First *a priori* Theoretical Evaluation of the Electroanalytical Cathodic Determination of Antibiotic Flavocillin

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For the first time, the possibility of flavocillin electrochemical determination, assisted by vanadium (III) oxyhydroxide has been evaluated. The electrochemical determination will be given by gradual reduction of both flavonyl and penicyllyl moieties in mildly acidic medium, close to neutral. The analysis of the mathematical model, correspondent to the reaction mechanism, confirms the efficiency of cathodic electrochemical process for flavocillin electrochemical determination.

Graphical abstract
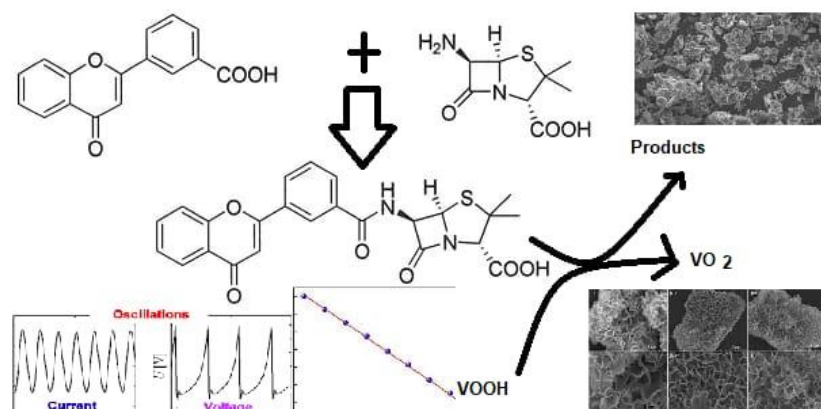
1. Introduction

The discovery of penicillin by Alexander Flemming in 1929 has changed the history of medicine forever [1 – 3]. The cure for many dangerous diseases became more efficient and safer, as it didn't need any dangerous compounds like corrosive sublimate or salvarsan anymore. Penicillins were nearly the first antibiotics successfully applied to the vast variety of infections caused by staphylococci and streptococci. They are still widely used worldwide. Nevertheless, many types of bacteria have developed resistance, due to β-lactamase enzyme action. In this aspect, penicillin antibiotic structure undergoes modification, in order to provide β-lactamase inhibition.

Flavocillin (Fig. 1) is an antibiotic, newly reported by Mustafa Pehlivan and his group [4 – 5]. Containing both flavone and penicillin derivatives, it is claimed to either increase the suscebility of various bacteria to β-lactam group, or relief the oxidative stress, due to the flavonoid group antioxidant properties. Nevertheless, the independent

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investigation of flavocillin properties are still in course. Moreover, the investigation of side and adverse effect is still pending. Either way, the development of an efficient quantification methodology for flavocillin is really actual, and the electrochemical methods, yet applied to both flavonoids and penicillin [6 – 14], may be easily applied to it.
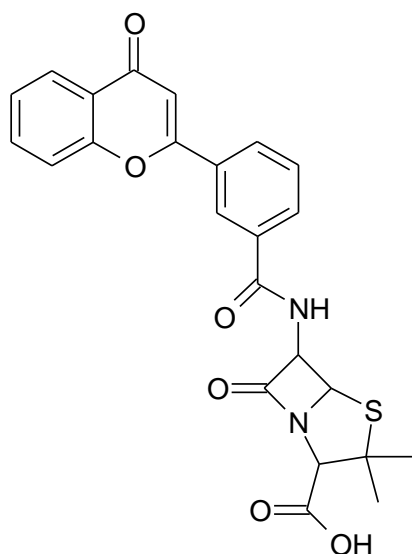

Fig. 1. Flavocillin.

Considering the flavocillin structure, we may conclude that both anodic and cathodic determination may be viable for this molecule, being the cathodic route the most preferable, due to the presence of stong acceptors. In this process, vanadium (III) oxyhydroxide, a semiconducting material, similar to cobalt oxyhydroxide, but with more expressed reductant properties [15 – 16] may be used as an efficient electrode modifier for flavocillin determination in neutral and mildly acidic medium. Nevertheless, there are some objections concerning the reaction mechanisms and critical phenomena, accompanying the electroabalytical process [17 – 19].

