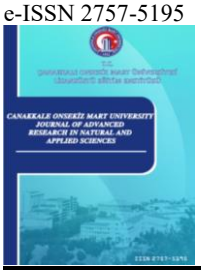
e-ISSN 2757-5195



Çanakkale Onsekiz Mart University

Journal of Advanced Research in Natural and Applied Sciences

Open Access

doi.org/10.28979/jarnas.845147 2020, Vol. 6, Issue 2, Pages: 342-352 dergipark.org.tr/tr/pub/jarnas

Reduction Behavior of Olanzapine and Its Differential Pulse Voltammetric Determination in Human Urine and Pharmaceuticals

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Article History

Received: 27.02.2020

Accepted: 06.11.2020

Published: 29.12.2020

Research Article

Abstract – The electrochemical reduction behavior of olanzapine was investigated by DPV (differential pulse voltammetry) and CV (cyclic voltammetry) techniques using a glassy carbon electrode. The measurements were carried out in different buffer solutions in a pH range from 0.50 to 12.05. The behavior of the peak potential and the peak current were examined by changing the pH, and a pH= 7.0 Britton-Robinson buffer solution was selected as the supporting electrolyte. To designate the electron and proton numbers that participated in the reaction, the changing peak potentials of olanzapine with increasing pH were investigated. The number of transferred electrons was found equal to the number of the hydrogen ions taking part in the electrode reaction. Equal electron and proton numbers were also supported with suggested reduction mechanism. For DPV analysis, the linear calibration curve of olanzapine was plotted between concentrations $2x10^{-5}$M and $1x10^{-4}$M at the pH= 7.0 Britton-Robinson buffer solution. The limit of detection (LOD) and the limit of quantification (LOQ) were found to be $1.88x10^{-6}$ M and $6.29x10^{-6}$M, respectively. Lastly, the developed technique was applied to spiked urine and pharmaceutical preparations for recovery studies of olanzapine. A reaction mechanism related to the reduction of olanzapine was also proposed with this study.

Keywords – *Human urin, olanzapine, pharmaceutical preparation, reduction, voltammetry*

1. Introduction

Olanzapine (Figure 1) is a drug with antipsychotic effects that is used to treat mainly schizophrenia and bipolar disorder (manic depressive disorder) in adults and teenagers. It treats the patients by changing the activity of certain natural substances in their brain (Medline Plus).

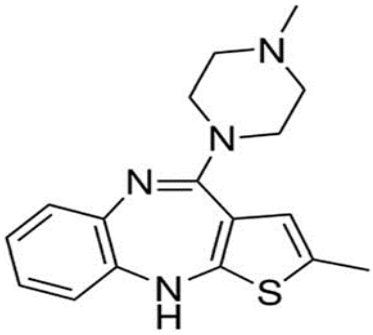

Figure 1. Chemical structure of olanzapine

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In the literature, for the determination of olanzapine in biological samples and tablets, different techniques have been reported such as the optimized UPLC-MS/MS method (Du et al., 2019), the gas chromatography / tandem mass spectrometry method (Rosado et al., 2018), the validated HPLC method (Karaca & Yeniceli, 2018), calorimetry (Adegoke et al., 2016), LC-MS/MS (Bonde et al., 2014), field-amplified sample injection coupled with the pseudo-isotachophoresis technique (Dziomba et al., 2014), GC-nitrogen phosphorus detection (Samanidou et al., 2013), HPLC-MS/MS coupled with column-switching technique (Zheng et al., 2012), UV spectrophotometry (Firdous et al., 2005), flow injection spectrophotometry (Jasinska & Nalewajko, 2004), tandem mass spectrometry (Berna et al., 2002), capillary zone electrophoresis (Pucci et al., 1999), and high performance liquid chromatography (Kasper et al., 1999). However, pre-treatment samples for these reported methods require a long time, and the equipment and reagents are expensive and thus are not useful for routine analysis. But with low-cost, high sensitivity and accuracy, and direct and fast practicality, voltammetry is an appropriate analytical technique for practical analysis. There are also electroanalytical techniques such as potentiometry (Rouhani & Soleymanpour, 2019), amperometry with HPLC (Raggi et al., 2000), and voltammetry. Voltammetric methods are used for the determination of many antipsychotics including olanzapine (Karadurmus et al., 2019; Kul, 2019), the oxidative behavior of olanzapine with modified electrodes (Azab & Amany, 2019; Behzad et al., 2016; Ahmed et al., 2015; Shahrokhian et al., 2014; El Shal, 2013; Mashhadizadeh & Afshar, 2012; Merli et al., 2012), and the oxidative behavior of olanzapine on a glassy carbon electrode (Yılmaz et al., 2017; Biryol & Erk, 2013). However, an electroreduction study of olanzapine has not yet been reported.

