THE POSSIBILITY OF THE DORZOLAMIDE DETERMINATION BY VANADIUM (III) OXYHYDROXIDE AS A MARKER OF VISION DISTURBANCES, CAUSED BY STUDY COMPUTERIZATION

V.V. Tkach[1,2], S. M. Lukanova[1], S. I. Seliverstov[1], M. V. Kushnir[1], S. C. de Oliveira[2], P. I. Yagodynets'[1]

[1]Chernivtsi National University, 58012, Kotsyubyns'ky Str., 2, Chernivtsi, Ukraine

[2]Universidade Federal de Mato Grosso do Sul, Av. Sen. Felinto. Müller, 1555, C/P. 549, 79074-460, Campo Grande, MS, Brazil

Abstract : The possibility of the use of vanadium oxyhydroxide (VO(OH)) as an electrode modifier for dorzolamide electrochemical determination, used as a marker of vision disturbances of students in the conditions of study computerization, has been theoretically evaluated. The correspondent mathematical model has been developed and evaluated by means of linear stability theory and bifurcation analysis. It was shown that, despite of expressively cathodic behavior, vanadium (III) oxyhydroxidemay serve as an anode modifier for the dorzolamide electrochemical determination. The electrochemical response has to be clear and easy to interpret. The possibility of the oscillatory and monotonic instabilities has also been verified.

Keywords: medication safety, dorzolamide, vanadium (III) oxyhydroxide, electrochemical sensors, stable steady-state

1. INTRODUCTION

The use of computer has been expanded among the pupils and students [1 – 6]. The computerization of the study: not only in class, but also by doing the homework and search of the information has enhanced the cases of the called Computer Vision Syndrome, also referred to as Digital Eye Strain (DES). Its most common symptoms [1] are:

- eyestrain
- headaches
- blurredvision
- enhance of eye pressure
- dryeyes

These symptoms may be caused by:

- poorlighting
- glareon a digitalscreen
- improperviewingdistances
- poorseatingposture
- uncorrectedvisionproblems

- acombinationofthesefactors

The DES at itself doesn't provoke serious symptoms. Nevertheless, the excessive and lasting use of the computer may enhance the risks of aging macular dystrophy, glaucoma and cataracts. Another negative factor is the incorrect sitting position. The correct position is represented on the Figure 1:

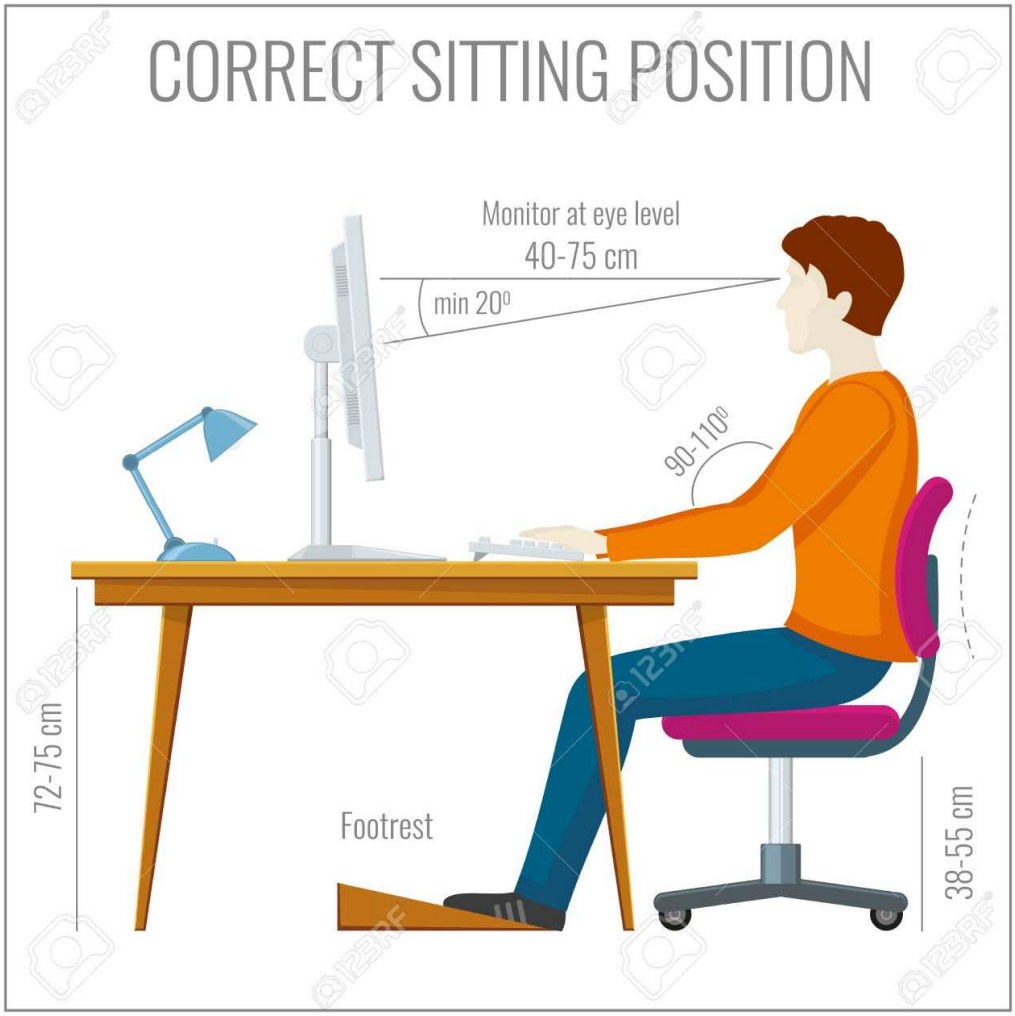

Fig. 1. The correct sitting position

By the enhance of the concentration of the eye drugs and their metabolites in tears, blood and nose liquids of students, it is possible to judge about the presence of DES and its frequency in their organisms. As the tear evaporation is more rapid and the blinking is more seldom during the use of the computer, the tears are more concentrated.

Dorzolamide is [7- 9] is a topical carbonic anhydrase inhibitor. It is an anti-glaucoma agent, and acts by decreasing the production of aqueous humor. It is indicated for the reduction of elevated intraocular pressure in patients with ocular hypertension who are insufficiently responsive to beta blockers, which may lower the learning capacity and quality. Dorzolamideis only found in individuals that have used or taken this drug. It is a carbonic anhydrase (CA) inhibitor. It is used in ophthalmic solutions (Trusopt) to lower intraocular pressure (IOP) in open-angle glaucoma and ocular hypertension.

Dorzolamide is a sulfonamide and a highly specific carbonic anhydrase II (CA-II) inhibitor, which is the main CA isoenzyme involved in aqueous humor secretion. Inhibition of CA-II in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Dorzolamide also accumulates in red blood cells as a result of CA-II binding, as CA-II is found predominantly in erythrocytes. However, sufficient CA-II activity remains so that adverse effects due to systemic CA inhibition are not observed.

Besides of its principal activity, dorzolamide possesses some side effects like burning, dry or itching eyes, discharge from the eye, excessive tearing. Rarely, blood in the urine, blurring vision, nausea or vomiting and skin rash may be observed [7, 10 – 12]. The lastly mentioned effects are linked with the presence of sulphonamine group in the side chain. Thus, the development of a method, capable to detect its concentration efficiently and rapidly is really actual [13 – 18].

An interesting technique for dorzolamide electrochemical determination has been described in [19], using anodic oxidation of dorzolamide in moderately acid media. This may lead us to think that vanadium (III) oxyhydroxide, a compound with the possibility of semiconducting behavior, could be an interesting electrode modifier for dorzolamide electrochemical determination. Its stability is given if $3 \leq pH \leq 14$.

Nevertheless, VO(OH) is a compound with the flexible electrochemical behavior, but more inclined to reducent properties. Moreover, no works, concerning electroanalytical function of VO(OH) with dorzolamide or other analytes, have been published for now. Only one work concerning the use of vanadium oxyhydroxide as an electrode modifier for condensers [20] is known. On the other hand, the development of a principally new electrode modifier may confront some problems, like:

- the indecision about the mechanism of electrochemical action of the electrode modifier with the analyte;

- the possibility of the appearance of electrochemical instabilities, characteristic for the electrosynthesis and action of CoO(OH), a similar compound [21 – 22].

These problems may be solved, if the experimental essays are preceded by an *a priori* theoretical investigation of the electroanalytical system. So, in this work, the theoretical mechanistic investigation of VO(OH)-assisted dorzolamide electrochemical determination is given ($3 \leq pH \leq 7$, T = 298 K). Also, the behavior of this system is compared with that of the similar electroanalytical processes [23 – 25].

SYSTEM AND ITS MODELING

It is possible to show that VO(OH) may be used as an anode modifier, if it is oxidized to yield vanadium (IV) oxide:

$$VO(OH) - e^- \rightleftarrows VO_2 + H^+ \quad (1)$$

This compound oxidizes dorzolamide, restoring vanadium (III) oxyhydroxide, as:

$$2VO_2^+ \rightarrow 2VO(OH)^+ \quad (2)$$

As in [19], the mildlyor moderately acidic media may be used in order to maintain the electroanalytical system, based on the pair $VO(OH)/VO_2$, H^+, stable in these conditions. Nevertheless, the use of lower pH values may provoke protonicattacks of the analyte, difficulting its oxidation. Thus, in order to describe the behavior of this system, we introduce three variables:

c – dorzolamide concentration in the pre-surface layer;

v – vanadium dioxide surface coverage degree;

h – proton concentration in the pre-surface layer.

