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New insights on diclofenac electrochemistry using graphite as working electrode

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ABSTRACT

This paper reports new investigation on the electrochemical behavior of diclofenac using a bare graphite electrode. The electrochemical oxidation of diclofenac was studied using cyclic voltammetry (CV), an anodic peak was found at 0.557 V as reported earlier by other authors, reversing the cycle results in a new cathodic peak at 0.272 V, which is proposed to be related with the reduction of 2-(2hydroxyprop-2-enyl) acetic acid. During the second cycle a new cathodic peak is observed at 0.333 V, associated to the oxidation of 2-(2hydroxyprop-2-enyl) acetic acid to 1-hydroxy-2-(hydroxyphenyl) ethanalate. Both electrochemical processes resulted to be adsorption-controlled, statistical fit of theoretical information with the experimental voltammograms, one electron transference is demonstrated which supports the proposed mechanism. From an analytical point of view, it was demonstrated that direct quantification of diclofenac using the anodic oxidation peak results less favorable when compared with an indirect quantification using the 2-(2hydroxyprop-2-enyl) acetic acid oxidation peak. The modified Simplex method was used to optimize differential pulse voltammetry parameters to achieve an exact and precise quantification of diclofenac in standard and real samples obtaining very competitive results compared with other more sophisticated working electrodes.

1. Introduction

Diclofenac ([2 - [(2,6-Dichlorophenyl) amino] phenyl] acetic acid) (Fig. 1) is one of the most used nonsteroidal anti-inflammatory drugs (NSAID), which blocks the cyclooxygenase enzyme and degrades prostaglandins produced by cells that cause inflammation, pain and fever [1]. Due to its low solubility, it is usually used as its sodium salt. Since 1974, diclofenac is widely prescribed for the treatment of pain, joint injuries, chronic inflammation, degenerative diseases, rheumatism, rheumatoid arthritis, osteoarthritis and musculoskeletal injuries [2,3].

Diclofenac is used as tablets, capsules, suppositories, intravenous solutions and gels for dermal application.

Due to the high demand of diclofenac in the pharmaceutical industry, a large number of analytical methods have been proposed for its quantification, usually high performance liquid chromatography (HPLC) [4–7], gas chromatography [8,9], capillary zone electrophoresis (CZE) [10], spectrophotometry [11], spectrofluorometry [12], and layer chromatography [13]. All these methods have some disadvantages such as: sample pretreatment (extractions or chemical reactions), previous derivatization, time-consuming analysis, the high analysis cost due to the technicians needed and the maintenance of the equipment.

Electrochemical techniques for the characterization and quantification of this drug have recently rise as a promising alternative due to its many advantages: shorter analysis times compared with routine techniques, lower cost per analysis, good sensitivity and selectivity, in some cases the sample does not requires pre-treatment and/or is not destroyed. In electrochemical techniques, the working electrode plays an important role since the analytical parameters depend on the electrode's response. Different materials for the working electrodes used for diclofenac quantification have already been reported in literature: modified with nickel hydroxide [14], edge-plane pyrolytic graphite with or without single walled carbon nanotubes [15,16], potentiometric electrode [17], bismuth [18], modified carbon paste [19–23], modified glassy carbon [24], and boron-doped diamond [25]. So far, the use of graphite as working electrode has been extensively

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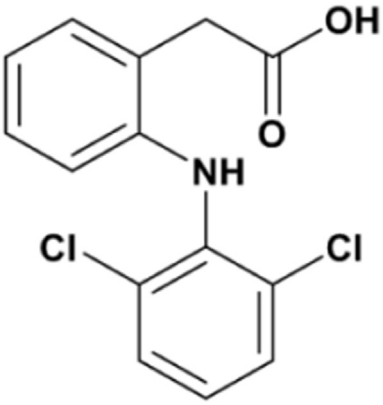

Fig. 1. Chemical structure of diclofenac.

reported in literature due to the great working potential window and the low cost of this material [26–28], even though, no diclofenac has not been reported to be studied with such electrodes.

There exist very few reports about the electrochemical characterization of diclofenac. Goyal et al. reported a cyclic voltammetry study of diclofenac using an edge-plane pyrolytic graphite electrode (EPPGE) coated with single wall carbon nanotubes. In the anodic sweep, a maximum current for diclofenac's oxidation was observed at a potential of 0.55 V with the production of 5-OH diclofenac, which is reduced in the successive cathodic sweep to diclofenac-2,5-quinone imine. During the second anodic sweep, a new oxidation peak is observed and related to the oxidation of diclofenac-2,5-quinone imine, involving $2e^-$ and $2H^+$ [15]. Afkhami et al. reported almost the same electrochemical behavior for diclofenac but using an Au-nanoparticles/Multi Walled Carbon Nanotubes/Glassy Carbon electrode, establishing an adsorption process for the reduction of 5-OH diclofenac [29]. Recently, Cid-Cerón et al. demonstrated that the electrochemical oxidation of diclofenac using a carbon paste electrode (CPE) involves a $1e^-$ EC mechanism, with a consecutive chemical reaction where 2,6 dichloroaniline and 2-(2hydroxiprop-2phenyl) acid acetic are formed [30].

