Role of Green Chemistry in Antipsychotics’ Electrochemical Investigations Using a Nontoxic Modified Sensor in McIlvaine Buffer Solution

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ABSTRACT: A new low-cost green electrochemical sensor based on nontoxic polyethylene glycol (PEG) and silver nanoparticles was used to improve the sensitivity of the carbon paste electrode for the investigation of olanzapine (OLZ) in dosage arrangements and in the existence of its coadministered drug fluoxetine and in the drug formulation. Scanning electron microscopy measurements were carried out to emphasize the morphology of the electrode surface. Cyclic voltammetry and differential pulse voltammetry were used to explore the diffusion and linearity behaviors of OLZ. Impedance spectroscopy measurements were determined to investigate the ac behavior of OLZ and then an ideal electrical circuit was modeled. A linear calibration was obtained from $1.0 \times 10^{-8}$ to $1.25 \times 10^{-4}$ M. The limit of detection was $1.5 \times 10^{-9}$ M, whereas the limit of quantification was $5 \times 10^{-9}$ M. The way has been wholly authenticated concerning linearity, precision, accuracy, reproducibility, sensitivity, and selectivity.

1. INTRODUCTION

Olanzapine (OLZ) is a first-line antipsychotic medicine used for the dealing of schizophrenia and depressive episodes connected with bipolar disorder [with fluoxetine (FLX)]. It has also been used as an antiemetic for the control of chemotherapy-induced nausea and vomiting. OLZ is a very active drug; so it is administered at very low dosages; so very sensitive analytical approaches are necessary for its determination. High-performance liquid chromatography, capillary electrophoresis technique, and spectrophotometry were used for its determination. Although electrochemical methods are sensitive techniques for drug determination, only few works were done on OLZ using cyclic voltammetry and differential pulse voltammetry to explore the diffusion behavior of OLZ at a glassy carbon electrode; a magnetic nanocomposite with a core–shell structure was also used. OLZ was finally investigated in tablets and human urine samples using a modified carbon paste electrode incorporating gold nanoparticles (NPs) and glutamine in a micellar medium and with a bilayer of multiwalled carbon nanotube/benzene disulfonate-doped poly pyrrole.

Green chemistry is the design of processes that reduce or eliminate the illumination of hazardous substances. It focuses on technological approaches to prevent pollution and reduce consumption of nonrenewable resources. Most of the important nonhazardous additive formulations used to control the electrodeposition of metals include polyethylene glycols (PEGs). PEG is a nontoxic, commercially available polymer which is used in clinical research. Many procedures of PEG surface adjustment have been used to shrink a surface protein resistant and to improve surface biocompatibility. PEG is passive to constituents of the cell environment because they avoid adsorption of proteins. It has been used incorporated with a carbon paste electrode (CPE) in several applications providing high sensitivity and selectivity.

Novel metallic NPs, especially silver NP-modified sensors, show high electrocatalytic activities toward the redox process because of their good conductivity. Moreover, from the economic point of view the cost for preparation of AgNPs is lower than that of Au and Pt NPs; also, silver is the least toxic metal for humans, so it has been used in wide fields of applications including as catalysts as an antibacterial, as a biosensor for bioimaging and in chemical analysis. The aim of this work is to implement a novel and simple sensor based on PEG and AgNPs to improve the sensitivity and selectivity of OLZ. Then, the utility of the sensor for its quantitative determination in the pharmaceutical formulation will be investigated.

