















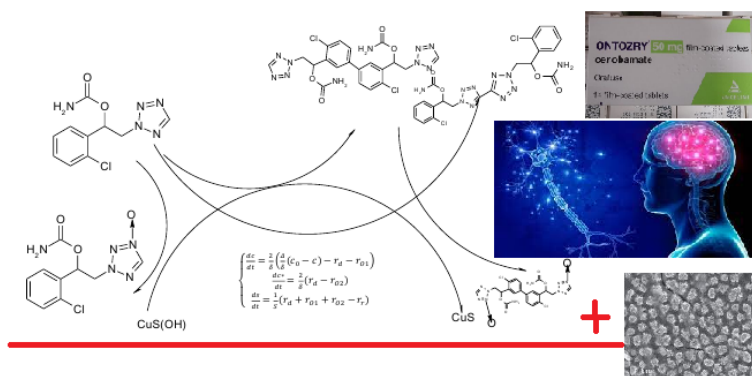
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The Theoretical Description for Cenobamate CuS-Assisted Electrochemical Determination in Pharmaceutical Formulations and Wastewater

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For the first time, the theoretical description for cenobamate antiepileptic drug on anode, assisted by copper sulfide nanoparticles in alkaline medium, has been given. Two mechanisms, involving either tetrazolic ring, or the carbocyclic aromatic moiety, are possible for this process, reason why the concentration of the drug will be identified and quantified by two peaks. Despite of the mechanism hybrid nature, both of the peaks will produce an easy interpretable analytical signal, being thereby possible to confirm the efficiency of the electroanalytical signal.

Graphical abstract



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1. Introduction

Epilepsy [1 – 4] is one of the most widespread chronic brain diseases, affecting people of all ages. It is esteemed that one of each 160 people has epilepsy, most of them from developing countries.

As for now, no complete epilepsy treatment is known.

Nevertheless, the patient state may be controlled by uptake of certain drugs, one of them cenobamate (Fig. 1) [5 – 7], known in the US as XCopri and in the EU as Ontoxry. It is used to treat partial-onset seizures in adults, like also focal-onset seizures with or without secondary generalization. It is in fact a tetrazolic carbamate (ester of unstable aminomethanic acid).

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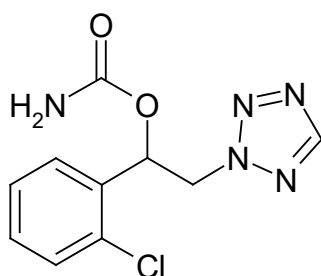


Fig. 1. Cenobamate.

Nevertheless, as cenobamate shortens the QT interval of the heart rhythm, it is contraindicated to people with heart electrical system disorder [5 – 7]. The most common side effects are dizziness, drowsiness and fatigue, like also potassium hyperconcentration, sight disorders and headache. For this reason the development of an efficient analytical method for cenobamate quantification is really actual, and the electroanalytical processes, yet used for the similar analytes [8 – 14] would give it a good service.

Considering the cenobamate structure, we may conclude that both cathodic and anodic processes may be applicable to its determination, but cathodic process is preferable, due to the presence of highly accepting groups, including the electronically deficient tetrazolic moiety. As for the anodic process, it is also possible, although requires the presence of the strong oxidants, one of which is trivalent copper, *in situ* obtained by copper sulfide nanoparticles electrooxidation in basic medium.

