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Boron-doped Diamond Film Electrode as Voltammetric Sensor for Cetirizine

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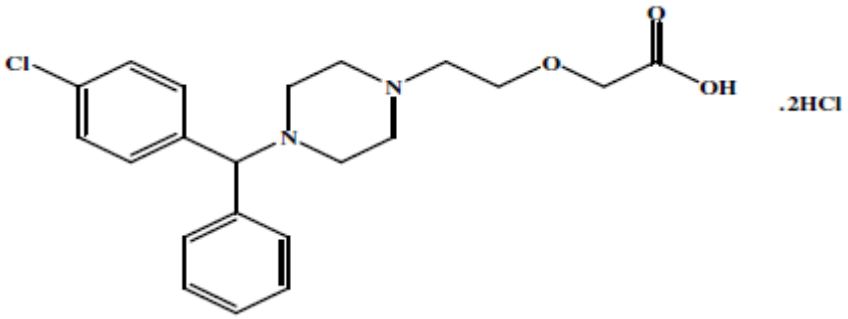
Electrochemical behaviour of cetirizine on bare boron-doped diamond electrode was investigated by cyclic voltammetry in supporting electrolytes with various values of pH. Signal of cetirizine is strongly affected by pH value of media. It was found that cetirizine provides one well developed irreversible oxidation peak at the potential of 1 V vs. Ag/AgCl in phosphate buffer solution (pH = 8) and no reduction peak. Oxidation process of cetirizine is limited by diffusion and involves equal number of electrons and protons. Kinetics of charge transfer was characterized by estimation of basic kinetic parameters as formal potentials (1.310 – 0.821 V), charge transfer coefficients (0.18 – 0.30) and standard heterogeneous rate constants ($2.3 – 1.4 \times 10^{-4}$ cm s^{-1}). Analytical performance of this reaction was examined by optimized differential pulse voltammetry. Rather low detection limit of 1.6×10^{-8} M was achieved. This value is significantly lower than on glassy carbon electrode. The practical applicability of proposed sensing platform was confirmed by analysis of pharmaceutical preparates and human urine as typical real samples.

Keywords: cetirizine, boron-doped diamond electrode, voltammetry, pharmaceuticals, urine

1. INTRODUCTION

Cetirizine dihydrochloride (CTZ), (±) - [2- [4- [(4-chlorophenyl)phenylmethyl] -1- piperazinyl] ethoxy]acetic acid, dihydrochloride (Scheme 1A) [1] is carboxylated metabolite of hydroxyzine and belongs to the second-generation class of antihistamines based on piperazine. Due to its structure CTZ negligibly enters into the central nervous system (CNS). It has less anticholinergic side effects (dry

mouth and sedation) in comparison with other antihistamines [2]. Cetirizine as a potent histamine H_1-receptor antagonist with marked affinity for peripheral histamine H_1-receptors has some antiallergic effects. Furthermore CTZ inhibits histamine release and eosinophil chemotaxis during the secondary phase of the allergic response [3]. This drug is used for the treatment and prevention of chronic and seasonal allergic rhinitis as well as for allergic urticaria. In addition, it was also found to be well tolerated by patients with asthma. Cetirizine as pharmaceutical is available in tablets, syrup and various oral drops [4].



Scheme 1A. Chemical structure of cetirizine dihydrochloride (CTZ).

Drug analysis plays very important role in pharmaceutical quality control, therefore it is necessary to develop simple, sensitive and selective methods. For the determination of cetirizine several analytical methods have been proposed. The most commonly used are separation techniques, because they are suitable for the determination of CTZ in human plasma. As example may serve high-performance liquid chromatography coupled with tandem mass spectrometric detection (HPLC-MS/MS) with detection limit of 3.3×10^{-10} M [5]. Very sensitive and selective is high performance thin layer chromatography (HPTLC) with LOD of 5.2×10^{-10} M [6]. In addition isocratic reversed phase liquid chromatography (RP-HPLC) with LOD of 8×10^{-7} M [7, 8], and capillary electrophoresis (CE) where LOD was estimated to be 6.5×10^{-9} M [9] may be used for the determination of above mentioned analyte in biological samples and pharmaceutical preparations.

As for optical analytical techniques, Gowda at al. have been described two simple and sensitive extractive spectrophotometric methods based on the formation of complexes between CTZ and bromocresol purple (BCP) or bromophenol blue (BPB) soluble in chloroform at pH of 2.64. These methods have linear responses in concentration range of 2.2×10^{-6} - 3.5×10^{-5} M for BCP and 3.2×10^{-6} – 4.5×10^{-5} M for BPB [10]. Next, spectrophotometric technique involving first derivative (1D) ultraviolet spectrophotometry was applied for determination of cetirizine in pharmaceuticals at 217 and 335 nm respectively. The detection limit of 2.4×10^{-7} M for CTZ was obtained [11]. Cetirizine is possible to determine also indirectly by inductively coupled plasma-atomic emission spectrometric (ICP-AES) method based on the reaction of CTZ with BiI_4^- in an acidic aqueous solution forming a precipitate (LOD = 2.1×10^{-5} M) [12]. However, separation and spectrophotometric methods are time consuming, laborious, and require sample pretreatment as well as expensive devices and solvents.

