Electrochemical determination of cefotaxime, a cephalosporin group drug, at a boron-doped diamond electrode

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ABSTRACT: In this study, electrochemical analysis of cefotaxime, one of the third-generation cephalosporins, the semi-synthetic antibiotic group of the β-Lactam family, with an anodic pre-treated boron-doped diamond electrode (APT-BDDE) were investigated in a wide pH range. The cyclic voltametric (CV) and square-wave voltametric (SWV) techniques were applied for the rapid, sensitive, cheap, simple, and precise detection of CEF. The compound yielded two well-defined oxidation steps (Ia=1.1; IIa=1.5 V) in acidic, neutral, and alkaline media by employing SWV. Experimental conditions, namely pH, modulation amplitude, step potential, frequency, interference, and effect of scan rate were optimized. By employing SWV, there was a linear dependence of the oxidation peak current at +1.1 V and CEF concentration in the range of 1.0-20.0 μg mL^{-1} (2.1×10^{-6} – 4.2×10^{-5} mol L^{-1}), with a detection limit of 0.22 μg mL^{-1} (4.6×10^{-7} mol L^{-1}) in 0.1 mol L^{-1} phosphate buffer solution (pH 2.5). The practical applicability of the proposed method was tested with the quantification of CEF in the drug formulation.

KEYWORDS: Cephalosporins; cefotaxime analysis; boron-doped diamond electrode; voltammetry; determination in drug formulation

1. INTRODUCTION

Antibiotics, which have provided great benefits to humanity, are powerful drugs that have been used for many years. Thanks to antibiotics, it is thought that the life expectancy of today's people is extended. The production of synthetically produced antibiotics is usually fungi. Cephalosporins are a group of antibiotics class drugs, which are quite numerous. The common structure in the main biochemical structure of Cephalosporins in the β-lactam group is 7-aminocephalosporinic acid. Cephalosporins are semisynthetic antibiotics of the β-lactam family [1,2]. β-Lactam antibiotics are most commonly used in human medicine due to their broad spectrum of antibacterial activity and low toxicity [3,4]. The presence of the methoxy-imino group in the cefotaxime (Figure 1, CEF) molecule is very important in terms of its chemical and electrochemical behavior. Cefotaxime (6*R*,7*R*)-3-(acetyloxymethyl)-7- [[(2*Z*)-2-(2-amino-1,3-thiazol-4-yl) -2-methoxyiminoacetyl] amino] -8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid; Pubchem) is used in the lower respiratory tract, urinary tract, gynecological infections, skin, and central nervous system infections [5,6].
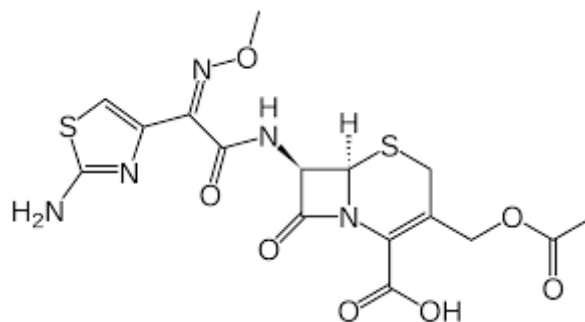

Figure 1. Chemical structure of cefotaxime

Boron-doped diamond electrode (BDDE), which has electrochemical properties compatible with graphite materials, is much more chemically inert and mechanically resistant to corrosion. It has a very low and stable background current and a very large potential range in both organic media and aqueous media [7-9]. These unique features have made BDDE a significant instrument in electrochemistry. The electrochemical properties of this electrode are extremely dependent on the surface termination. The activation process is generally performed in the presence of sulfuric acid [10,11]. The high negative potential (hydrogen generation site) cathodic pretreatment causes a reduction in the surface and thus hydrogen-terminated (H-terminated). The anodic pretreatment takes place at a high positive potential, causing the surface to be oxidized and terminated with oxygen (O-termination) [12,13]. Compared to other carbon-based electrodes, it has advantages in terms of fast response, working range, sensitivity, durability, and precision [14,15]. According to the literature research, many analytical methods such as high-performance liquid chromatography, spectrophotometric and potentiometric have been used for the determination of cefotaxime drug active ingredient. The few quantitative determination studies examining the electrochemical properties of the CEF active substance using various working electrodes are given in Table 1.