For this reason, the aim of this work is to investigate *a priori* the possibility for flavocillin electrochemical determination on vanadium (III) oxyhydroxide-modified electrode, which includes the mechanism suggestion and the correspondent mathematical model investigation with the comparison of the behavior of this system with that of the similar ones [20 - 21].

2. Material and Methods

Considering the flavocilin composition, we may conclude that the electrochemical reduction will be firstly given by the chromonic ring, being thereby followed by lactam and peptidic group reduction (Fig. 2):
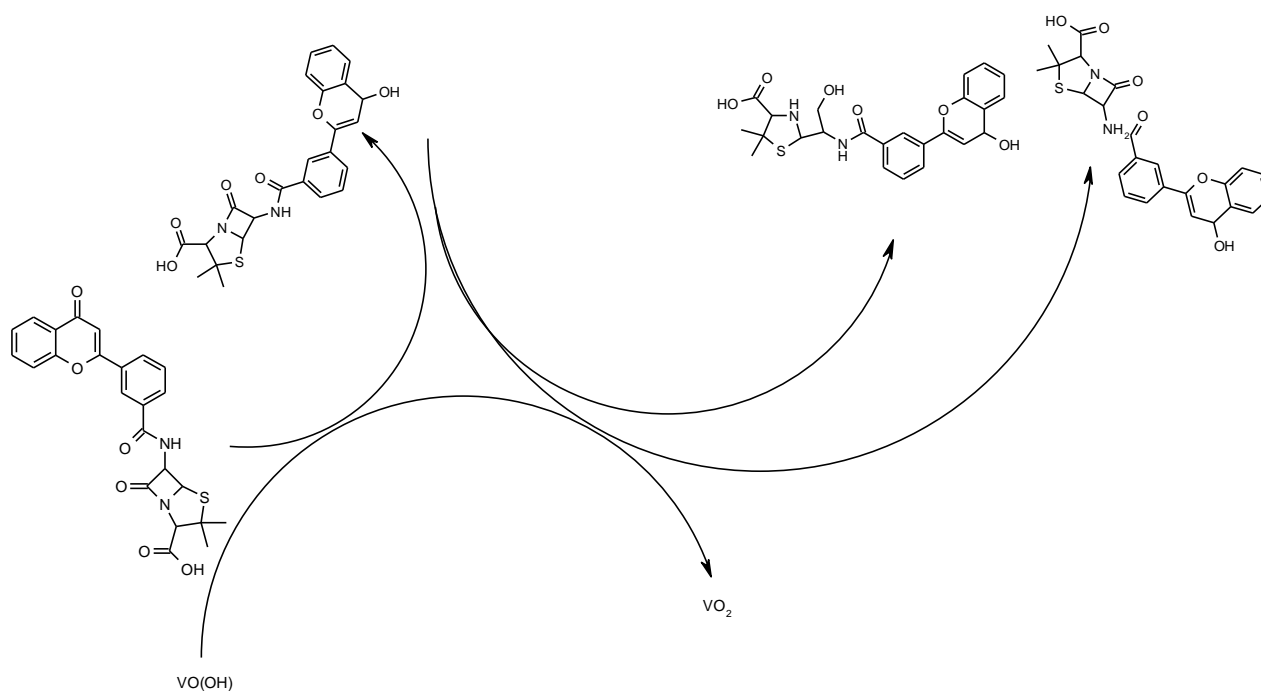

Fig. 2. The scheme for VO(OH)-assisted flavocillin cathodical determination.

