate leads to a decrease in the value of the pseudocapacitance of Q_2 by half (Table 2). Thus, at a ratio of molar concentrations of doxycycline hyclate and iron (III) chloride 1:1 for both the resistance of charge transfer R_S and for the pseudocapacitance Q_2 , a change in the dynamics is observed, which is a confirmation of the complexation process at this point.

To further quantify the stability of complexation according to the indicators of electrochemical resistance of charge transfer (Tab. 2), the molar conductivities of the investigated solutions were calculated, the dependence of which on the ratio of molar concentrations $[\text{Dox}]:[\text{Fe}^{3+}]$ are given in Fig. 4.

Table 2
Parameters of electrochemical impedance of solutions of doxycycline hydrochloride and FeCl_3 in different ratios of molar concentrations $[\text{Dox}]:[\text{Fe}^{3+}]$

$[\text{Dox}]:[\text{Fe}^{3+}]$	R_Ω , Ohm	Q_1 , $10^{-12} \text{ F} \cdot \text{s}^{(a_1-1)}$	a_1	C_d , 10^{-12} F	R_{ct} , 10^3 Ohm	σ_2 , $\text{Ohm} \cdot \text{s}^{-1/2}$	Q_2 , $10^{-9} \text{ F} \cdot \text{s}^{(a_2-1)}$	a_2	C_3 , 10^{-9} F	R_3 , Ohm	σ_3 , $\text{Ohm} \cdot \text{s}^{-1/2}$
1:6	39.33	5.698	1	5.698	0.486	45925	1301.00	0.680	6.542	10.7	60563
1:5	35.11	5.158	1	5.158	0.550	49898	1061.00	0.689	6.317	19.7	68920
1:4	36.80	5.382	1	5.382	0.659	57248	987.70	0.684	5.66	22.4	74358
1:3	35.20	5.235	1	5.235	0.809	57760	504.60	0.732	6.87	29.5	85653
1:2	33.41	5.074	1	5.074	1.064	58678	169.40	0.807	8.654	78.4	112917
1:1	31.36	4.912	1	4.912	1.606	75640	75.16	0.845	8.182	450.4	5524
2:1	32.79	5.016	1	5.016	1.196	61743	71.64	0.863	13.45	378.1	13.94
3:1	33.28	5.079	1	5.079	1.081	61545	94.75	0.844	10.23	350.9	18.89
4:1	33.91	5.131	1	5.131	0.977	55162	98.67	0.839	11.44	329.0	21.84
5:1	34.65	5.170	1	5.170	0.882	53196	141.60	0.826	12.00	292.3	38.33
6:1	34.90	5.196	1	5.196	0.854	50668	161.50	0.821	12.65	274.7	108.90

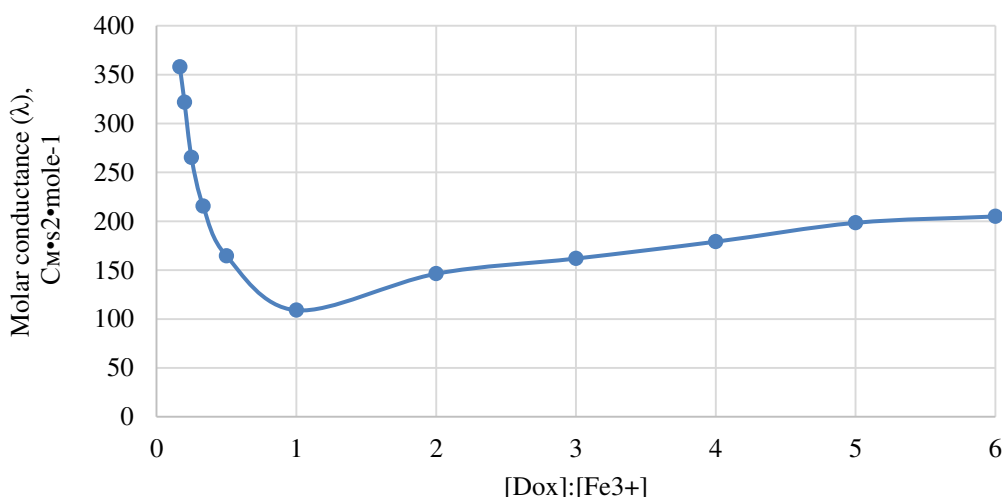


Fig. 4. Dependence of molar conductivity on the ratio of molar concentrations $[\text{Dox}]:[\text{Fe}^{3+}]$ dissolved in water at a temperature of 295 K

As can be seen from Fig. 4, there is a constant decrease in the molar conductivity of solutions for Fe^{3+}

cations. This clearly indicates that the complexes formed were less mobile than the free solvated cations. Further,

the slope of the molar conductivity curve changes at the point where the molar ratio of doxycycline hyclate and Fe^{3+} concentrations is 1:1, which indicates the formation of complexes at this point.

