the theoretical evaluation of COO(OH)-assisted metformin electrochemical detection in alkaline media

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Abstract
The metformin electrochemical detection, assisted by cobalt (III) oxyhydroxide has been evaluated from the 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 CoO(OH) may be applied as an efficient electrode modifier in the detection of metformin in neutral and lightly alkaline media. The electrochemical response has to be clear and easy to interpret. The possibility of the oscillatory and monotonic instabilities has also been verified.

Keywords: drug safety, metformin, chemically modified electrodes, cobalt(III) oxyhydroxide, electrochemical detection, stable steady-state

Introduction
The use of chemically modified electrodes (CME) is a very important step in electroanalytical chemistry [1 – 3]. 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.
Type 2 diabetes comprises about 70 – 90 % of all cases of diabetes, and approximately one half of them remain undetected [4]. It has already reached epidemic proportions, currently affecting more than 200 million people worldwide. A significant growth is predicted, generally in developing countries of Asia, Africa and Latin America. It is not a single disease, but a heterogeneous collection of phenotypically and genotypically different hyperglycemic syndromes. Some 90% of cases have a multifactorial pathogenesis due to unhealthy life-style habits (overnutrition, lack of physical activities, overconsumption of alcohol, sedentary life-style etc) [5].

One of the the first-line medication for the treatment of type 2 diabetes is metformin (Fig. 1) [4 - 8]. It is also used in the treatment of polycystic ovary syndrome.[9] Limited evidence suggests metformin may prevent the cardiovascular disease and cancer complications of diabetes [10 - 11]. It is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents [12 – 13].

Although metformin is generally well tolerated [13], side effects are possible [14 – 17], including diarrhea, nausea and abdominal pain, muscle pain, decreased appetite and sleepiness. Lactic acidosis and the vitamin B12 deficit are a concern if the drug is prescribed inappropriately and in overly large doses [18 - 20]. It should not be used in those with significant liver disease or kidney problems [21 - 22]. Thus, the development of the efficient and rapid methods of its quantification is really actual [23 – 25].

Many electrochemical techniques, involving metformin electrochemical detection have been developed [26 – 29], generally using alkaline solutions with high pH. This statement may bring a hypothesis that the cobalt (III) oxyhydroxide CoO(OH), seen by many researchers as a substitute to titanium dioxide [30 - 31] and yet used in the detection of ascorbic acid [32], oxalic acid [32– 33], phenolic and hydroquinonic compounds [34], which are oxidized in the similar conditions, may be an interesting alternative.

On the other hand, its electroanalytic properties’ investigation has only begun, and a CoO(OH)-assisted electrochemical oxidation may confront the 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 electrochemical synthesis of cobalt (III) oxyhydroxide [34 – 35], and electrochemical oxidation and electrooxidative polymerization of organic molecules [36 - 41].

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 metformin CoO(OH)-assisted electrochemical quantification. In order to achieve it, we realize the specific goals:

- suggestion of the mechanism of the electroanalytical reaction sequence, including the participation of hydroxyl ions, 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 [42 - 47].

**System And Its Modeling**

In the majority of the systems, the pH used for metformin electrochemical detection was high, which presumes that hydroxyl takes part in the reaction. In the presence of CoO(OH) its mechanism may be described as:

\[
\text{glycine} + \text{OH}^- + \text{CoO(OH)} \rightarrow \text{glycine} + \text{CoO} + \text{H}_2\text{O} \quad (1)
\]

And the reversibility of the electrode is achieved by the reaction:

\[
\text{CoO} + \text{OH}^- - e^- \rightarrow \text{CoO(OH)} \quad (2)
\]

On the other hand, in very high pH values, and, especially in hot solutions, CoO(OH) may be dissolved according to the equation

\[
\text{CoO(OH)} + 3\text{OH}^- + \text{H}_2\text{O} \rightarrow [\text{Co(OH)}_6]^{3-} \quad (3)
\]

Taking into account the exposed above and assuming the excess of the hydroxyl in the solution, we introduce two variables:

- m – metformin concentration in the pre-surface layer;
- \( \theta \) – CoO(OH) 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 \( \delta \), and the concentration profile in it is supposed to be linear. It’s also supposed that at the beginning of the reaction CoO covers the entire electrode surface.
It’s possible to show that the two-dimensional mathematical model for this case will be described as:

\[
\begin{align*}
\frac{dc}{dt} &= \frac{2}{d} \left( \frac{\Delta (m_0 - m) - r_1}{\delta} \right) \\
\frac{d\theta}{dt} &= \frac{1}{G} (r_2 - r_1 - r_3)
\end{align*}
\]

in which \(m_0\) is metformin bulk concentration, \(G\) is CoO(OH) surface coverage degree, and the variables \(r_1\), \(r_2\) and \(r_3\) are the correspondent reaction rates, which may be calculated as:

\[
\begin{align*}
\dot{r}_1 &= k_3 m \theta \\
\dot{r}_2 &= k_2 (1 - \theta) \exp \left( \frac{F \gamma \theta}{RT} \right) \\
\dot{r}_3 &= k_3 \theta \exp (-\beta \theta)
\end{align*}
\]

in which the parameters \(k\) are correspondent reaction rate constants, \(F\) is the Faraday number \(\gamma\) is the parameter, describing the influences of the coverage degree on the potential slope in the double electric layer (DEL), referent to the zero-charge degree, \(\beta\) is the variable, describing the interaction between CoO(OH) particles during their dissolution, \(R\) is the universal gas constant, and \(T\) is the solution absolute temperature.

