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Theoretical Description for Dexketoprofen Electrochemical Determination, Assisted by VO(OH) Composite with Polypyrrole

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Abstract: An interesting electroanalytical process for dexketoprofen electrochemical determination over a polypyrrole-VO(OH)-modified electrode has been described. The electroanalytical process is realized by a cathodic reduction by two parallel mechanisms. The electroanalytical process kinetics is pH-dependent. The analysis of the mathematical model for this case has shown that the neutral and mildly acidic media is slightly more favorable to dexketoprofen electrochemical determination. The steady-state stability and electroanalytical efficiency of the process have been proven. The process may be used *in vitro* and *in vivo* to evaluate the drug delivery efficiency.

Keywords: dexketoprofen; electrochemical sensors; vanadium (III) oxyhydroxide; polypyrrole; stable steady-state.

1. Introduction

Dexketoprofen (dextrorotary ketoprofen, Fig. 1) [1–4] is widely used as a non-steroid painkiller for a short-time treatment of mild to moderate pain. The chiral switch from ketoprofen to dexketoprofen enhances the drug's therapeutical efficiency.

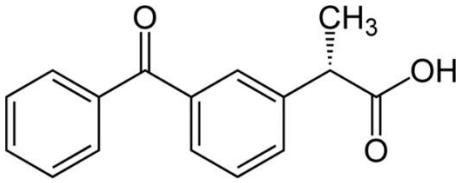

Figure 1. Dexketoprofen.

The side effects of dexketoprofen include dizziness, nausea, vomiting [5–10]. Also, it may increase the alcohol and sedative drugs action. Moreover, it may be intolerant in certain persons, which is why the development of an efficient method for dexketoprofen determination is actual [11,12].

Considering the presence of the electroactive groups, we may conclude that the electroanalytical methods apply to dexketoprofen determination [13–16]. Moreover, the cathodic processes are more convenient, so the vanadium (III) oxyhydroxide may be suitable for cathode modifiers. To enhance the VO(OH) efficiency in the electroanalytical process, it is used in the form of nanoparticles, stabilized by conducting a polymer layer [17–21].

Nevertheless, we can't proceed with the practical use of the electroanalytical system without the theoretical mechanistic stability investigation of its behavior. This analysis includes the probability of the instabilities, typical for electrooxidation and electropolymerization processes [22–24]. Also, this analysis includes the "virtual" comparison of the electroanalytical systems. Therefore, we analyze the VO(OH)-doped conducting polymer electrode efficiency in the dexketoprofen electrochemical determination in this work. This analysis includes the mechanism suggestion and analysis by means of the correspondent mathematical mode like also the virtual comparison of this system with that of the similar electroanalytical processes [25 – 34]

2. Materials and Methods

Dexketoprofen molecule contains two moieties capable of reducing electrochemically. As for the carbonyl, moiety is reduced at the first turn, yielding the correspondent hydroxy acids. It is thereby reduced by the carboxyl group, yielding the correspondent diol (Fig. 2):

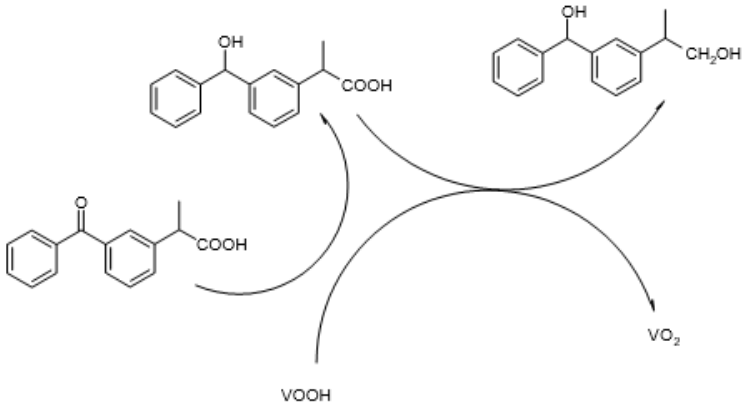

Figure 2. The scheme of dexketoprofen reduction.

As for polypyrrole, it plays a dual role in the composite, stabilizing the VO(OH) nanoparticles and providing electron transfer mediation.

Therefore, to describe the behavior of this system, we introduce three variables:
c – dexketoprofen concentration in the pre-surface layer;
c* - dexketoprofen primary reduced form concentration in the pre-surface layer;
v – vanadium dioxide surface coverage degree.

Taking some assumptions [27 – 34], we expose the balance differential equation-set for this system as:

$$\begin{cases} \frac{dc}{dt} = \frac{2}{\delta}\left(\frac{\Delta}{\delta}(c_0 - c) - r_1\right) \\ \frac{dc*}{dt} = \frac{2}{\delta}(r_1 - r_2) \\ \frac{dv}{dt} = \frac{1}{V}(r_1 + r_2 - r_r) \end{cases} \quad (1)$$

Herein, Δ is the diffusion coefficient, c_0 is drug bulk concentration, V is vanadium dioxide maximal surface concentration, and the parameters r are the correspondent reaction rates, calculated as:

$$r_1 = k_1 c(1-v)^2 \exp(-ac) \quad (2)$$

$$r_2 = k_1 c*(1-v)^4 \exp(-bc*) \quad (3)$$

$$r_r = k_r v \exp\left(-\frac{F\varphi_0}{RT}\right) \quad (4)$$

In which the parameters k are the correspondent reaction rate constants, F is the Faraday number, $\varphi_0$is the zero-charge potential related potencial slope, R is the universal gas constant and T is the reactor absolute temperature.

