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THE MATHEMATICAL MODELING FOR THE PHENOTHIAZINE-ASSISTED CAPTOPRIL ELECTROCHEMICAL DETECTION

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Abstract

The possibility of the captoprilphenothiazine-assisted electrochemical detection in neutral and weakly acidic media has been analyzed from the mechanistic theoretical point of view. The correspondent mathematical model has been developed and analyzed by means of linear stability theory and bifurcation analysis. It was shown that phenothiazine derivatives may serve as a modifier for captopril electrochemical detection in neutral media, although the oxidation mechanism contains radical recombination. The electroanalytical process is diffusion-controlled. The possibility of oscillatory and monotonic instabilities has also been verified.

Keywords

captopril, phenothiazine, electrochemical sensors, electrochemical oscillations, stable steady-state

1. Introduction

The use of chemically modified electrodes (CME) is a very important step in electroanalytical chemistry [1 – 5]. Compared to the bare electrodes, they have some advantages, like:

- Rapidity; Low cost; Precisity; Exactity; Flexibility; Versatility in use;

Affinity between the electrode modifier and the analyte.

Captoprilis a potent and specific inhibitor of peptidyl-dipeptitase A. It blocks the conversion of angiotensin I to angiotensin II, a vasoconstrictor and important regulator of arterial blood pressure [6]. Captopril acts to suppress the renin-angiotensin system and inhibits pressure responses to exogenous angiotensin. It is a sulfhydryl-containing analog of proline and has been used in the treatment of essential hypertension [7] and to reduce mortality in patients with acute myocardial infraction

[7]. Captopril, as a chelating agent, has been proposed to complex cysteine in the treatment of cystinuria, an autosomal recessive genetic defect of the transepithelial transport of cystine and other dibasic amino acids in the kidney [8–10]. Some studies indicate that captopril acts as an antioxidant both by scavenging reactive oxygen species (ROS) and by increasing the activities of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase [11].

On the other hand administering captopril for therapeutic purposes leads to undesirable side effects like a light-headed feeling, little or no urination, or urinating more than usual, respiratory depression, swelling, rapid weight gain, chest pain or pressure, pounding heartbeats or fluttering in your chest, high potassium , nausea, slow or unusual heart rate, weakness, loss of movement, ill feeling, fever, chills, sore throat, painful mouth sores, pain when swallowing, skin sores, cold or flu symptoms[12]. Preliminary research has indicated significant loss of zinc in urine due to the intake of captopril [13]. Although details remain unclear, it now appears that chronic use of captopril may lead to a zinc deficiency [13]. Captopril is metabolized in the liver (it is oxidized into the corresponding disulfide) and is excreted mainly with the urine with 40–60% of the drug excreted unchanged [14]. An uncommon yet potentially serious side effect of CPL treatment (incommon with other angiotensin-converting enzyme inhibitors) is increased blood potassium levels [15–16]. Therefore, the determination of this drug is important from a physiological point of view as well as for the purposes of quality control [17 – 18], and electrochemical methods may be an interesting solution for this task.

Only few works concerning captopril electrochemical detection are known so far [19 – 22]. In the work [22] phenothiazine derivatives have been used as electrode modifiers. The mechanism included phenothiazine cation-radical formation and may be applied not only for captopril, but also to other analytes.

Nevertheless, the development of new electroanalytical techniques includes the solution of problems like:

- the indecision in the modifier mechanism of action;
- the compatibility of the modifier with the tissue or biological object (some modifiers, used *in vitro* may be non-compatible with *in vivo* sensing);
- the presence of electrochemical instabilities, accompanying both and electrochemical oxidation and electrooxidative polymerization of organic molecules [23 - 29].

