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ORIGINAL ARTICLE

Electrochemistry of cefditoren pivoxil and its voltammetric determination

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Methods

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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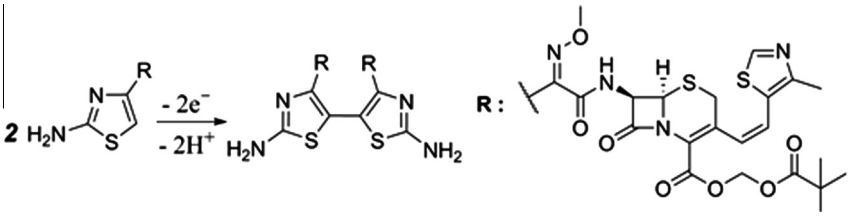


Scheme 1 Proposed oxidation mechanism of CTP on GCE.

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

calculation was done, with the popular polarized basis set, 6-31 + G(d) which adds d functions on heavy atoms.

4. Results and discussion

Electrochemical characteristics of CTP were studied on both HMDE (reduction side) and on GCE (oxidation side). In these studies, methods such as cyclic voltammetry (CV), square-wave voltammetry (SWV) and constant-potential bulk electrolysis (BE) were used.

4.1. Electrochemical behavior of CTP on GCE and HMDE

In CV studies on GCE, single well-defined oxidation peak at 0.8 V at positive-going scan in BR of pH 4.0 (Fig. 1A) was observed and peak current of oxidation peak was found to be increased with increasing concentration of CTP, on the other hand, at negative-going scan on HMDE, one reduction peak at *ca.* −0.7 V in BR of pH 6.0 was observed (Fig. 1B) and currents of this peak also increase with increasing CTP concentration. Since there is no voltammetric signal when only blank BR was scanned and peak currents increase with increasing concentration of CTP these peaks should belong to CTP. Since no cathodic peak on reverse scan on GCE and no anodic peak on that for HMDE were observed, irreversible nature for oxidation on GCE and reduction on HMDE could be suggested (Brett and Oliviera-Brett, 1996; Wang, 2000; Bard and Faulkner, 2001; Bond, 2002).

4.1.1. Effect of pH

Electrochemical behavior was studied in detail. As a first step, effects of pH on peak parameters were studied using SWV on GCE and CV on HMDE between pH of 2.0 and 12.0. As could be seen from Fig. 2A, oxidation potential on GCE shifted to less positive potentials with increasing pH between the pH values from 2.5 to 7.5 by obeying Eq. (1) (Fig. 2B):

$$Ep/V = 0.044 \pm (0.007) + 0.051(\pm 0.008)\ \text{pH};\quad (R^2 = 0.9804) \qquad (1)$$

Oxidation peak disappeared at pH values higher than 8.0 on GCE. On the other hand potential of reduction on HMDE shifts to more negative values with increasing pH (Fig. 2C) with linear relation given as Eq. (2) (Fig. 2D):

$$Ep/V = -0.65 \pm (0.03) - 0.06(\pm 0.004)\ \text{pH};\quad (R^2 = 0.9837) \qquad (2)$$

Changing the potentials of both oxidation and reduction with pH was concluded as the evidence of existence of proton on both mechanisms (Brett and Oliviera-Brett, 1996; Wang, 2000; Bard and Faulkner, 2001; Bond, 2002). For oxidation processes on GCE, shifting of peak potential to less positive potentials with increasing pH may be caused by the initial deprotonation of a functional group before electron transfer. Besides, shifting of reduction peak potential to more negative

