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The theoretical description for omeprazole electrochemical determination, assisted by the composite poly(1,2,4-triazole)-Ag_2O_2

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Summary

Introduction: Omeprazole is one of the most used proton-blocking molecules applied in the gastric ulcer treatment. Its blocking effect is achieved by the presence of both acidic and basic nitrogen heteroatoms in its composition. Nevertheless, due to its collateral effects, which may be moderate to severe, the development of its electrochemical determination is really actual. **Methods**: In this work, we describe theoretically the possibility of omeprazole electrochemical determination, assisted by the composite, containing the silver (I, III) oxide as an active substance and the polymer of 1,2,4-triazolic derivative as a mediator. In this case, the omeprazole molecule is gradually oxidized yielding firstly phenolic and then quinonic derivative. The pyridinic nitrogen is oxidized later. **Results**: The electroanalytical process is described by a trivariant equation-set, analysis of which confirms the efficiency of the composite of poly(1,2,4-triazole) with Ag_2O_2. The electrochemical oscillations are also possible, being realized beyond the detection limit. **Conclusion**: The composite of poly(1,2,4-triazole) with Ag_2O is suitable for omeprazole electrochemical determination both *in vivo* and *in vitro*.

Keywords: Omeprazole, electrochemical sensors, silver (I, III) oxide, conducting polymers, stable steady-state.

Resumo

A descrição teórica da detecção eletroquímica de omeprazol, assistida pelo compósito poli(1,2,4-triazol)-Ag_2O_2

Introdução: o omeprazol é um dos bloqueadores de protons mais usados no tratamento de úlceras gástricas. O seu efeito de bloqueio se dá pela presença dos heteroátomos de nitrogênio de carizes acídico e básico. Entretanto, vistos os seus efeitos colaterais, que podem ser moderados a severos, o desenvolvimento de um método da sua determinação eletroquímica é realmente atual. **Métodos**: neste trabalho, nós descrevemos teoricamente a possibilidade da determinação electroquímica de omeprazol, assistida pelo compósito, que contém o óxido de prata (I, III) como substância ativa e o polímero 1,2,4-triazólico como mediador. Neste caso, a molécula do omeprazol se oxida gradualmente, rendendo primeiro o seu derivado fenólico, depois, o quinônico. O nitrogénio piridínico se oxida depois. **Resultados**: o processo eletroanalítico se descreve por um conjunto de equações diferenciais trivariante, cuja análise confirma a eficácia do compósito de poli(1,2,4-triazol) com Ag_2O_2. As oscilações eletroquímicas também são possíveis, realizando-se além do limite de detecção. **Conclusão**: o compósito de poli(1,2,4-triazol) com Ag2O é idóneo para a detecção eletroanalítica de omeprazol tanto *in vivo* como *in vitro*.

Palavras-chave: Omeprazol, sensores eletroquímicos, óxido de prata (I, III), polímeros condutores, estado estacionário estável.

Resumen

Descripción teórica de la detección electroquímica de omeprazol, asistida por el compuesto poli(1,2,4-triazol)-Ag_2O_2

Introducción: el omeprazol es uno de los bloqueadores de protones más comunes en el tratamiento de úlceras gástricas. Su efecto de bloqueo se da por la presencia de los heteroátomos de nitrógeno de tipos ácido y básico. Entretanto, sus efectos colaterales pueden variar de moderados a severos, y el desarrollo de un método de su determinación electroquímica es realmente actual. **Métodos**: en este trabajo, nosotros describimos teóricamente la posibilidad de la determinación electroquímica de omeprazol, asistida por el compuesto, que contiene el óxido de plata (I, III) como sustancia activa y el polímero 1,2,4-triazólico como mediador. En este caso, la molécula de omeprazol se oxida gradualmente, rindiendo primero su derivado fenólico, después, el quinónico. El nitrógeno piridínico se oxida ulteriormente. **Resultados**: el proceso electroanalítico se describe por un conjunto de ecuaciones diferenciales trivariante, cuyo análisis confirma la eficiencia del compuesto de poli(1,2,4-triazol) con Ag_2O_2. Las oscilaciones electroquímicas también son posibles, realizándose lejos del límite de detección. **Conclusión**: el compuesto de poli(1,2,4-triazol) con Ag_2O es idóneo para la detección electroanalítica de omeprazol *in vivo* e *in vitro*.