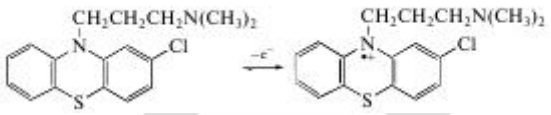
The mentioned problems may only be solved by means of an analysis of a mathematical model, capable to describe adequately the electroanalytical system. By modeling it is also capable compare the behavior of this system with that for the similar ones without any experimental essay.

So, the goal of this work is the mechanistic theoretic analysis of the possibility of captopril phenothiazine-assisted electrochemical quantification. In order to achieve it, we realize the specific goals:

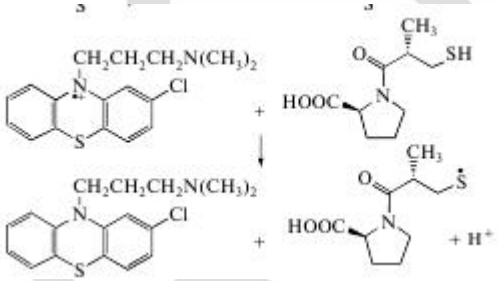
- suggestion of the mechanism of the electroanalytical reaction consequence, leading to the appearance of analytical signal;
- development of the balance equation mathematical model, correspondent to the electroanalytical system;
- analysis and interpretation of the model in terms of the electroanalytical use of the system;
- the seek for the possibility of electrochemical instabilities and for the factor, causing them;
- the comparison of the mentioned system´s behavior with the similar ones [30 – 35].

2. System and its modeling

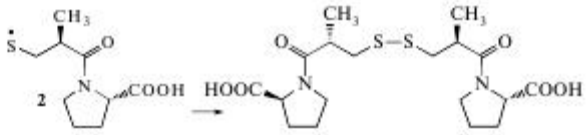
The mechanism of captopril electrochemical determination on phenothiazine derivative chlorpromazine may be described as:



1)



(2)



(3)

Taking into account the reactions (1 – 3), it is possible to conclude that the mathematical model, described in [30] for conducting polymers, will be accomplished by the appearance of one more variable, related to the captopril radical-cation, so the equation set in this case will be trivariant with the variables, described as:

c – captopril concentration in the pre-surface layer;
c* - captopril cation-radicals´ concentration in the pre-surface layer;
θ - phenothiazine derivative surface coverage degree.

To simplify the modeling, we suppose that the reactor is intensively stirred, so we can neglect the convection flow. Also we assume that the background electrolyte is in excess, so we can neglect the migration flow. The diffusion layer is supposed to

be of a constant thickness, equal to δ, and the concentration profile in it is supposed to be linear.

It is possible to show that the electrochemical system´s behavior may be described as:

$$\begin{cases} \frac{dc}{dt} = \frac{2}{\delta}\left(\frac{\Delta}{\delta}(c_0 - c) - r_2\right) \\ \frac{dc*}{dt} = \frac{2}{\delta}(r_2 - r_3) \\ \frac{d\theta}{dt} = \frac{1}{G}(r_2 - r_1) \end{cases} \quad (4)$$

In which Δ is the diffusion coefficient, c_0 is captopril bulk concentration, G is phenothiazine derivative maximal concentration and the parameters r (r_1, r_2, r_3) are correspondent reaction rates, defined as:

$$r_1 = k_1\theta \exp\left(\frac{F\varphi_0}{RT}\right) \quad (5)$$

$$r_2 = k_2 c(1-\theta) \quad (6)$$

$$r_3 = k_3 c^{*2} \quad (7)$$

in which the parameters k (k_1, k_2, k_3) are correspondent rate constants, F is the Faraday number, φ_0 is the potential slope in the double electric layer (DEL), related to the zero-charge potential, R is the universal gas constant and T is the absolute temperature.

The presence of radical formation and recombination influences strongly the system's behavior, and this influence will be described below.