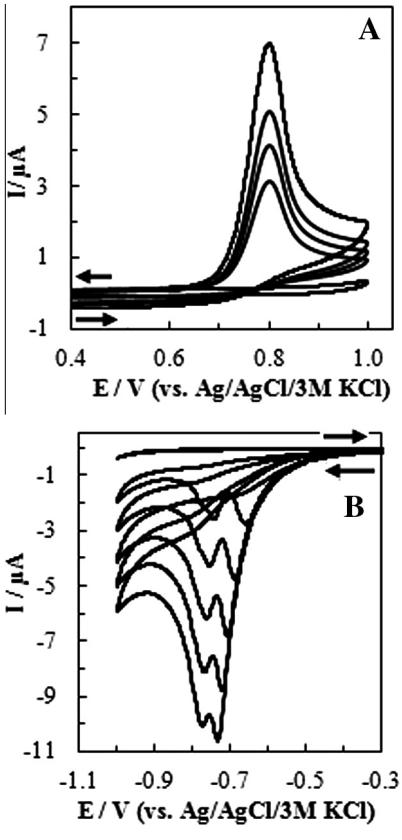


Figure 1 CVs of various CTP solutions in 0.04 M BR with scan rate of 0.10 V/s, on (A) GC (concentrations from lower to higher; blank, 0.25, 0.45, 0.65, 0.85 mM; pH 4.0 (B) HMDE concentrations from lower to higher; blank, 0.10, 0.25, 0.48, 0.75, 1.00 mM; pH 6.0.

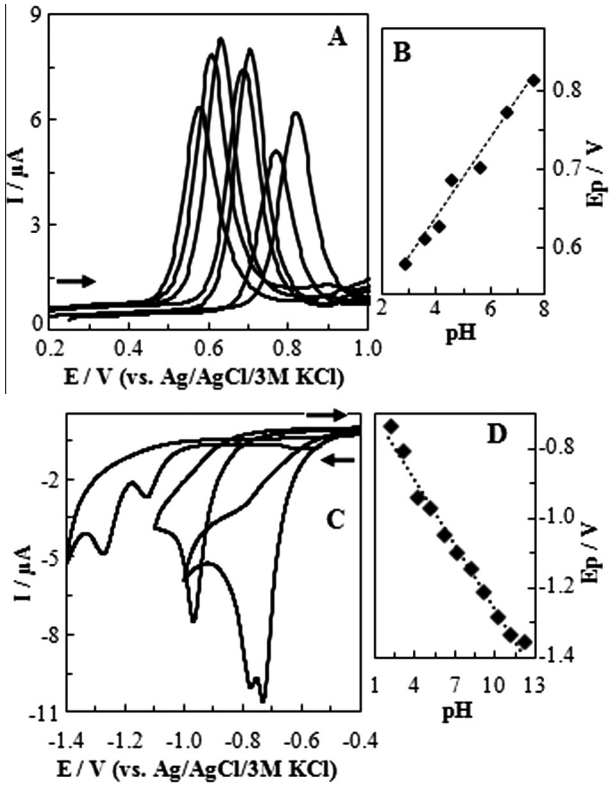


Figure 2 (A) SWVs of various CTP solutions with different pH (pH values from right to left), 2.8, 3.5, 4.0, 4.5, 5.5, 6.5, 7.5 in 0.04 M BR, with scan increment of 2 mV and frequency of 25 Hz, on GC (B) dependency of peak potential to pH (C) CVs of various CTP solutions with different pH (pH values from right to left; 2.0, 6.0, 12.0 in 0.04 M BR with scan rate 0.10 V/s, and (D) dependency of peak potential to pH.

(more cathodic) values with increasing pH on HMDE may be concluded as presence of protonation step before electron transfer (Taşdemir et al., 2012; Pamuk et al., 2013; Zorluoğlu et al., 2013).

Subsequently, slope of the graph *pH* versus *Ep* should be equal to $2.303RT\delta/nF$ where δ is the number of protons involved in the electrode reaction, n is the number of electrons transferred, R is gas constant (8.314 J/mol/K), T is temperature (298 ± 3 K), F is Faraday's constant (96,485 C/mol) (Brett and Oliviera-Brett, 1996; Wang, 2000; Bard and Faulkner, 2001; Bond, 2002). In this study, δ/n values were calculated as 0.86 and 1.0, for oxidation on GCE and reduction on HMDE, respectively. These values for δ/n show us the transfer of same number of electrons and protons in the oxidation on GCE and same number of electrons and protons in reduction mechanism on HMDE. Peak current, peak shape and symmetry were taken into account and finally the optimum pH was selected as 4.0 for GCE and 6.0 for HMDE.