On other hand, electrochemical methods are simple, cheap, fast, sensitive and selective allowing direct measurements with minimal sample pretreatment. We may mention an electrochemical approach for CTZ detection based on carbon paste electrode modified with multiwalled carbon nanotubes and platinum nanoparticles (MWCNT-PtNPs) nanocomposite which has been proposed for simultaneous voltammetric determination of paracetamol (PCT), cetirizine (CTZ) and phenylephrine (PHE) in pharmaceutical formulations, blood serum and urine samples. The electrochemical oxidation of these drugs has been examined in phosphate buffer solution (pH=5.5). The detection limits were estimated to 2.79×10^{-8} M, 5.86×10^{-8} M and 2.83×10^{-8} M for PCT, CTZ and PHE respectively [13]. A multi-walled carbon nanotubes (MWCNT) film-modified glassy carbon electrode (GCE) was also applied for the cetirizine analysis in pharmaceutical and urine samples. Oxidation of cetirizine was irreversible with peak potential shifted from 1.17 V for bare GCE to 1.08 V in the case of MWCNT-modified GCE. The voltammetric signal was found to be linear in the concentration range from 5.0×10^{-7} to 1.0×10^{-5} M whereas detection limit reached value of 7.07×10^{-8} M for 180 s accumulation [14]. The electrochemical oxidation of cetirizine dihydrochloride was also studied similarly on bare glassy carbon (GC) electrode using cyclic voltammetry and differential pulse voltammetry and the lowest value of LOD was 4.3×10^{-6} M [15].

Rizk et al. proposed potentiometric method for determination of cetirizine using CTZ membrane on conventional (CE) and carbon paste (CPE) electrode (LOD = 5×10^{-6} M for CE and LOD = 5×10^{-6} M for CPE) with very good selectivity [1]. The potentiometric sensor based on molecularly imprinted polymer (MIP) added into carbon paste was successfully employed for analysis of above mentioned analyte in tablets in biological fluids with relatively low detection limit of 7.0×10^{-7} M [16].

Because only a few electroanalytical methods dealing with cetirizine detection have been published up to date in the literature, we decided to develop a new method for determination of cetirizine using boron-doped diamond (BDD) as chemically unmodified highly stable electrode material. It has extremely low background signal ensuring high sensitivity of voltammetric measurements. Consequently we would like to show boron-doped diamond electrode (BDDE) as fast, cheap and environmentally acceptable voltammetric sensor enabling a simple detection of CTZ in common samples containing cetirizine.

2. EXPERIMENTAL

2.1. Instrumentation

All voltammetric experiments were conducted in three electrode arrangement in a glass electrochemical cell maintained at 25.0 ± 0.5 °C. Ag/AgCl (3 M KCl) reference electrode and counter platinum macroelectrode with area of 1 cm^2 were used. Commercially available bare boron-doped diamond film electrode with microcrystalline structure inserted in polyetherether ketone (PEEK) tube with a diameter of 3 mm, thickness of 0.5 mm, resistivity of 0.75×10^{-3} Ω m and boron doping level of 1000 ppm (or 10^{20} boron atoms cm^{-3}) (Windsor Scientific Ltd., UK) served as working electrode. The

surface of BDDE was cathodically pretreated using the potential of -3 V during 300 s in 0.6 M H_2SO_4 and rinsed with distilled water. Autolab PGSTAT 302N (Metrohm Autolab BV, The Netherlands) controlled by NOVA 2.0 software was employed for all electrochemical measurements. The measurements were performed by cyclic voltammetry (CV), linear sweep voltammetry (LSV) and differential pulse voltammetry (DPV) in phosphate buffer solution. In the first set of electrochemical experiments cyclic voltammetry with a scan rate of 50 mV s^{-1} and LSV using scan rates of 10-300 mV s^{-1} were used. DPV was optimized before applying and subsequently measurements were realized with scan rate of 25 mV s^{-1}, modulation amplitude of 40 mV and modulation time of 40 ms.

2.2. Chemicals

All chemicals were of p. a. purity. All aqueous solutions were prepared using deionized water (EUROWATER, Bratislava). As supporting electrolyte served 0.1 M phosphate buffer solution (PBS) with pH value of 7 prepared from 0.2 M $Na_2HPO_4.12H_2O$ (LACHEMA, Brno) and 0.2 M $NaH_2PO_4.H_2O$ (LACHEMA, Brno). The value of pH of this media was adjusted by NaOH (0.2 M, CENTRALCHEM, Bratislava) and H_3PO_4 (0.2 M, LACHEMA, Brno).

A standard stock solution of 2×10^{-2} M cetirizine dihydrochloride was used for preparation of other solutions with various concentrations by dilution with deionized water. 20 mL of supporting electrolyte was pipetted into electrochemical cell as well as various additions of CTZ solution. Before each voltammetric measurement solutions were bubbled with pure N_2 for 10 minutes. The known amounts of cetirizine were spiked to human urine without CTZ and standard addition calibration plot method was applied for determination its amount.

2.3. Sample analysis

Commercially available pharmaceutical preparations and human urine were analyzed as real samples. One tablet containing CTZ - Zodac (Zentiva, CZE) and Alerid (Cipla UK Ltd., GB) was powdered in a mortar and dissolved in water. Subsequently the solution was filtered after 10 min of sonification and the filtrate was transferred into 50 mL volumetric flask. From this solution 0.5 mL was added into electrochemical cell and filled with supporting electrolyte to 25 mL. The sample of fresh urine (2.5 mL) was diluted with supporting electrolyte to the volume of 25 mL and then directly analyzed.

