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ORIGINAL ARTICLE

Electrochemistry of cefditoren pivoxil and its voltammetric determination

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Abstract Electrochemical behavior of cefditoren pivoxil (CTP) was studied via experimental electrochemical methods and theoretical calculations performed at B3LYP/6-31+G(d)//AM1 level. Experimental studies were carried out based on an irreversible 4e−/4H+ reduction peak at ca. −0.8 V on hanging mercury drop electrode (HMDE) and irreversible 1e−/1H+ oxidation of CTP at ca. 0.8 V on glassy carbon electrode (GCE) versus Ag/AgCl, KCl (3.0 M) in Britton–Robinson buffer at pH 6.0 and 4.0, respectively. Tentative reduction and oxidation mechanisms were proposed based on computational and experimental results. Square-wave adsorptive stripping voltammetric methods have been developed and validated for quantification of CTP in different samples. Linear working range was established as 0.15–15.0 μM for HMDE and 1.0–50.0 μM for GCE. Limit of quantification (S/N = 10) was calculated to be (0.10 ± 0.02) μM and (0.80 ± 0.03) μM for HMDE and GCE, respectively. Methods were successfully applied to assay the drug in tablets and human serum with good recoveries between (99.2 ± 11.6) % and (102.5 ± 9.5) % having relative standard deviation less than 10%.

1. Introduction

Cefditoren pivoxil (CTP) chemically known as (6R)-7-[[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2-methoxyiminoacetyl]amino]-3-[(Z)-2-(4-methyl-1,3-thiazol-5-yl) ethenyl]-8-oxo-5-thia-1-aza bicyclo [4.2.0]oct-2-ene-2-carboxylic acid (Scheme 1) is third generation member of cephalosporin. According to (Brunton et al., 2001) it has antibacterial activity against both gram-positive and gram-negative pathogens and it is used in the treatment of biotic disorders such as mild to moderate pharyngitis, tonsillitis, uncomplicated skin, skin structure infections, and acute exacerbations of chronic bronchitis.

Since it is newly introduced as a drug, there are few determination methods for its assay in different samples: Ion selective electrode (Al-Tamimi et al., 2013), different kind of chromatography such as, planar chromatography (El-Bagary et al., 2013), gas chromatography (Telko and Hickey, 2007), inverse gas chromatography (Stapley et al., 2006), HPLC (Dhoka et al., 2011; Rieck and Platt, 2000; Srinivasa and Saraswathi, 2011; Dewani et al., 2010), LC (Annapurna et al., 2012), UPLC (Garg et al., 2011), spectrophotometric

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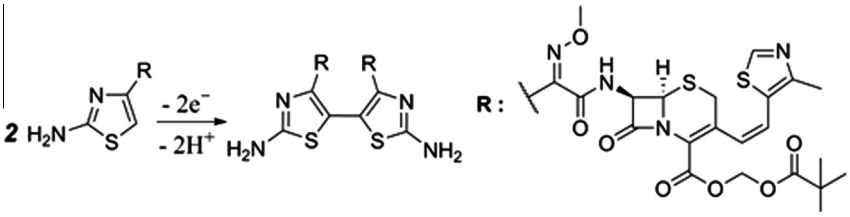

Scheme 1 Proposed oxidation mechanism of CTP on GCE.

methods (Raju et al., 2009; Narala and Saraswathi, 2011) and stability indicating chromatographic method (Jayswal et al., 2011) have been devised for its determination.

Beside it has reducible and oxidizable parts on its structure, to the best of literature knowledge, there is no study dealing with its electrochemical behavior and its voltammetric determination. Since results of electrochemical studies might be used in investigating many physical, chemical and redox behavior of species such properties and their evaluation may be important. In this instance evaluation of electrochemical parameters of CTP may be of great importance. Theoretical calculations by which molecular orbitals could be mapped according to their relative energies were also found to be useful as a value added tool to enlighten oxidation-reduction mechanisms by (Taşdemir et al., 2012; Pamuk et al., 2013; Zorluoğlu et al., 2013).

The present study was designed to investigate the redox behavior of CTP on both glassy carbon electrode (GCE) and hanging mercury drop electrode (HMDE). Tentative reaction mechanisms were also proposed. Computational studies were performed to enlighten the electrode reaction mechanisms. In addition, it was also aimed to develop rapid, simple and novel voltammetric methods for direct determination of CTP in pharmaceutical dosage forms and human serum samples.

2. Experimental

2.1. Apparatus

Voltammetric measurements on both electrodes were carried out using Reference 3000 (Gamry Instruments, Warminster, USA) electrochemical work station. Three electrode system consisted of working electrodes (hanging mercury drop electrode (HMDE); BAS CGME 1108, 0.0145 cm^2 and glassy carbon electrode (GCE); BAS, MF 2012, 0.071 cm^2), reference electrode (Ag/AgCl; 3 M KCl; MF-2052, RE-5B) and a Pt auxiliary electrode (BAS MW-1034) were used. Prior to each experiment, GCE was polished manually with slurries prepared from 0.01 μm aluminum oxide on a smooth polishing pad (BAS velvet polishing pad), then rinsed with double-distilled water thoroughly.

pH measurements were made with Thermo Orion Model 720A pH ion meter having an Orion combined glass pH electrode (912600; Thermo Fisher Scientific). Double-distilled deionized water was supplied from Ultra-Pure Water System (ELGA as PURELAB Option-S). All measurements were performed at room temperature.

2.2. Reagent and solutions

CTP standard was kindly given as a gift by Bilim Pharmaceuticals. All chemicals used were of analytical grade. Stock solutions of CTP (5.0×10^{-3} M) were prepared in absolute ethanol and kept in the dark and below 4 °C. Working CTP solutions were prepared by sufficient dilution of stock solution with optimized supporting electrolyte on desired pH and used within the day to avoid possible 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 Britton–Robinson buffer solution (BR) in which each component had an analytical concentration of 0.04 M. All chemicals were used as received.

2.3. Procedure

For voltammetric measurements, a known volume of CTP solution was pipetted into 5.0 mL supporting electrolyte with optimized pH. Measurements were carried out after degassing with argon for 5 min. Voltammograms were then recorded by scanning the potential toward the positive direction on GCE (oxidation studies) and negative direction on HMDE (reduction studies) versus reference electrode.

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

2.4. Preparation of Spectraceft tablets and human serum samples

Spectraceft® tablets were taken commercially from the local pharmacy in Amasya and were used as pharmaceutical dosage form that contains 200 mg CTP per tablet. Then the same procedures given in our previous studies (Taşdemir et al., 2012; Pamuk et al., 2013; Zorluoğlu et al., 2013) were followed to prepare tablet solutions and serum samples.

3. Computation

In order to have supported and enlightened mechanisms to be proposed, theoretical calculations were performed and these calculations were run with the Gaussian 09 suite of programs (Frisch et al., 2009). In these calculations, geometry of CTP was fully optimized at AM1 level. Frequency calculations were computed at the same level to verify that the optimized geometry is a real minimum on the potential energy surface without any imaginary frequency. Then by using AM1-optimized geometry at DFT/B3LYP level of theory single point energy