Table 1. Electrochemical studies of CEF using various working electrodes

Working Electrode	LOD (mol L^{-1})	References
HMDE	7.2×10^{-9}	[16]
GCE	2.8×10^{-7}	[17]
AuNPs/P$_{ARG}$/CPE	2.3×10^{-9}	[18]
ZnO /nanorod/GCE	2.0×10^{-7}	[19]

HDME; Hanging Mercury Drop Electrode, GCE; Glassy carbon electrode, AuNPs/Parg/CPE; Gold nanoparticle/polyarginine modified carbon paste electrode, ZnO /nanorod/GCE; Zinc oxide nanoparticle modified glassy carbon electrode

However, Feier et al. [22] evaluated to the determination of seven cephalosporins at high potential with BDD electrode. The influence on the analytical response of the cephalosporin side chains was investigated by this work. No detailed study has been found in the literature examining the electrochemical behavior of CEF on a BDD electrode. The aim of this work was to develop a faster, sensitive, cheaper, and selective voltammetric method and also to establish the experimental conditions, to investigate the voltammetric behavior of CEF using CV, SWV methods in the drug dosage form. There are no sample preparation and time-consuming extraction steps for the determination of CEF. The proposed method might be an alternative to the HPLC techniques.

2. RESULTS AND DISCUSSION

To understand the electrochemical reaction occurring on the BDD electrode surface, three-consecutive cyclic voltammograms of 80.0 µg mL^{-1} CEF in 0.1 mol L^{-1} phosphate buffer solution (pH 2.5, optimal conditions for analytical analysis, as will be shown later) were obtained in the anodic scan direction with a potential range of 0.5 to 1.8 V and a scan rate of 100 mV s^{-1} are given in Figure 2. When comparing the curves of solutions containing supporting electrolytes and 80.0 µg mL^{-1} CEF, it is observed that CEF gives two well-defined anodic oxidation peaks at approximately (Ia) +1.1 and (IIa) 1.50 V, and no reduction peaks are observed when scanning in the cathodic direction. Hence, it is clear that it is an irreversible reaction.
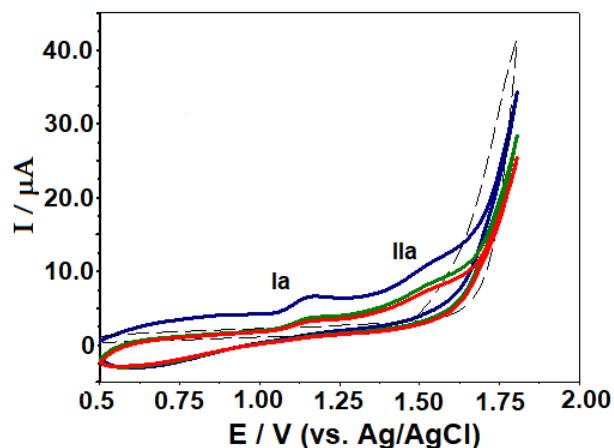
Figure 2. Three consecutives cyclic voltammograms of 80.0 µg mL^{-1} CEF on the BDD electrode in 0.1 mol L^{-1} phosphate buffer (pH 2.5). The scan rate, 100 mV s^{-1}, dashed line indicates supporting electrolyte solution.