Taking this into account and accepting some assumptions [20 – 21], we describe the system's behavior by a trivariant equation-set (1):

$$\begin{cases} \dfrac{df}{dt} = \dfrac{2}{\delta}\left(\dfrac{\Delta}{\delta}(f_0 - f) - r_c\right) \\ \dfrac{df*}{dt} = \dfrac{2}{\delta}(r_c - r_l - r_p) \\ \dfrac{dv}{dt} = \dfrac{1}{V}(r_c + r_c + r_l - r_r) \end{cases} \quad (1)$$

in which f and f_0 stand for the pre-surface and bulk flavocillin concentration, Δ for its diffusion coefficient, f* for its first reduction product, δ for pre-surface layer thickness, v for vanadium dioxide surface coverage degree, V for its maximal surface concentration, and the parameters r for the reaction rates, calculated as:

$$r_c = k_c f (1 - v)^2 \quad (2)$$
$$r_l = k_l f * (1 - v)^2 \exp(-af *) \quad (3)$$
$$r_p = k_p f * (1 - v)^2 \exp(-af *) \quad (4)$$

$$r_r = k_r v \exp\left(-\frac{F\varphi_0}{RT}\right) \qquad (5)$$

In which the parameters k are the correspondent reaction rate constants, a is the DEL ionization influence parameter, becoming nil in the neutral medium and non-nil in acidic, F is the Faraday number, φ_0 is the zero-charge related potential slope, R is the universal gas constant and T is the absolute temperature.

As the first stage does not yield highly ionic compounds in neutral or acidic media, it won´t affect the DEL strongly. As for two second stages, they will influence the DEL ionic force, impedance and conductivity, provoking the oscillatory behavior. Nevertheless, in general the electroanalytical process is expected to be efficient, as shown below

3. Results and Discussion

We describe the behavior of the system with flavocillin electrochemical determination on VO(OH)-modified cathode by means of linear stability theory and describe the steady-state Jacobian matrix members as (6):

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

Herein:

$$a_{11} = \frac{2}{\delta}\left(-\frac{\Delta}{\delta} - k_c(1-v)^2\right) \qquad (7)$$

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

$$a_{13} = \frac{2}{\delta}(2k_c f(1-v)) \qquad (9)$$

$$a_{21} = 0 \qquad (10)$$

$$a_{22} = \frac{2}{\delta}\big(ak_l f*(1-v)^2\exp(-af*) - k_l(1-v)^2\exp(-af*)) + ak_p f*(1-v)^2\exp(-af*) - k_p(1-v)^2\exp(-af*)\big) \qquad (11)$$

$$a_{23} = \frac{2}{\delta}\big(2k_l f*(1-v)\exp(-af*) + 2k_p f*(1-v)\exp(-af*)\big) \qquad (12)$$

$$a_{31} = \frac{1}{v}(k_c(1-v)^2) \qquad (13)$$

$$a_{32} = \frac{1}{v}\big(-ak_l f*(1-v)^2\exp(-af*) + k_l(1-v)^2\exp(-af*)) - ak_p f*(1-v)^2\exp(-af*) + k_p(1-v)^2\exp(-af*)\big) \qquad (14)$$

$$a_{33} = \frac{1}{v}\big(-2k_c f(1-v) - 2k_l f*(1-v)\exp(-af*) - 2k_p f*(1-v)\exp(-af*) - k_r\exp\left(-\frac{F\varphi_0}{RT}\right) + jk_r v\exp\left(-\frac{F\varphi_0}{RT}\right)\big) \qquad (15)$$

Observing the main diagonal elements (7), (11) and (15), we may conclude that the *oscillatory behavior* in this system is possible. Moreover, it is more probable than in the most simple cases, in which only one factor causes this type of behavior (the DEL impact of the electrochemical stage, described by the positivity of $jk_r v\exp\left(-\frac{F\varphi_0}{RT}\right) > 0$, if j>0) [20 – 21], as the chemical stages also affect the DEL ionic force, leading to the cyclic conductivity changes, manifested mathematically in the case of the positivity of the elements $ak_p f*(1-v)^2\exp(-af*) > 0$ and $ak_l f*(1-v)^2\exp(-af*) > 0$ if a>0. Both of the types of the oscillatory behavior foresee the dependence of its frequency and amplitude on background electrolyte composition, including

pH [18 – 21]. Moreover, considering that a=0 in the neutral medium, only electrochemical stage influence will be manifested by the oscillatory behavior in that case.