4.1.2. Effect of scan rate

Effect of potential scan rate on peak potential was investigated while CTP concentration was held constant at 0.85 mM for GCE and 0.75 mM for HMDE. It is clear from Fig. 3A that oxidation potential on GCE shifts to more positive (more anodic) potentials with increasing scan rate and linear relation between peak potential and logarithm of scan rate (Fig. 3B) was established as given in Eq. (3):

$$Ep/V = 0.081 \pm (0.01) + 0.046(\pm 0.007)\log(\mathrm{v/V/s}); \quad (R^2 = 0.9908) \tag{3}$$

Potential of reduction on HMDE was found to be shifted to more negative (more cathodic) potentials with increasing scan rate (Fig. 3C), and linear dependency of peak potential to logarithm of scan rate (Fig. 3D) is expressed as given in Eq. (4):

$$Ep/V = -0.81 \pm (0.09) - 0.071(\pm 0.009)\log(\mathrm{v/V/s}); \quad (R^2 = 0.9937) \tag{4}$$

Changing of the peak potential with scan rate should be explained by quasireversible or irreversible mechanism (Brett and Oliviera-Brett, 1996; Wang, 2000; Bard and Faulkner, 2001; Bond, 2002). Since there is no peak at reverse scan for measurements on both electrodes, mechanisms should be irreversible. Slope values of Eqs. (3) and (4) were used to calculate the charge transfer coefficient (α). Value for αn (n is number of electrons) was calculated as 0.56 and 1.37 for GCE and HMDE, respectively. Accordingly, number of electrons in oxidation on GCE and reduction on HMDE should be different.

Effect of scan rate on peak current was also studied. Logarithm of peak current changes linearly with logarithm of scan rate with the slope value of 0.57 (Fig. 4A) on GCE and peak current is not changed linearly with scan rate, and peak current linearly changes with the square-root of scan rate (Fig. 4B). As a result, oxidation on GCE is not surface confined and it should take please on electrode-solution interface (Brett and Oliviera-Brett, 1996; Wang, 2000; Bard and Faulkner, 2001; Bond, 2002). Parallel studies were performed for reduction on HMDE and it was found that peak current changes linearly with scan rate (Fig. 4C), logarithm of peak current linearly changes with logarithm of scan rate by the slope value of 0.86 (Fig. 4D) and peak current has no linear dependency to square root of scan rate. This observation may be explained by the adsorption effect on the reduction mechanism on HMDE. As could be seen in Figs. 1B and 2C, reduction peak was splitted. Splitting behavior is concentration and scan rate dependent. Furthermore, peak potential shifts to more negative potentials as concentration increases. These results may indicate the effect of adsorption on mechanism (Brett and Oliviera-Brett, 1996; Wang, 2000; Bard and Faulkner, 2001; Bond, 2002).