The aim of the study was to research the properties of the reduction process of olanzapine by glassy carbon electrode for the first time and detect olanzapine in tablets and urine. In this method, CV and DPV techniques were used, and there were no time-consuming processes such as plating and cleaning of the electrode. For this reason, our method is fast and easy, and it is the first electroreduction technique for olanzapine. The developed technique was applied to spiked urine and pharmaceutical preparations for recovery studies of olanzapine. In addition, a reaction mechanism related to the reduction of olanzapine was also proposed for the first time with this study.

2. Materials and Methods

2.1. Apparatus

The pH values of each solution were measured by a Metrohm 744 pH meter instrument at about 20 °C temperature. Deionized water was supplied by Sartorius Ultra-Pure Water Systems.

Voltammetric measurements were taken by a Metrohm 757 VA Trace Analyzer instrument which has three electrodes. In this system, a glassy carbon electrode was used as the working electrode, platinum wire was used as the auxiliary electrode, and Ag/AgCl (KCl 3 mol/L) was used as reference electrode. Before each measurement, the GCE surface was polished with Al_2O_3 (aluminum oxide, 0.01 μm). After that, it was rinsed first with deionized water and then with ethanol. Before the measurements, Ar gas was crossed over the supporting electrolytes for about five minutes, and, after sample additions, Ar gas was crossed over the voltammetric cell for about one minute.

For the analytical application, the following parameters were employed: for DPV analysis, a pulse amplitude of 50 mV, a pulse time of 0.04 s, a voltage step of 0.009 V, a voltage step time of 0.04, a potential step of 10 mV; and, for CV analysis, a scan rate in the range of 10-1000 mVs^{-1}.

2.2. Reagents

Our drug agent olanzapine and its tablet form Rexapin (One Rexapin tablet contains 10 mg of olanzapine) were supplied by the Abdi İbrahim Drug Company. A stock solution of olanzapine ($1.0x10^{-2}$ M) was prepared

daily with deionized water containing 20 µL HNO_3 in a 10 mL solution. Diluted solutions of olanzapine were prepared with deionized water from a stock solution. To avoid decomposition, all solutions were used within 24 hours and were protected from light.

An acetate buffer (pH 3.55-5.55), a phosphate buffer (pH 4.50-7.50), a Britton Robinson buffer (pH 2.03-12.05), and a 0.5 M H_2SO_4 solution (pH 0.55) were used as supporting electrolytes in the experiments.

2.3. Quantitative Analysis of Olanzapine

Diluted olanzapine solutions were prepared from a stock olanzapine solution with deionized water. For the best results in the experimental section, a calibration graph was created in the concentration range of $2x10^{-5}$ M - $1x10^{-4}$ M linearly with the DPV technique. The accuracy, precision, and repeatability parameters of the measurements were checked.

2.4. Voltammetric Analysis of Olanzapine in Spiked Tablet Form

Ten Rexapin tablets were weighed and crushed. An adequate amount was taken for a $1x10^{-2}$ M stock Rexapin solution and dissolved in deionized water in a 10 mL-calibrated flask. For complete dissolution, the flask was centrifuged at 4000 rpm for 20 min. Diluted Rexapin solutions were prepared from stock a Rexapin solution with deionized water. By comparing obtained regression equations and plotted calibration plots, the quantity of olanzapine in pharmaceuticals was calculated.