3. RESULTS AND DISCUSSION

3.1. Electrochemical behaviour of CTZ on bare BDDE

At first, we investigated voltammetric behaviour of cetirizine on bare boron-doped diamond electrode by cyclic voltammetry in various supporting electrolytes based on PBS with pH values of (2, 4, 6, 7, 8). From cyclic voltammograms on the Fig. 1 it was noticed one oxidation peak for CTZ in

PBS (pH = 8) at the potential of 1 V but no reduction peak. The highest anodic signal of cetirizine was obtained in 0.1 M phosphate buffer solution with pH = 8 at the scan rate of 50 mV s^{-1}. Based on these observations the electron transfer for cetirizine oxidation on BDDE is apparently irreversible. This observation is similar as on previously reported voltammetric sensors for cetirizine as carbon paste electrode modified with multiwalled carbon nanotubes and platinum nanoparticles (MWCNT-PtNPs-CPE) [13], glassy carbon electrode modified with multiwalled carbon nanotubes (MWCNT-GCE) [14], bare GCE [15] and carbon black modified glassy carbon electrode (CB-GCE) [21]. As for peak potential for anodic oxidation of cetirizine a slight higher values (1.05 -1.08V vs. Ag/AgCl) were reached, but in the case of sensor based on time consuming chemical modification including platinum nanoparticles synthesis [13] this value is only slightly decreased (0.95V vs. Ag/AgCl).

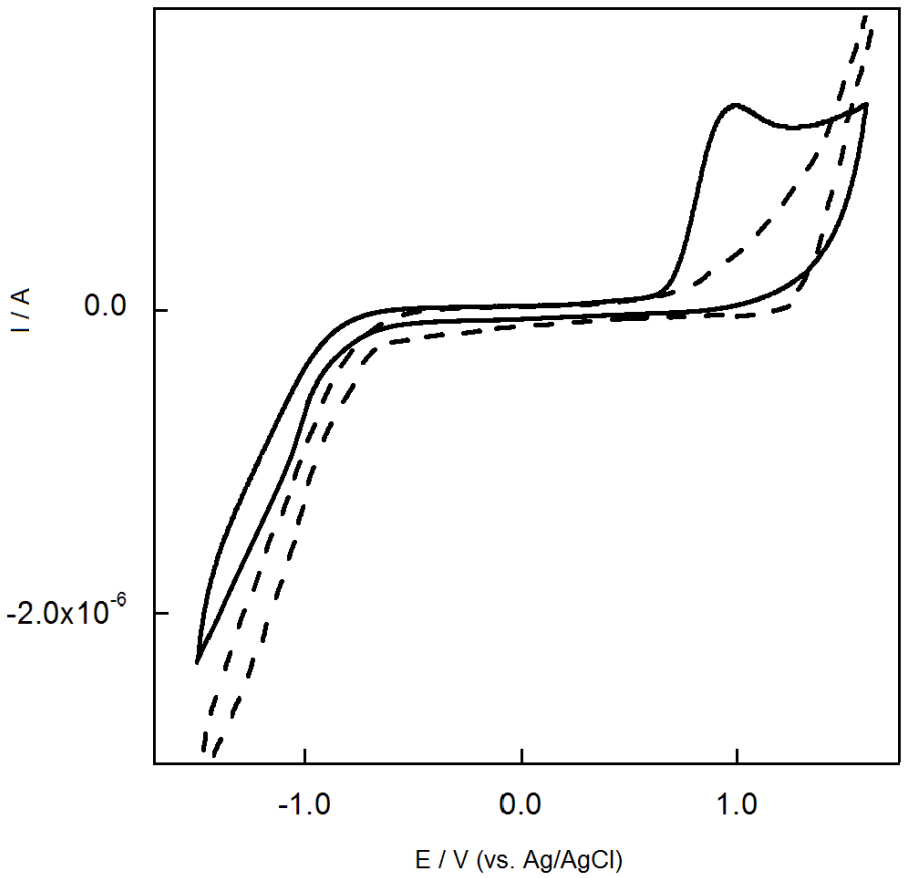


Figure 1. Cyclic voltammograms of 1×10^{-3} M cetirizine solution in 0.1 M PBS (pH = 8) (solid line) and alone PBS (pH = 8) (dashed line) on BDD electrode at scan rate of 50 mV s^{-1}.

3.2. Effect of scan rate and pH

Linear sweep voltammograms for CTZ at various scan rates (10-300 mV s^{-1}) are depicted in Fig. 2A. It was observed that anodic peak currents (I_p) increase with rising value of scan rate. Peak current magnitudes are linearly proportional to the square root of scan rate ($v^{1/2}$) in the studied range (Fig. 2B), the parameters of this dependence are: A = -3.487×10^{-7} A, $s_A = 4.11 \times 10^{-8}$ A,

B = 2.767 × 10^{-7} A s mV^{-1}, s_B = 3.99 × 10^{-9} A s mV^{-1}, R^2 = 0.999. They are indicating that the oxidation of cetirizine on boron-doped diamond electrode is limited by diffusion while adsorption or other surface processes are negligible, as in the case of bare GCE electrode [15], while for chemically modified voltammetric sensors [13, 14, 21] also adsorption takes place in the anodic oxidation process of cetirizine.