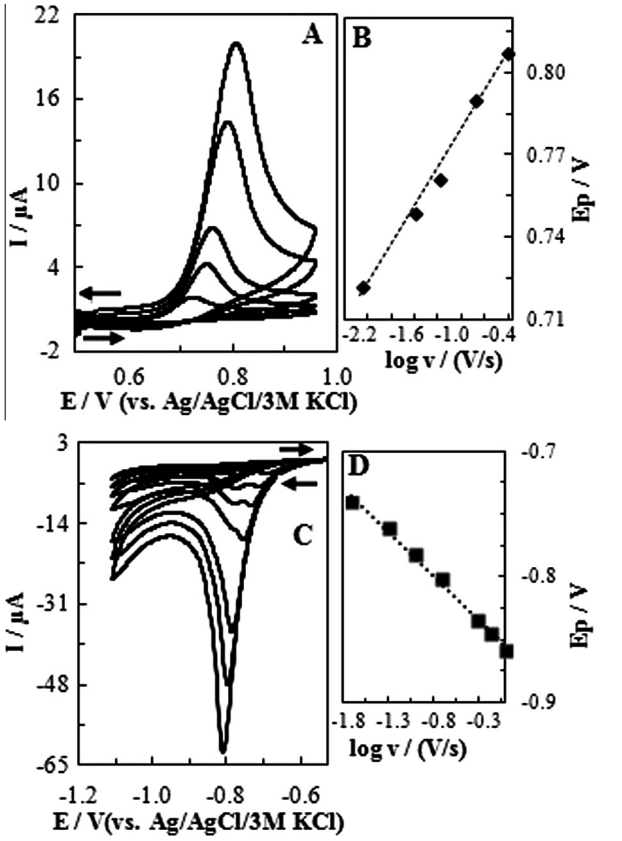


Figure 3 CVs of CTP solutions with different scan rates in 0.04 M BR on (A) GC (scan rates from lower to higher; 0.01, 0.05, 0.30, 0.75 V/s, pH 4.0, C_{CTP} = 0.85 mM, (B) dependency of peak potential to logarithm of scan rate, (C) HMDE (scan rates from lower to higher; 0.02, 0.05, 0.10, 0.30, 0.50, 0.70, 1.00 V/s, pH 6.0, C_{CTP} = 0.75 mM), and (D) dependency of peak potential to logarithm of scan rate.

4.1.3. Bulk electrolysis (BE)

BE studies at 1.0 V were carried out to find the number of electrons in the oxidation mechanisms on GCE and at −1.0 V for that of HMDE. After BE, Faraday equations were used to calculate the number of electrons and it was found to be 1 for each of CTP molecule for oxidation on GCE and 4 for reduction on HMDE.

4.2. Theoretical investigations and tentative mechanisms

Electrons flow from the electrode into the lowest unoccupied molecular orbital (LUMO) of the molecule as reduction takes

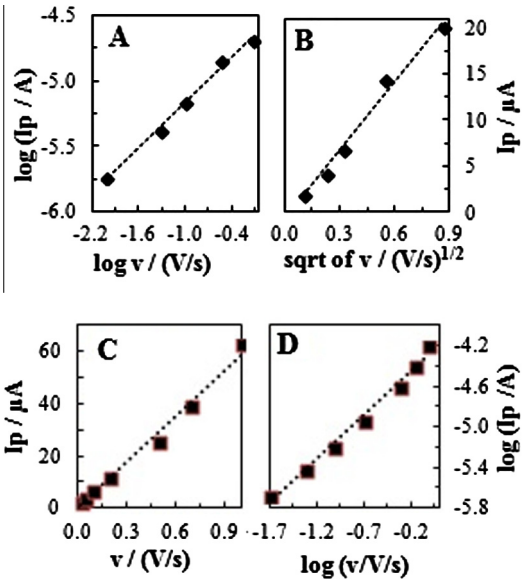


Figure 4 (A) dependency of logarithm of peak current to logarithm of scan rate on GCE, (B) dependency of peak current to square-root of scan rate on GCE, (C) dependency of peak current to scan rate on HMDE, and (D) dependency of logarithm of peak current to logarithm of scan rate on HMDE.

place. When the oxidation occurs, the electron from the highest occupied molecular orbital (HOMO) is involved. Consequently, the arrangement of these frontier molecular orbitals is important to determine the most relevant part/atoms of the molecule for redox reactions. It is therefore necessary to determine the HOMO–LUMO of the molecule to support the electrode mechanisms in more accurate way. For this reason, in order to predict HOMO and LUMO, CTP geometry was firstly optimized, using semi empirical methods (AM1). These methods are fast but often fail to predict accurate energy values of compounds. Hence a more accurate basis set was found necessary to obtain energy values that match experimental accuracy. Accordingly, single point energy calculation processes were performed at B3LYP/6-31 + G(d). As a result of theoretical investigations HOMO and LUMO together with their corresponding energies are depicted in Fig. 5.

