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The Theoretical Evaluation of the Work of Cp-based Sulfoacids as Electrode Modifiers for Daclatasvir Electrochemical Detection

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Abstract- The possibility of daclatasvir electrochemical detection, assisted by conducting polymer-based sulfoacid, was analyzed by theoretical point of view. It was shown, that the conducting polymer sulfoacid may serve as an excellent electrode modifier, permitting the use of more flexible pH-window for analysis. The steady-state may be maintained stable in the vast parameter region. The electroanalytical response has to be clear and easy to interpret. The possibility for electrochemical instabilities (electrochemical oscillations and monotonic instability) in this system has also been studied.

Keywords- Daclatasvir, conducting polymer, Electrochemical detection, Electrochemical sensing, Stable steady-state

1. INTRODUCTION

Hepatitis C is a liver disease caused by the hepatitis C virus: the virus can cause both acute and chronic hepatitis infection, ranging in severity from a mild illness lasting a few weeks to a serious, lifelong illness. The hepatitis C virus is a bloodborne virus and the most

common modes of infection are through unsafe injection practices, inadequate sterilization of medical equipment, and the transfusion of unscreened blood and blood products. Globally, 130 to 150 million people globally have chronic hepatitis C infection.A significant number of those who are chronically infected will develop liver cirrhosis or liver cancer.Approximately 700 000 people die each year from hepatitis C-related liver diseases [1].

Antiviral drug combintions can cure approximately 90% of persons with hepatitis C infection, thereby reducing the risk of death from liver cancer and cirrhosis, but access to diagnosis and treatment is low. There is currently no vaccine for hepatitis C; however research in this area is ongoing.

Daclatasvir(Fig. 1), sold under the trade name Daklinza, is a medication used in combination with other medications to treat hepatitis C (HCV) [2-4]. Its mechanism of action includes the inhibition of non-structural protein 5A which is an essential component in HCV replication [5]. The other medications used in combination include sofosbuvir, ribavirin, and interferon, vary depending on the virus type and whether the person has cirrhosis[6-8]. It is taken orally once a day.

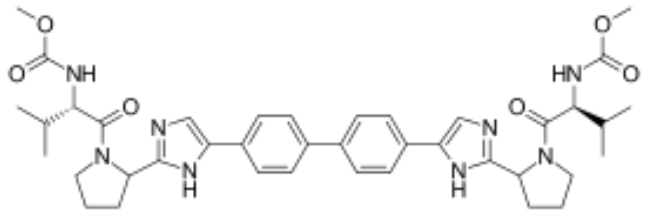

Fig. 1. Daclatasvir chemical composition

Common side effects with sofusbivir and daclatasvir include headache, feeling tired, and nausea. With daclatasvir, sofusbivir, and ribavirin the most common side effects are feeling tired, fatigue, headache, insomnia, influenza-like illness, dry skin, nausea, decreased appetite, alopecia, asthenia, irritability, myalgia, anemia, pyrexia, cough, dyspnea, neutropenia, diarrhea, arthralgia and anemia [9-11]. So, the development of the method of the efficient detection of daclatasvir is really actual problem [12-13], and the use of electrochemical methods involving chemically modified electrodes may be an interesting solution to it [12].

In [12] daclatasvir electrochemical determination has been realized for the first time. The electrode modifier used was a cobalt-chitosane nanocomposite. So, it is possible to predict that conducting polymers may be an interesting electrode modifier for them. The use of conducting polymers as electrode modifier for electrochemical analysis is one of the most important aspects of their application [14-24]. Combining the properties of plastics (versatility in shaping, flexibility, corrosion resistance, light weight) and metals (conductivity, magnetic properties) with the facility of modification [25-26], they take part in sensing processes either as active substances, or as mediators.

