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The Theoretical Description for Fluoxetine Electrochemical Determination, Assisted by CoO(OH)-Nanoparticles, Deposited Over the Squaraine Dye

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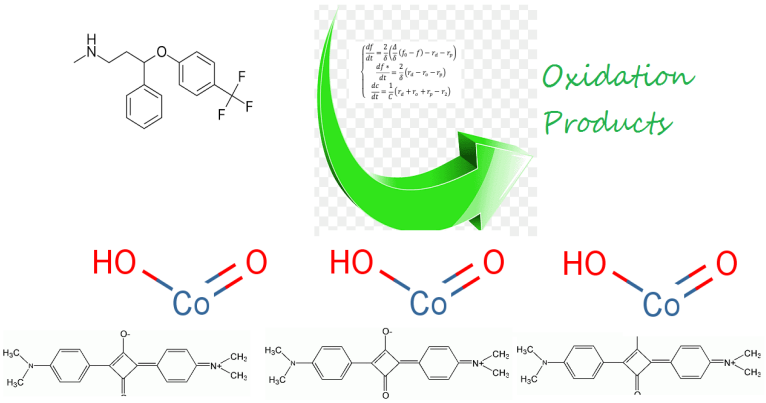
The theoretical description of the fluoxetine electrochemical determination over a CoO(OH) – Squaraine Dye composite has been carried out in this work. The correspondent mathematical model has been developed and analyzed by means of the linear stability theory and bifurcation analysis. It has been shown that the cobalt(III) oxyhydroxide, stabilized by squaraine dye layer, may be efficient electrode modifier for fluoxetine electrochemical determination. The possibility for the oscillatory and monotonic instabilities has also been verified.

Graphical abstract



Keywords

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1. Introduction

Over the past decades, the widespread occurrence of human pharmaceuticals in the environment has increasingly come to light [1,2]. The selective serotonin reuptake inhibitor (SSRI) fluoxetine (Fig. 1) (Adofen; Depres, Docutrix; Erocap; Fluctin; Fluctine; Fluoxeren; Fontex; Foxetin; Lorien; Lovan; Mutan; Prozac; Prozyn; Reneuron; Sanzur; Zactin), prescribed as an antidepressant in people, has received considerable attention regarding its effects on wildlife. Its active demethylated metabolite, norfluoxetine, is also a SSRI and similarly considered to pose an environmental risk, albeit to a

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lesser extent [3]. Fluoxetine white or almost white crystalline powder.

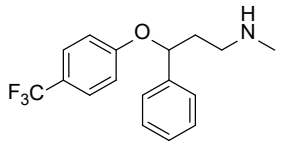

Fig. 1. Fluoxetine.

SSRIs are most widely prescribed antidepressant drugs for mental diseases and personality disorders. Fluoxetine is a prototype drug of SSRIs group of antidepressants. SSRIs inhibit the presynaptic serotonin or 5-Hydroxytryptamine (5-HT) Reuptake Transport system of serotonergic neurons [4]. Normally in serotonergic neurons after the release of serotonin, a portion of it is recycled by reuptake into presynaptic serotonergic neurons [5].

Fluoxetine (structures shown in Figure 1) is used for the treatment of major depressive disorder, obsessive–compulsive disorder (OCD), bulimia nervosa, panic disorder, and premenstrual dysphoric disorder. Fluoxetine has also been used to treat premature ejaculation. It is taken by mouth [6,7]. Despite the widespread use of fluoxetine in medical practice the cases of the manifestation of their toxic effects are not excluded (in overdose and individual hypersensitivity), as evidenced by cases of acute and chronic poisoning with these drugs described in the literature [8, 9]. Fluoxetine is associated with the increased suicide risk in different age groups: in youth, adolescents and adults. Therefore, the development of a rapid and efficient fluoxetin determination method is really actual, and the electroanalytical methods could provide it a good service [9 – 13].