Nevertheless, the development of a novel electrochemical

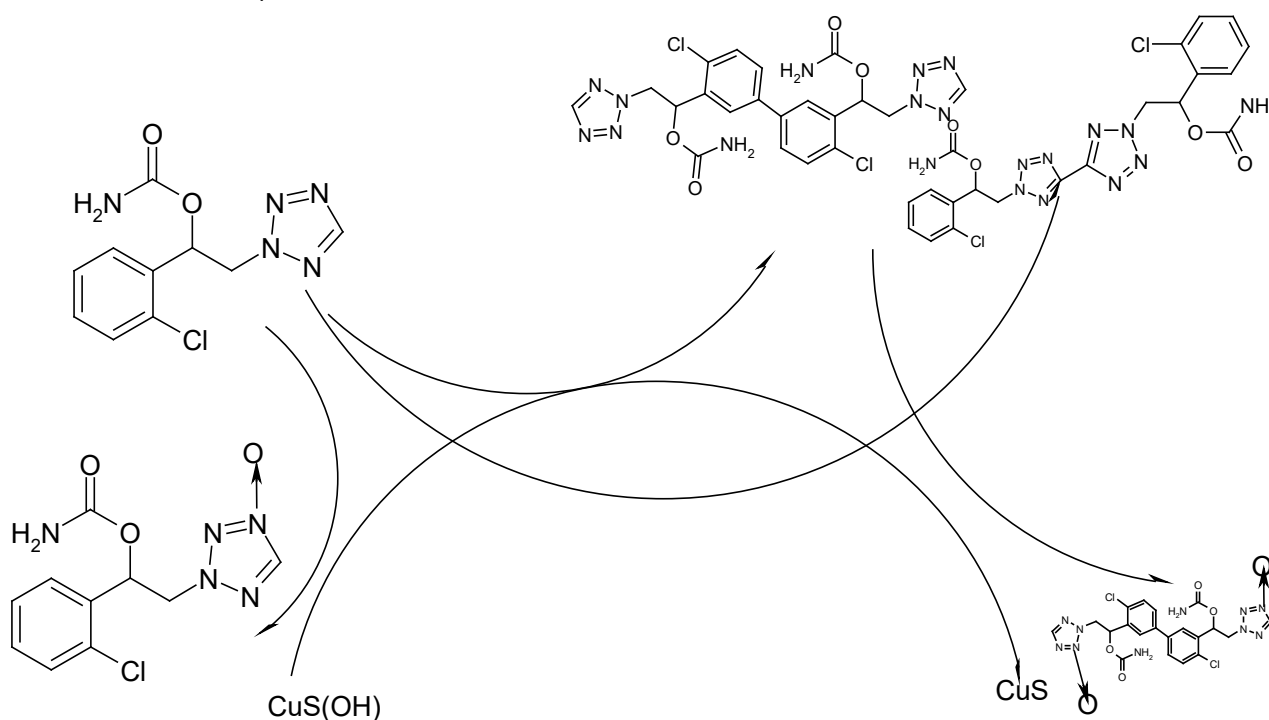


Fig. 2. The scheme of electroanalytical process.

Therefore, considering only one of two dimerization scenarios (as the second one will be similar in terms of behavior to the first of them) and taking some assumptions [18 – 21], we describe the behavior of this process by a trivariant equation-set (2)

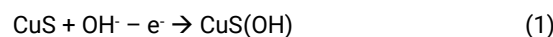
$$\begin{cases} \frac{dc}{dt} = \frac{2}{\delta} \left(\frac{\Delta}{\delta} (c_0 - c) - r_d - r_{O1} \right) \\ \frac{dc^*}{dt} = \frac{2}{\delta} (r_d - r_{O2}) \\ \frac{ds}{dt} = \frac{1}{s} (r_d + r_{O1} + r_{O2} - r_r) \end{cases} \quad (2)$$

sensor for cenobamate determination in biological liquids and pharmaceutical wastewater, on cathode or anode, requires a previous theoretical mechanistical investigation of the behavior of the hypothetic sensor. This investigation may also show the possibility of electrochemical instabilities [15 – 17], capable of affecting the behavior of the system and, consequently, the sensor precisiy and analytical signal interpretation.

For this reason, the goal of this work is to investigate, from the mechanistic point of view, the behavior of the electrochemical anodic sensor for cenobamate determination on CuS nanoparticles. The correspondent mathematical modeling includes two cenobamate oxidation scenarios, and its analysis includes stability investigation and the comparison of the behavior of this system with that of the similar ones [18 – 21].