In order to describe the behavior of the system with captopril electrochemical detection, assisted by phenothiazine, we analyze the equation set (4) by means of linear stability theory. The Jacobian functional matrix steady-state elements may be rewritten as:

$$\begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix} \quad (8)$$

in which:

$$a_{11} = \frac{2}{\delta}\left(-\frac{\Delta}{\delta} - k_2(1-\theta)\right) \quad (9)$$

$$a_{12} = 0 \quad (10)$$

$$a_{13} = \frac{2}{\delta}(k_2 c) \quad (11)$$

$$a_{21} = \frac{2}{\delta}(k_2(1-\theta)) \quad (12)$$

$$a_{22} = \frac{2}{\delta}(-k_3 c^{*2}) \quad (13)$$

$$a_{23} = \frac{2}{\delta}(-k_2 c) \quad (14)$$

$$a_{31} = \frac{1}{G}(k_2(1-\theta)) \quad (15)$$

$$a_{32} = 0 \quad (16)$$

$$a_{33} = \frac{1}{G}\left(-k_2 c - k_1\theta \exp\left(\frac{F\varphi_0}{RT}\right) + jk_1\theta \exp\left(\frac{F\varphi_0}{RT}\right)\right) \quad (17)$$

Similarly to [30 – 35], *the oscillatory behavior* for this system is possible and it will be caused uniquely by influences of phenothiazine electrochemical oxidation on DEL capacitances, described by the positivity of main-diagonal element $\mathrm{jk_1\theta exp}\left(\frac{\mathrm{F\varphi_0}}{\mathrm{RT}}\right)$ (positive main-diagonal elements describe the positive callback). This is the common oscillatory behavior cause for all the analogous electroanalytical systems [30 – 35].

In order to analyze the *steady-state stability*, we apply the Routh-Hurwitz criterion to the equation set (4). In order to simplify the analysis, avoiding cumbersome expressions, we introduce new variables, so the matrix determinant will be described as:

$$\frac{4}{\delta^2 G}\begin{vmatrix} -\kappa - \Xi & 0 & \Omega \\ \Xi & -P & -\Omega \\ \Xi & 0 & -\Omega - X \end{vmatrix} \quad (18)$$

Opening the brackets and applying the condition Det J<0, salient from the criterion, we obtain the steady-state stability requirement described as:

$$-P(\kappa\Omega + \kappa X + \Xi X) < 0 \quad (19)$$

As the variables P, κ, Ω and Ξ are always positive, the condition Det J<0 is always satisfied if the variable X is also positive, describing the fragility of DEL influences during the electrochemical stage. Thus, the expression on the left side of the inequation (19) will be negative, describing the steady-state stability.

In this case, the steady-state stability is electroanalytically efficient, being correspondent to the linearity of the dependence between the electrochemical parameter and concentration. The process is diffusion-controlled, tending to be

reaction-controlled in the case of the relatively small electrodes and relatively high analyte concentrations.

The *monotonic instability* in this system is possible, being caused by the equality between the stabilizing influences and the destabilizing ones of the electrochemical process influences on DEL. It is correspondent to the detection limit and its condition may be described as:

$$-P(\kappa\Omega + \kappa X + \Xi X) = 0 \quad (20)$$

If the reaction is realized in alkaline media on a bare carbon electrode, the *Kolbe* electrooxidation of captopril is possible. The surface phenomena begin to influence the system's behavior and the radical recombination will result in the appearance of surface instabilities. This case will be described in our next works.

3. Conculsions

From the theoretical investigation of the possibility of phenothiazine – assisted captopril electrochemical detection it is possible to conclude that:

- Phenothiazine may serve as an excellent modifier for captopril quantification. The stable steady-state is maintained easily, so the electroanalytical signal is easy to interpret;
- The system is electroanalytically efficient, and, depending on the electrode size and on analyte concentration, the process may be diffusion- or reaction-controlled. The linearity of the dependence between electrochemical parameter and concentration is observed in a vast zone of parameter values, which is confirmed by experimental data;
- The oscillatory behavior in this system is possible, being caused only by DEL influences of the electrochemical process.

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