Taking into account the composition of fluoxetine, it is possible to conclude that it may be electrochemically active, due to the presence of electronically-enriched aromatic fragments and aminogroup. One of the potential electrode modifiers for this purpose may be cobalt (III) oxyhydroxide [14 – 16]. It is a p-type semiconductor, suggested as a TiO_2 replace in the semiconducting systems with more flexible electrochemical behavior, as it possesses cobalt in the median oxidation state.

Nevertheless, the use of novel electrode modifiers with novel analytes may be impeded by:

- the indecision concerning the exact mechanism of electrochemical reaction;
- necessity of determination of the parameter region, correspondent to the most efficient active substance and mediating action;
- the presence of electrochemical instabilities, yet described for the CoO(OH) synthesis [17 - 19].

The mentioned problems may only be solved by means of an analysis of a mathematical model, capable to describe adequately the fluoxetine electrochemical determination Moreover, 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 fluoxetine electrochemical determination, assisted by CoO(OH) – Squaraine dye composite. 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 [20 – 21].

2. Material and Methods

In this work, the dynamic electrochemical system is evaluated as a set of state functions, time change of which is described by balance equations, derived from the physical laws describing its behavior, taking into account the chemical behavior of the described substances.

These equations form a set:

$$\begin{cases} \frac{dA}{dt} = f_1(A,B,C) \\ \frac{dB}{dt} = f_2(A,B,C) \\ \frac{dC}{dt} = f_3(A,B,C) \end{cases} \quad (1)$$

permitting stable and unstable solutions. As even the most stable steady-states permit fluctuations, in the concrete point, the most stable state, in other words, most susceptible to the fluctuations is realized.

The steady-state stability is evaluated by linear stability theory, investigating the behavior of the system after the little perturbations of the steady-state. The unstable states are considered deviations, in relation on steady-states – the less is the deviation from a steady-state, more stable this state is. If we consider

$$A=A_{SS}+ a;\ B=B_{SS}+b;\ C= C_{SS}+b \quad (2-4)$$

where a, b and c are deviations from the stable steady-state, the functions f_1, f_2 and f_3 may be linearized, described as:

$$\begin{cases} \frac{dA}{dt} = a_{11}a + a_{12}b + a_{13}c \\ \frac{dB}{dt} = a_{21}a + a_{22}b + a_{23}c \\ \frac{dC}{dt} = a_{31}a + a_{32}b + a_{13}c \end{cases} \quad (5)$$

Herein the elements a_{xx} are the correspondent steady-state Jacobian matrix members, calculated as the derivatives of the functions f_1, f_2 and f_3 on the variables A. B and C.

Due to the linearity, the equation-set (5) permits the solutions, exposed as normal modes:

$$A=A_0e^{wt},\ B=B_0e^{wt},\ C=C_0e^{wt} \quad (6-8)$$

Imputing of them into the equation (5), we obtain the linear equation system, related to the coefficients A_0, B_0 and C_0, solution of which gives the pass to characteristic equation, analysis of which derives the stability and instability requisites, as shown below. More developed description for this methodology is given in [36].

3.1 System and its Modeling

As for fluoxetine, two oxidation mechanisms are possible for it, involving intramolecular assisted heterocyclization with subsequent polymerization (Fig. 2):

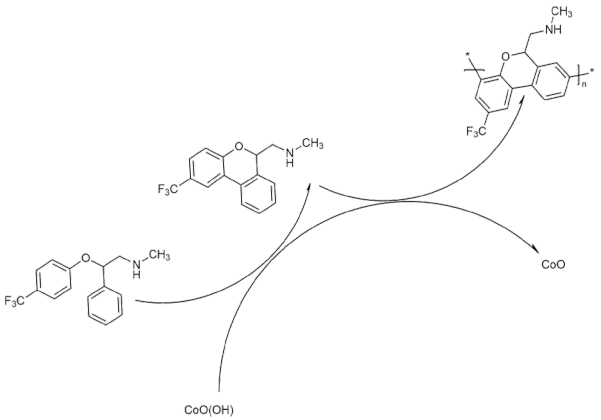

Fig. 2. Electrocyclization and polymerization scenario for fluoxetine.

and intermolecular dimerization via amino group, followed by the dimer participation in the electropolymerization (Fig. 3):