2.5. Voltammetric Analysis of Olanzapine in Spiked Human Urine

Urine analysis was performed by the standard addition method (Yagmur et al., 2018; Nosal-Wierciñska et al., 2014; Sadikoglu et al., 2011) For this purpose, urine was supplied daily from a volunteer not taking any medication and was diluted (1 mL urine + 9 mL deionized water). The voltammogram was recorded at pH=7.0 in 0.04 M BR buffer (9.4 mL) (blank). After adding a diluted urine solution (0.6 mL) to the blank, the voltammogram was also measured (blank for urine). For a 4×10^{-5} M cell concentration, a 40µL sample (1×10^{-2} M olanzapine stock solution of 1 mL / 8 mL deionized water/1 mL urine) was added and measured. The 1×10^{-2} M olanzapine (20 µL) standard solution was added and measured three times. The urine calibration curve was plotted according to these measurement results.

3. Results and Discussion

3.1. Electrochemical Reduction Behavior of Olanzapine

The best shaped and the highest peak current was observed at pH 7.00 in 0.04 M BR buffer. Therefore, this pH and this type of buffer solution were chosen for the electroanalytical studies (Figure 2). Consequently, the DP voltammetric technique and the BR buffer (pH 7.00) were chosen for further work. The voltammetric results were found to be pH dependent.

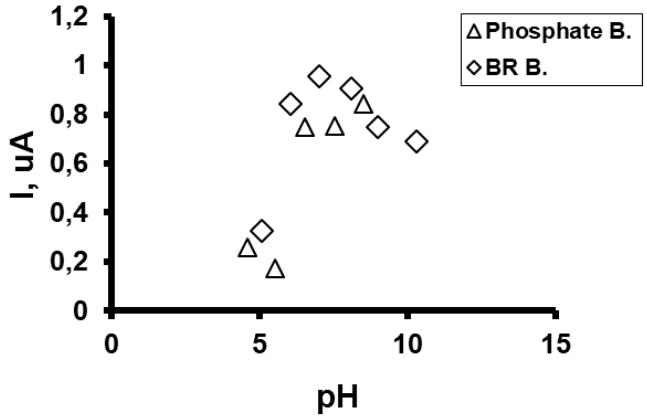

Figure 2. Changing peak currents of $5x10^{-5}$M olanzapine with increasing pH for the DPV technique in different buffer solutions

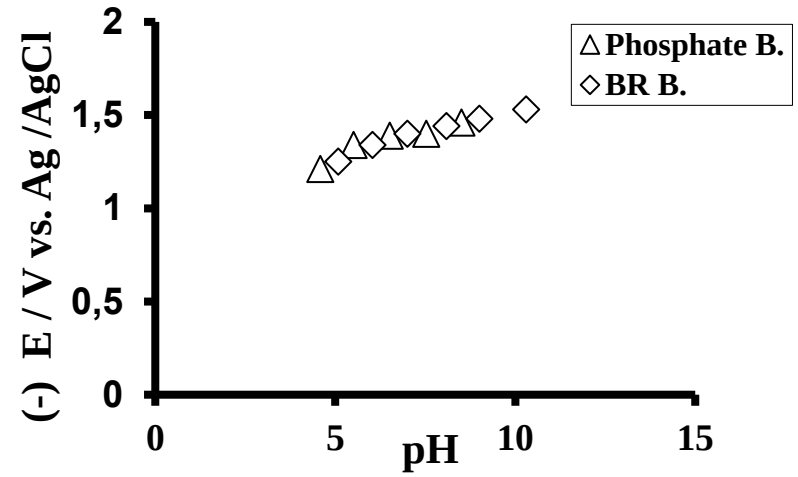

Figure 3. Changing peak potentials of $5x10^{-5}$M olanzapine with increasing pH with the DPV technique in different buffer solutions

To designate the electron and proton numbers that participated in the reaction, the changing peak potentials of olanzapine with increasing pH were investigated. As the pH values of solutions increased, peak potential values shifted to more negative regions (Figure 3), showed that there was a proton transfer participation in the electrode reaction (Yılmaz, 2016).

The relation between Ep_k and pH may be seen below:

Ep_k (mV) = a x + b;
Ep_k: cathodic peak potential, a = slope, x = pH, b = intercept.