In this work, diclofenac is characterized electrochemically using a bare graphite electrode, in order to have a better understanding of the chemical processes happening, and with this knowledge and the use of chemometrics, establish a simple, inexpensive, but competitive methodology to quantify diclofenac in pharmaceutical and biological samples.

2. Material and methods

2.1. Material and equipment

All chemical reagents used were analytical grade. Pharmaceutical samples were purchased at local pharmacies. All solutions used were prepared using deionized high purity water (18.2 MΩ/cm). Electrochemical tests were performed using an AUTOLAB PGSTAT302N potentiostat connected to a PC. A three electrode system was used, where the reference electrode is a double-junction saturated Ag/AgCl (KCl saturated) electrode, high purity graphite rods are used as auxiliary and working electrodes. pH measurements were performed using a Corning digital pH meter pH/ION 450; also a Sartorius CPA224S analytical balance was used. UV–vis absorbance spectra were recorded on a HACH (DR 3900) spectrophotometer with a 1.0 cm quartz cell.

Sodium diclofenac (Sigma-Aldrich) solutions were bubbled with high purity nitrogen before each experiment in order to remove oxygen. A 0.1 mol L^{-1} pH 7 phosphate buffer was used to maintain a constant working pH (monobasic potassium phosphate and dibasic potassium phosphate from Sigma-Aldrich). All electrical potentials in this work are referred to the Ag/AgCl (KCl saturated) reference electrode.

2.2. Construction of the support for the working electrode

A ϕ = 6 mm (Sigma Aldrich, purity 99.999%) graphite rod was used as working electrode. In order to maintain a constant working surface, Teflon tubes ϕ = 9 mm were used to support the graphite rod, using epoxy resin (Araldite-HY) to immobilize the graphite. To harden the resin, the electrodes were treated for 12 h at 60 °C. After this, one of the ends was sanded until graphite was exposed.

2.3. Electrochemical analysis of diclofenac by means of cyclic voltammetry using graphite as working electrode

Cyclic voltammetry (CV) is performed to a 0.1 mol L^{-1} phosphate buffer (pH 7) with and without the presence of diclofenac (1×10^{-3} mol L^{-1}), starting at the equilibrium potential in anodic direction using a potential window of -1.3 to 1.3 V at different scan rates. Anodic and cathodic peaks are analyzed in order to stablish the relation between the maximum current intensity of the anodic peak with the scan rate.

2.4. Differential pulse voltammetry optimization for diclofenac quantification

Diclofenac quantification was performed using differential pulse voltammetry (DPV). DPV variables were optimized with the modified Simplex method: pulse width (ms), pulse amplitude (mV), step potential (mV) and pulse period (ms), in order to achieve the higher analytical response (anodic current).

Multisimplex ® v. 2.1 was used to perform the simplex optimization. A simplex is a geometric structure having a number of vertex of $k + 1$, where k is the number of factors to be optimized. The optimization uses an algorithm which consists of a series of rules that forces the simplex to "move" towards the optimal response region. After 18 experiments, the optimum parameters were obtained: a pulse width of 73 ms, a pulse amplitude of 123 mV, a step potential of 13 mV and a pulse period of 178 ms.

2.5. Analytical characterization of the optimized methodology

Statistical analysis of the calibration curves obtained with the optimized system was performed in order to establish the detection (LOD) and quantification (LOQ) limits, along with the sensitivity of the proposed analytical method. LOD and LOQ were estimated as $a + 3s_{y/x}$ and $a + 10s_{y/x}$ respectively, where the value of a, the calculated intercept of the adjusted calibration curve and $s_{y/x}$ is the standard deviation.

Interference effect of other chemical species was evaluated as the relative error percentage related to the variation of the analytical response with and without the presence of the interference. The study was conducted using solutions with the same diclofenac concentration but different interference concentrations: equal, 10, 100 and 1000 times higher than diclofenac concentration.

Reproducibility of the electrode's response was determined constructing five different graphite electrodes and measuring several times the maximum anodic current obtained in a solution with a fixed diclofenac concentration (5×10^{-5} mol L^{-1}). The relative standard deviation was used to determine the reproducibility. Repeatability was evaluated almost the same way, but measuring nine consecutive times with just one of the electrodes, using a 7×10^{-5} mol L^{-1} sodium diclofenac solution.

2.6. Diclofenac quantification in real samples

For the analysis of real samples, two different commercial tablets (A and B, both from different brands) are analyzed. For this, ten tablets of each commercial product were crushed to fine powder. A sample of this