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Original Article

Electrochemistry and determination of cefdinir by voltammetric and computational approaches

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ABSTRACT

The oxidation and reduction behavior of cefdinir (CEF) was studied by experimental methods and computational calculations at B3LYP/6-31+G (d)//AM1. Voltammetric studies were carried out based on two irreversible reduction peaks at approximately −0.5 and −1.2 V on a hanging mercury drop electrode (HMDE) and on one irreversible oxidation peak at approximately 1.0 V on a glassy carbon electrode (GCE) versus Ag/AgCl, KCl (3.0M) in Britton–Robinson (BR) buffer at pH 4.2 and 5.0, respectively. Differential pulse adsorptive stripping voltammetric methods have been developed and validated for determination of CEF in different samples. The linear range was established as 0.25–40.0 μM for HMDE and 0.40–10.0 μM for GCE. Limit of quantification was calculated to be 0.20 and 0.26 μM for HMDE and GCE, respectively. These methods were successfully applied to assay the drug in tablets and human serum with good recoveries between 92.7% and 107.3% having relative standard deviation less than 10%.

1. Introduction

Cefdinir (CEF), chemically known as [(6*R*,7*R*)-7-[[(2*Z*)-(2-amino-4-thiazolyl)(hydroxyl imino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid] (Fig. 1), is a broad-spectrum oral third-generation cephalosporin that has been approved for the treatment of some kind of bacterial infections [1,2].

Many kind of analytical methods have been described for the determination of CEF in pharmaceutical samples and biological fluids, including high-performance liquid chromatography (HPLC)–tandem mass spectrometry [3], HPLC–solid-phase extraction [4,5], stability indicating chromatography [6,7], reverse-phase HPLC with UV deduction [8], different kinds of liquid chromatography [9–13], resonance Rayleigh scattering spectra [14], and spectrophotometry [15,16]. Because the CEF molecule contains electroactive groups, reports have been published regarding its reduction behavior on mercury electrode [17–19]. It could be possible to evaluate the redox characteristics, adsorption–diffusion properties, and charge transfer mechanisms for electroactive molecules by electrochemical methods. These parameters and their evaluation are of great importance for distribution, metabolism, pharmacological, toxicological, and pharmacokinetic behaviors of drug molecules [17–25]. Theoretical calculations were also found to be useful as a value-added tool to enlighten oxidation–reduction mechanisms [22,23].

Voltammetric techniques are used for the quantitative determination of a variety of organic and inorganic

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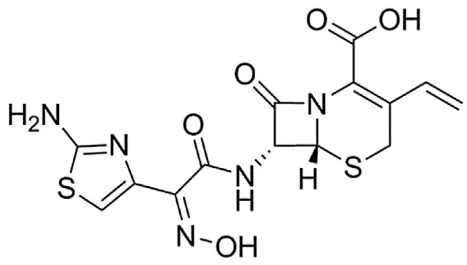

Fig. 1 – Chemical structure of cefdinir.

substances including drug-active ingredients and excipients in pharmaceutical dosage and their possible metabolites in biological fluids. In addition, voltammetric stripping technique extends the use of these methods ensuring lower detection limits. Many applications of voltammetric stripping methods have been reported in literature to determine environmentally and biologically important substances [17–33].

At present, there is no electrochemical study dealing with the oxidation behavior of CEF and its determination on carbon-based electrodes. This study was designed to investigate the reduction and oxidation behavior of CEF on both glassy carbon electrode (GCE) and hanging mercury drop electrode (HMDE). Tentative reaction mechanisms on both electrodes were also proposed. Computational studies were performed to enlighten the proposed mechanisms. In addition, it was also aimed to develop rapid, simple, and novel voltammetric methods for direct determination of CEF in pharmaceutical dosage forms and human serum.

