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The theoretical description for bromfenac electrochemical determination in tears and eye drops on CoO(OH)

Volodymyr V. Tkach [1,*], Tetiana V. Morozova [2], Sílvio C. de Oliveira [3], Maria João Monteiro [4], Yana G. Ivanushko [5], Igor G. Biryuk [5], Tetiana B. Sykyrytska [5], Jarem R. Garcia [6], Necdet Karakoyun [7], Petro I. Yagodynets´ [1,*], Zholt O. Kormosh [8,*], Karina V. Palamarek [9], Iryna R. Loshenyuk [9], Konon L. Bagrii [9], José Inácio Ferrão da Paiva Martins [10], Inesa M. Khmeliar [11], Lesya O. Kushnir [11], Rostyslav O. Sabadyshyn [11], Dmytro L. Lysytsia [11], Riboba G. Sharipova [12], Sabina Nasirova [12], Markhabo R. Rakhmatova [12], Vazira Z. Jalalova [12], Yulia V. Palytsia [13], Alla V. Grekova [14], Ianina F. Burdina [14], Viktoria O. Khrutba [2]

1 Chernivtsi National University, 58000, Kotsyubyns´ky Str. 2, Chernivtsi, Ukraine
2 National Transport University, 02000, Omelianovych-Pavlenko Str. 1, Kyiv, Ukraine
3 Universidade Federal de Mato Grosso do Sul, Av. Sen. Felinto. Müller, 1555, C/P. 549, 79074-460, Campo Grande, MS, Brazil
4 University of Trás-os-Montes e Alto Douro, Quinta de Prados, 5001-801, Folhadela, Vila Real, Portugal
5 Bukovinian State Medical University, 58001, Teatralna Sq., 9, Chernivtsi, Ukraine,
6 Universidade Estadual de Ponta Grossa, Campus de Uvaranas, Av. Gal. Carlos Cavalcanti, 4748, 84030-900, Ponta Grossa, PR, Brazil
7 Yüzüncü Yil University of Van, Bardakçı, 65090, Tuşba/Van, Türkiye
8 Volyn National University, 43000, Voli Ave., 13, Lutsk, Ukraine
9 Chernivtsi Institute of Trade and Economics of Kyiv National University of Trade and Economics, 58001, Central Sq. 6, Chernivtsi, Ukraine
10 Faculdade de Engenharia da Universidade do Porto, 4200-465, Rua Dr. Roberto Frias, s/n, Porto, Portugal
11 Rivne State Basic Medical Academy, 33000, Mykola Karnaukhov Str., 53, Rivne, Ukraine
12 Abu Ali Ibn Sino Bukhara State Medical Institute, 705018, Navoi Str., 1, Bukhara, Uzbekistan
13 National University of Life and Environmental Science of Ukraine, 03041, Heroiv Oborony Str, 15, Kyiv, Ukraine
14 Odesa National Medical University, 65000, Valikhovsky Ln. 2, Odesa, Ukraine
* Correspondence: nightwatcher2401@gmail.com (V.V.T.), ved1988mid@rambler.ru (P.I.Y.), zholt1971@ukr.net (Z.O.K.);

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Abstract: The bromfenac electrochemical determination over cobalt (III) oxyhydroxide-modified electrode has been described theoretically for the first time. Depending on the solution pH, the electroanalytical process will be carried out differently. It is hydrolyzed in a basic medium, correspondent to tears, thereby oxidized by electrochemical phenolization, followed by quinone-hydroquinonic mechanism. The correspondent mathematical model confirms that despite the high double electric layer impact of each stage, including the analyte hydrolysis, cobalt (III) oxydroxide may be suitable for the bromfenac electrochemical determination in tears and eye drops.

Keywords: bromfenac; electrochemical sensors; cobalt (III) oxyhydroxide; electrochemical oscillations; stable steady-state

1. Introduction

Bromfenac (Fig. 1) is an NSAID analogous to diclopfenac [1 – 4], but with more specific use. It is used to treat eye inflammation and pain in post-operative states. It is used as an ophthalmic solution for eye drops. It has been shown to reduce macular edema and retinal thickness, augmenting the visual acuity.

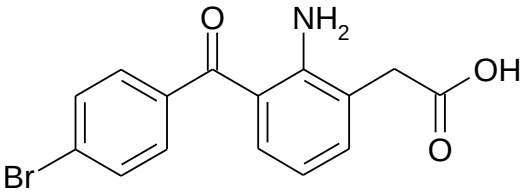


Figure 1. Bromfenac.