2. Material and Methods

On the first stage, copper sulfide nanoparticles are oxidized, being thereby transformed into the copper (III) sulfhydroxide.



Copper (III) sulfhydroxide becomes thereby aggressive and oxidizes the analyte by either pyridinic nitrogen atoms, or benzenic ring, yielding a dimer. 4-4'-dimerization via tetrazolic cycle is also possible, but it is rarer, as it requires certain conditions to be realized (Fig. 2):

Herein, c and c^* are cenobamate and its dimer pre-surface layer concentrations, c_0 stands for cenobamate bulk concentration, Δ is its diffusion coefficient, s is copper sulfide nanoparticles matrix coverage degree, S is its maximal matrix concentration and the parameters r are the correspondent reaction rates, calculated as:

$$r_d = k_d c(1 - s) \quad (3)$$

$$r_{O1} = k_{O1} c(1 - s)^2 \quad (4)$$

$$r_{O2} = k_{O2} c * (1 - s)^2 \quad (5)$$

$$r_r = k_r s \exp\left(\frac{F\phi_0}{RT}\right) \quad (6)$$

In which the parameters k are the correspondent reaction rate constants, F is the Faraday number, ϕ_0 is the zero-charge related potential slope, R is the universal gas constant and T is the absolute temperature.

In neutral medium, the phenolic compounds are less ionized and thereby their chemical transformations DEL effect will be less expressed, than in the similar systems [18 – 21]. For this reason, the use of neutral and mildly alkaline pH values ($7 \leq pH \leq 11$) and copper sulfide nanoparticles as anode modifier at high potential in alkaline medium (generally inorganic) may be efficiently used for cenobamate electrochemical determination, as shown below.

3. Results and Discussion

We investigate the behavior of the cenobamate electrochemical determination over CuS nanoparticles in alkaline medium, we analyze the equation-set (2), considering the algebraic relations (3 – 6) by means of linear stability theory and depict the Jacobian matrix members as (7):

$$\begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix} \quad (7)$$

Herein:

$$a_{11} = \frac{2}{\delta} \left(-\frac{\Delta}{\delta} - k_d(1 - s) - k_{O1}(1 - s)^2 \right) \quad (8)$$

$$a_{12} = 0 \quad (9)$$

$$a_{13} = \frac{2}{\delta} (k_d c + 2k_{O1} c(1 - s)) \quad (10)$$

$$a_{21} = \frac{2}{\delta} (k_d(1 - s)) \quad (11)$$

$$a_{22} = \frac{2}{\delta} (-k_{O2}(1 - s)^2) \quad (12)$$

$$a_{23} = \frac{2}{\delta} (-k_d c + 2k_{O2} c(1 - s)) \quad (13)$$

$$a_{31} = \frac{1}{S} (k_d(1 - s) + k_{O1}(1 - s)^2) \quad (14)$$

$$a_{32} = \frac{1}{S} (k_{O2}(1 - s)^2) \quad (15)$$

$$a_{33} = \frac{1}{S} \left(-k_d c - 2k_{O1} c(1 - s) - 2k_{O2} c(1 - s) - k_r \exp\left(\frac{F\phi_0}{RT}\right) + jk_r s \exp\left(\frac{F\phi_0}{RT}\right) \right) \quad (16)$$

In order to simplify the stability analysis, we introduce new variables, rewriting thereby the determinant as:

$$\frac{4}{\delta^2 S} \begin{vmatrix} -\kappa - \varepsilon - \Sigma & 0 & T + Y \\ \varepsilon & -P & T - Y \\ \varepsilon + \Sigma & P & -T - Y - \Omega \end{vmatrix} \quad (17)$$

Opening the brackets we obtain the determinant value, calculated as (18):

$$P(2\kappa Y + \kappa\Omega + \varepsilon\Omega + \Sigma\Omega - 3\varepsilon T + 2\varepsilon Y - \Sigma T) \begin{cases} > 0, \text{linear dependence range} \\ = 0, \text{detection limit} \end{cases} \quad (18)$$

If $-\text{Det } J > 0$, the Routh-Hurwitz stability criterion is valid, and the steady-state is thereby stable, providing an efficient bisphenols electrochemical determination. Moreover, the wide stability region permits us to use this system as electroanalytical, for sensing purposes.