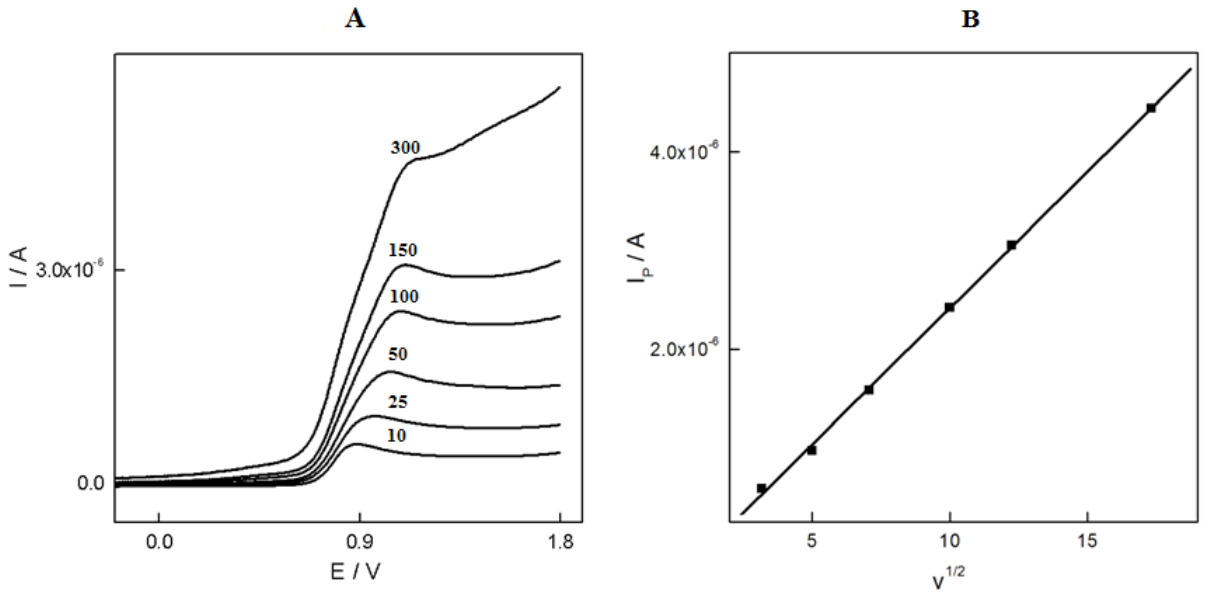


Figure 2. (A) Linear sweep voltammograms of 1 × 10^{-3} M cetirizine solution in 0.1 M phosphate buffer solution (pH = 8) on BDD electrode at scan rate of 10, 25, 50, 100, 150, 300 mV s^{-1}. (B) The dependence of anodic peak current I_p vs. $v^{1/2}$ for 1 × 10^{-3} M cetirizine solution

In Figure 3A baseline corrected LSV – voltammograms of CTZ oxidation at various pH values of supporting electrolyte are displayed. From this figure it is evident that the oxidation peak potential was shifted towards the more negative values with increasing of pH value. This shift is typical for redox processes of organic molecules where protons taking part in electrode reaction and was noticed in the all cases of previous voltammetric sensors for cetirizine [13, 14, 15, 21]. Further, the effect of pH phosphate buffer solution on peak current magnitude was investigated using different voltammetric methods (LSV, DPV and CV). It was found that signal is influenced by pH of media and its magnitude changed variously whereas the maximal value was achieved in PBS with pH=8 [13], pH = 3 [14] and pH = 4 [21]. In our work anodic signal of CTZ growing with alkality of media to pH = 8, then it will be diminished and no signal was noticed in solutions with pH of 9 and 10 as observed also in ref. [15].

The dependence E_p vs. pH (Fig. 3B) was used for calculation of number of protons involved in cetirizine oxidation. It was found that relationship between peak potential and pH is linear with parameters: A = 1.544 V, B = -0.0662 V, s_A = 1.34 × 10^{-2} V, s_B = 2.3 × 10^{-3} V, R^2 = 0.998. The slope (B) of this dependence is given by formula:

$$B = -\frac{2.3026nRT}{zF} \quad (1)$$

where n is number of protons and z is number of electrons participated in electrochemical reaction, the other physical symbols are generally known.

This slope (0.066) of above mentioned dependence was close to the Nerstian value (0.059 V) and revealed that equal number of protons and electrons are involved in the oxidation of cetirizine on BDDE. From equation (1) it was calculated that 1.1 protons for one electron taking part in the electrooxidation of cetirizine which is in close agreement with result published in ref. [13] confirming that one electron and one proton participates in this process (Scheme 1B) forming cation-radical followed by radical dimerization. However NMR data shows also several minor oxidation products [21].