To obtain information about the electrode reaction mechanism, the cyclic voltammograms of 80.0 µg mL^{-1} CEF were recorded by the CV technique in the range of 25 - 500 mV s^{-1} in 0.1 mol L^{-1} (pH 2.5) phosphate buffer solution. As seen in the equations given below, there is a linear relationship between the potential scan rate and the peak current intensity (1), as well as the linear relationship between the logarithm of the scan rate and logarithm of the peak current (2), with a slope of less than 0.5, indicating that the electrochemical reaction of the CEF is diffusion-controlled.

$$i_p \, (\mu A) = 0.014 \, v \, (mV \, s^{-1}) + 3.0755, \, r = 0.994 \quad (1)$$

$$\log i_p \, (\mu A) = 0.395 \log v - 0.0988, \, r = 0.997 \quad (2)$$

In order to ascertain the electron number (n) involved in CEF oxidation process at BDD electrode, the n value was determined by CV voltammogram using the equation $\Delta E_p = E_p - E_p/2 = 47.7 mV / \alpha n$ [20,47], where E_p is peak potential, $E_p/2$ is half-peak potential, α is the charge transference coefficient (generally, assumed as 0.5 for totally irreversible system) and n is the number of electrons. Using the cyclic voltammogram obtained for CEF oxidation at 100 mV s^{-1} the value of $E_p - E_p/2$ was 71.0 mV, so n value was found to be 1.34 (≈1). This result indicates that the irreversible oxidation of CEF involves one-electron per molecule at BDD electrode in 0.1 mol L^{-1} phosphate buffer solution (pH 2.5).

2.1. Effect of pretreatment on BDD electrode

The pretreatment step applied to the ordinary BDD electrode can have different effects on the responses of the electrochemically active species. To evaluate this effect, two pretreatment procedures were used. The first, the BDD electrode consists of an anodic polarization (APT-BDD) at +1.8 V for 60 seconds, and a second procedure consists of a cathodic polarization (CPT-BDD) at −1.80 V for 60 seconds (see the experimental section for the details of this pretreatment). Figure 3 depicts square wave voltammograms obtained from CPT-BDD and APT-BDD electrodes containing 30.0 µg mL^{-1} CEF in 0.1 mol L^{-1} phosphate buffer (pH 2.5). The Ia oxidation peak current showed a better result when the electrode cleaning was applied in the anodic direction (APT) compared to the application in the cathodic direction (CPT). In these studies, analytical analysis was evaluated according to Ia (both in terms of reproducibility and sensitivity). In this sense, in the following analysis, the oxidation peak was selected as Ia and anodic pretreatment was applied to obtain a clean, repeatable surface.
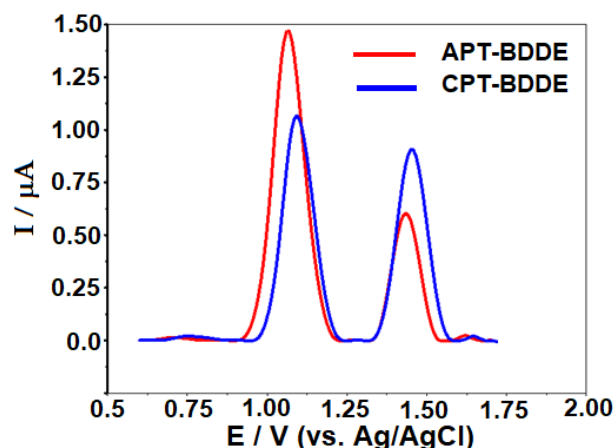
Figure 3. Voltamograms of 30.0 µg mL^{-1} CEF were obtained by different pretreatments in 0.1 mol L^{-1} phosphate buffer (pH 2.5). SWV parameters; Frequency: 25 Hz; amplitude: 30 mV, step potential: 8 mV.

2.2. Effect of solution pH

Further experiments were conducted to examine the effect of the supporting electrolyte at different pH values using SWV, which is a more sensitive pulse voltammetric technique than a CV to expand our knowledge of the electrochemical oxidation of CEF and find the optimum conditions for its sensitive determination. To obtain the best voltammetric results, in the following stage of experimental work, the effect of pH on oxidation peak current for the CEF molecule was investigated using the APT-BDD electrode in several supporting electrolyte solutions with different pH values. The electrochemical behavior of 30.0 µg mL^{-1} CEF in the potential range of 0.5 – 2.0 V was investigated using BR buffer solution from pH 2.0 to pH 10.0 (Figure 4A). As seen in Figure 4A, the Ia oxidation peak potential of the CEF compound shifts towards lower potentials with pH, but the IIa oxidation peak potential is at an almost constant potential.