According to Fig. 5, less tightly held electrons in the molecule (HOMO) lie mainly on the 5-membered ring contains N and S atoms (aminothiazolyl moiety), whereas LUMO, which will be the easiest route to the addition of electrons to the molecule, is located around carboxylic and etheric oxygens. Aminothiazolyl groups are known to be oxidized by 1 electron, dimerization occurs and related mechanisms are postulated in the literature (Jouikov and Simonet, 2007). The reported oxidation mechanism is irreversible which is initiated by removal of proton from the 5-membered ring and followed by a transfer of electron and finally dimerization. Therefore, the oxidation of CTP is also expected to proceed in the same way which agrees well with both theoretical and experimental findings. As a result, mechanism figured out in Scheme 1 is proposed for oxidation reaction.

Several reduction mechanisms may be proposed, for the fact that there are different functional groups on CTP that are available to be reduced. The first one is the protonation of the etheric oxygen followed by electron transfer and finally irreversibly fragments into the corresponding alcohol and saturated hydrocarbon. But this obviously would be two-electron processes which will not meet with our experimental findings. Reduction and fragmentation of two similar oxygen groups may be the plausible one but at this time reductions should take place at different potentials. Another possibility is the reduction of carbonyl groups into their corresponding alcohols without undergoing any fragmentation. This mechanism is also supported by computational study which shows that the reduction centers are located around carbonyl oxygen groups. In this mechanism, prior to electron transfer, protonation of carbonyl oxygen takes place first, indicating that this is a classical acid catalyzed reaction. The reduction of carbonyl group will be more favorable at low pHs. Similarly, protonation step will be more difficult in higher pHs and higher potential will be needed as investigated in pH studies, but again, reduction of carbonyl oxygen needs two electrons. To meet our experimental results there should be four electrons and four protons. Besides, more than one carbonyl group are present in the structure and since they have completely different relative

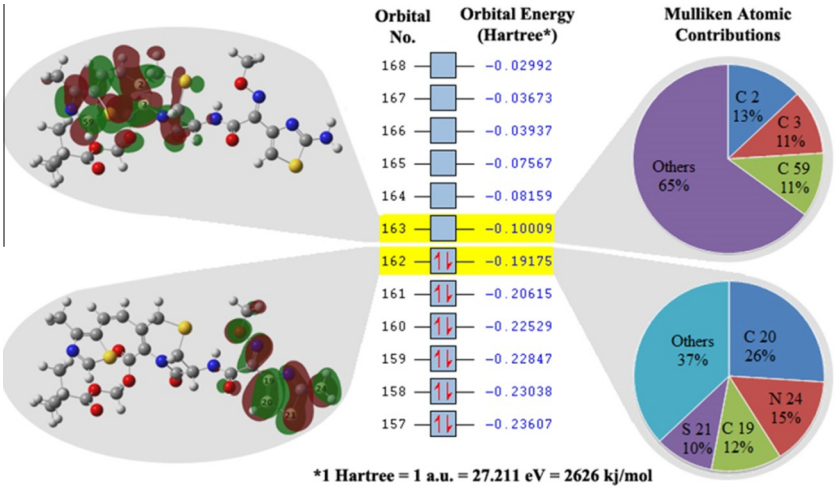
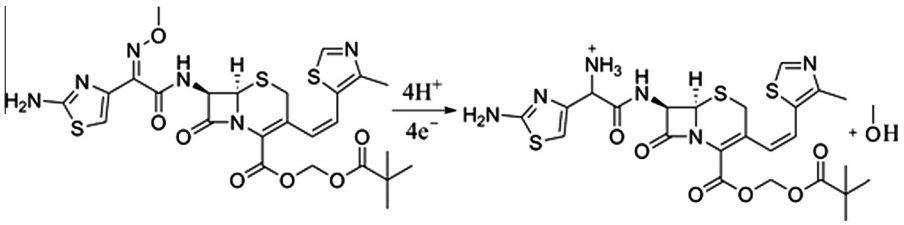


Figure 5 Frontier molecular orbitals mapped on optimized molecular structure of CTP, their corresponding energies calculated at B3LYP/6-31 + G(d)//AM1 and contribution of atoms to HOMO and LUMO.