CoO(OH) use for metformin detection in alkaline solutions may be compromised by the CoO(OH) destruction reaction. The concurrence between these two reactions and its stability aspects will be discussed below.

**Results And Discussion**

To investigate the behavior with CoO(OH)-assisted metformin electrochemical detection, we analyze the equation set (1) by means of linear stability theory and bifurcation analysis. The Jacobian functional matrix steady-state elements for it may be described as:

\[
\begin{pmatrix}
  a_{11} & a_{12} \\
  a_{21} & a_{22}
\end{pmatrix}
\]

in which:

\[
\begin{align*}
  a_{11} &= \frac{2}{d} \left( \frac{\Delta}{\delta} - k_1 \theta \right) \\
  a_{12} &= \frac{2}{d} \left( -k_1 m \right) \\
  a_{21} &= \frac{1}{G} \left( -k_1 \theta \right) \\
  a_{22} &= \frac{1}{G} \left( -k_2 \exp \left( \frac{F \gamma \theta}{RT} \right) + \gamma k_2 (1 - \theta) \exp \left( \frac{F \gamma \theta}{RT} \right) - k_3 \theta - k_3 \exp (-\beta \theta) + \beta k_3 \theta \exp (-\beta \theta) \right)
\end{align*}
\]

*The oscillatory behavior* is capable to be realized in the Andronov-Hopf bifurcation conditions – \(\text{Det} J > 0, \text{Tr} J = 0\), in which \(\text{Tr} J = a_{11} + a_{22}\), and \(\text{Det} J = a_{11} a_{22} - a_{21} a_{12}\). As the condition \(\text{Det} J > 0\) is, generally, satisfied, the main one is that described as \(\text{Tr} J = 0\). It may be satisfied, if at least one of the main diagonal elements is positive.

Two positive elements are present in the main diagonal. One of them, \(\gamma k_2 (1 - \theta) \exp \left( \frac{F \gamma \theta}{RT} \right) > 0\) if \(\gamma > 0\), defines the oscillatory behavior, caused by the DEL influences of the electrochemical process.
The second one, $\beta k_3 \theta \exp(-\beta \theta) > 0$ if $\beta > 0$, describes the oscillatory behavior, caused by the attraction of the CoO(OH) particles during its dissolution. The oscillatory behavior causes are correspondent to those, described for the similar systems in [43 – 47]. The oscillations are expected to be frequent, and their amplitude will depend on solution pH.

The steady-state stability condition for a two-dimensional system may be described as: $\text{Tr } J < 0$, $\text{Det } J > 0$. In order to avoid the cumbersome expressions, we introduce new variables, so, the matrix determinant will be rewritten as:

$$\frac{2}{\partial \mathcal{G}} \begin{vmatrix} -\kappa - \Xi & -\Sigma \\ -\Xi & -\Sigma - \Omega - X \end{vmatrix}$$

Opening the brackets, we obtain the steady-state stability condition as:

$$\begin{cases} -\kappa - \Xi - \Sigma - \Omega - X < 0 \\ \kappa \Xi + \kappa \Omega + \Xi \Omega + \kappa X + \Xi X > 0 \end{cases}$$

And it is warranted to be satisfied in the case of the positivity of $\Omega$ and $X$, describing the fragility of DEL influences of the electrochemical process and the repulsion between CoO(OH) particles. The process is diffusion-controlled, tending to be reaction-controlled in the case of the relatively small electrodes and relatively high analyte concentrations.

The steady-state is maintained stable easily. Nevertheless, its electroanalytical efficiency will depend on pH and electrode size. If the electrode size is relatively small in hot solutions with the concentrated alkaline media, the material will be destroyed, and the process won’t be electroanalytically efficient, although the steady-state remains stable. So, it is recommended to use relatively big electrodes with relatively cold solutions.

Being the requirements satisfied, he steady-state stability is correspondent to the linear dependence between the electrochemical parameter and analyte concentration, or, better saying, to the electroanalytical efficiency. This efficiency is maintained easily, so CoO(OH) may be an excellent candidate as electrode modifier for metformin electrochemical detection.

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:

$$\begin{cases} -\kappa - \Xi - \Sigma - \Omega - X < 0 \\ \kappa \Xi + \kappa \Omega + \Xi \Omega + \kappa X + \Xi X = 0 \end{cases}$$

As in CoO(OH) cobalt is trivalent, cobalt (III) oxyhydroxide may act either as oxidant, or as a reductant, forming cobalt dioxide.

$$\text{CoO(OH)} + \text{OH}^- - e^- \rightarrow \text{CoO}_2 + \text{H}_2\text{O}$$

So, the use of this pair in electroanalytical investigation not only of metformin, but also for other compounds, inclusively, those hardly oxidized, may be also used. This possibility will be evaluated in our next works.
Conclusions
From the theoretical investigation of the possibility of CoO(OH) – assisted metformin electrochemical detection it is possible to conclude that:

- CoO(OH) may serve as an excellent modifier for metformin quantification. The stable steady-state is maintained easily;
- The system is electroanalytically efficient, if the electrode size pH and temperature do not promote the rapid CoO(OH) dissolution. The electrode must be relatively big, and the solution temperature, relatively low;
- Depending on the electrode size and on analyte concentration, the process may be diffusion- or reaction-controlled;
- The oscillatory behavior in this system is possible, being caused by DEL influences of the electrochemical process and surface instabilities, accompanying the dissolution;
- The monotonic instability in this system is also possible, being caused by the equality of the destabilizing influences in DEL to the stabilizing ones.

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