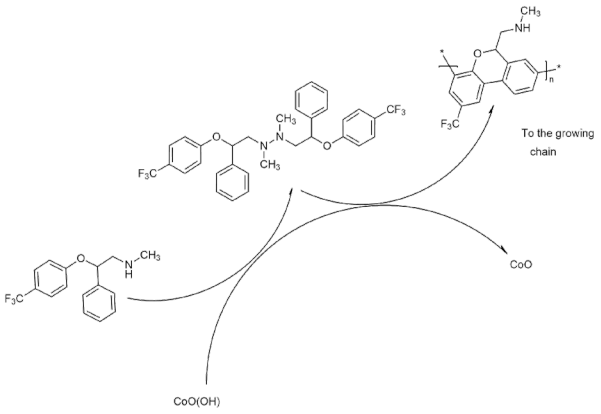

Fig. 3. Dimerization scenario with dimer joining the growing chain.

Dimer may also undergo the electrocyclization, yielding the oligomer with well-developed conjugated structure (Fig. 4).

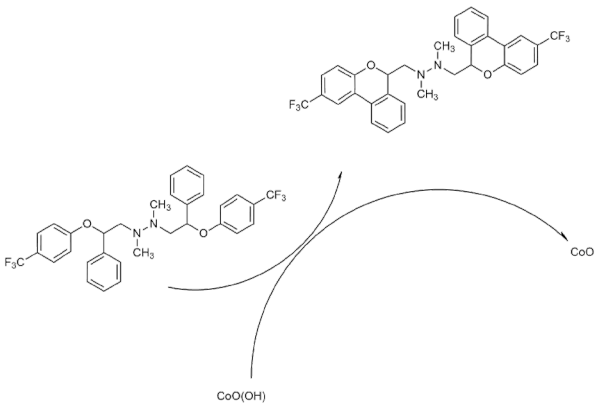

Fig. 4. Dimer oxidation to oligomer.

Taking this into account, in order to describe the behavior of this system we introduce three variables:

f – fluoxetin concentration in the pre-surface layer;

f* - fluoxetin dimer concentration in the pre-surface layer;

c – cobalt (II) 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. Also, we assume that olygomer, while formed, diffuses off the pre-surface layer and does not intervent in the electropolymerization process.

It is possible to show that the behavior of this system will be described by three balance equations, written as:

$$\begin{cases} \frac{df}{dt} = \frac{2}{\delta}\left(\frac{\Delta}{\delta}(f_0 - f) - r_d - r_p\right) \\ \frac{df*}{dt} = \frac{2}{\delta}(r_d - r_o - r_p) \\ \frac{dc}{dt} = \frac{1}{C}(r_d + r_o + r_p - r_2) \end{cases} \quad (7)$$

Herein, Δ is the diffusion coefficient, f_0 is the fluoxetine bulk concentration, C is the maximal CoO surface concentration, and the parameters r are the correspondent reaction rates, calculated as (2 – 5):

$$r_d = k_d f^2 (1-c)^2 \quad (8)$$

$$r_o = k_o f * (1-c)^4 \quad (9)$$

$$r_p = k_p f^x f *^y (1-c)^{2(x+y-1)} \quad (10)$$

$$r_2 = k_2 c \exp\left(\frac{F\varphi_0}{RT}\right) \quad (11)$$

in which the parameters k are rate constants of the reactions, x and y are monomer and dimer reaction orders in the electropolymerization (the expression 2(x+y-1) may be derived from the generalized Diaz electropolymerization mechanism), F is the Faraday number, φ_0 is the potential slope in double electric layer (DEL), relative to the zero-charge potential, R is the universal gas constant, and T is the absolute temperature.

This model describes the behavior of the system in neutral and basic media, in which secondary aminogroups are not protonized. In this case, the electroanalytical and electrosynthetical process will be more branched, than for the acidic media. Nevertheless, it will be more stable, than on lower pH, as shown below.