Scheme 2 One of the possible reduction mechanisms for CTP on HMDE.

energies, reduction of these should take place at different potentials and this investigation does not meet our results. In fact, as could be seen in Figs. 1B and 2C there is a splitting of peak and this may be evaluated as two peaks. But this splitting disappears on scan rates higher than 0.2 V/s and it is considered as adsorption-effected splitting. If the reduction of two same groups with different environments and different location and of course different relative energies is thought to be possible at the same potential, and this splitting could be considered as two different peaks than it is plausible to propose the reduction of two etheric or more possibly two carbonyl oxygen to corresponding alcohols as reduction mechanism. Otherwise, there is only one group possible to be reduced with participation of four electrons and four protons and this mechanism was shown in Scheme 2 with support of similar mechanisms in the literature (Jain et al., 2007, 2008) although it is not met our theoretical investigations.

4.3. Voltammetric determination of CTP

In an effort to develop a voltammetric method for CTP determination, quantitation of peak current resulting from the reduction on HMDE and oxidation on GCE were examined for 2.0 μM CTP solution. Square-wave voltammetric (SWV) and differential pulse voltammetric (DPV) techniques were applied first without using stripping mode. In such studies, SWV method was found to be more suitable and reproducible than DPV for both electrodes, to get more sensitive methods, square-wave anodic adsorptive stripping voltammetry (SWAAdSV) on GCE and square-wave cathodic adsorptive stripping voltammetry (SWCAdSV) on HMDE were applied.

4.3.1. Optimization of variables

Nature of supporting electrolyte affects the peak response of the CTP. Thus, various electrolytes, such as BR, phosphate and acetate buffer solutions were examined to find the optimum conditions for quantification. BR gave the highest peak current and better peak shape than other media, therefore, BR was selected for further studies. The effect of pH was also investigated and results for pH were given in Section 4.1.1.

For tested techniques, variation of peak current and its shape with instrumental conditions such as frequency (f), scan increment (ΔE_i), pulse height (ΔE), step increment (ΔE_i), accumulation time (t_{acc}), and accumulation potential (E_{acc}) was investigated using 2.0 μM CTP in a BR at optimum experimental conditions. As a result, optimum instrumental parameters were found as follows: f = 25 Hz, ΔE_i = 2 mV, pulse width 0.01 s and ΔE = 65 mV, and as a result for accumulation optimization, 0.25 V and 90 s for GCE and −0.45 V and 60 s were found optimal for HMDE.