In Figure 4B, the baseline-corrected SWV voltammograms are depicted in several supporting electrolyte solutions with different pHs for 30.0 µg mL^{-1} CEF. As can be seen in Figure 4B, the highest response was obtained in terms of the magnitude of the peak current [P$_{A1}$ (1.12 V; 1.48 µA), P$_{A2}$ (1.43 V; 0.55 µA)] in 0.1 mol L^{-1} (pH 2.5) phosphate buffer. Therefore, this medium was employed in the next steps for analytical studies.
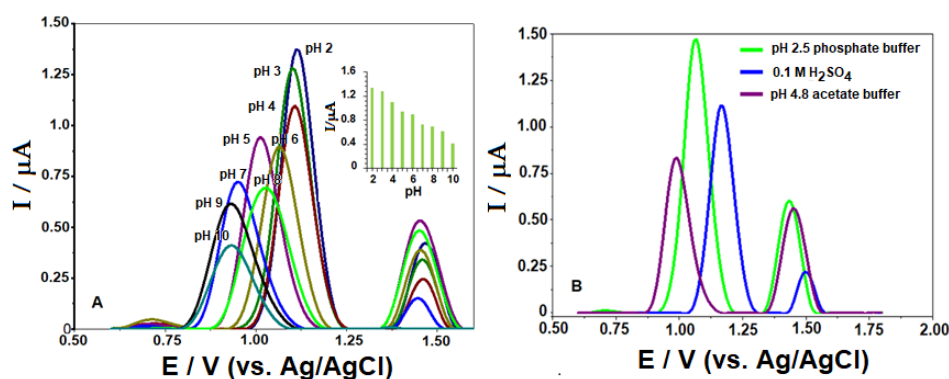

Figure 4. SW voltammograms of 30.0 µg mL^{-1} CEF in different supporting electrolytes. A: 0.1 mol L^{-1} BR buffer (pH: 2-10), B: 0.1 mol L^{-1} H$_2$SO$_4$, 0.1 mol L^{-1} acetate buffer (pH 4.8), and 0.1 mol L^{-1} phosphate buffer (pH 2.5). Electrode, anodically pretreated BDD electrode. SW voltammetry parameters; Frequency: 25 Hz; amplitude: 30 mV, step potential: 8 mV.

2.3. Optimization of SWV parameters

Next, the effect of pulse parameters was optimized such as step potential (ΔE_s), pulse amplitude (ΔE_{sw}), and frequency (f) on the voltammetric signal of CEF to obtain the best peak morphology and the highest sensitivity. These parameters of SWV were studied for a 30.0 µg mL^{-1} CEF solution. For this purpose, variables of the SW voltammetry technique were carried out in the range of 15-125 Hz to examine the optimum value

for frequency (constant ΔE_s of 8 mV, ΔE_{sw} of 30 mV). As a result, the optimum frequency value was chosen as 75 Hz. Besides, measurements were taken in the range of 2−16 mV to examine the optimum step potential value (constant *f* of 75 Hz and ΔE_{sw} of 30 mV) and 10 mV was chosen as the optimum value.
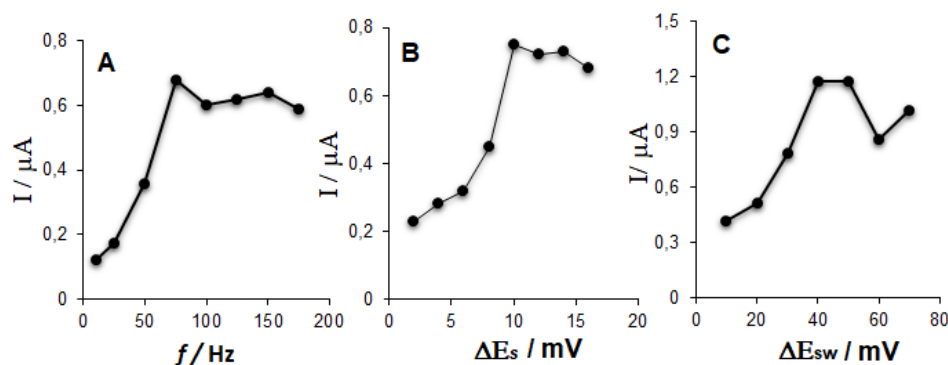