Palabras clave: Omeprazol, sensores electroquímicos, óxido de plata (I, III), polímeros conductores, estado estacionario estable.

Introduction

Nowadays, the frequency of verticular and chronic gastritis and gastritic ulcers occurrences has been grown slightly [1-4] in both urban and rural areas. Gastritis and ulcers may be treated by the H2-blocking molecules, detaining the proton transfer. One of this molecules is omeprazole (6-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl) methylsulfinyl]-1H-benzimidazole, M= 345 g/mol, PubChem Number=4594, CAS N: 73590-58-6, Fig. 1).

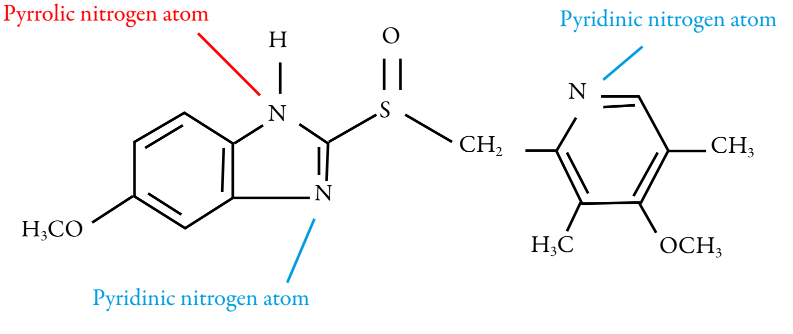

Figure 1. Omeprazole molecule.

Its blocking effect is achieved by the formation of its sulphenamide metabolite, forming complex with both H+K+ATPase+ and gastric mucosa carbonic anhydrase [3, 4], inhibing the proton transfer into the gastric lumen. This effect is possible, due to the presence of both pyrrolic and pyridinic nitrogen atoms, in its composition. Nevertheless, may present various collateral effects, like headache, vertigo, nausea, diarrhea and flatulence, which may cause discomfort [5-8]. Moreover, the concentration control is also important for successful treatment of patients with liver and kidney insufficiency or older people. Thus, the search of a precise, exact, rapid and sensitive method for its quantification is a really actual problem [9-12].

Many electrochemical methods have been proposed for omeprazole [13-15] electrochemical determination. Nonetheless, the bare electrodes may not be suitable, due to high overvoltage needed to commence the electrochemical reaction, thus the electrode must be chemically modified by a hybrid composite, possessing both the active substance and mediator.

This composite may contain inorganic oxidant nanoparticles as active substance, stabilized by organic conducting polymer [16-22], acting as a mediator.

> Nevertheless, the organic electrooxidation processes (including the electropolymerization) tend to be accompanied by electrochemical instabilities. These instabilities include the oscillatory changes in electrochemical potential and monotonic instabilities [23-25] and influence the sensing properties of the composite.

Thus, in order to investigate the parameter values, correspondent to the most efficient monomer and polymer formation, like also verify the possibility and probability of the electrochemical instabilities in this system, an *a priori* theoretical observation of the electrochemical determination.

In this work, we analyze the omeprazole electrochemical determination, assisted by the composite of silver (I, III) oxide nanoparticles, stabilized by poly (1,2,4-triazole). In order to achieve it, we realize the specific goals:

- Suggestion of the mechanism of the 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, involving omeprazole electrochemical determination [26-28].

System and its modeling

The mechanism of the Ag_2O_2 assisted electrochemical determination may be schematically depicted as on the Fig. 2.