2. RESULTS AND DISCUSSION

2.1. Surface Characterization. Scanning electron microscopy (SEM) micrographs of (A) bare CPE, (B) CPE/PEG, and (C) CPE/PEG/AgNPs are presented in Figure 1. The
CPE surface is uniform and smooth, whereas the CPE/PEG surface shows large spherical holes. At the CPE/PEG/AgNP surface, AgNPs appear spherical in shape, giving a larger surface area than bare CPE. The transmission electron microscopy (TEM) micrograph (Figure 1D) shows spherical irregular distribution of AgNPs with an average diameter of 22 nm. Energy-dispersive X-ray spectroscopy (EDX) of the CPE/PEG/AgNP sensor (Figure 1E) proves the presence of AgNPs on the surface at its binding energy of 3 keV, whereas the elemental mapping (inset) shows that silver NPs are arranged homogeneously and covering the whole surface area. Also, the effect of changing the electrodeposition time of silver was examined (Figure 1F). The increasing current response of OLZ toward the electrodeposition time was monitored from 5 to 60 s, where a maximum peak of OLZ was obtained when the electrodeposition time of silver was 40 s. The electron transfer of OLZ was enhanced because the increase of AgNP concentration on the PEG surface leads to an increase of the charge capacity; also, the electrostatic attraction force between the positively charged OLZ and the negatively charged AgNPs enhances the current values. However, upon increasing the electrodeposition time to higher than 40 s, a drop in the OLZ current response was observed. This may be attributed to the growth of AgNPs on the surface of the CPE/PEG that blinds the sensor and hinders the charge transfer process.15,26

2.2. Electrochemical Behavior of OLZ. A reversible oxidation process of 1.0 × 10^{-3} M OLZ in McIlvaine (Mc) buffer, pH 2.2, at a scan rate 50 mV·s^{-1} was recorded at bare CPE, CPE/PEG, and CPE/PEG/AgNPs (Figure 2). It is clear that OLZ gives an anodic peak current at +0.59 V when bare CPE is used because of the oxidation of the amine group.

Figure 1. SEM image of (A) CPE, (B) CPE/PEG, (C) CPE/PEG/AgNPs. (D) TEM of AgNPs, (E) EDX and elemental mapping of CPE/PEG/AgNPs. (F) Effect of the electrodeposition time of silver NPs on 1 mM OLZ.

Figure 2. Cyclic voltammograms of 1.0×10^{−3} mol L^{−1} of OLZ in Mc buffer, pH 2, at a scan rate of 50 mV s^{−1} recorded for bare CPE, CPE/PEG, and CPE/PEG/AgNPs.
However, CPE/PEG gives a higher oxidation peak current, as it rises from 36.2 to 110.2 μA. Upon the addition of AgNPs, it reaches 244.8 μA, because the capping agents of PEG have the capability of stabilizing the newly formed AgNPs in the polymer matrix, which induce a larger surface area.\textsuperscript{17,19} The oxidation mechanism of OLZ at CPE/PEG/AgNPs is illustrated in Scheme 1.

### 2.3. Optimization of the Experimental Conditions.

#### 2.3.1. Effect of pH

The current response diagram of 1.0 × 10^{-3} M OLZ in the Mc buffer with different pH values (2.2 → 8) at a scan rate 100 mV·s\(^{-1}\) has been studied in Figure 3. OLZ is a weak base with \(pK_a\) values of 4.69 and 7.37. At a pH higher than 7.37, there is no charge and the current intensity is almost the same. A supreme oxidation current signal is reached at pH 7, \(\gamma = 0.998\), which implies that the oxidation process of OLZ with diﬀusion-controlling process.\textsuperscript{22} Also, the relation between the square root of the scan rate and the peak current is related to a linear line at low frequency, indicating a diffusion process.\textsuperscript{33} The diameter of the semicircle rises in the order: bare CPE > CPE/PEG > CPE/PEG/AgNPs.

#### 2.3.2. Effect of Scanning Speed

Studying the impact of scan rate on the electrochemical oxidation of 1 × 10^{-3} M OLZ is presented using CPE/PEG/AgNPs in Figure 4. A linear relationship between the square root of the scan rate and the anodic current (inset A) between 10 and 300 mV·s\(^{-1}\) results in a linear equation: \(I_p (\mu A) = 13.9S_n^{1/2} (V \cdot s^{-1})^{1/2} - 21.32\) (\(n = 7, \gamma = 0.998\)), which implies that the oxidation process of OLZ is a diffusion-controlling process.\textsuperscript{22} Also, the relation between the log of the anodic peaks of OLZ with the log of the scan rate gives a linear relationship with a slope of 0.641 (inset B), signifying that OLZ oxidation is organized by diffusion with some adsorption sustenance.

