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Electrochemical properties of active substances contained in non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) contain active substances i.a. salicylic acid (SA), acetylsalicylic acid (ASA), N-acetyl-p-aminophenol (AAP) and 2-(p-isobutylphenyl)propionic acid (IB) which are responsible for their therapeutic effect.

In recent years, electrochemical methods have become more important in the study of active substances contained in NSAIDs. They allow to determine the properties of NSAIDs under the conditions of electrochemical oxidation and reduction as well as to know the mechanisms and products of their decomposition, these compounds may be important for the assessment of the effect of the used drug on the human body and health.

In this work, electrochemical oxidation and reduction of active substances (SA, ASA, AAP and IB) contained in NSAIDs at the Pt electrode were performed. The tests were carried out using cyclic (CV) and differential pulse voltammetry (DPV) in an aqueous solution.

Based on CV measurements, it was found that the tested substances are oxidized irreversibly in at least two (SA, ASA, IB) or one (AAP) electrode steps at potentials lower than the potential at which oxygen evolution starts. They are reduced quasi-reversibly in at least two (ASA) or one (SA, IB) electrode steps at potentials higher than the potential at which hydrogen evolution starts. Based on the determined physicochemical parameters such as: peak potential (E_p), half-peak potential ($E_{p/2}$) and half-wave potential ($E_{1/2}$), kinetic parameters were calculated: transfer coefficients (βn_β, αn_α), rate constants (k_{bh}, k_{fh}) and reaction order (z_{utl}, z_{red}) electrode reactions. These parameters are important not only in estimation of anti-oxidative and anti-reductive properties of drugs but also in understanding of their oxidation and reduction mechanisms.

It has been shown that the dependence of the logarithm of the peak current (ln i_p) on the logarithm of the scan rate (ln v) for SA, ASA, AAP and IB is linear, so the rate of the electrode reaction can be controlled by adsorption or diffusion of the substrate to the electrode surface. Slopes of the above dependence for electrooxidation of SA (0,649) and ASA (0,626) indicate the diffusion control of the electrode process but preceded by a chemical reaction. In the case electrooxidation of AAP and IB, the slopes are equal to 0,396 and 0,729, respectively, which indicates the diffusion (AAP) and adsorption-diffusion (mixed) (IB) character of the electrode process.

In the case of the SA (0,486), ASA (0,384) i IB (0,309) electroreduction of the slope of the dependence of ln i_p = f (ln v) indicates the diffusion control of the reduction process.

It was found that the concentration and pH of the reaction media have an influence on the electrooxidation and electroreduction of the investigated substrates. The linearity the dependence of the peak current (i_p) of electrooxidation and electroreduction versus the concentrations of SA, ASA, AAP and IB makes it possible to determine the concentration of the above-mentioned substances in different samples, e.g. pharmaceutical products, using voltammetric methods. However, depending on the pH of the reaction medium, different products may be formed as a result of electrode processes of the tested substances, which in a consequence leads to a change in the mechanism of oxidation and reduction of the tested substrates.

Analysis of electrooxidation and electroreduction of tested compounds under potentiostatic conditions in separated electrode spaces with controlled potential, allowed for analysis and identification of products formed in the electrode processes SA, ASA, AAP and IB using voltammetry CV and DPV, UV-Vis spectroscopy and gas chromatography coupled with mass spectrometry (GC-MS).

It was found that in the electrooxidation process under potentiostatic conditions SA, ASA, AAP and IB are oxidized irreversibly in at least seven (SA), five (ASA) and three (AAP and IB), while in the electroreduction process in at least three (SA and ASA) and four (IB) electrode steps.

Spectrophotometric analysis of solutions after electrolysis at a controlled potential showed the presence of new absorption bands with respect to spectra observed for the stock solutions. This indicates the creation of products with a different chemical structure than the tested substrates. GC-MS analysis enabled the identification of products created in the electrooxidation process of SA, ASA, AAP and IB and electroreduction SA, ASA, IB.

Electrodes reactions were confirmed by quantum chemical calculations. The distribution of electron charge in the molecules of the tested compounds is not uniform, which determines the reactivity of individual bonds and substituents in the molecule. The calculated energy of the highest occupied orbital (E_{HOMO}) determines the ease of electron release and indicates that AAP is most easily oxidized (E_{HOMO} = -8,462 eV), while ASA is the most difficult to oxidize (E_{HOMO} = -9,634). The most susceptible places for oxidation in AAP molecule are the amino group and the bond between the carbon of the benzene ring and the hydroxyl group, while in ASA the bond between the carbon of the benzene ring and the ester group. While, the energy of the lowest unoccupied orbital (E_{LUMO}) for SA equal to -0,457 eV and indicates that this compound is reduced more easily than IB (E_{LUMO} = 0,198 eV). The most susceptible place for reduction in SA and IB molecules is the carboxyl group.

On the basis of performed electroanalytical tests, analytical determinations and quantum-chemical calculations, the mechanisms of electrooxidation and electroreduction of the investigated substrates were proposed.

The final stage of the work was to determine the concentration of active substances in selected pharmaceutical products using CV, DPV and UV-Vis spectrophotometry methods and to determine and calculate the validation parameters of the above research methods.

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