As for the parameters a and b, they describe the DEL influence of the transformation of the ionic form on the chemical stage and, taking into account the acidic nature of the analyte; their values are conditioned to (5):

$$a, b \begin{cases} = 0, & pH \leq 7 \\ \neq 0, & pH > 7 \end{cases} \quad (5)$$

Describing the pH-dependent feature of the ionic transformations on the chemical stage of the electroanalytical process.

As for the process, its behavior is expected to be pH-dependent. The oscillatory behavior in this system is expected to be less probable in neutral and acidic media and more probable in alkaline media. Nevertheless, the electroanalytical process is expected to be efficient, as shown below.

3. Results and Discussion

To describe the system's behavior with dexketoprofen VO(OH)-PPy assisted electrochemical determination, we analyze the balance differential equation-set (1) using linear stability theory and bifurcation analysis. The steady-state Jacobian functional matrix members for it may be described as:

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

in which:

$$a_{11} = \frac{2}{\delta}\left(-\frac{\Delta}{\delta} - k_1(1-v)^2 \exp(-ac) + ak_1 c(1-v)^2 \exp(-ac)\right) \quad (7)$$

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

$$a_{13} = \frac{2}{\delta}(2k_1 c(1-v)\exp(-ac)) \quad (9)$$

$$a_{21} = \frac{2}{\delta}(k_1(1-v)^2 \exp(-ac) - ak_1 c(1-v)^2 \exp(-ac)) \quad (10)$$

$$a_{22} = \frac{2}{\delta}(bk_1 c*(1-v)^4 \exp(-bc*) - k_1(1-v)^4 \exp(-bc*)) \quad (11)$$

$$a_{23} = \frac{2}{\delta}(4k_1 c*(1-v)^3 \exp(-bc*) - 2k_1 c(1-v)\exp(-ac)) \quad (12)$$

$$a_{31} = \frac{1}{V}(2k_1 c(1-v)\exp(-ac) - ak_1 c(1-v)^2 \exp(-ac)) \quad (13)$$

$$a_{32} = \frac{1}{V}(2k_1 c(1-v)\exp(-ac) - bk_1 c*(1-v)^4 \exp(-bc*)) \quad (14)$$

$$a_{33} = \frac{1}{V}\left(-2k_1 c(1-v)\exp(-ac) - 4k_1 c*(1-v)^3 \exp(-bc*) - k_r \exp\left(-\frac{F\varphi_0}{RT}\right) + jk_r v \exp\left(-\frac{F\varphi_0}{RT}\right)\right) \quad (15)$$

Taking into account the Jacobian main diagonal elements (7), (11), and (15), we may conclude that the oscillatory behavior for this system is possible. Moreover, considering the

conditions (5), we may conclude that it will be more probable for alkaline pH than neutral and acidic.

Really, if the element $jk_r v \exp\left(-\frac{F\varphi_0}{RT}\right) > 0$, if j>0, typical for all the similar systems [25 – 28] describes the oscillatory behavior on the electrochemical stage at both alkaline and non-alkaline pH, the elements $ak_1c(1-v)^2\exp(-ac) > 0$ and $bk_1c*(1-v)^4\exp(-bc*) > 0$, if a,b>0, describe the oscillatory behavior caused by ionic forms transformations on the chemical stage. As in neutral and acidic media, the dexketoprofen molecule is less ionized, the DEL is less affected, and this effect may be neglected. The values of a and b will thus be equal to nil, reducing the probability of the oscillatory behavior.

As for the steady-state stability, its region augments neutral and mildly acidic media and diminishes the alkaline media. Applying the Routh-Hurwitz criterion to the equation-set (1), rewriting the matrix determinant as (16):

$$\frac{4}{\delta^2 V}\begin{vmatrix} -\kappa-\Xi & 0 & \Lambda \\ \Xi & -\Sigma & P-\Lambda \\ \Xi & \Sigma & -\Lambda-P-\Omega \end{vmatrix} \quad (16)$$

and investigating the Det J<0 requisite, salient from the criterion, we obtain the steady-state stability condition, expressed as (17):

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

Conveniently rewritten as (19)

$$(\kappa+\Xi)(2\Sigma\Lambda+\Sigma\Omega) > 2\Lambda\Xi\Sigma \quad (19)$$

Indicating either diffusion or kinetically controlled electroanalytical efficient process. The less alkaline is the media, the vaster is the topological area, correspondent to the realization of the condition (19). Also, as no side reaction compromising the analyte and(or) modifier stability occur in this process, the steady-state stability will correspond to the linear dependence between electrochemical parameter and concentration.

As the pH value of the inflamed tissue tends to be mildly acidic, this sensor may easily be used *in vivo* in order to monitor the drug delivery and release.

The detection limit is defined by the *monotonic instability*, describing the margin between the stable and unstable states. Its condition is Det J = 0, or (20).

$$(\kappa+\Xi)(2\Sigma\Lambda+\Sigma\Omega) = 2\Lambda\Xi\Sigma \quad (20)$$

The lowermost pH limit for this model is correspondent to the pH=3, in which VO(OH) becomes dissolved (21):

$$VO(OH) + 3H^+ \rightarrow V^{3+} + 2H_2O \quad (21)$$

The VO(OH) dissolution will be thereby accompanied by both surface and DEL instabilities. This case will be described in our next papers.

4. Conclusions

The theoretical analysis for the possibility of VO(OH) – PPy-assisted dexketoprofen electrochemical determination let us conclude that the system is more efficient in neutral and acidic media and less efficient in alkaline solutions. As for the oscillatory behavior is more probable in alkaline solutions and less probable in the acidic. The system's behavior permits us to use this electroanalytical process for drug release and delivery monitoring.

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Conflicts of Interest

The authors declare no conflict of interest.

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