The surface area of CPE/PEG/AgNPs was evaluated using 1.0 mM K\(_3\) Fe (CN)\(_6\) at different scan rates based on the Randles–Sevcik equation.\textsuperscript{29–32}

\[
I_p = 2.69 \times 10^4 n^{3/2} A D^{1/2} v^{1/2} C
\]

For K\(_3\)Fe(CN)\(_6\), \(n = 1\) and \(D = 7.6 \times 10^{-6}\) cm\(^2\)/s, the surface area of CPE/PEG/AgNPs was found to be 0.181 cm\(^2\). The diffusion coefficient of OLZ was calculated by the same equation and was found to be 1.03 × 10^{-9} cm\(^2\)/s.\textsuperscript{31}

#### 2.4. EIS Study

Electrochemical impedance spectroscopic (EIS) technique is used mainly to test the conductivity of the modified electrode surface that is directly proportional to the current and inversely proportional to the impedance. EIS scans measured at the peak potential (590 mV) for bare CPE, CPE/PEG, and CPE/PEG/AgNPs are shown in Figure 5 as Nyquist plots. It shows a semicircle at high frequency, signifying a charge-transfer process connected to a linear line at low frequency, indicating a diffusion process.\textsuperscript{33} The diameter of the semicircle rises in the order: bare CPE > CPE/PEG > CPE/PEG/AgNPs. The Nyquist plots’ data were simulated with two time constants’ equivalent circuit (inset) with 2% error. Analysis was performed by Thales software delivered with a Zahner-Electric workstation.\textsuperscript{34} The model consists of \(R_w Z_w C_1\) and \(R_1 C_2\) in series with the solution resistance (\(R_s\)). \(C_1\) and \(C_2\) are inner and outer layer capacitances; \(R_1\) and \(R_2\) are the respective internal and external layer resistances. \(Z_w\) is the Warburg component linked to diffusion phenomena.\textsuperscript{35} Constant phase element (CPE) is presented instead of ideal capacitance to validate the ideal behavior and surface roughness. CPE is connected to an empirical exponent (\(\alpha = 0\)–1) to justify the surface inhomogeneity.\textsuperscript{36} Generally, the data show that upon adding PEG and AgNPs, the oxidation of OLZ gives a lower impedance value (\(R_1\)) of 16 kΩ cm\(^2\) (highest conductivity) and the highest diffusion process (\(W = 611 \Omega cm^2 s^{-1/2}\)) compared to \(R_1 = 153 k\Omega cm^2\) and \(W = 187 \Omega cm^2 s^{-1/2}\) for the bare CPE. Thus, the mechanism of the reaction depends on both charge-transfer and diffusion processes.
Electrochemical processes, which confirms the CVs and the scan rate calculations.

3. ANALYTICAL APPLICATIONS

3.1. Simultaneous Determination of OLA and FLX. The drug combination of OLZ with the serotonin reuptake inhibitor FLX29 has no official method for their determination. Thus, an interference study including FLX was performed to test the selectivity of CPE/PEG/AgNPs. As shown in Figure 6, both OLA and FLX exhibit a well-defined DPV with good separations in the M& buffer, pH 7.4 (physiological pH of the body). As the safety doses above 18 mg of OLZ with 75 mg of FLX have not been estimated in clinical trials, the projected modified electrode can discriminate OLZ from FLX, by changing the concentration of both, OLZ (2 → 18 mg/mL) and FLX (5 → 75 mg/mL). The current comebacks due to the oxidation of OLA (at 260 mV) and FLX (at 450 mV) with a peak separation of 190 mV were observed, giving good calibration curves for both drugs (inset). This indicates the electrocatalytic activity of OLZ and FLX in the presence of each other.

3.2. Calibration Curve and Detection Limit. The current intensity of the developed sensor in M& buffer, pH 2.2, with a scan rate of 10 mV s⁻¹ using DPV at CPE/PEG/AgNPs increased linearly with OLZ in the range of 1.0 × 10⁻⁸ to 1.25 × 10⁻⁴ M (Figure 7) with a regression equation of \( I_p (\mu A) = 0.209c (\mu M) + 1.242 \) and a correlation coefficient equal to 0.9961. The limit of detection (LOD) and limit of quantification (LOQ) were calculated using the following equations: LOD = 3s/m and LOQ = 10s/m, where s is the standard deviation and m is the slope of the calibration curves, and were established to be 1.5 × 10⁻⁹ M and 5 × 10⁻⁹ M, respectively.