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, in the case of analyteprotonic attacks, the system's behavior will be described by the following equation set:

$$\begin{cases} \frac{dc}{dt} = \frac{2}{\delta}\left(\frac{\Delta}{\delta}(c_0 - c) - r_2 - r_h\right) \\ \frac{dv}{dt} = \frac{1}{G}(r_1 - r_2) \\ \frac{2}{\delta}\left(\frac{D}{\delta}(h_0 - h) + r_1 - r_h\right) \end{cases} \quad (3)$$

Δ and D are is the diffusion coefficients of dorzolamide and protons, c_0 is dorzolamide' bulk concentration, G is VO(OH) maximal surface concentration and the parameters r are correspondent reaction rates, which may be calculated as:

$$r_1 = k_1(1 - v)exp\left(\frac{F\varphi_0}{RT}\right) \quad (4)$$

$$r_2 = k_2 c v^2 \quad (5)$$

$$r_h = k_h c h \quad (6)$$

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

This article describes the electroanalytical process in mildly acidic pH, in which the VO(OH) dissolution is relatively slow. So, the oscillatory behavior will be less probable than if pH were lower, which will be shown in the next section.

RESULTS AND DISCUSSION

In order to investigate the behavior of the system with dorzolamide VO(OH)-assisted electrochemical determination, we analyze the equation set (3) by means of linear stability theory. The Jacobi functional matrix steady-state elements may be described as:

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

in which:

$$a_{11} = \frac{2}{\delta}\left(\frac{-A}{\delta} - k_2 v^2 - k_h h\right) \quad (8)$$

$$a_{12} = \frac{2}{\delta}\left(-2k_2 v\right) \quad (9)$$

$$a_{13} = \frac{2}{\delta}\left(-2k_2 v\right) \quad (10)$$

$$a_{21} = \frac{1}{G}\left(-k_2 v^2\right) \quad (11)$$

$$a_{22} = \frac{1}{G}\left(-k_1 exp\left(\frac{F\varphi_0}{RT}\right) - jk_1(1-v)exp\left(\frac{F\varphi_0}{RT}\right) - k_2 v\right) \quad (12)$$

$$a_{23} = 0 \quad (13)$$

$$a_{31} = \frac{2}{\delta}\left(-k_h ch\right) \quad (14)$$

$$a_{32} = \frac{2}{\delta}\left(k_1 exp\left(\frac{F\varphi_0}{RT}\right) + jk_1(1-v)exp\left(\frac{F\varphi_0}{RT}\right)\right) \quad (15)$$

$$a_{33} = \frac{2}{\delta}\left(\frac{-D}{\delta} - 2k_2 v\right) \quad (16)$$

It is possible to show that the *oscillatory behavior* for this system is possible and it will be caused uniquely by influences of the electrochemical stage on the double electric layer, described by the positivity of main-diagonal element $-jk_1(1-v)exp\left(\frac{F\varphi_0}{RT}\right)$ (positive main-diagonal elements describe the positive callback). The oscillations are expected to be frequent and of small amplitude.

In order to analyze the *steady-state stability,* we apply the Routh-Hurwitz criterion to the equation set (3). In order to simplify the analysis, avoiding cumbersome expressions, we introduce new variables, so the matrix determinant will be described as:

$$\frac{2}{\delta GM}\begin{vmatrix} -\kappa-\Xi-X & \Lambda & -\Omega \\ -\Xi & -\Lambda-\Sigma & 0 \\ -X & \Sigma & -\Omega-\lambda \end{vmatrix} \quad (17)$$

Applying the requisite Det J<0, salient from the criterion, we obtain the steady-state stability condition rewritten as:

$$-\Omega(\Xi\Sigma+\kappa\Lambda+2\Xi\Lambda+\kappa\Sigma+\Xi\Sigma)-\lambda(\kappa\Lambda+2\Xi\Lambda+X\Lambda+\kappa\Sigma+\Xi\Sigma+X\Sigma)<0 \quad (18)$$

It is warranted to be satisfied, in the case of the positivity of the element j, describing the fragility or absence of the destabilizing influences on the electrode surface and in DEL. So, the steady-state is maintained stable easily. The expression (18) is typical for diffusion-controlled systems.

In the terms of electroanalytical efficiency of stable steady-state at the analytical conditions, in which either VO(OH), or analyte are stable to proton attacks, and in which the reduction is realized by most efficient level($3 \leq pH \leq 7$, T = 298 K), it will be correspondent to the linear dependence between dorzolamide concentration and electrochemical parameter. So, it is possible to conclude that in lightly and moderately acidic solutions, the electroanalytical process will be efficient.