When the peak potential values were plotted versus concentrations, a linear graphic was obtained. By using this graphic, a 52 mV / pH (r = 0.99) slope was found, and it was closer to the theoretical value of 59 mV / pH (Nernst value). It also indicated that the number of transferred electrons was equal to the number of the hydrogen ions taking part in the electrode reaction (Yılmaz, 2016; Can et al., 2015). Equal electron and proton numbers were also supported as two (Rodrigo & Waldvoge, 2019) at the suggested reduction mechanism (Figure 8).

The influence of the scan rate on the peak current and the peak potential of olanzapine were investigated. The cyclic voltammograms for olanzapine at different scan rates in 0.04 M BR buffer (pH 7.00) are given in Figure 4.

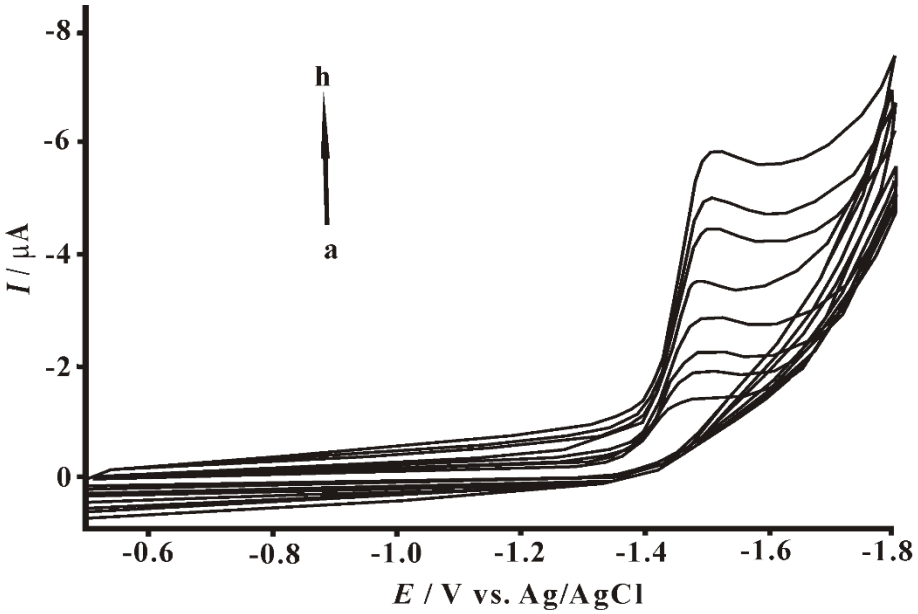

Figure 4. $1x10^{-4}$ M olanzapine cyclic voltammograms in 0.04 M BR buffer (pH 7.00). Scan rate (mV s^{-1}) a) 50 b) 100 c) 150 d) 250 e) 400 f) 600 g) 750 h) 1000

Because the correlation coefficient of I_p / µA= $0.0936\upsilon^{1/2}$ - 0.1596 equation was 0.999 and the slope of (logarithm of peak current-logarithm of scan rate) was approximately 0.5 (0.5838), the reduction process was determined to be diffusion-controlled (Yagmur et al., 2018; Engin et al., 2015; Citak et al., 2007) .One cathodic peak with no reverse was seen in the cyclic voltammograms of olanzapine, and as the scan rate increased, more negative peak potentials were seen. This indicated an irreversible electrode reaction

3.2. Validation and Analytical Studies of the Suggested Voltammetric Technique

According to the optimized experimental conditions, a linear relationship was found in the range $2x10^{-5}$ M - $1x10^{-4}$ M between the peak current and the concentration of olanzapine (Figure 5).

