RESEARCH ARTICLE

THE POSSIBILITY OF NALBUPHIN CoO(OH)-ASSISTED ELECTRO-CHEMICAL DETECTION AND ITS MATHEMATICAL DESCRIPTION

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Abstract. **The possibility of nalbuphin electrochemical determination over a CoO(OH)-modified electrode has been studied 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 nalbuphin 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.**

Introduction. The use of chemically modified electrodes (CME) is a very important step in electroanalytical chemistry [1–4]. Compared to the bare electrodes, they have some advantages, like, rapidity, low cost, precisity, exactity, flexibility, versatility in use and affinity between the electrode modifier and the analyte. On the other hand, nalbuphine is a semi-synthetic opioid pain-relieving drug, used as an analgesic to relieve the moderate and severe pains. It is an agonist at kappa opioid receptors and an antagonist or partial agonist at mu opioid receptors [5]. Nalbuphine is the only opioid analgesic that is not a controlled substance in the United States. In Ukraine it is included in the first aid box of the sanitary instructors. In Brazil it is sold as Nubain and is commercialized only to hospitals. It may be used as a supplement to balanced anesthesia, for preoperative and post-operative analgesia, and for obstetrical analgesia during labor and delivery [5–8]. Its plasma half-life is about 5 hours and in clinical studies the duration of analgesic activity has been reported to range from 3 to 6 hours [9]. Its excess can create side effects, like dizziness, drowsiness, feeling of constant movement of self or surroundings, nausea, relaxed and calm sensation of spinning, slumber, sweaty, clammy skin, vomiting, rarely, dry mouth and headache [10–14]. So, the development of an efficient and rapid method for its quantification is, without a doubt, an actual problem [15–17]. In the work [18] an electroanalytical process for naphlubine electrochemical detection on Pt:Co nanostructure has been suggested. The sensor has shown efficient selectivity in the presence of diclofenac. Nevertheless, its modifier contained platinum, with may enhance the cost of its use, so the cobalt (III) oxyhydroxide CoO(OH), seen by many researchers as a substitute to titanium dioxide [19] and yet used in the detection of ascorbic acid [20], oxalic acid [20–21], phenolic and hydroquinonic compounds [22], 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 electrochemi-cal instabilities, accompanying both electrochemical synthesis of cobalt (III) oxyhydroxide [23–24], and electrochemical oxidation and electrooxidative polymerization of organic molecules [25-28]. 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 nalbuphine CoO(OH)-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 [29–35].

System and its modeling. In general, the mechanism of CoO(OH)-assisted nalbuphine electrochemical oxidation in neutral media may be described as:
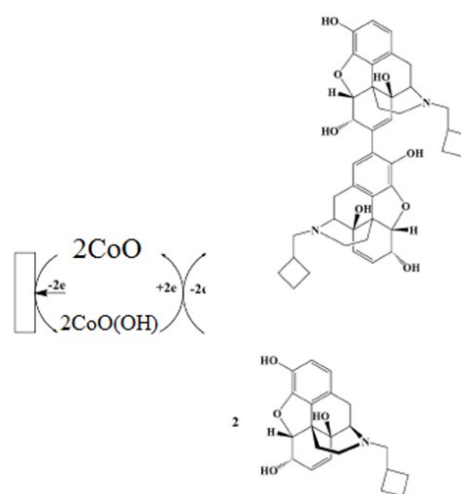

Fig. 1 Nalbuphine CoO(OH)-assisted oxidation mechanism

and it is accomplished, while compared with the similar systems [29 – 35], by dimerization. In this system we may introduce three variables: c – nalbuphine concentration in the pre-surface layer; c* - nalbuphine radical-cation concentration in the pre-surface layer; θ – CoO surface concentration. Nevertheless, if the radical-cations do not provoke side reactions on the surface or in the solution, the variable c* is easily eliminated, and the system will be bivariant with the variables c and θ. This case will be described in this system.

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'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:

$$\begin{cases} \dfrac{dc}{dt} = \dfrac{2}{\delta}\left(\dfrac{\Delta}{\delta}(c_0 - c) - r_1 \right) \\ \dfrac{d\theta}{dt} = \dfrac{1}{G}(r_1 - r_2) \end{cases} \qquad \text{Eq. [1]}$$

In which Δ is the diffusion coefficient, c_0 is nalbuphine bulk concentration, G is CoO maximal concentration and r_1 and r_2 are the reaction rates of the electroanalytical process stages, shown on the Fig. 1, which may be calculated as:

$$r_1 = k_1 c^2 (1-\theta)^2 \qquad \text{Eq. [2]}$$

$$r_2 = k_2 \theta \exp\left(\frac{2F\gamma\theta}{RT} \right) \qquad \text{Eq. [3]}$$

In which the parameters k are reactions' rate constants, F is Faraday number, γ is the parameter describing the influence of the electrochemical process on double electric layer (DEL) capacitance, R is the universal gas constant, and T is the solution absolute temperature. Contrariously to the CP-based systems [32–35], in which the radical coupling influenced the polymer composition and properties, leading to surface instabilities, in this system, it gives less impact, which will be discussed below.