Its mechanism of action is somehow analogous to that of diclofenac and aceclophenac, but in basic eye solution, the phenolization following quinone-hydroquinone oxidation becomes more expressed.

Bromfenac is contraindicated for people who do not tolerate NSAIDs. Its side effects include eye irritations and mild erosion of the cornea [5 – 8]. Moreover, the use of bromfenac in exceeded doses or other inflammatory processes except for ocular may provoke hepatic disorders [8]. For this and other reasons, the determination of bromfenac is actual in order to control adequate medical care for post-surgery ophthalmologic patients [9 – 12].

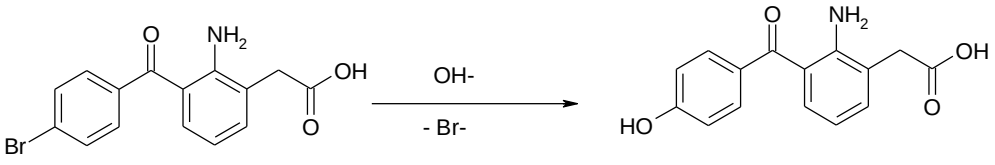
Being similar in either chemical structure or biological action to diclofenac, bromfenac is electroactive. Therefore, its electrochemical behavior will become similar, and considering that diclofenac is a very popular analyte in electroanalysis [13 – 19], these methods will be acceptable for bromfenac. Taking this into account, we may conclude that cobalt (III) oxyhydroxide, yet used for similar compounds [20 – 23], may also be applied as an electrode modifier for bromfenac determination in tears.

Similar compounds may also be used in metal complexes [24], in which they are used to model the proton interaction. They may also used as conducting polymer dopants for electroanalytics.

Therefore, in this work, we theoretically describe the electrochemical determination of bromfenac on anode modified by cobalt (III) oxyhydroxide. In this work, by the suggestion and the analysis of the mechanism and the corresponding mathematical model, we investigate the possibility of the practical use of the electrochemical process and compare the behavior of this system with similar electroanalytical processes [25 – 28].

2. Materials and Methods

Similarly to diclofenac, bromfenac will be hydrolyzed in an alkaline medium, yielding a phenolic compound (1):



(1)

The phenolic compound then undergoes CoO(OH)-assisted phenolization with further oxidation to the correspondent quinonic derivative. This mechanism mimics bromfenac metabolism in the eye (Fig. 2):