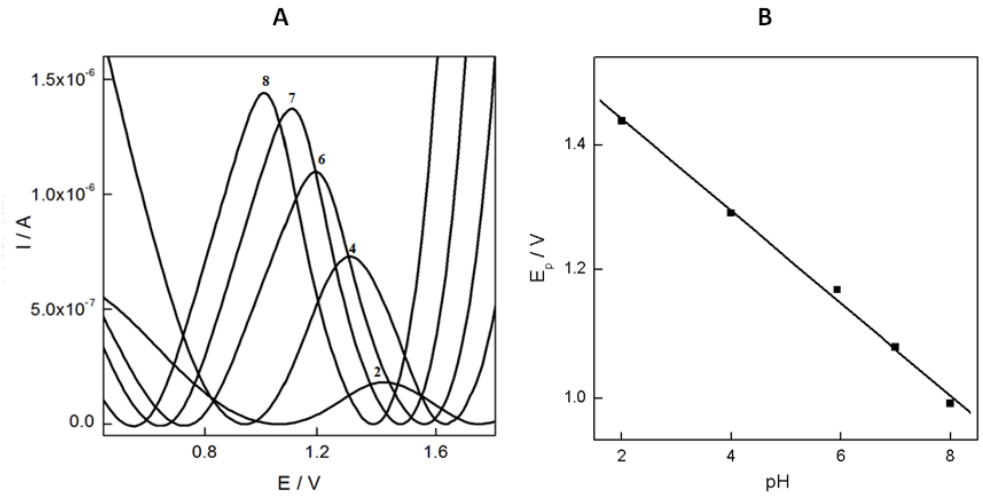
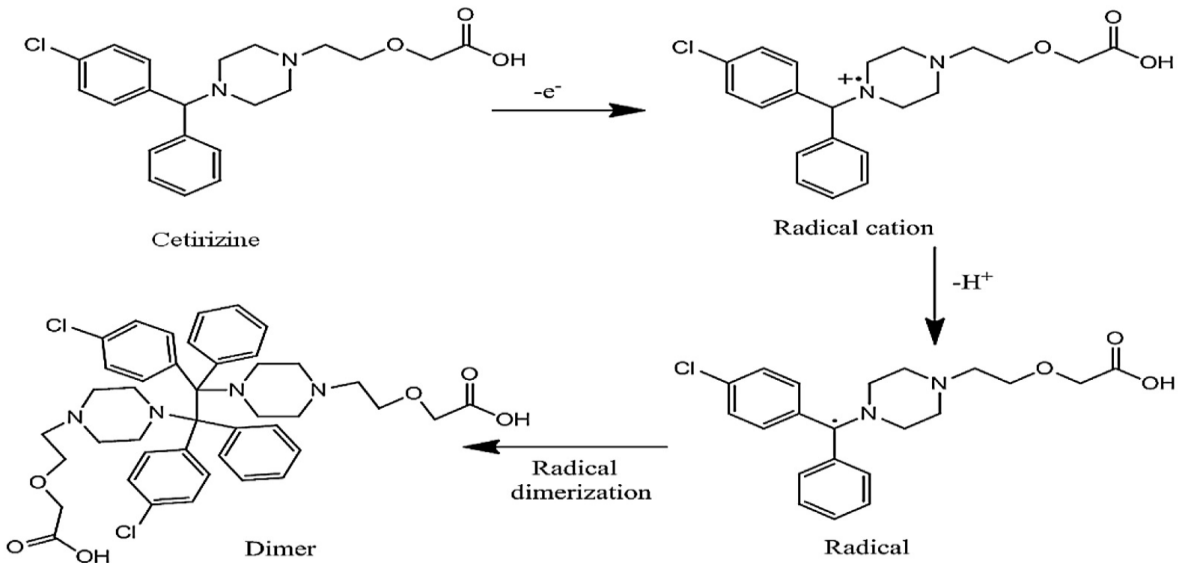


Figure 3. (A) Background corrected linear sweep voltammograms of oxidation of 1×10^{-3} M cetirizine solution measured at various pH values of 0.1 M supporting electrolytes (phosphate buffer solution with pH value of 2, 4, 6, 7, 8). Scan rate was 50 mV s^{-1}. (B) The dependence of anodic peak potential of 1×10^{-3} M cetirizine solution at various pH values of 0.1 M phosphate buffer solutions (pH = 2, 4, 6, 7, 8). Scan rate was 50 mV s^{-1}. Background was subtracted.



Scheme 1B. Mechanism of oxidation of CTZ [13].

3.3. Charge transfer characterization

Next, the kinetics of charge transfer for oxidation of cetirizine on BDD electrode in different media was studied by linear sweep voltammetry. The dependence of peak potential of CTZ in PBS with value of pH = 8 on scan rate is shown in Fig. 4. Anodic peak potential (E_p) rises rather linearly with an enhancement of scan rate but this growth is slower at higher scan rates with a slight curvature. This dependence was nonlinearly fitted according to this three parametric equation:

$$E_p = A + \frac{B\nu}{C + \nu} \quad (2)$$

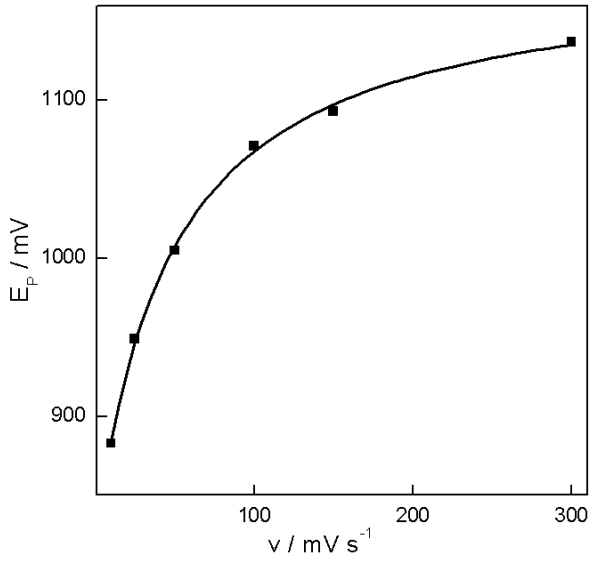


Figure 4. Dependence of LSV anodic peak potential of 1×10^{-3} M cetirizine solution in 0.1 M PBS (pH = 8) on scan rate (10, 25, 50, 100, 150, 300 mV s^{-1}). Results of nonlinear fitting: A = 0.821 V, s_A = 0.009 V, B = 0.364 V, s_B = 0.007 V, C = 0.048 V s^{-1}, s_C = 0.005 V s^{-1}, R^2 = 0.999.

This increase was also observed in work [14], but in this case different dependence E_P vs. log ν was used for charge transfer characterization according to Laviron´s theory.

Formal potential $E^{o\prime}$ corresponds to calculated potential for scan rate ν equal to zero (parameter A = $E^{o\prime}$, parameters B, C are empirical constants) [17]. In ref. [14] $E^{o\prime}$ was also found from the intercept of E_p vs. ν plot by extrapolating to the vertical axis at ν=0. From results summarized in Table 1 it is evident that the formal potential is in the range of 1.310 – 0.821 V and is shifted to more negative values with growing pH value. The similar value [14] of $E^{o\prime}$=0.998 was achieved on MWCNT-GCE, but in PBS at pH = 3

Table 1. Data characterizing the charge transfer for cetirizine oxidation on boron-doped diamond electrode for various supporting electrolytes with concentration of 0.1 M.

electrolyte	α	SD_α	$E^{0'}$(V)	SD_{E^0} (V)	k^0 (10^4 cm s^{-1})
A	0.18	0.01	1.310	0.003	2.33
B	0.20	0.01	1.157	0.005	2.22
C	0.25	0.02	1.000	0.010	2.18
D	0.30	0.02	0.821	0.009	1.40

Abbreviations: A-PBS pH = 2, B-PBS pH = 4, C-PBS pH = 6, D-PBS pH = 8.