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:

$$-\Omega(\Xi\Sigma+\kappa\Lambda+2\Xi\Lambda+\kappa\Sigma+\Xi\Sigma)-\lambda(\kappa\Lambda+2\Xi\Lambda+X\Lambda+\kappa\Sigma+\Xi\Sigma+X\Sigma)=0 \quad (18)$$

The simplest model, described here is applicable to the system only in the case of the solutions, in which VO(OH) is stable (like blood plasma or tears pretreated tissues). In the case of VO(OH) dissolution in the acid media, the surface and DEL factors of the dissolution and formation of V^{3+} ions will influence the system. This case will be aborded in our next works.

The use of this sensor with the blood and tears tissues of students of different academic groups may help us to evaluate (by drug concentration) the influence of study computerization on the occurence of some consequences of DES (eye hypertension) and their influence on the students' learning quality.

CONCLUSIONS

From the theoretical investigation of the possibility of the Dorzolamide electrochemical detection, assisted by the VO(OH) – polypyrrole composite it is possible to conclude that:

- VO(OH) may serve as an excellent modifier for Dorzolamide quantification. The stable steady-state is maintained easily.
- the system is electroanalytically efficient;

- the electroanalytical process is diffusion -controlled;
- the oscillatory behavior in this system is possible, being caused only by DEL influences of the electrochemical process. The amplitude is dependent on the solution composition;
- the development of this sensor may contribute on the determination of negative vision influences of digital eye syndrome and their impact on worsening of the learnimg quality of the students.

REFERENCES

1. http://proglaza.ru/bolezniglaz/komputerniy-zritelniy-syndrom.html, accessed at the 8th of January 2018
2. https://www.aoa.org/patients-and-public/caring-for-your-vision/protecting-your-vision/computer-vision-syndrome, accessed at the 8th of January 2018
3. C. Blehm, S. Vishnu, A. Khattak *et al.,* Surv. Ophthalmolg., 50(2015), 253
4. K. M. Arif, M. J. Alam, Faridpur Med Coll. J., 10(2015), 33
5. J. Bali, N. Neeraj, R. T. Bali, J. Clin. Ophthalmol. Res., 2(2014), 61
6. S. Kokab, M. I. Khan, J. Evol. Med. Dent. Sci., 1(2012), 1223
7. https://www.drugs.com/pro/dorzolamide.html, accessed at the 8th of January 2018
8. J. A. Balfour, M. I. Wilde, Drugs Aging 10(1997), 394
9. https://pubchem.ncbi.nlm.nih.gov/compound/dorzolamide, accessed at the 8th of January 2018
10. M. R. Razeghinejad, A. K. Sawchyn, L. J. Katz, Expert Opin. Pharmacother., 11(2010), 959
11. K. D. Tripari, Essentials of Medical Pharmacology, Jaypee Brothers Medical Publishers(P) Ltd, Delhi, 2004
12. http://www.medbroadcast.com/drug/getdrug/sandoz-dorzolamidetimolol, accessed at the 8th of January 2018
13. M. Constanzer, C. Chavez, B. Matuszewski *et al.,* J. Pharm. Biomed. Anal., 15(1997), 1001
14. A. Maltese, C. Bucolo, Biomed. Chromatogr., 16(2002), 274
15. A. Zammataro, R. Saletti, C. Civale *et al.,* J. Chromatogr. B., 878(2010), 807
16. N. Erk, Die Pharm. Int. J. Pharm. Sci., 58(2003), 491
17. L. I. Bebawy, J. Pharma. Biomed. Anal., 27(2002), 737
18. N. Erk, J. Pharma. Biomed. Anal., 28(2002), 391
19. H. Hendawy, H. Elwy, A. Fekry, Int. J. Pharm. Pharm. Sci., 9(2017), 43
20. Y.Y. Zhao, L. Li, T. Chen, X. Chu, Anal. Meth., 37(2017), 5518
21. 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
22. Stadnik O. Synthesis, Electrochemical and Photoelectrochemical Properties of the Oxide-hydroxide Compounds of Cobalt, Diss. Kand. Chim. N. – Kyiv. – 2011
23. V.V. Tkach, Ya. G. Ivanushko, Iryna L. Kukovs´ka *et al.,*Revista Química Hoy, 6(2016), 14
24. V. Tkach, S.C. de Oliveira, G. Maia *et. al.,* Mor. J. Chem., 4(2016), 112
25. V. Tkach, S.C. de Oliveira, F.J. Anaissi *et. al.,* Anal. Bioanal. Electrochem., 8(2016), 1

JACEP

ISSN: 2509-1468