Results and Discussions   To investigate the behavior with CoO(OH)-assisted nalbuphine 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:

$$\begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix} \qquad \text{Eq. [4]}$$

$$a_{11} = \frac{2}{\delta}\left(-\frac{\Delta}{\delta} - 2k_1 c(1-\theta)^2 \right) \qquad \text{Eq. [5]}$$

$$a_{12} = \frac{4}{\delta}\left(k_1 c^2 (1-\theta) \right) \qquad \text{Eq. [6]}$$

$$a_{21} = \frac{2}{G}\left(k_1 c(1-\theta)^2 \right) \qquad \text{Eq. [7]}$$

$$a_{22} = \frac{1}{G}\left(-k_1 c^2 (1-\theta) - k_2 \exp\left(\frac{2F\gamma\theta}{RT}\right) - \gamma k_2 \theta \exp\left(\frac{2F\gamma\theta}{RT}\right) \right) \qquad \text{Eq. [8]}$$

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

$$-\gamma k_2 \theta \exp\left(\frac{2F\gamma\theta}{RT} \right) > 0$$

positive if γ<0, describing strong influences of the electrochemical processes on DEL. It is common for all similar systems [29–35]. The steady-state stability condition for a two-dimensional system may be described as: Tr J<0, Det J>0. In order to avoid the cumbersome expressions, we introduce new variables, so, the matrix determinant will be rewritten as:

$$\frac{2}{\delta G}\begin{vmatrix} -\kappa - \Xi & \Sigma \\ \Xi & -\Sigma - \Omega \end{vmatrix} \qquad \text{Eq. [9]}$$

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

$$\begin{cases} -\kappa - \Xi - \Sigma - \Omega < 0 \\ \kappa\Sigma + \kappa\Omega + \Xi\Omega > 0 \end{cases} \qquad \text{Eq. [10]}$$

And it is warranted to be satisfied in the case of the positivity of Ω, describing the fragility of DEL influences of the electrochemical process. The process is diffusion-controlled, tending to be reaction-controlled in the case of the relatively small electrodes and relatively high analyte concentrations (see the Table).

Analyte concentration	Electrode size	Steady-state stability defining process
Low	Small	Diffusion or reaction
High		Reaction
Low	Large	Diffusion
High		Diffusion or reaction

Tab. 1 The optimal conditions for nalbuphin electroanalysis

For the electroanalytical effects the steady-state stability is correspondent to the linear dependence between the electrochemical parameter and analyte concentration, or, better saying, to the electroanalytical efficiency. It isn't compromised even by radical recombination effects, if they do not provoke side reactions. 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:

$$\begin{cases} -\kappa - \Xi - \Sigma - \Omega < 0 \\ \kappa\Sigma + \kappa\Omega + \Xi\Omega = 0 \end{cases} \qquad \text{Eq. [11]}$$

In the case of *side reactions* of radical cations, the variable c* can't be eliminated, and the equation set used becomes trivatiant. it's possible to mention that CoO(OH) may change its modification during the electroanalytical process. If so, an additional variable, describing another CoO(OH) modification coverage degree, is introduced, and the modification change effects strongly the system's behavior. This system will be described in our next works.

Conclusions.   From the theoretical investigation of the possibility of CoO(OH) – assisted nalbuphin electrochemical detection it is possible to conclude that: CoO(OH) may serve as an excellent modifier for nalbuphin quantification, despite of the presence of radical recombination. The stable steady-state is maintained easily, and the system is electroanalytically efficient; 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; The monotonic instability in this system is also possible, being caused by the equality of the destabilizing influences in DEL to the stabilizing ones; The presence of side reactions of the cation-radicals and also modification changes in CoO(OH) may influence the system, making its behavior more complicated.