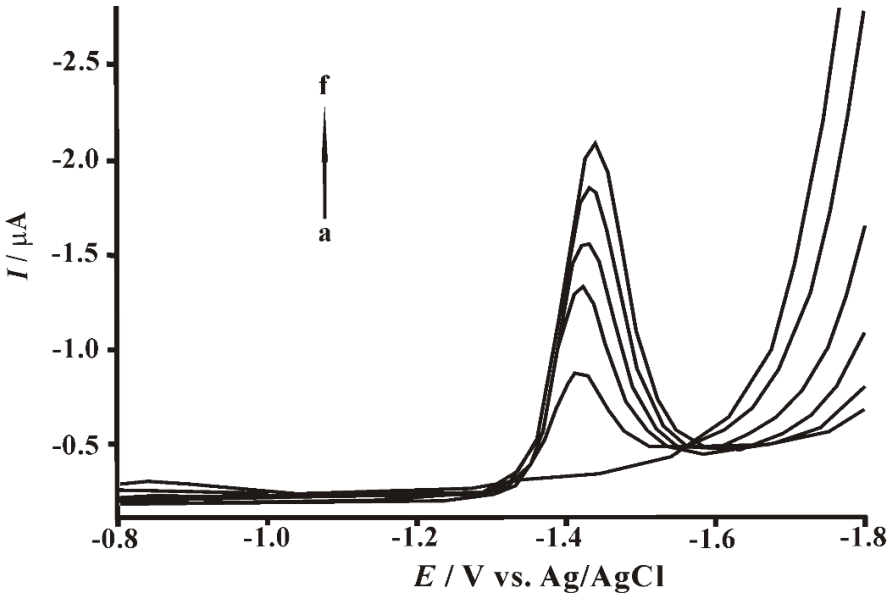

Figure 5. Voltammograms of different concentrations of olanzapine in 0.04 M BR buffer (pH 7.00) by DPV technique a) blank b) $2x10^{-5}$ c) $4x10^{-5}$ d) $6x10^{-5}$ e) $8x10^{-5}$ f) $1x10^{-4}$ M.

When the current values obtained from the voltammograms in Figure 5 were plotted versus concentrations in the graph, a linear graphic was obtained (Figure 6).

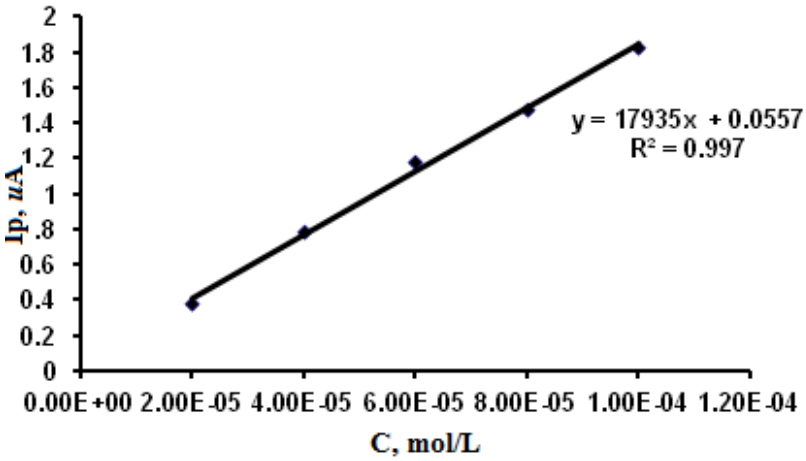

Figure 6. Calibration plot for olanzapine

The equation of the linear calibration graph was found to be $I_p/\mu A = 17935\ (\mu A/M)) + 0.055$, and the correlation coefficient (r) was 0.998 for 10 measurements. The SD of the slope and the SD of the intercept are given. For the quantitative detection of olanzapine, the LOD (limit of detection; 3*s*/m) and the LOQ (limit of quantification; 10 *s*/m) were calculated (*s* is the standard deviation of the peak current for five runs, and *m* is the slope of the calibration curve) (Yılmaz et al., 2013; Engin et al., 2015; Yagmur et al., 2018). For the validation procedure, repeatability and reproducibility of the peak current and the peak potential were examined. Calculated parameters are given in Table 1.

Table 1

Analytical and validation parameters for olanzapine in BR buffer (pH 7.00) with DPV technique

Parameters	**Results**
Linear concentration range (M)	$2x10^{-5}$- $1x10^{-4}$
Measured potential (V)	-1.4
Slope (µA/M)	17935
SD of slope	321
Intercept (nA)	0.055
SD of intercept	0.02
Correlation coefficient (r)	0.998
LOD (M)	1.88×10^{-6}
LOQ (M)	$6.29x\ 10^{-6}$
Repeatability of peak current (% RSD)	1.05 for $8x10^{-5}$ M
Reproducibility of peak current (% RSD)	1.97 for $8x10^{-5}$ M
Repeatability of peak potential (% RSD)	0.505 for $8x10^{-5}$ M
Reproducibility of peak potential (% RSD)	0.71 for $8x10^{-5}$ M

3.3. Voltammetric Determination of Olanzapine in Pharmaceutical Preparations

The amount of olanzapine in Rexapin tablets was calculated according to the calibration curve for olanzapine. The recovery results for olanzapine from Rexapin tablets were recorded (Table 2).

