Pencil graphite electrode as an electrochemical sensor for the voltammetric determination of chlorpromazine


Department of Chemistry, School of Chemical Science, Kuvempu University, Shankaraghatta, 577451, Shimoga, Karnataka, India

**1. Introduction**

A phenothiazine class of drug, chlorpromazine (CPZ, 2-chloro-10-(3-dimethylaminophenyl) phenothiazine), has been widely used to treat major depressive illness, bipolar disorder and also for schizophrenia [1]. CPZ reacts by blocking postsynaptic dopaminergic D2 receptors in the mesolimbic and prefrontal cortex regions of the brain and acts as a competitive antagonist of dopamine. The blockade of D2 receptor is responsible for decreasing the positive symptoms of schizophrenia [2]. Over dosage or excess concentration which may causes several problems such as interpalpebral conjunctiva, abnormal pigmentation of eyelids, tract disorders, and cataract and accommodation interference [3]. Thus, emerging and accurate analytical method for detecting chlorpromazine became an important topic of research.

Various analytical methods have been reported on the investigation of CPZ such as gas chromatography [4,5], spectrophotometry [6–8], HPLC [9,10], chemiluminescence [11–13], electrochemical methods potentiometry [14,15], polarography [16] and capillary zone electrophoresis [17]. Although chromatographic and spectrophotometric methods are widely used for the determination of CPZ, the instruments involved are often costly to run and maintain, and the pretreatment process for samples is usually time-consuming and complicated. Among these, the analytical methods based on electrochemical sensors exhibited distinctive and unique properties such as rapid response, inexpensive, simple operation procedure, time saving, high selectivity and sensitivity [18–24]. The various electrodes have been employed for the determination of CPZ, such as, carbon paste electrode (CPE) [18], boron-doped diamond electrode (BDDE) [3], glassy carbon electrode (GCE) [19], graphene paste electrode (GPE) [20] and rhenium electrodes [21].

Among various carbon based electrodes, pencil graphite electrodes (PGEs) have widespread attention due to their sp² hybridized carbon which shows good adsorption, conductivity, high sensitivity, smaller background current, and ease of preparation and surface modification properties [25,26]. As compared to the other electrodes such as glassy carbon electrode, the renewal of surface plays an important role for subsequent analysis because of electrochemical reactions of the molecule may cause a change in surface properties of the electrode [27]. Thus subsequent renewal of surface of the PGE for the each trial may lead to the selective and
sensitive electrochemical investigation of chlorpromazine. In this work, the sensitive and selective determination of CPZ presented in pharmaceutical formulations using cyclic voltammetry (CV) and differential pulse voltammetry (DPV) methods has been carried out using PGEs. To the best of our knowledge, no literature has been found on this research direction.

2. Experimental

2.1. Chemicals, reagents and instrumentation

All the chemicals were of analytical grade and used without any further purification. CPZ was procured from Tokyo Chemical Industry Co., Ltd. K2HPO4, KH2PO4 and KCl were procured from Merck, Mumbai, India. Potassium ferricyanide was procured from HiMedia Laboratories Pvt. Ltd. The Equiptronics pH meter (EQ-611) was used to measure pH of the solution. Pencil graphite lead of 0.5 mm diameter and length of 60 mm were procured from Kokuyo Camlin Ltd., Mumbai, India. EMETIL-25 tablets were procured from local pharmaceutical shop. Doubly distilled water was used for the preparation of solutions. All the electrochemical measurements were carried out using electrochemical workstation CHI660D (CH Instruments, USA) using three electrode system. The PGE was used as working electrode. Saturated calomel and platinum wire were used as reference and counter electrodes, respectively.

2.2. Preparation of pencil graphite electrode

The HB pencil lead of 0.5 mm diameter and length of 60 mm was used as PGE for the investigation of CPZ. The electrical contact has been made at one end of the pencil lead using copper wire and it was inserted into the plastic tube containing araldite mixture (epoxy resin, 1:1). After 24 h of drying, the edge of the PGE was renewed by using sharp blade and then smoothened using emery paper followed by butter sheet.