References

1. C.C. Vishvanatha, B. Kumara Swamy, K. Vasantakumar Pai, J. Anal. Bioanal. Techn., 6(2015), 237

2. M.A. Sheikh-Mohseni, S. Pirsa, Anal. Bioanal. Electrochem., 8(2016), 777

3. M. Maximiano, C. A. Lima Cardoso, G. J. Arruda, Orbital Elec. J. Chem., 8(2016), 232

4. D. Zane, G. B. Appetecchi, C. Bianchini et.al., Electroan., 23(2011), 23, 1134

5. https://www.drugbank.ca/drugs/DB00844, accessed at the 18th of January 2017

6. M.W. Gunion, A.Marchionne, C.T.M. Anderson, Acute Pain 6(2004), 29

7. R.D. Jowey *et al.,* Pain Res. Manage, 8(2003), 3A

8. http://www.medicinanet.com.br/bula/3811/nubain.htm, accessed at the 18th of January 2017

9. H. Krenn, W. Oczenski, H. Jellinek *et al.,* Eur. J. Pain., 5(2001), 219

10. https://www.drugbank.ca/drugs/DB00844, accessed at the 18th of January 2017

11. https://www.drugs.com/sfx/nalbuphine-side-effects.html, accessed at the 18th of January 2017

12. Z. Zeng, J. Lu, Ch. Shu *et al.,* Sci. Rep., 5 (2015), 10927

13. J. Ouaki, A. Rochette, O. Raux *et al.,* Eur. J. Anaest., 24(2007), 138

14. S.E. Cohen, E.F. Ratner, T.R. Kreizman *et al.,* Anesteth. Analg., 75(1992), 747

15. P.W. Huang, H. Ta Liu, Ch. Huei Hsiong *et al.,* Biomed. Chromatogr., 27(2013), 831

16. A. M. El-Didamony, M.Z. Saad, N.O. Saleem, J. Chil. Chem. Soc., 58(2013), 1907

17. H.M. Elquaby, H.A.M. Hendawy, E.R. Souaya *et al.,* Int. J. Electrochem., 2016(2016), ID: 8621234, 9 pages

18. S. Cheraghi, M.A. Taher, H. Karimi-Maleh, R. Moradi, J. Electrochem. Soc., 160(2017), B60

19. C. J. Raj, B. Ch. Kim, W. J. Cho et. al., 747(2015), 130

20. A. Stadnik, Aplicação de eletrodos, modificados com cobalto como sensor eletroquímico, M.Sc. Thesis, Universidade Estadual de Centro-Oeste do Paraná, Guarapuava, 2011, 110 pages

21. A. Stadnik, E.M. Caldas, A. Galli, F.J. Anaissi, Orbital. Elec. J. Chem., 7(2015), 122

22. J.S. Bonini, F.Q. Mariani, E. Guimarães Castro et. al., Orbital Elec. J. Chem., 7(2015), 318

23. O. Stadnik, N. Ivanova, Y. Boldyrev, 218th Int. Electrochem. Soc.Meeting.Abstract#2240,

http://ma.ecsdl.org/content/MA2010-02/38/2240.full.pdf Accessed at 8th of August 2015

24. Stadnik O. Synthesis, Electrochemical and Photoelectrochemical Properties of the Oxide-hydroxide Compounds of Cobalt, Diss. Kand. Chim. N. – Kyiv. – 2011

25. A.J. Pearlstein, J.A. Johnson, J. Electrochem. Soc, 136(1991), 1290

26. S.U. Rahman, M.S. Ba-Shammakh, Synth. Met. 140(2004), 207.

27. I. Das, N.R.Agrawal, S.A.Ansari, S.K.Gupta,Ind. J. Chem, 47(2008), 1798.

28. K. Aoki, I. Mukoyama, J. Chen., Russ. J. Electrochem., 40(2004), 319

29. V. Tkach, S.C. de Oliveira, F.J. Anaissi *et. al.,* Anal. Bioanal. Electrochem., 8(2016), 1

30. V. Tkach, S.C. de Oliveira, F.J. Anaissi *et. al.,* Anal. Bioanal. Electrochem., 8(2016), 557

31. V. Tkach, Ya. Ivanushko, S.C. de Oliveira *et. al.,* Anal. Bioanal. Electrochem., 8(2016), 749

32. V. Tkach, S.C. de Oliveira, V. Neves *et. al.,* Mor. J. Chem., 4(2016), 678

33. V. Tkach, Ya. Ivanushko, O. I. Aksimentyeva *et. al.,* Anal. Bioanal. Electrochem., 8(2016), 856

34. D. Zane, G. B. Appetecchi, C. Bianchini et.al., Electroan., 23(2011), 23, 1134

35. A. Ramanavicius, A. Ramanaviciene, A. Malinauskas, Electrochim. Acta, 51(2006), 6025