Table 2

DPV Applications for olanzapine in pharmaceutical preparations

Parameters	Results
Spiked olanzapine (mg)	0.5
Found olanzapine (mg)	0.505
Average recovery (%)	101
Relative standard deviation (%),	2.80
Bias (%)	1
Labeled olanzapine (mg)	10
Found olanzapine (mg)	10.5
Relative Standard deviation (%)	1.24
Bias (%)	5
Number of measurements	5

According to the test, none of the excipients in the tablets had any effect on the analysis. In conclusion, olanzapine was found to be determined quantitatively in pharmaceutical preparations with no excipients.

3.4. Application to Human Urine Samples

For quantitative detection and recovery studies for olanzapine in spiked urine, the developed technique was applied to human urine samples by the standard addition method as in the experimental section (Yagmur et al., 2018; Nosal-Wierciñska et al., 2014; Sadikoglu et al., 2011). The voltammograms are given in Figure 7.

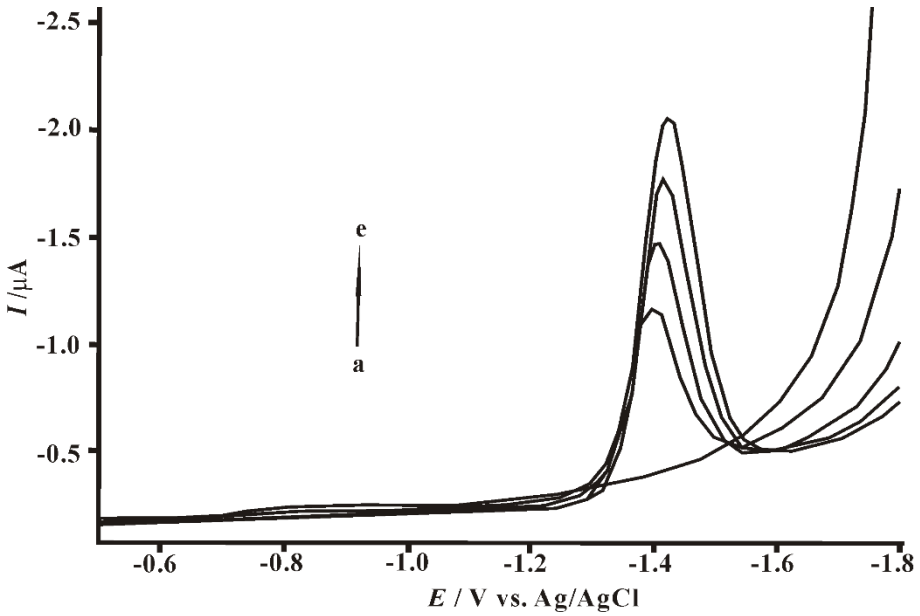

Figure 7. DP voltammograms of olanzapine in human urine; a) 0.04 M BR buffer (pH 7.00) Blank + 600 µL Urine (1:9); b) $4x10^{-5}$ M Olanzapine with Urine; c) $2x10^{-5}$ M d) $4x10^{-5}$M e) $6x10^{-5}$ M olanzapine

The voltammetric parameters for olanzapine in human urine are calculated as in Table 3.

Table 3

DPV applications and recovery studies for olanzapine in human urine samples

Parameters	**Results**
Olanzapine (Spiked, M)	$4x10^{-5}$
Olanzapine (Found, M)	$4.12x10^{-5}$
Average recovery (%)	103
RSD (%)	1.37
Bias (%)	3
Number of measurements	5

3.5. Suggested Reduction Mechanism for Olanzapine

Lastly, an electrochemical mechanism for the reduction of olanzapine was suggested (Figure 8). The possible mechanism is given below. As seen from the possible mechanism, after the imine double bond is reduced by two electrons, it is protonated, taking $2H^+$ to form the amine (Rodrigo & Waldvoge, 2019). The reduction reaction takes place in three steps. First, in the imine molecule, the C=N bond opens towards nitrogen, the carbon atom is positively charged, and the nitrogen atom is negatively charged. Then, the C atom acquires an electron and forms radical carbon. In the second stage, the radical carbon atom gets one more electron and becomes negatively charged. In the last step, the negatively charged N and C in the molecule take one H^+, and the final product, amine (CH-NH), is formed.