2. Experimental analysis

2.1. Apparatus

All voltammetric measurements were carried out using a Gamry instruments framework electrochemical analyzer (reference 3000; Gamry Instruments, Warminster, PA, USA). The three-electrode system consisted of working electrodes (HMDE; BAS CGME 1108, 0.0145 cm^2, and GCE; BAS, MF 2012, 0.071 cm^2), reference electrode (Ag/AgCl; 3M KCl; MF-2052, RE-5B), and a Pt auxiliary electrode (BAS MW-1034). Before performing each experiment, GCE was polished manually with slurries prepared from 0.01-μm aluminum oxide on a smooth polishing pad (BAS velvet polishing pad), and then thoroughly rinsed with double-distilled water.

All pH measurements were obtained using Thermo Orion Model 720A pH ion meter having an Orion combined glass pH electrode (912600; Thermo Fisher Scientific). Double-distilled deionized water was obtained from an ultrapure water system (ELGA as PURELAB Option-S). All measurements were performed at room temperature (23 ± 2 °C).

2.2. Reagents and solutions

The CEF standard was purchased from Bilim Pharmaceuticals (Istanbul, Turkey). All chemicals used were of analytical grade and used as received.

The CEF stock solutions (5.0 mM) were prepared in absolute ethanol and kept in dark and stored at <4°C. Working CEF solutions were prepared by sufficient dilution of stock solution with supporting electrolyte having optimum pH and used within the same day to avoid decomposition. Phosphoric acid (Riedel-de-Haen, Honeywell Specialty Chemicals Seelze GmbH, Germany), boric acid (Riedel-de-Haen, Honeywell Specialty Chemicals Seelze GmbH, Germany), and acetic acid (Merck KGaA, Darmstadt, Germany) were used in the preparation of BR solution in which each component had an analytical concentration of 0.04 M. Double-distilled deionized water was used in preparing of all the solutions.

2.3. Procedure

For voltammetric measurements, a known volume of CEF solution was pipetted into a 10.0-mL supporting electrolyte. The cell contents were degassed with argon for 5 minutes during the first run and for 30 seconds between successive runnings. Voltammetric measurements were carried out after degassing with argon for 5 minutes. Voltammograms were then recorded by scanning the potential toward the positive direction on GCE (oxidation studies) and toward the negative direction on HMDE (reduction studies) versus the reference electrode.

A three-electrode combination system for bulk electrolysis (BE) was used. The system included a mercury pool (55.4 cm^2), a glassy sieve as working electrode, a coiled platinum wire as an auxiliary electrode [BAS MW-1033 (23 cm)], and Ag/AgCl as reference electrode (BAS MF-2052 RE-5B in 3.0 M KCl). In BE studies, 25 mL of 10 μM solutions were used for both electrodes.

2.4. Preparation of Cefnet tablets

Cefnet tablets were obtained from a local market in Amasya and were used as the dosage form obtained. Each tablet contains 600 mg CEF. Ten tablets were accurately weighed and crushed into a homogeneous fine powder in a mortar and mixed well. The average weight of one tablet was calculated. A powdered sample, equivalent to one tablet, was weighed and transferred into a calibrated flask containing approximately 100 mL of absolute ethanol. The contents of the flask content were then sonicated for 10 minutes. After standing at room temperature for approximately 30 minutes, the volume of this flask was increased to 250 mL by adding double-distilled water. Then, to prepare the final concentration, a required amount of sample from the clear supernatant liquor was withdrawn and quantitatively diluted with the supporting electrolyte solution. Quantitations in all proposed methods were performed by the calibration curve method from the related calibration equations.

2.5. Preparation of spiked human serum

Drug-free human serum samples were obtained from healthy volunteers and stored frozen until assay. After gently thawing the samples, 2.0 mL of an aliquot volume of serum sample was spiked with CEF in BR buffer to maintain 0.1 mM CEF concentration in serum, and acetonitrile was added to precipitate serum proteins. The mixture was then vortexed for 25 seconds