For all supporting electrolytes charge transfer coefficients (α) according to the known equation were calculated [18]:

$$\left|E_p - E_{1/2}\right| = \frac{47.7}{\alpha z}\,\text{mV at } 25\,^{\circ}\text{C} \tag{3}$$

where $\left|E_p - E_{1/2}\right|$ is difference between peak potential and potential corresponding to halfheight of peak. IR drop is significant on BDD surface and causes a slight dependence of charge transfer coefficient on scan rate, so the voltammograms were IR corrected before each calculation [19]. As can be seen from Table 1 after this procedure the potential difference remains statistically constant and α values are statistically the same at each scan rate (10 – 300 mV s^{-1}). In article [14] α value was set to 0.5 and value αn, was calculated from the slope of E_p vs. log ν plot. This value was found to be equal 0.4549, and subsequently the interval for number of electrons n was calculated to be 0.9098-1.

Knowing formal potentials and charge transfer coefficients we also calculated the estimates of standard heterogeneous rate constants k^o in scan rate range of 10 – 300 mV s^{-1} for typical value of diffusion coefficient of cetirizine [20] in water D = 3.86 × 10^{-6} cm^2 s^{-1} according to this equation:

$$E_p = E^{o'} + \frac{RT}{\alpha zF}\left[0.78 + \ln\frac{D^{1/2}}{k^o} + \ln\left(\frac{\alpha zF\nu}{RT}\right)^{1/2}\right] \tag{4}$$

Physical sense of parameters $E^{o'}$, α, z and ν has been already mentioned above. Calculated k^o for all supporting electrolytes are in the order of 10^{-4} cm s^{-1} (Table 1). It was observed that with rising alkality of media peaks of CTZ are more wider and values of k^o are lower.

Standard heterogeneous rate constant k^o can be also determined from the intercept of the above mentioned dependence E_p vs. log ν with known $E^{o'}$. Calculated value k^o=3.951 × 10^{-3} cm s^{-1} may be found from Laviron equation. In the case of MWCNT-GCE [14] this value is ten times higher than on our unmodified electrode. On the base of these facts we can conclude, that charge transfer is faster on glassy carbon electrode in more acidic media of PBS with pH 3.

3.4. Differential pulse voltammetric experiments

Next, more sensitive differential pulse voltammetry was used for the investigation on analytical performance for cetirizine oxidation on BDD electrode. We optimized DPV parameters as modulation amplitude and modulation time influencing height and shape of oxidation peak. During this optimization every parameter was modified whereas other remained constant. First, we measured the dependence of peak height at different pulse amplitudes: 30, 40, 50 and 60 mV at constant modulation time (50 ms) and scan rate (25 mV s^{-1}). Modulation amplitude of 40 mV was determined as optimal with the best developed peak. Similarly we optimized modulation time from various values: 50, 40 and 60 ms with constant modulation amplitude 40 mV and 25 mV s^{-1} scan rate. We observed that with increasing of modulation time peak current decreased and the stable signal was achieved at 40 ms. The highest current response for oxidation of 1×10^{-5} M CTZ was reached at modulation amplitude of 40 mV, modulation time of 40 ms and scan rate of 25 mV s^{-1}.

At these optimal parameters anodic DPV voltammograms for various concentrations of cetirizine (Fig. 5A) were measured in the potential range of 0.6 - 1.4 V. The dependence of peak current on cetirizine concentration shows good linearity in studied concentration range of 6.7×10^{-8} - 5.4×10^{-7} M with following parameters: A = 4.10×10^{-9} A, s_A = 1.15×10^{-9} A for the intercept and B = 0.217 A M^{-1}, s_B = 3.4×10^{-3} A M^{-1} for the slope, R^2 = 0.999 (Fig. 5B). The detection limit calculated according to $3s_A/B$ criterion was found to be 1.6×10^{-8} M. This value is comparable with values found for formerly published techniques for cetirizine detection (Table 2). The relative standard deviation less 4% calculated from ten consecutive runs shows good repeatability of measurements.