3.3. Analysis of OLZ Tablets. Five tablets were balanced and the average mass per tablet was determined. Four aliquots of the drug solution were introduced and the standard addition method was carried out. The recovery and relative standard deviation are provided in Table 1. The outcomes suggested that CPE/PEG/AgNPs have high reproducibility and that the auxiliary materials in tablets have no vital interferences for the samples analyzed.

| formulation | free OLZ 1.0 × 10⁻⁶ M | added OLZ 1.0 × 10⁻⁶ M | found OLZ 10⁻⁹ M | recovery % RSD % |
|-------------|------------------------|------------------------|------------------|-----------------|
| OLZ 10.00   | 15.03                  | 100.2                 | 0.02             |
| 40.00       | 44.66                  | 99.24                 | 1.03             |
| 80.00       | 83.80                  | 98.58                 | 0.53             |
| 120.0       | 126.92                 | 101.53                | 3.07             |

3.4. Stability and Robustness of the Modified Electrode. The stability of the electrochemical sensor was tested by recording cyclic voltammograms of OLZ in M& buffer, pH 2.2. After 50 successive scans, the anodic peak currents at CPE/PEG/AgNPs decreased by 3.3%. This indicates that the AgNP film formed is mechanically stable. The immobilization of AgNPs into the polymeric matrix through the hydrophobic part of the surfactant avoids the movement of the NPs out of the polymer structure, which
leads to the nonmechanical alteration of the polymer matrix that maintains the stability of the sensor. These results prove the reliability of the proposed method for the determination of OLZ so it can be considered robust.

4. CONCLUSIONS

A novel nontoxic carbon paste sensor with an excellent performance for the sensitive electrochemical determination of OLZ based on ethylene glycol polymer and silver NPs was prepared. The proposed methods have the advantage of using feasible analytical procedures and the electrode exhibits good sensitivity, selectivity, and reproducibility for OLZ determination in pure and dosage form with an LOD value of 1.5 × 10^{-9} M, whereas the LOQ was 5 × 10^{-8} M. The analytical procedure has been fully validated regarding linearity, precision, accuracy, reproducibility, sensitivity, and selectivity.

5. EXPERIMENTAL SECTION

5.1. Materials and Reagents. OLZ was kindly supplied from Etipco, Egypt; PEG and AgNO₃ were purchased from sigma. Mc buffer is a buffer solution prepared in the pH range from 2.2 to 8.0 by mixing 0.2 M disodium hydrogen phosphate and 0.1 M citric acid.

5.1.1. Preparation of Bare CPE. CPE was arranged by collaborating graphite powder (0.5 g) with drops of nujol oil in a glassy mortar. The carbon paste was filled into the hole of the electrode and pressed on a filter paper.

5.1.2. Preparation of the Modified CPE. CPE was arranged by collaborating graphite powder (0.5 g) with drops of nujol oil in a glassy mortar. The carbon paste was filled into the hole of the electrode and pressed on a filter paper.

5.2. Instrumental and Experimental Setup. All voltammetric and impedance measurements were achieved by the three-electrode electrochemical workstation EC-Lab SP-150 potentiostat. A platinum wire was served as the auxiliary electrode and the calomel as the reference electrode. SEM tests were achieved by SEM Model Quanta 250 FEG (field emission gun) committed with an EDX unit, with accelerating voltage of 30 kV, magnification 14 up to 1 000 000 (FEI company, the Netherlands).

5.3. Validation in Pharmaceutical Samples. Ten tablets of the commercial pharmaceutical olazine (10 mg/tablet) were weighed, powdered, and dissolved in deionized water and the average mass per tablet was determined to obtain the concentration of OLA in the working range and then DPV was recorded with the following parameters: scan rate of 10 mV/s^{-1}, pulse width of 25 ms, pulse period of 200 ms, and pulse amplitude of 10 mV, using CPE/PEG/AgNPs with the standard addition technique.

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Notes
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