3. Results and Discussion

In order to investigate the behavior of electrochemical determination of fluoxetine, we analyze the equation-set (7), alongside with the algebraic relations (8 – 11) by means of linear stability theory. The steady-state Jacobian matrix members will be exposed as:

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

Where:

$$a_{11} = \frac{2}{\delta}\left(-\frac{\Delta}{\delta} - 2k_d f(1-c)^2 - xk_p f^{x-1} f *^y (1-c)^{2(x+y-1)}\right) \quad (13)$$

$$a_{12} = \frac{2}{\delta}\left(-yk_p f^x f *^{y-1} (1-c)^{2(x+y-1)}\right) \quad (14)$$

$$a_{13} = \frac{2}{\delta}\left(2k_d f^2(1-c) + 2(x+y-1)k_p f^x f *^y (1-c)^{2(x+y-2)}\right) \quad (15)$$

$$a_{21} = \frac{2}{\delta}\left(2k_d f(1-c)^2 - xk_p f^{x-1} f *^y (1-c)^{2(x+y-1)}\right) \quad (16)$$

$$a_{22} = \frac{2}{\delta}\left(-k_o(1-c)^4 - yk_p f^x f *^{y-1} (1-c)^{2(x+y-1)}\right) \quad (17)$$

$$a_{23} = \frac{2}{\delta}\left(-2k_d f^2(1-c) + 4k_o f * (1-c)^3 + 2(x+y-1)k_p f^x f *^y (1-c)^{2(x+y-2)}\right) \quad (18)$$

$$a_{31} = \frac{1}{C}\left(2k_d f(1-c)^2 + xk_p f^{x-1} f *^y (1-c)^{2(x+y-1)}\right) \quad (19)$$

$$a_{32} = \frac{1}{C}\left(k_o(1-c)^4 + yk_p f^x f *^{y-1} (1-c)^{2(x+y-1)}\right) \quad (20)$$

$$a_{33} = \frac{1}{C}\left(-2k_d f^2(1-c) - 4k_o f * (1-c)^3 - 2(x+y-1)k_p f^x f *^y (1-c)^{2(x+y-2)} - k_2 \exp\left(\frac{F\varphi_0}{RT}\right) + jk_2 c \exp\left(\frac{F\varphi_0}{RT}\right)\right) \quad (21)$$

As in the similar systems [20 – 21], the oscillatory behavior is possible in this system. Nevertheless, as on the chemical stages no ionic compounds formation, destruction and transformation occurs (in basic media), the unique factor responsible for the oscillatory behavior is the influence of the electrochemical stage on double electric layer capacitance and conductivity. It is described by the positivity of the element $jk_2 c \exp\left(\frac{F\varphi_0}{RT}\right) > 0$ if j<0. The oscillations frequency and amplitude are dependent on the background electrolyte composition, directly related to DEL structure and conductivity. Nevertheless, the proper oscillations are expected to be frequent and of small amplitude.

Yet if this condition is not satisfied, the steady-state stability condition is realized. In order to investigate the steady-state stability, we apply the Routh-Hurwitz criterion to the equation-set (7). Introducing new variables, we avoid the cumbersome expressions and rewrite the matrix determinant as:

$$\frac{4}{\delta^2 C}\begin{vmatrix} -\kappa-\Xi-\Lambda & -\Sigma & T+K \\ \Xi-\Lambda & -P-\Sigma & -T+K \\ \Xi+\Lambda & P+\Sigma & -T-K-\Omega \end{vmatrix} \quad (22)$$

Which, taking into account the properties of the determinant, will be transformed into (23):

$$\frac{4}{\delta^2 C}\begin{vmatrix} -\kappa-\Xi-\Lambda & -\Sigma & T+K \\ \Xi-\Lambda & -P-\Sigma & -T+K \\ 2\Xi & 0 & -2T-\Omega \end{vmatrix} \quad (23)$$

Opening the straight brackets and applying the requisite Det J<0, salient from the criterion, we derive the stability requirements, which, after rearrangement ans sign changes, will be exposed as:

$$(2T+\Omega)(\kappa P + \Xi P + \Lambda P + \kappa\Xi + 2\Xi\Sigma) > 2\Xi(2\Sigma T + PT + PK) \quad (24)$$

Which will be readily satisfied in the case of the positivity of the parameter $\Omega = k_2 \exp\left(\frac{F\varphi_0}{RT}\right) - jk_2 c \exp\left(\frac{F\varphi_0}{RT}\right)$, defining the fragility of DEL influences of the electrochemical stage. Really, putting $\Omega > 0$, the expression to the left side of the inequity (24) will be more positive, stabilizing the system. Also, as the kinetical parameters contribute more to the steady-state stability, the electroanalytical and electrosynthetical process will be kinetically controlled.