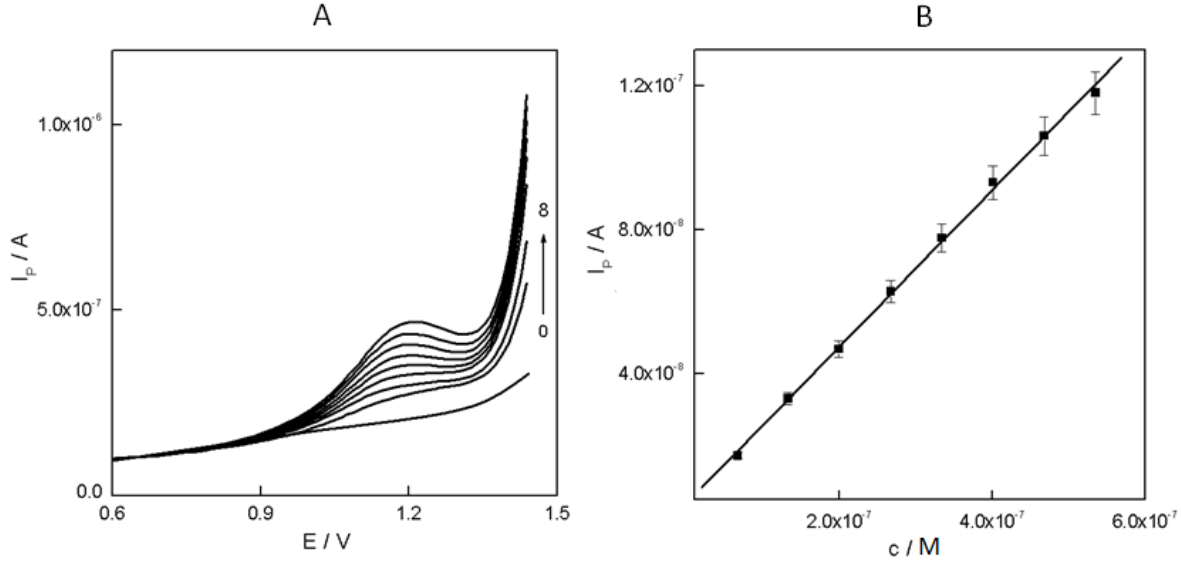


Figure 5. (A) Differential pulse voltammograms for 1 µL of 1×10^{-5} M CTZ additions in 0.1 M phosphate buffer solution (pH = 8). Concentrations of CTZ: (0) 0, (1) 6.7×10^{-8}, (2) 1.3×10^{-7}, (3) 2.0×10^{-7}, (4) 2.7×10^{-7}, (5) 3.3×10^{-7}, (6) 4.0×10^{-7}, (7) 4.7×10^{-7} and (8) 5.4×10^{-7} M of CTZ on BDD electrode. Parameters: scan rate 25 mV s^{-1}, modulation amplitude 40 mV and modulation time 40 ms. (B) Calibration curve for this experiment. Linearity was verified by F-test.

Comparison of the analytical performance of our method and other electrochemical methods for detection of cetirizine is presented in Table 2. Modification of bare electrodes based on carbon - glassy carbon electrode and carbon paste electrode results in lower detection limits and enhances their sensitivity. MWCNT-GCE showed higher sensitivity for cetirizine than GCE and allows to determine lower concentrations by cyclic voltammetry [14]. The widest linear dynamic range was obtained by potentiometric study [1] using carbon paste electrode, but with the highest LOD, which is one order higher than in the case of MIP-CPE in work [16]. Nevertheless, the lowest detection limit for cetirizine was achieved on boron-doped diamond electrode without chemical modification connected with differential pulse voltammetry presented in this paper.

Table 2. Electrochemical methods for the detection of cetirizine.

Method	Electrode	LOD (µM)	LDR (µM)	Sensitivity	Ref.
AdSDPV	MWCNT-PtNPs-CPE	0.0586	0.19 – 193	0.024 µA μM^{-1}	[13]
CV	MWCNT-GCE	0.0707	0.5 – 10	13.32 µA μM^{-1}	[14]
CV	GCE	4.3	20 – 100	0.375 A M^{-1}	[15]
DPV	GCE	4.5	20 – 100	0.0545 A M^{-1}	[15]
POT	CPE	7.0	7.0 – 100,000	57.4 mV	[1]
POT	MIP-CPE	0.7	1.0 – 10,000	28 ±0.9 mV	[16]
SWAdASV	CB-GCE	0.4	0.497 – 10.8	7,31 µA μM^{-1}	[21]
DPV	BDDE	0.016	0.067 – 0.54	0.217 A M^{-1}	This paper

Abbreviations: AdSDPV: adsorptive stripping differential pulse voltammetry, MWCNT-PtNPs: multiwalled carbon nanotube-platinum nanoparticles, CPE: carbon paste electrode, CV: cyclic voltammetry, GCE: glassy carbon electrode, DPV: differential pulse voltammetry, POT: potentiometry, MIP: molecularly imprinted polymer, SWAdASV: square-wave adsorptive anodic stripping voltammetry, CB: carbon black, BDDE: boron-doped diamond electrode, LOD: limit of detection, LDR: linear dynamic range.

3.5. Interference studies

In order to examine the selectivity of the proposed method, the effect of some interfering compounds such as glucose, tartaric acid, urea, uric acid, dopamine, ascorbic acid, citric acid, oxalic acid, 4-aminophenol, starch, tyrosine on peak current of 1×10^{-5} M CTZ solution was studied using DPV on bare boron-doped diamond electrode. The signal of CTZ has been statistically the same in 10-fold excess of glucose, tartaric acid, urea, ascorbic acid, tyrosine and 4-aminophenol. Citric acid, oxalic acid and starch did not interfere till 5-fold excess. The species such as Ca^{2+}, K^{+}, Mg^{2+}, Cl^{-} and NO^{3-} had no effect on peak current of CTZ in the ratio of 1:100. The most problematic species like uric acid and dopamine are oxidized at the potential of 0.5 V vs. Ag/AgCl and 0.66 V vs. Ag/AgCl respectively. The voltammetric signal of cetirizine remains non affected, because potential

corresponding to the cetirizine oxidation (1.0 V) is sufficiently positive, therefore these species did not interfere in 10-fold excess (Table 3).

In paper [13] voltammetric signal of 2×10^{-5} M cetirizine was interfered by ascorbic acid and 4-aminophenol above the ration of 1/8 and 1/15 on MWCNT-PtNPs-CPE. Other substances such as sucrose and gum acacia did not interfere till 10-fold excess, however glucose caused growth and citric acid with oxalic acid drop of CTZ signal to 10% on MWCNT-GCE [14] while the BDDE signal is not affected by these species. In potentiometric study [1] on carbon paste electrode no effect of lactose, maltose, talc powder, mannitol, carboxymethyl cellulose and magnesium stearate was found, and these compounds did not influenced of cetirizine response up to 10^4-fold excess.