Figure 5. The graphs of 30.0 µg mL-1 CEF for the effect of pulse parameters. A: shows the plot of *i*p against the frequency (*f*), B: shows the plot of *i*p against the step potential (ΔE_s), C: shows the plot of *i*p against the pulse amplitude (ΔE_{sw}). Electrode, anodically pretreated BDD electrode.

Finally, the optimum amplitude was determined as 40 mV after evaluation of the results taken by measurements in the pulse amplitude range of 10−50 mV (constant *f* of 75 Hz and ΔE_s of 10 mV) (As can see in Figure 5A-B-C).

2.4. Application of CEF on a boron-doped diamond electrode

Analytical performance was tested after optimizing chemical conditions and instrumental parameters by measuring oxidation peak currents for Ia as a function of CEF concentration. Electrochemical oxidation of CEF was observed at APT-BBD in 0.1 mol L-1 phosphate buffer (pH 2.5). The sensitive and rapid electroanalytical technique, SWV, was developed for the determination of CEF in 0.1 mol L-1 phosphate buffer (pH 2.5). Ia's calibration curves are presented in Fig. 5 and the relevant analytical parameters are summarized in Table 1.

The Ia peak exhibited a more favorable linear concentration range considering our findings. Therefore, the Ia oxidation peak current was chosen for further experiments. Fig. 5 shows an elevation in oxidation peak currents achieved as the function of the added standard CEF solutions in the range from 1.0 - 20.0 µg mL-1 (2.1×10^{-6} – 4.2×10^{-5} mol L-1) in 0.1 mol L-1 phosphate buffer (pH 2.5) at 1.12 V. A linear relationship among the SW voltammograms obtained in response to the addition of CEF is as follows:

$[i_p$ (µA) = (0.0605±0.0005) C (µg mL-1) + (0.0183±0.002)], r=0.9988; where r the correlation coefficient, i_p is the oxidation peak current for Ia.

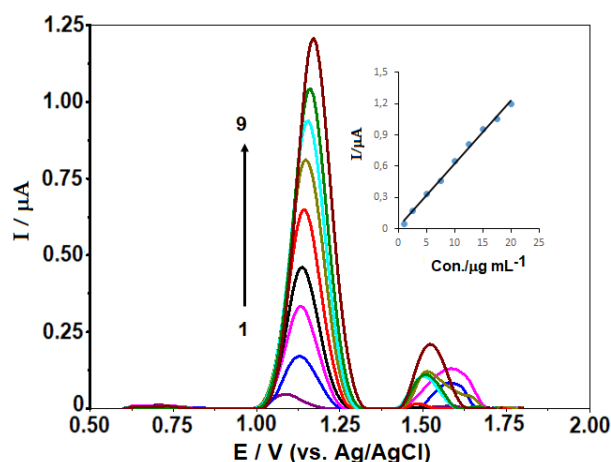**Figure 5.** SW voltammograms of CEF levels of (1-9) 1.0, 2.5, 5.0, 7.5, 10.0, 12.5, 15.0, 17.5 and 20.0 µg mL^{-1} in 0.1 mol L^{-1} phosphate buffer (pH 2.5). Inset shows the corresponding calibration curve for CEF. Square wave parameters (pulse amplitude, 40 mV, frequency, 75 Hz, step potential, 10 mV).