The stability constant (complexation) was calculated by the formula (1) [17]:

$$K_{ML+} = \frac{a_1 a_2}{a_2 a_3 [L]_t - a_1 a_3 [M]_t}, \quad (1)$$

where $a_1 = \lambda_{M+} - \lambda$, $a_2 = \lambda_{M+} - \lambda_{ML}$, $a_3 = \lambda - \lambda_{ML}$,

$$\lambda = \frac{1000 \cdot k}{C},$$

λ_{M+} , λ_{ML} – molar conductivities of the metal salt solution, as well as the test solution of the antibacterial drug and the corresponding metal salt, $[L]_t$ – molar concentration of ligand (doxycycline), $[M]_t$ – molar concentration of cation (metal salt).

Taking into account the previously calculated molar conductivities of the investigated solutions, it was determined that at $T=296 \pm 3$ K and in purified water the constant formation of the solution of doxycycline hyclate and iron (III) chloride is $\log_{10}(K_{ML+})=2.9$ units. This value of the complexation constant indicates that doxycycline hyclate forms a stable metal-ligand complex with iron (III) ions.

5. Discussion

EIS analysis of Nyquist curves of doxycycline hyclate and iron (III) chloride aqueous solutions in the range of molar ratios 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1 showed a change in the dynamics of electrical resistance at a ratio of 1:1, which can be considered a qualitative sign of complexation at this point.

It is also important to note that the charge transfer resistance of the studied electrochemical systems significantly exceeds the value of the Warburg impedance $R_S > R_3$ (Table 2). This means that the activity of iron (III) ion transfer is higher than the activity of the diffusion transfer process in the oxidation of doxycycline hyclate, despite the fact that with decreasing concentration of iron (III) ions, the mass transfer coefficients σ_2 and σ_3 increase. At the same time, both for the previous electrochemical parameters and for the dynamics of mass

transfer coefficients σ_2 and σ_3 , the ratio $[\text{Dox}]:[\text{Fe}^{3+}]=1:1$ is the transition point of dynamics from decrease to increase.

In general, the study confirmed the complexation of iron(III) and doxycycline as it is reported in the results of previous studies conducted using other physicochemical methods [18, 19]. Khammas et al. studied and reported the formation of iron (III)-doxycycline metal complexes in acidic medium by UV-spectrophotometry; by using Job's method they have estimated the ratio of $[\text{Fe}^{3+}]:[\text{Dox}]$ as 1:2 [18]. Javed and Zahir also reported the presence of complexation at the metal-ligand molar ratio 1:2 estimated by UV-spectrophotometry and thermodynamic studies. The variation between the results can be explained by the differences of the methodology approaches. The first and foremost is the different pH of the studies, as in our research the neutral solvent was used, and the acidic one was used in the studies referred above.

Research limitations. The choice of dissolution medium, study cell and electrode material can influence the electrochemical process significantly, hence should be carefully considered.

Prospects for further research. It is planned to further conduct a study of the complexation of doxycycline by the EIS method with other metal salts that may interact. Moreover, to expand research to study the interaction of other antibiotics, using the developed model.

6. Conclusions

Conducted study of the possibility of using the EIS method as a tool for assessing the complexation of antibacterial drugs and metal salts on the example of the interaction of doxycycline hyclate and salts of iron (III). Possibility of doxycycline and iron (III) complexation was confirmed both qualitatively and quantitatively. According to the change in the slope of the molar conductivity curve, as well as the maximum value of electrical resistance, the ratio at which the complexes are formed is 1:1. The constant of the complex formation was calculated using estimated molar conductivities values is 2.9. The obtained results showed the effectiveness and possibility of using the EIS to further study the chemical interactions of drugs and metal salts.

Conflict of interest

The authors declare that they have no conflicts of interest.

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