Taking into account the basic properties of daclatasvir, it´s possible to suppose that the use of the conducting polymers, doped by –COOH and $–SO_3H$ groups may enhance the immobilization of the drug. Nevertheless, the development of new electroanalytical systems may confront the problems like:

- the indecision in the modifier mechanism of action;
- the compatibility of the modifier with the tissue or biological object (some modifiers, used *in vitro* may be non-compatible with *in vivo* sensing);
- the presence of electrochemical instabilities, accompanying both electrochemical synthesis of conducting polymers, or their modification [27-30].

The mentioned problems may only be solved by means of an analysis of a mathematical model, capable to describe adequately the electroanalytical system. By modeling 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 possibility of daclatasvir CP-assisted electrochemical quantification. In order to achieve it, we realize the specific goals:

- suggestion of the mechanism of the electroanalytical reaction sequence, 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 [31-35].

2. SYSTEM AND ITS MODELING

Daclatasvir terminal groups firstly react with sulfogrups, achieving daclatasvir immobilization. It is then electrooxidized, forming a salt with pyridinium nitrogen atoms as in [12].

So, due to the presence of a strong acid on the surface, it is possible to use less acidic solutions, than in [12] and even neutral media.

Taking this into account, to describe the CP-assisted daclatasvir electrochemical detection, we introduce three variables:

c–daclatasvir concentration in the pre-surface layer;

θ–the coverage degree of daclatasvir-modified conducting polymer;

θ*-the coverage degree of the oxidized form of daclatasvir-modified conducting polymer.

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's also supposed that at the beginning of the reaction the initial monomer covers the entire electrode surface.

It is possible to show that the system's behavior may be described as:

$$\begin{cases} \frac{dc}{dt} = \frac{2}{\delta}\left(\frac{\Delta}{\delta}(c_0 - c) - r_1\right) \\ \frac{d\theta}{dt} = \frac{1}{G}(r_1 - r_2) \\ \frac{d\theta*}{dt} = \frac{1}{G*}(r_2 - r_3) \end{cases} \quad (1)$$

In which c_0 is the daclatasvir concentration in the pre-surface layer, G and G* are the maximal concentrations of the reduced and oxidized forms of the modified conducting polymer, r_1, r_2 and r_3 are the three reaction rates of the chemical and electrochemical reactions, forming the electroanalytical process.

The correspondent reaction rates may be calculated as:

$$r_1 = k_1 c(1 - \theta - \theta *) \quad (2)$$

$$r_2 = k_2 \theta \exp\frac{4F\gamma\theta}{RT} \quad (3)$$

$$r_3 = k_3 \theta * \exp(-\alpha\theta *) \quad (4)$$

In which the parameters k are the correspondent reaction rate constants, F is the Faraday number, γ and α are coefficients, relating the DEL capacitances influences of the electrochemical oxidation and salinization, R is the universal gas constant and T is the absolute temperature.

In general, this system doesn't have to differ much from the similar systems involving conducting polymer-based sensors [31-35]. Nevertheless, the presence of one more stage in the electroanalytical process, and its influences to DEL, contribute strongly to the system's behavior, and this contribution will be discussed below.

3. RESULTS AND DISCUSSION

In order to investigate the behavior of the system with the electrochemical detection of daclatasvir over a CP-based sulfoacid, we analyze the equation set (1) by means of linear stability theory. The steady-state members of Jacobian functional matrix may be described as:

$$\begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix} \quad (5)$$

In which:

$$a_{11} = \frac{2}{\delta}\left(-\frac{\Delta}{\delta} - k_1(1 - \theta - \theta *)\right) \quad (6)$$

$$a_{12} = \frac{2}{\delta}(k_1 c) \quad (7)$$

$$a_{13} = \frac{2}{\delta}(k_1 c) \quad (8)$$

$$a_{21} = \frac{1}{G}(k_1(1 - \theta - \theta *)) \quad (9)$$

$$a_{22} = \frac{1}{G}\left(-k_1 c - k_2 \exp\frac{4F\gamma\theta}{RT} - \gamma k_2 \theta \exp\frac{4F\gamma\theta}{RT}\right) \quad (10)$$