LOD and LOQ were found to be at 0.22 µg mL^{-1} (4.6×10^{-7} mol L^{-1}) and 0.73 µg mL^{-1} (1.53×10^{-6} mol L^{-1}), respectively. It should be mentioned once more that no reports on the electrochemical determination of CEF have been published. The simplicity of the current methodology allows it to be used with sufficient analytical precision for application to commercial products. To determine the method's precision, intra-day repeatability (seven measurements in one day) and inter-day reproducibility (five measurements over five consecutive days) were researched for 1.0 and 5.0 µg mL^{-1} CEF. The relative standard deviation (RSD) values were calculated as 2.7% and 3.1% (for 1.0 µg mL^{-1} CEF) and 4.6% and 5.3% (for 5.0 µg mL^{-1} CEF) respectively, which suggest that BDD electrode produces acceptable recoveries in CEF measurements.

The selectivity of the proposed method was also evaluated before the analysis of the samples. In particular, biological samples such as urine represent a complex biological matrix with greater interference potential. When the presence of uric acid, dopamine, and ascorbic acid in the presence of 5.0 and 10.0 µg mL^{-1} CEF was tested in the selectivity study, these compounds did not coincide with Ia. As can be seen from Figure 6, the voltammogram of ascorbic acid (d), dopamine (e), and uric acid (c), it could be concluded that the suggested method has adequate selectivity and may be used for biological matrices. In the voltammograms in Figure 6, dopamine was oxidized at 0.56 V (0.44 µA), uric acid at 0.78 V (1.11 µA), and ascorbic acid at 0.63 V (1.13 µA).
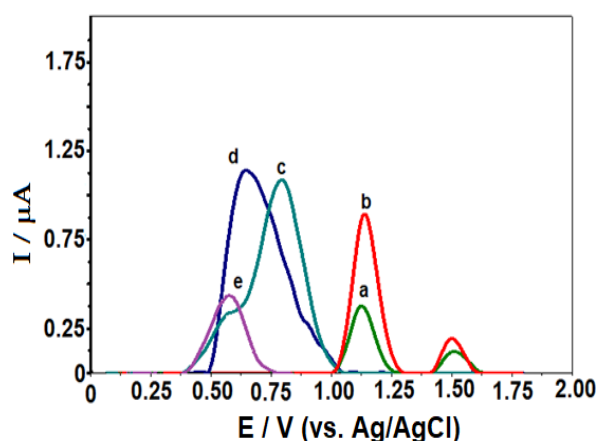

Figure 6. SW voltammograms of 5.0 (a) and 15.0 (b) µg mL^{-1} CEF, 2.0 µg mL^{-1} uric acid (c), 4.0 µg mL^{-1} ascorbic acid (d) and 2.0 µg mL^{-1} dopamine (e) in 0.1 mol L^{-1} phosphate buffer (pH 2.5). The variables are as in Figure 5.

In this part of the study, the developed methodology was applied to define the CEF content in a commercial pharmaceutical formulation (injectable solution). Sample solutions were prepared after dilution of the final solution to a target concentration within its workable linear range. Analysis of the sample was made using the calibration curve method from the relevant regression equation for 'Ia' as mentioned earlier.

After the necessary dilutions were made from the injectable sample, the standard addition method was applied to the sample taken into the supporting electrolyte solution. It can be concluded that the increase in peak current after each standard CEF addition is due to CEF oxidation of the oxidation peak seen at about +1.1 V. The linear equation obtained after plotting the concentration versus peak current values is [ip (µA) = (0.0649±0.004) C (µg mL^{-1}) + (0.1184±0.006)], r=0.9934. The % recovery and % BSS values obtained in this linear relationship are shown in table 2.

Table 2. Results of recovery and relative standard deviation of the pharmaceutical sample

Added (µg mL^{-1})	Founded (µg mL^{-1})	%Recovery ± %RSD
2.5	2.8	110±2
5.0	5.4	108±2
7.5	7.4	99±3

4. CONCLUSION

In this study, the electrochemical properties of cefotaxime, an antibiotic from the cefolosporin group, were investigated for the first time, using an anodic pre-treated BDD electrode, and a square wave voltammetric method was developed for its quantification. The sensitivity, selectivity, accuracy, reproducibility, and applicability of the developed voltammetric method were demonstrated by the findings. This developed method can be an alternative to the chromatographic and spectroscopic methods in the bibliography, by developing a cheap and sensitive method, which is fast and working with small volumes of sample, without the need for any pre-concentration process, as well as time-consuming separation processes.