As no reactions, capable to compromise the analyte or modifier stability are characteristic for this case, the steady-state stability will be correspondent to the linear dependence between the current and concentration and the deposition of well-developed polymer surface. Also, as the condition (19) is readily satisfied for a vast parameter region, the electrochemical process will be efficient from either analytical or synthetical points of view.

As for the detection limit, it will be described by monotonic instability, putting the margin between the stable steady-states and unstable states. For this system, it will be described as Det J=0, or:

$$(2T+\Omega)(\kappa P + \Xi P + \Lambda P + \kappa\Xi + 2\Xi\Sigma) = 2\Xi(2\Sigma T + PT + PK) \quad (25)$$

In acidic media, the aminogroups are protonized, forming the fluoxetine salts. The only possible oxidation scenario will be the electrochemical oxidation of the protonized form of the drug by heterocyclization mechanism. By this, the variable f* will leave the equation-set, making it bivariant. Nevertheless, as in this case, the chemical stages will involve the conversion of ionic forms, they will also give strong impact on DEL, as in [20 – 21]. Therefore, the behavior of this system will be bit less efficient and bit more dynamic.

4. Conclusions

From the analysis of the system with the fluoxetine electrochemical determination as an anodic process, assisted by CoO(OH) – Squaraine Dye composite it is possible to conclude that;

- The system's behavior is less dynamic, while compared to the similar systems in acidic media, due to the less intense influence of the process of double electric layer conductivity and capacitance.
- The electroanalytical process tends to be kinetically controlled with the easy realization of linear dependence between the concentration and the current.
- The oscillatory behavior tends to have less probability to be realized, compared with the acid media, due to the impossibility of DEL influence of the electrochemical stage.
- The acidic media suppresses the dimerization of fluoxetine, but ionizes it, augmenting its influence on the DEL ionic force, reason why it is less suitable for fluoxetine electrochemical determination on anode.

Author Contributions

Volodymyr V. Tkach (Investigation, Conceptualization, Supervision, Validation, Writing – Original Draft, Writing – Review and Editing); Marta V. Kushnir (Data Curation, Conceptualization, Investigation); Sílvio C. de Oliveira (Conceptualization, Investigation, Supervision, Formal Analysis), Hanifa Zh. Salomova (Investigatioon, Conceptualization, Data Curation, Methodology, Validation, Visualization), Fazliddin Jalilov (Investigatioon, Conceptualization, Data Curation, Methodology, Validation,

Visualization), Feruza Jalilova (Investigatioon, Conceptualization, Data Curation, Methodology, Validation, Visualization), Laziz N. Niyazov (Conceptualization, Investigation, Data Curation, Methodology, Validation, Visualization, Formal Analysis), Dilfuza M. Musayeva (Conceptualization, Investigation, Supervision, Formal Analysis), Yana G. Ivanushko (Conceptualization, Investigation, Formal Analysis), Oleksandra V. Ahafonova (Conceptualization, Investigation, Formal Analysis), Mariia P. Mytchenok (Conceptualization, Investigation, Formal Analysis), Petro I. Yagodynets´ (Investigation, Conceptualization, Methodology, Supervision, Validation, Writing – Original Draft, Writing – Review and Editing), Zholt O. Kormosh (Investigation, Conceptualization, Supervision, Validation, Writing – Original Draft, Writing – Review and Editing), Lucinda Vaz dos Reis (Data Curation, Conceptualization, Investigation); Yulia V. Palytsia (Data Curation, Conceptualization, Investigation).

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