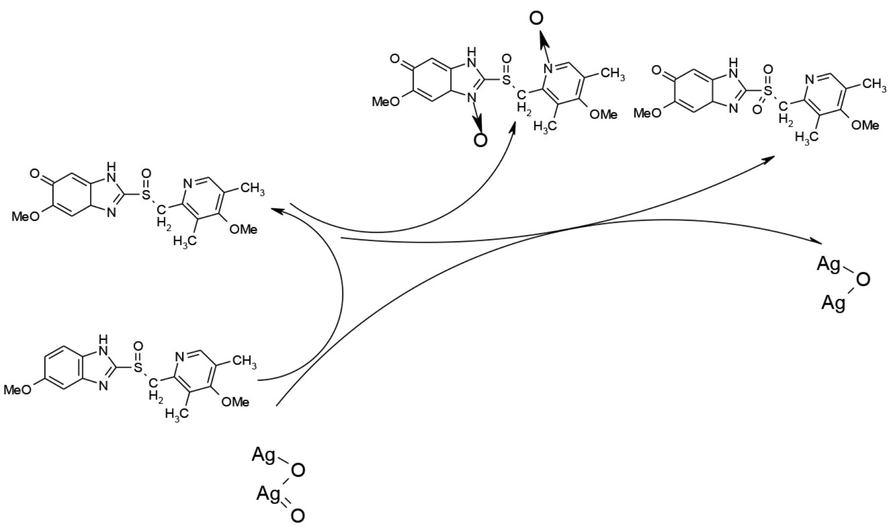

Figure 2. The mechanism for omeprazole electrochemical determination, assisted by a Ag_2O_2-Poly (1,2,4-triazole) composite.

On the first stage, the omeprazole is oxidized, yielding the quinonic derivatives [13-15, 26-28]. Then, the resulting quinone is oxidized by either nitrogen or sulfur atom, yielding N-oxide and sulfone, respectively. Therefore, in order to describe the behavior of the electroanalytical system, we introduce three variables:

c: omeprazole concentration in the pre-surface layer;

q: quinonic form concentration in the pre-surface layer;

s: silver (I) oxide 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 electroanalytical process will be described by the three-dimensional equation set, exposed as:

$$\begin{cases} \frac{dc}{dt} = \frac{2}{\delta}\left(\frac{\Delta}{\delta}\left(c_0 - c\right) - r_1\right) \\ \frac{dq}{dt} = \frac{2}{\delta}\left(r_1 - r_{21} - r_{22}\right) \\ \frac{ds}{dt} = \frac{1}{S}\left(r_1 + r_{21} + r_{22} - r_3\right) \end{cases} \tag{1}$$

Herein, Δ is the diffusion coefficient, c_0 is the omeprazole bulk concentration, S is the silver (I) oxide maximal surface concentration and the parameters r are the correspondent reaction rates, expressed as:

$$r_1 = k_1 c(1 - s)^3 \tag{2}$$

$$r_{21} = k_{21} q(1 - s)^2 \tag{3}$$

$$r_{22} = k_{22} q(1 - s) \tag{4}$$

$$r_3 = k_3 s \exp\frac{2F\varphi_0}{RT} \qquad (5),$$

in which the parameters k are the correspondent rate constants, F is the Faraday number, R is the universal gas constant and T is the absolute temperature.

In this system, the electrochemical determination of omeprazole is gradual, due to the electrochemical oxidation of the benzenic ring to quinonic derivative, followed by N-oxide and sulfone formation. Nevertheless, as all of the additional chemical stages do not influence the DEL capacitance and ionic force, the electroanalytical system will resemble the described in [26-28], as shown below.

Results and discussion

In order to describe the behavior of the system with omeprazole electrochemical determination, assisted by a composite Ag_2O_2-poly(1,2,4-triazoles), we analyze the equation set (1) by means of linear stability theory and bifurcation analysis. The steady-state Jacobian matrix members will be exposed as:

$$\begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix} \quad (6),$$

in which:

$$a_{11} = \frac{2}{\delta}\left(-\frac{\Delta}{\delta} - k_1(1-s)^3\right) \quad (7)$$

$$a_{12} = 0 \quad (8)$$

$$a_{13} = \frac{2}{\delta}\left(3k_1c(1-s)^2\right) \quad (9)$$

$$a_{21} = \frac{2}{\delta}\left(k_1(1-s)^3\right) \quad (10)$$

$$a_{22} = \frac{2}{\delta}\left(-k_{21}(1-s)^2 - k_{22}(1-s)\right) \quad (11)$$