5. MATERIALS AND METHODS

All chemicals were purchased from Sigma-Aldrich and Merck companies (Istanbul, Turkey). 0.1 mol L^{-1} Britton-Robinson (BR) buffer was used as a supporting electrolyte. The phosphoric acid (purity of 85%, boric acid, and acetic acid (glacial, 100%) were purchased from Merck companies. 0.1 mol L^{-1} phosphate buffer (pH 2.5 and 7.4), 0.1 mol L^{-1} acetate buffer (pH 4.8), 0.1 mol L^{-1} HNO$_3$ (purity of 65%), and 0.1 mol L^{-1} H$_2$SO$_4$ (purity of 95-97%), supporting electrolyte solutions were also used. Cefotaxime sodium salt were provided by Sigma (Istanbul, Turkey). CEF stock solution was prepared in methanol as 1000 µg mL^{-1} and stored at +4^{0}C when not in use. Experimental studies were carried out using ultrapure water (18.2 MΩ, Millipore Simplicity) at room temperature. Voltammetric studies and electrode characterization studies were performed using the electrochemical analyzer AUTO LAB TYPE III (GPES 4.9 software package (EcoChemie, Netherlands)). In the voltammograms obtained as a result of all square wave voltammetric experiments, the ground correction [baseline correction, Savitzky and Golay filter (level 2), peak width of 0.01 V) was made in the software program of the instrument. Boron doped diamond electrode (with a diameter of 3 mm and boron content of 1000 ppm, Windsor Scientific Ltd., UK) was used as the working electrode. Ag/AgCl electrode (3.0 mol L^{-1} NaCl; MF 2012, BASi®, USA) was used as the comparison electrode (reference electrode) and the platinum wire electrode (MW 1032, BASi®) was used as the auxiliary electrode (counter electrode). Electrochemical test cells (10 milliliters) are made of pyrex glasses, and the electrodes are contacted with the solution with the test cell cover with three-electrode inlets (C-3 Cell Stand; BASi®). There is a magnetic stirrer at the bottom of the assembly, and a magnet is used in cases where the solution medium is mixed. WTW, the in-lab pH 720 device was used for pH measurements. A commercial sample of Eqitax® injectable solution (Tüm - Ekip İlaç A.Ş, Turkey) was obtained from the local hospital. The required amount was taken from the vial bottle and the necessary dilutions were made and directly analyzed in the selected buffer solution medium. Quantification was made from the calibration curve obtained by the standard addition method. An anodic or cathodic (for comparative purposes) pretreatment of the BDD electrode was carried out once a day, before starting any other electrochemical experiments, in the presence of 0.5 mol L^{-1} H$_2$SO$_4$ applying either +1.8 or -1.8 V (both for the period of 180 s). Between individual measurements, an activation program was applied for 60 s under the same conditions in order to obtain reproducible and reliable results.

Cyclic voltammetry (CV) was employed for preliminary studies on the electrochemical behavior of CEF, followed by square-wave voltammetry (SWV) to assess the analytical performance and the method's applicability. The pre-concentration of CEF was performed by immersing the previously treated BDD electrode in the sample solution. After a fixed rest period (5 s) to settle the solution and decrease the

background current, anodic scans were carried out over the range from +0.5 to +1.8 V using the SW waveform. For analytical application, the optimized instrumental parameters for SWV were as follows: frequency, 75 Hz; pulse amplitude, 40 mV; scan increment, 10 mV. Successive measurements were carried out by repeating the above assay protocol on the working electrode. All measurements were performed in triplicate at laboratory temperature. Limits of detection (LOD) and quantification (LOQ) were calculated as the three and ten times the standard deviation of the peak currents (ten runs) of the lowest concentration of the related linearity range divided by the slope of the particular calibration curves, respectively. The formulae used were LOD = 3.3s / m and LOQ = 10s / m, respectively, where s is the standard deviation and m is the slope.

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