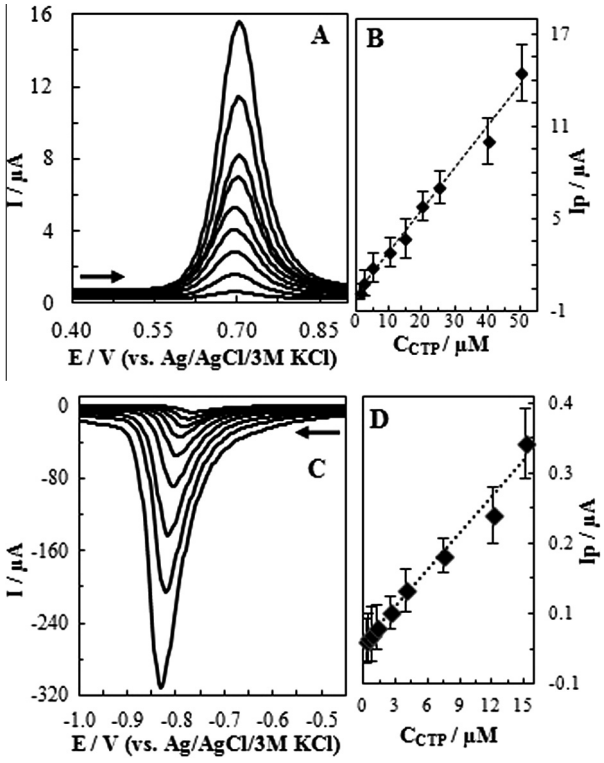


Figure 6 SWAdSVs of CTP solutions with various concentration in 0.04 M BR, f = 25 Hz, ΔE_i = 2 mV, pulse width 0.01 s and ΔE = 65 mV, on (A) GCE, pH = 4.0 with accumulation time of 90 s at 0.25 V, (B) calibration graph, concentrations from lower to higher: 1.0, 2.5, 5.0, 10.0, 15.0, 20.0, 25.0, 40.0, 50.0 μM, linear (C) HMDE, pH = 6.0 with accumulation time of 60 s at −0.45 V, and (D) calibration graph, concentrations from lower to higher: 0.15, 0.35, 0.65, 1.20, 2.45, 3.85, 7.35, 12.0, 15.0 μM.

4.3.2. Method validation

The proposed voltammetric methods were validated investigating the following parameters: Linearity range, sensitivity, limits of detection (LOD) and quantitation (LOQ), accuracy, reproducibility and repeatability according to (ICH; Al-Ghamdi and Hefnawy, 2012; Elqudaby et al., 2013; Pamuk et al., 2013; Zorluoğlu et al., 2013).

Linearity was checked by preparing more than ten standard solutions of CTP with different concentration levels for each electrode. Five serial measurements were taken for each concentration and subsequent to evaluation of the required statistical test (Q-test) for 95% confidence level; the average was used as a peak current of related concentration. Oxidation peak current on GCE was found to change linearly with

Table 1 Validation parameters of proposed methods.

Validation parameter	GCE[a]	HMDE[b]
Linearity range (μM)	1.0–50.0	0.15–15.0
Slope of calibration curve (AL/mol)	0.273	0.017
Intercept (μA)	0.16	0.01
SD[c] of regression (μA)	0.52	0.01
SD of slope (μA L/mol)	0.011	0.001
SD of intercept (μA)	0.021	0.00017
Limit of detection (LOD) (μM)	0.24	0.03
Limit of quantification (LOQ) (μM)	0.80	0.10
Determination coefficient (R^2)	0.9892	0.9829
Within-day repeatability of peak current (RSD)[d]	7.75	5.87
Between-day repeatability of peak current (RSD)	12.5	8.23
Within-day repeatability of peak potential (RSD)	2.68	1.25
Between-day repeatability of peak potential (RSD)	4.56	2.79

[a] GCE: Glassy carbon electrode.
[b] HMDE: Hanging mercury drop electrode.
[c] SD: Standard deviation .
[d] RSD: Relative standard deviation of 5 serial measurements.

Table 2 Results of proposed methods for Spectracef® tablets.

	Nominal value (mg)	Calculated values (mg)	Recovery[a] (%)	RSD (%)
GCE	200	189; 195; 202; 215; 223	102.4 ± 8.7	6.9
HMDE	200	185; 192; 205; 212; 226	102.0 ± 10.1	8.0

[a] Value = average ± $ts/\sqrt{N}$ (N = 5 and at 95% confidence level).

Table 3 Results of proposed methods for spiked human serum.