$$a_{23} = \frac{1}{G}\left(-k_1 c - \alpha k_2 \theta \exp\frac{4F\gamma\theta}{RT} \quad \right) \quad (11)$$

$$a_{31} = 0 \quad (12)$$

$$a_{32} = \frac{1}{G*}\left(k_2 \exp\frac{4F\gamma\theta}{RT} + \gamma k_2 \theta \exp\frac{4F\gamma\theta}{RT} - \gamma k_3 \theta * \exp(-\alpha\theta *)\right) \quad (13)$$

$$a_{33} = \frac{1}{G*}\left(\alpha k_2 \theta \exp\frac{4F\gamma\theta}{RT} - k_3 \exp(-\alpha\theta *) + \alpha k_3 \theta * \exp(-\alpha\theta *)\right) \quad (14)$$

Analyzing the expressions (6), (10) and (14) it is possible to see that the *oscillatory behavior* for this system may be realized. Moreover, it is more probable than for the similar systems, as there is more than one process influencing DEL capacitances. These influences, causing oscillatory behavior are represented by the positivity of the members $-\gamma k_2 \theta \exp\frac{4F\gamma\theta}{RT}$, $\alpha k_2 \theta \exp\frac{4F\gamma\theta}{RT}$ and $\alpha k_3 \theta * \exp(-\alpha\theta *)$. The oscillation are expected to be frequent and of little amplitude.

To investigate the *steady-state stability,* we analyze the equation set (1) by means of the Routh-Hurwitz criterion. In order to avoid the appearance of cumbersome expressions, we introduce new variables, so the Jacobian determinant will be described as:

$$\frac{2}{\delta G G*}\begin{vmatrix} -\kappa - \Xi & \Lambda & \Lambda \\ \Xi & -\Lambda - \rho - \Omega & -\Lambda - T \\ 0 & \Omega - \Sigma & T - \sigma - K \end{vmatrix} \quad (15)$$

Opening the brackets and applying the condition of Det J<0, salient from the criterion, we obtain the steady-state stability requirement expressed as:

$$(-\kappa - \Xi)(\rho T + \Omega T - \Lambda T + \rho\sigma + \Omega\sigma - \Lambda\sigma + \rho K + \Omega K - \Lambda K) + \Xi\Lambda(\Omega - \Sigma - T + \sigma + K) < 0 \quad (16)$$

The steady-state stability condition is is warranted to be satisfied in the case of the positivity DEL influences of two reactions. The electroanalytical process is diffusion-controlled.

The steady-state stability is correspondent to the linear dependence between the electrochemical parameter and analyte concentration, or, better saying, to the electroanalytical efficiency. So, the system is electroanalytically 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:

$$(-\kappa - \Xi)(\rho T + \Omega T - \Lambda T + \rho\sigma + \Omega\sigma - \Lambda\sigma + \rho K + \Omega K - \Lambda K) + \Xi\Lambda(\Omega - \Sigma - T + \sigma + K) = 0 \quad (17)$$

So, the presence of a strong acid on the electrode surface let us use less acid solutions for the electrochemical detection, without problems of the electroanalytical inefficiency.

4. CONCLUSION

The theoretical analysis of the system with daclatasvir electrochemical detection let us conclude that the oscillatory behavior for this case is possible, being even more probable, than for general case of CP-based electrochemical sensor. It may be caused by DEL-influences of electrochemical and chemical stage. Also, the steady-state stability is warranted by the fragility of DEL-influences of two reactions. Nevertheless, the topological stability zone is vast, and the sensor is very sensitive. Moreover, the process is, in general, diffusion-controlled and electroanalytically efficient, permitting us use of higher pH values, up to neutral in daclatasvir electrochemical detection in these conditions.

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