Table 3. Influence of potential interferences on the voltammetric response of 1×10^{-5} M CTZ.

Interferent	Concentration (M)	Signal change (%)
glucose	1×10^{-4}	-0.20
tartaric acid	1×10^{-4}	+1.36
urea	1×10^{-4}	+2.40
ascorbic acid	1×10^{-4}	+0.86
tyrosine	1×10^{-4}	-0.59
4-aminophenol	1×10^{-4}	+1.84
uric acid	1×10^{-4}	-1.23
dopamine	1×10^{-4}	+0.97
citric acid	5×10^{-5}	-3.40
oxalic acid	5×10^{-5}	+0.38
starch	5×10^{-5}	-0.98
Ca^{2+}	1×10^{-3}	+1.73
K^{+}	1×10^{-3}	+2.05
Mg^{2+}	1×10^{-3}	-0.69
Cl^{-}	1×10^{-3}	+0.26
NO^{3-}	1×10^{-3}	-3.24

3.6. Model, spiked and real sample analysis

The proposed analytical method was validated by analysis of five model samples (Table 4). The mean of six parallel determinations does not statistically differ from given values and coverage interval for 95 % probability is also acceptable. In [14] known amounts of the drug in the range of 2×10^{-6} M to 8×10^{-6} M was added before analysis of CTZ formulations and recovery test by cyclic voltammetry with results 98.9 – 101.47% and RSD of 0.68%.was performed.

Next, we tested three human urine samples spiked with cetirizine. The recovery values (95 – 103%) show good accuracy and applicability of proposed method for real samples analysis (Table 5).

In previous literature, urine and blood serum samples were spiked with CTZ by standard addition method [13] and RSD values to 1.5% for urine and 0.7% in the case of blood serum were achieved. The recoveries were determined from drug free urine samples spiked with cetirizine (1×10^{-6} M to 8×10^{-6} M) in range 99.5-100.84 % [14]. In the case of CB-CPE reached higher value of recovery 96%-108% by SWAdASV method and RSD lower than 10% [21]. Potentiometric method based on MIP-CPE was applied for detection of cetirizine in spiked human serum as well as urine (5×10^{-6} M to 1×10^{-4} M) and recoveries are from the interval of 96.6-110.2% and 102-108% respectively confirming accuracy of proposed procedure [16].

Table 4. CTZ model samples analysis (6 parallel determinations).

CTZ (10^7 M)	CTZ found (10^7 M)[a]	SD (10^7 M)
1	1.2 ± 0.2	0.2
2	2.1 ± 0.3	0.3
3	2.9 ± 0.3	0.3
4	4.2 ± 0.3	0.3
5	4.6 ± 0.3	0.3

Method: DPV

[a] The coverage interval for 95 % probability: $\bar{x} \pm t_{n-1,\alpha} SD/n^{1/2}$ ($t_{5;0.05} = 2.0150$).

Table 5. Analysis of CTZ spiked human urine samples by DPV (n=6).

Added (μM)	Found (μM)[a]	SD (μM)	Recovery (%)
2	1.9 ± 0.1	0.1	95.0
4	3.9 ± 0.2	0.2	97.5
6	6.1 ± 0.3	0.3	101.7

[a] The coverage interval for 95 % probability: $\bar{x} \pm t_{n-1,\alpha} SD/n^{1/2}$ ($t_{5;0.05} = 2.0150$).

Table 6. Real sample analysis of CTZ (n=3).

Real sample	Found (mg)	SD (mg)	Declared by manufacturer (mg)	SD (mg)
Zodac (Zentiva, CZE)	8.9	1.0	10	-
Alerid (Cipla UK Ltd., GB)	10.8	1.0	10	-
Human urine*	5.5×10^{-7}	5×10^{-8}	5.3×10^{-7}**	3×10^{-8}**

Method: DPV

* all data in this row are in M

** determined by HPLC-UV as independent technique

As real samples served pharmaceutical formulations and human urine. The results obtained from real samples analysis (Table 6) are in correspondence with results declared by manufacturer as well as with data obtained by independent HPLC-UV method. In [14] determined content of CTZ in tablets Zyntec is in good agreement with content marked in the label with 98.5% recovery. Cetirizine was also analysed by potentiometry in other drugs – Cetrak, Tomazine, Epirizine and Zyrtec on carbon paste electrode and results were statistically identical with values obtained by spectrophotometric method (UV-VIS) [1].

4. CONCLUSIONS

Bare boron-doped diamond electrode was employed for the first time on investigation of electrooxidation of antihistamine drug, cetirizine in phosphate buffer solution. Oxidation of cetirizine on BDD electrode is irreversible process limited by diffusion connected with transfer of one electron and one proton. Charge transfer was characterized by formal potentials (1.310 – 0.821 V), charge transfer coefficients (0.18 – 0.30) and standard heterogeneous rate constants ($2.3 – 1.4 \times 10^{-4}$ cm s^{-1}). During analytical studies relatively low detection limit of 1.6×10^{-8} M for cetirizine was achieved by differential pulse voltammetry in 0.1 M PBS with pH value of 8 like optimal media for this determination. Proposed method was after validation successfully applied to cetirizine analysis in pharmaceutical formulations and human urine which served as real samples. This analytical platform based on bare boron-doped diamond electrode seems to be more sensitive than other electrodes based on bare materials and less complicated than voltammetric methods based on electrode chemical modification as well as potentiometry which allows higher times for the equilibrium establishment as in this case there is also higher risk of analysis error due to antilogarithmization of Nernstian response of potentiometric sensor.

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