$$a_{23} = \frac{2}{\delta}\left(-3k_1c(1-s)^2 + 2k_{21}q(1-s) + k_{22}q\right) \quad (12)$$

$$a_{31} = \frac{1}{C}\left(k_1(1-s)^{3}\right. \quad (13)$$

$$a_{32} = \frac{1}{C}\left(k_{21}(1-s)^2 + k_{22}(1-s)\right) \quad (14)$$

$$a_{33} = \frac{1}{C}\left(-3k_1c(1-s)^2 - 2k_{21}q(1-s) - k_{22}q - k_3\exp\frac{2F\varphi_0}{RT} + jk_3s\exp\frac{2F\varphi_0}{RT}\right) \quad (15)$$

Contrarily to the similar systems [26-28], the oscillatory behavior in this system, despite of remaining possible, is of less probability. It is explained by the absence of DEL influences of chemical stages, present in the similar systems. Thus, the unique main-diagonal element, which may be possible (and, consequently, responsible to the positive callback, causing the Hopf bifurcation), is + $jk_3 s \exp\frac{2F\varphi_0}{RT}$ if j>0, describing the cyclic DEL capacitance changes during the electrochemical stage. This factor is common for the great majority of the electroanalytical systems and is realized in sufficient manner to cause significant oscillations far beyond the detection limit. The oscillations are expected to be frequent and of small amplitude.

Yet if the mentioned element is negative, the *steady-state stability* is warranted. Really, applying the Routh-Hurwitz criterion to the Jacobian matrix and introducing new variables, having it rewritten as (16):

$$\frac{4}{\delta^2 S}\begin{vmatrix} -\kappa-\Xi & 0 & \Lambda \\ \Xi & -\Sigma & \mathrm{P}-\Lambda \\ \Xi & \Sigma & -\mathrm{P}-\Lambda-\Omega \end{vmatrix} \tag{16}$$

and opening the brackets and applying the condition Det J<0, salient from the criterion, we obtain the steady-state stability requirement (17):

$$-\kappa\left(2\Sigma\Lambda+\Sigma\Omega\right)+2\Lambda\Xi\Sigma<0 \tag{17}$$

Contrarily to the similar systems [26-28], which are mostly diffusion-controlled, this system will be kinetically-controlled, due to the relative strong destabilizing influences on the first chemical stage.

Nonetheless, it defines the vast parameter region of the steady-state stability. From the electroanalytical point of view, it is correspondent to the linear dependence between the electrochemical parameter and the drug concentrations, describing an efficient diffusion-controlled electroanalytical process, even more stable than in similar systems [26-28].

Thus, it is possible to conclude that the Ag_2O_2-Poly (1,2,4-triazoles) composite is efficient electrode modifier for the omeprazole electrochemical determination.

The monotonic instability, correspondent to the detection limit, from the electroanalytical point of view, is also probable, if the destabilizing and stabilizing influences are equal. Its conditions will be described as:

$$-\kappa(2\Sigma\Lambda+\Sigma\Omega)+2\Lambda\Xi\Sigma=0 \tag{18}$$

The same model may be used for the electrochemical determination of omeprazole, assisted by silver (I, III) oxide, stabilized by conducting polymer of other monomers. Yet the use of cobalt (IV) oxide in some conditions excludes the N-oxide formation, annihilating the r_{21}. In the rest, the model will be similar to described above.

Conclusions

From the system with the electrochemical determination of omeprazole on a Ag2O2 – Poly(1,2,4-triazole) composite it was possible to conclude that:

- Contrarily to the similar systems involving omeprazole electrochemical detection, this electroanalytical system will be kinetically-controlled.
- The linear dependence between the electrochemical parameter and concentration of the pesticides is realized in a broad topological parameter region. The composite is efficient electrode modifier for omeprazole electrochemical determination.
- The oscillatory behavior in this system is less probable than in the similar systems, being caused uniquely and exclusively by the DEL influences of the electrochemical stage.

Disclosure statement

The authors declare that they have no conflict of interest.

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