It's important to mention that if the first stage with the flavonoic ring reduction does not affect significantly the DEL ionic force, the second stages with amide group and lactam ring reduction does yield compounds capable to ionize in acidic medium. Therefore, the first reaction rate equation does not contain the exponential element, and the second-stage related ones contain it. However, in neutral medium (a=0), the exponent argument will be set to zero, and the exponent value will be fixed to one, erasing the ionization factor expressions, which confirms that the oscillatory behavior in the neutral medium will be less probable than in acidic. This corresponds to the similar systems [18 – 21].

On the other hand, the neutral medium the steady-state stability tends to be manifested more clearly, as the steady-state stability condition becomes more ready to satisfy in neutral conditions than in the acidic ones. Really, if we apply the Routh-Hurwitz stability criterion and rewrite the determinant as (16):

$$\frac{4}{\delta^2 v}\begin{vmatrix} -\varphi - \Phi & 0 & -\Xi \\ 0 & -T & -P \\ \Phi & T & -\Xi - P - \Omega \end{vmatrix} \qquad (16)$$

opening the brackets, applying the steady-state stabiolity condition −Det J>0, salient from the criterion, we obtain the steady-state stability requisite as (17):

$$\varphi(T\Xi + TP) + \Phi TP > 0 \qquad (17)$$

defining an efficient system which may be both diffusion and kinetically controlled and warranted to be satisfied if j≤0, a=0. The role of the kinetic control grows in acidic medium, in which the ionization on the second chemical stage becomes to affect strongly the DEL ionic force. Either way, the electroanalytical process is efficient, even though in acidic medium it becomes somehow less stable, as no side reactions capable to compromise the analyte or modifier stability are realized in this case. By this, the steady-state stability will correspond to the linear dependence between the electrochemical parameter and concentration.

As for the *detection limit,* it is defined by the monotonic instability. It defines the margin between stable steady-states and unstable states, correspondent to the condition (18):

$$\varphi(T\Xi + TP) + \Phi TP = 0 \qquad (18)$$

Another option is to use the VO(OH)/VO or VO(OH)/V(OH)$_2$ redox pair, which will be accessible in lightly alkaline medium. In this case, vanadium oxyhydroxide will be reduced by (19 or 20):

$$VO(OH) + H_2O + e^- \rightarrow V(OH)_2 + OH^- \qquad (19)$$

$$VO(OH) + H_2O + e^- \rightarrow VO + H_2O + OH^- \qquad (20)$$
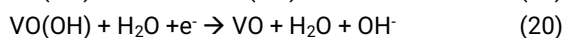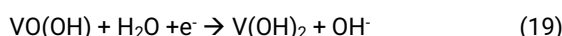
And the bivalent vanadium will become even more aggressive reducent for flavocillin determination.

As for the *anodic process* it may be given by sulfur atom and aromatic ring oxidation. It may also be realized by tertiary

nitrogen oxidation, if stonger oxidant is used. The anodic oxidation possibility will be analyzed in our next works.

4. Conclusions

From the system with the electrochemical determination of flavocillin on a VO(OH)-modified electrode it was possible to conclude that this electroanalytical system will be both diffusion and kinetically controlled. The oscillatory behavior in this case will be more probable than for the simplest situation, due to the ionic forms´ transformation in DEL. Also, although the linear dependence between the electrochemical parameter and concentration is realized in a more narrow parameter region in acidic medium, VO(OH) is efficient electrode modifier for flavocillin simultaneous electrochemical determination. Nonetheless, in order to obtain a wider linear range, the neutral medium is recommended.

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); Yana G. Ivanushko (Investigatioon, Conceptualization, Data Curation, Methodology, Validation, Visualization), Viktor V. Kryvetskyi (Investigatioon, Conceptualization, Data Curation, Methodology, Validation, Visualization), Inna I. Kryvetska (Investigatioon, Conceptualization, Data Curation, Methodology, Validation, Visualization), Igor V. Kryvetskyi (Investigatioon, Conceptualization, Data Curation, Methodology, Validation, Visualization), 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), José Inácio Ferrão da Paiva Martins (Investigation, Conceptualization, Supervision, Validation, Writing – Original Draft, Writing – Review and Editing).

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