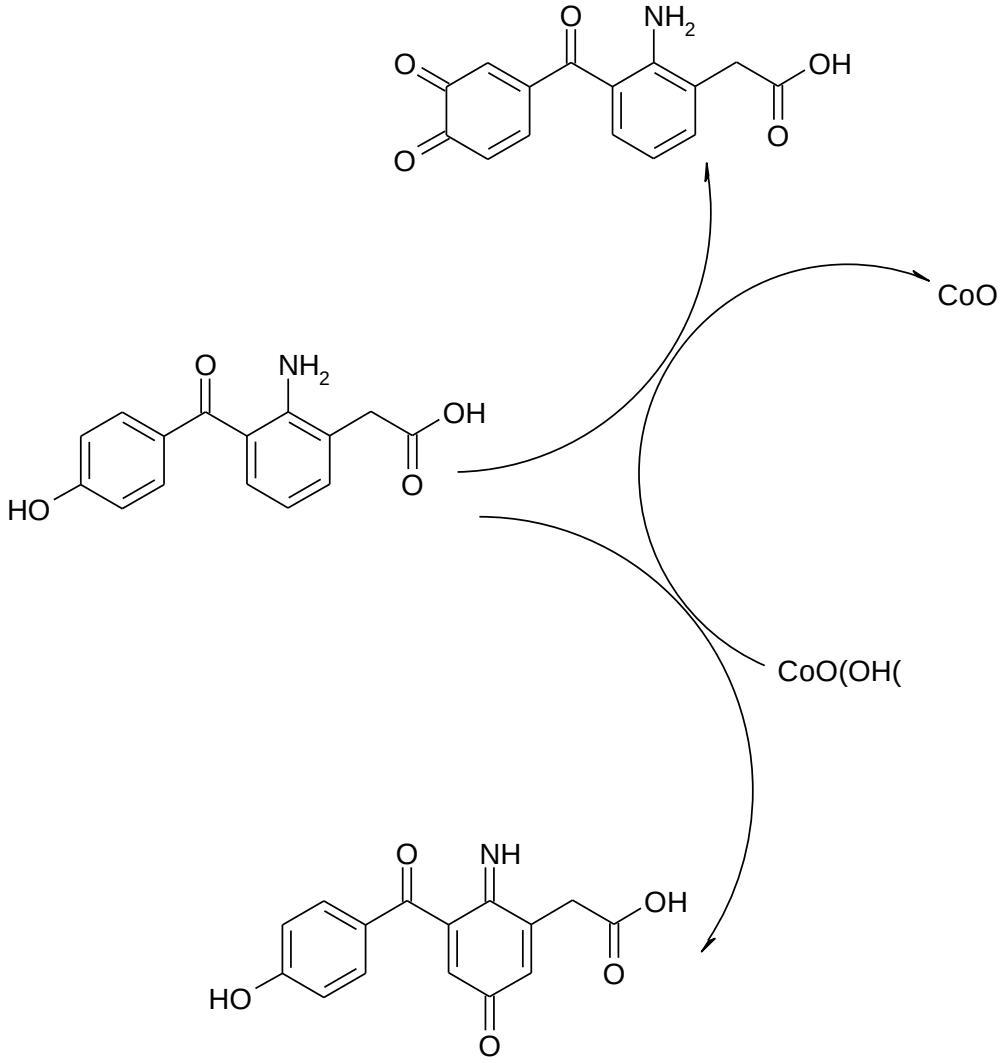


Figure 2. The scheme of the electroanalytical process, based on the bromfenac hydrolysis product

Therefore, if the pH is mild to moderate, which corresponds to tear alkalinity, bromfenac is quantified as its hydrolysis product.

Taking this into account and considering some assumptions [25 – 28], we describe the system´s behavior by a trivariant equation-set described as (2):

$$\begin{cases} \frac{db}{dt} = \frac{2}{\delta}\left(\frac{\Delta}{\delta}(b_0 - b) - r_h\right) \\ \frac{db*}{dt} = \frac{2}{\delta}\left(r_h - r_{q1} - r_{q2}\right) \\ \frac{dc}{dt} = \frac{1}{C}\left(r_{q1} + r_{q2} - r_O\right) \end{cases} \quad (2)$$

Similar to that observed for diclofenac [27 – 28].

Herein, b and b* are bromfenac and its hydrolysis product, Δ is the diffusion coefficient, b_0 is its bulk concentration, c is cobalt oxyhydroxide surface coverage degree, C is its maximal surface concentration, and the parameters r stand for the correspondent reaction rates, calculated as (3 – 6):

$$r_h = k_h b \exp(-ab) \quad (3)$$

$$r_{q1} = k_{q1} b * (1-c)^4 \exp(-vb) \quad (4)$$

$$r_{q2} = k_{q2} b * (1-c)^4 \exp(-vb) \quad (5)$$

$$r_O = k_O c \exp\left(\frac{F\varphi_0}{RT}\right) \quad (6)$$

In which the parameters k stands for the correspondent reaction rate constants, parameters a and v are the DEL-related parameters describing the DEL ionic force impact of the chemical stages, F stands for the Faraday number, φ_0 stands for the zero-charge-related potential slope, R is the universal gas constant, and T is the absolute temperature.

Despite the different behavior of bromfenac over CoO(OH)-modified electrodes in different pH values, cobalt (III) oxyhydroxide may be an efficient electrode modifier for bromfenac determination, as shown below.

3. Results and Discussion

The steady-state Jacobian matrix members, correspondent to the equation-set (1), may be exposed as:

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

In which:

$$a_{11} = \frac{2}{\delta}\left(-\frac{\Delta}{\delta} - k_h \exp(-ab) + ak_h b \exp(-ab)\right) \quad (8)$$

$$a_{12} = 0 \quad (9)$$

$$a_{13} = 0 \quad (10)$$

$$a_{21} = \frac{2}{\delta}(k_h \exp(-ab) - ak_h b \exp(-ab)) \quad (11)$$

$$a_{22} = \frac{2}{\delta}\left(-k_{q1}(1-c)^4 \exp(-vb) - k_{q2}(1-c)^4 \exp(-vb) + v\left(k_{q1} b * (1-c)^4 \exp(-vb) + k_{q2} b * (1-c)^4 \exp(-vb)\right)\right) \quad (12)$$