Added concentration (μM)	Calculated concentration (μM)	Recovery[a] (%)	RSD (%)
HMDE			
0.35	0.37	99.2 ± 11.6	9.4
1.50	1.65		
3.50	3.0		
6.0	5.85		
12.0	11.65		
GCE			
2.0	2.2	102.5 ± 9.5	7.5
8.0	7.65		
19.0	20.3		
28.0	26		
42.0	45		

[a] Value = average ± $ts/\sqrt{N}$ (N = 5 and at 95% confidence level).

CTP concentration between the range of 1.0 and 50.0 μM (Fig. 6A and B) when optimum instrumental and experimental variables were used and the linear relation between the peak current and CTP concentration was found to be expressed as given in Eq. (5):

$$Ip/\mu A = 0.16(\pm 0.02) + 0.27(\pm 0.011)\, C_{CTP}/\mu M; \quad (R^2 = 0.9892) \tag{5}$$

Reduction peak current on HMDE was found to change linearly with CTP concentration between the range of 0.15–15.0 μM (Fig. 6C and D) and the linear regression equation between the peak current and CTP concentration was found as given in Eq. (6):

$$Ip/\mu A = 0.01(\pm 0.0002) + 0.017(\pm 0.001)\, C_{CTP}/\mu M; \quad (R^2 = 0.9829) \tag{6}$$

The good linearity of the calibration graphs and negligible scatter of the experimental points (Fig. 6B and D) are clearly evident from the coefficient of determination (R^2).

Slope of related calibration equation was considered to be the sensitivity ($S = dI/dC_{CTP}$) of proposed method and calculated to be (0.27 ± 0.011) μA/μM for GCE and to be (0.017 ± 0.001) μA/μM HMDE.

Calibration parameters were assessed in least-square approach and results were given in Table 1 with repeatability values as well as values of LOD and LOQ calculated using equations given in the literatures (Taşdemir et al., 2012; Pamuk et al., 2013; Zorluoğlu et al., 2013). As could be seen in Table 1, method proposed for GCE has coefficient of determination (R^2) higher than 0.98. Repeatability and reproducibility of peak current and peak potential were found to be satisfactory for 2.0 μM CTP. In case of HMDE, method has R^2 higher than 0.98 and repeatability and reproducibility of peak current were better when compared to GCE because of surface properties of mercury drop. Proposed methods on both GCE and HMDE are advisable to use for pharmaceutical preparations and biological fluids.

4.3.3. Determination of CTP in tablets and spiked serum

In order to evaluate the applicability of the proposed methods to pharmaceutical preparations CTP was determined in Spectraceft® tablets. As shown in Table 2, mean results of each application for both electrodes lie around 102% (with RSD less than 10.0%) for tablet recovery. These results indicate the validity of proposed methods.

Recovery studies in spiked human serum samples were also performed. In these applications, voltammetric base line for CTP-free serum samples in BR solution was taken and no voltammetric signal in the potential range of CTP was found. It was concluded that there is no interference effect of any potential species found in human serum. As could be seen in Table 3, recovery values are around 100%. The differences between spiked and calculated concentrations are insignificant at 95% confidence level.

5. Conclusion

Electrochemical characteristics of CTP on GCE and HMDE with the help of ab-initio calculations were studied for the first time. The adsorptive stripping voltammetric techniques have been shown to be excellent for the determination of CTP in different samples. The use of electroanalytical measurements for determination of pharmaceutical compounds has increased greatly in recent years. In the present study, bare GCE and HMDE were used for the measurement of CTP. The entire analytical procedure to the determination was simple and convenient and completed in several minutes without needing any tedious sample preparation step and sophisticated instrumentation. A sensitivity of (0.27 ± 0.011) μA/μM and (0.017 ± 0.001) μA/μM obtained for GCE and HMDE, respectively. Low detection limit of 0.24 and 0.03 μM was achieved for GCE and HMDE. In further studies preparation of modified and composite electrodes will be taken place to achieve reliable results and to avoid the usage of HMDE for lower detection limits. Besides their determinations, redox properties and electrochemical parameters of drug molecules may be of critical importance in understanding the mechanism of action against their target/related organs.

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