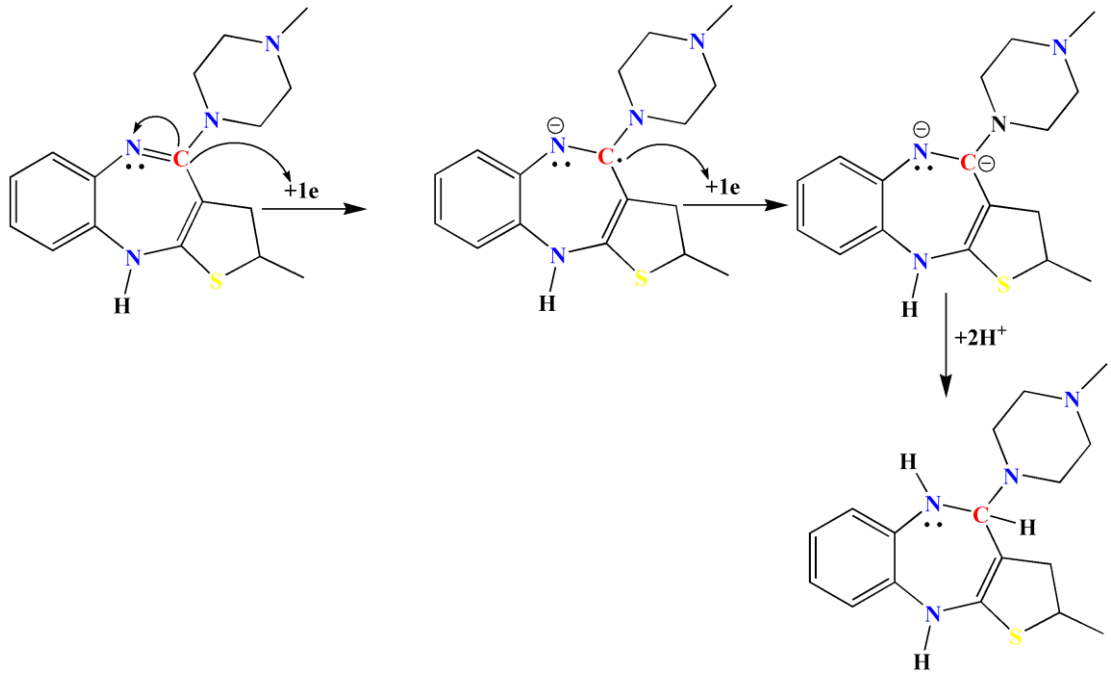

Figure 8. Suggested electrochemical reduction mechanism for olanzapine

4. Conclusion

A sensitive and simple electrochemical reduction technique was developed for the determination of the olanzapine quantity in pharmaceuticals and spiked human urine. Olanzapine could be determined on a glassy carbon electrode in BR buffer (pH 7.00) by the differential pulse voltammetry technique. Electrode reaction

was found to be pH dependent and irreversible. It was concluded that for accuracy in studies of olanzapine, the developed technique could easily be applied to biological and pharmaceutical preparations. In addition, voltammetric techniques have advantages over the other methods, and this easier and faster technique can also be an alternative to techniques with modified electrodes. Lastly, a reaction mechanism related to the reduction of olanzapine was also proposed for the first time with this study.

Acknowledgement

This study was supported by the Office of Scientific Research Projects Coordination at Çanakkale Onsekiz Mart University. Grant number: FBA-2018-2702. Author would like to thank Abdi İbrahim Drug Company (Istanbul, Turkey) for providing olanzapine and its tablet form Rexapine for the development the applied voltammetric techniques.

Author Contributions

Sultan YAĞMUR KABAŞ: Conceived and designed the paper, collected data, performed the analysis, and wrote the paper.

Conflicts of Interest

The author declares no conflict of interest.

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