$$a_{23} = \frac{2}{\delta}\left(4k_{q1} b * (1-c)^3 \exp(-vb) + 4k_{q2} b * (1-c)^3 \exp(-vb)\right) \quad (13)$$

$$a_{31} = 0 \quad (14)$$

$$a_{32} = \frac{1}{C}\left(k_{q1}(1-c)^4 \exp(-vb) + k_{q2}(1-c)^4 \exp(-vb) - v\left(k_{q1} b * (1-c)^4 \exp(-vb) + k_{q2} b * (1-c)^4 \exp(-vb)\right)\right) \quad (15)$$

$$a_{33} = \frac{1}{C}\left(-4k_{q1} b * (1-c)^3 \exp(-vb) - 4k_{q2} b * (1-c)^3 \exp(-vb) - k_O \exp\left(\frac{F\varphi_0}{RT}\right) - jk_O c \exp\left(\frac{F\varphi_0}{RT}\right)\right) \quad (16)$$

Avoiding the cumbersome expressions during the determinant analysis, we introduce new variables and rewrite the determinant as:

$$\frac{4}{\delta^2 C}\begin{vmatrix} -\kappa - \Xi & 0 & 0 \\ \Xi & -\Sigma & T \\ 0 & \Sigma & -T - \Omega \end{vmatrix} \quad (17)$$

Opening the brackets, we may calculate the negative determinant as (18):

$$\Sigma\Omega(\kappa+\Xi)\begin{cases}>0,\ in\ the\ case\ of\ steady-state\ stability\\ =0, at\ detection\ limit\end{cases} \quad (18)$$

If –Det J>0, the Routh-Hurwitz stability criterion is valid, and the steady state is thereby stable. In the absence of the side reactions or other factors capable of compromising the analyte and (or) modifier stability, excluding the reactions foreseen by the mechanism, the linearity between the electrochemical parameter and concentration is observed, providing an efficient analytical signal interpretation.

This criterion is readily satisfied if the kinetic parameters Σ and Ω have the same signs. In the vast majority of the cases, they both have positive signs, and considering that the other variables in the determinant are positive, it indicates the vast steady-state stability topological region. As for the negativity of both Σ and Ω it is extremely rare. The electroanalytical process is both diffusion and kinetically controlled, with the prevalence of kinetic factors.

The condition Det J=0 corresponds to the detection limit, manifested by the *monotonic instability*. It depicts the margin between the stable steady-states and unstable states and corresponds to the steady-state multiplicity. In other words, multiple steady-states, each one unstable, coexist at this point.

As for the oscillatory behavior, it is realized beyond the detection limit in the case of the Hopf bifurcation realization. Its realization requires the presence of the positive-callback related positive addendums in main diagonal elements.

Analyzing the main diagonal (8), (12), and (126), we may observe three elements capable of being possible, thereby describing a positive callback caused by the DEL influence of the electrochemical and chemical stages, including hydrolysis. This callback is described by the positivity of the addendums $jk_Oc\exp\left(\frac{F\varphi_0}{RT}\right)$, $ak_hb\exp(-ab)$ and $v\left(k_{q1}b*(1-c)^4\exp(-vb)+k_{q2}b*(1-c)^4\exp(-vb)\right)$, if j, a, and b, correspondently, are positive. This callback is typical for similar systems [25 – 28], and the oscillation imaging will depend on solution composition, including pH.

If the pH is closer to neutral, the bromfenac hydrolysis will become slower, and the system´s behavior will be thereby described by the bivariant equation set (19):

$$\begin{cases}\frac{db}{dt}=\frac{2}{\delta}\left(\frac{A}{\delta}(b_0-b)-r_1-r_2\right)\\ \frac{dc}{dt}=\frac{1}{C}(r_1+r_2-r_3)\end{cases} \quad (19)$$

Its analysis will come to the same conclusions that the analysis exposed above.

This process does not include the electropolymerization scenario, which is realized if the CoO(OH)/CoO_2 redox pair is used. This system will somehow become more accomplished due to the influence of the polymerization process.

4. Conclusions

From the theoretical description of bromfenac electrochemical determination over CoO(OH), it has been possible to conclude that it may be an excellent modifier for bromfenac quantification in tears and pharmaceutical formulations. The stable, steady state is maintained

easily. The process may be diffusion-controlled or kinetically controlled with the prevalence of the kinetic factor. The oscillatory behavior in this system may be caused only by DEL influences in both the electrochemical and chemical stages.

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Conflicts of Interest

The authors declare no conflict of interest.

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