This criterion is readily satisfied, if the kinetic parameter Ω is positive. In the vast majority of the cases, it has positive signs and, considering that the other variables in the determinant are positive, it indicates the vast steady-state stability topological region. The electroanalytical process is mostly kinetically controlled.

In the absence of the side reactions or other factors, capable to compromise the analyte and (or) modifier stability, excluding the reactions, foreseen by the mechanism, the linearity between the electrochemical parameter and concentration is observed, providing an efficient analytical signal interpretation, which is really important for bisphenol concentration monitoring.

The condition $\text{Det } J = 0$ corresponds to the detection limit, manifested by the *monotonic instability*. It may be seen as an N-shaped part of the steady-state voltammogram and depicts the margin between the stable steady-states and unstable states and corresponds to the steady-state multiplicity. In other words, multiple steady-states, each one unstable, coexist in this point.

The main condition for the Hopf bifurcation, responsible for the oscillatory behavior is the presence of the positive elements in the Jacobian main diagonal. They are responsible for the positive callback.

Contrarily to [18 – 21], only one of the main diagonal addendums is capable of being positive, and it is $jk_r s \exp\left(\frac{F\phi_0}{RT}\right) > 0$, if $k > 0$. It describes the cyclic conductivity changes in the electroanalytical cell during the electrochemical stage and correspond to the frequent and small-amplitude oscillations.

If acidic medium is used for this system, cenobamate and its dimer become ionized, reason why the ionization elements become included in the model. By this, the behavior of this system will be described by the models, exposed in [18 – 21].

4. Conclusions

From the analysis of the system with cenobamate electrochemical determination, assisted by nano-CuS modified electrode, it was possible to conclude that that it is an efficient process, in which the linear dependence between the analyte concentration and electrochemical parameter is easy to form in an efficient kinetically-controlled system. The pH range is recommended between 7 and 11, which is correspondent to blood plasma and some other biological liquids, like also some pharmaceutical wastewaters. For its turn, the oscillatory behavior is expected to be less probable than in the alkaline medium, being only caused by double electric layer structure changes during the process on both chemical and electrochemical stage.

Author Contributions

Volodymyr V. Tkach (Investigation, Conceptualization, Supervision, Validation, Writing – Original Draft, Writing – Review and Editing); Tetiana V. Morozova (Conceptualization, Investigation, Supervision, Formal Analysis); Viktoriia O. Khrutba (Conceptualization, Investigation, Supervision, Formal Analysis), Andrii O. Hlukhonets (Conceptualization, Investigation, Supervision, Formal Analysis), Marta V. Kushnir (Data Curation, Conceptualization, Investigation); Yana G. Ivanushko (Investigation, Conceptualization, Supervision, Data Curation, Methodology, Validation, Visualization), Viktor V. Kryvetskyi (Investigation, Conceptualization, Data Curation, Methodology, Validation, Visualization), Inna I. Kryvetska (Investigation, Conceptualization, Data Curation, Methodology, Validation, Visualization), Igor V. Kryvetskyi (Investigation, Conceptualization, Data Curation, Methodology, Validation, Visualization), Petro I. Yagodynets´ (Investigation, Conceptualization, Methodology, Supervision, Validation, Writing – Original Draft, Writing – Review and Editing), Zholt O. Kormosh (Investigation, Conceptualization, Supervision, Validation, Writing – Original Draft, Writing – Review and Editing), Mykhailo M. Kucher (Investigation, Conceptualization, Data Curation), Nadiia Yu. Chykun (Investigation, Conceptualization, Supervision, Validation, Writing – Original Draft, Writing – Review and Editing), Maria João Monteiro (Investigation, Conceptualization, Supervision, Data Curation, Methodology, Validation, Visualization).

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