After preparing the PGE, it has been electro-polymerized using alanine and glycine within the potential window 0–0.2 V (50 cycles).

3. Results and discussion

3.1. Cyclic voltammetric study of chlorpromazine on PGE

Voltammetric methods such as CV and DPV were employed to evaluate the electrochemical behaviour of CPZ. Electrochemical behaviour of 0.1 mM CPZ was investigated in phosphate buffer solution (at pH-7) with the scan rate of 0.1 Vs\(^{-1}\). In Fig. 1, PGE showed good sensitivity and increased peak current when compared to alanine and glycine modified PGEs in 0.1 mM CPZ (potential window 0–1.2 V). At PGE the anodic peak current is 3.16 \(\mu\)A at 0.759 V which was higher than that of alanine (2.19 \(\mu\)A) and glycine (2.30 \(\mu\)A) modified PGEs with the small shift in the positive potential (0.770 and 0.761 V). Thus, the PGE showed more desirable electrochemical response compared to alanine and glycine modified PGEs. In conclusion, PGE showed good conductivity, sensitivity, selectivity and electron transfer kinetics compared to alanine and glycine modified PGE for the electrochemical investigation of CPZ.

3.2. Study of electroactive surface area of PGE

The electrocatalytic activity of PGE can be studied by calculating the electroactive surface area of the electrode. The cyclic voltamograms of \([Fe(CN)]_6^{3-}/4^{-}\) redox system has been probed to different scan rates and for reversible processes, the Randles-Sevick equation has been used to calculate electroactive surface area of the electrode [28]:

\[
I_p = 2.69 \times 10^5 n^2 AD_0^{1/2} C_0 v^{1/2}
\]

Where \(I_p\) is anodic peak current (\(\mu\)A), \(n\) indicates the number of electrons transferred (\(n = 1\) for \(K_3[Fe(CN)_6]\)), \(A\) is the surface area of the electrode (cm\(^2\)), \(D_0\) is the diffusion coefficient (D\(_0\) = 7.6 \times 10\(^{-6}\) cm\(^2\) s\(^{-1}\) for \(K_3[Fe(CN)_6]\)), \(C_0\) is the concentration of electroactive species (mol cm\(^{-3}\)), and \(v\) is the scan rate (V s\(^{-1}\)). By plotting \(I_p\) vs. \(v^{1/2}\) the value of diffusion coefficient can be obtained. On substituting these values in the above equation, the electroactive surface area was found to be 6.85 cm\(^2\) on PGE.

3.3. Effect of solution pH

The anodic behaviour of CPZ on PGE at different pH values was studied using CV. As shown in the Fig. 2, the anodic peak current increases as increasing pH of the solution from pH 2.0 to 7.0. The better current response and well defined voltammogram shape observed at pH 7.0. Further increase in pH from pH 8.0 to 9.0 results in a decrease in the peak current. Hence, pH 7.0 was chosen as optimum pH for the further investigation. Scheme 1 shows possible oxidation mechanism of CPZ.

3.4. Study on effect of scan rate

The electrode reaction (diffusion or adsorption) processes were carried out by varying the scan rate. The effect of scan rate on the electrochemical response of CPZ at PGE in 0.1 M PBS of pH 7.0 was recorded by CV method as shown in Fig. 3a. As scan rate increased from 25 to 200 mVs\(^{-1}\) there was a small shifts in the peak potential with linear increase of peak current. The small shift in positive potential is due to the adsorption or double layer formation at the surface of the electrode which shows an irreversible nature of the electroactive molecule. The linear regression equation between the peak current (\(I_{pa}\)) vs. scan rate (\(v\)) expressed as \(I_{pa}\) (\(\mu\)A) = 2.12568 \times 10\(^{-6}\) + 1.15029 \times 10\(^{-8}\) \(v\) (V s\(^{-1}\)). For the plot of \(I_{pa}\) vs. \(v^{1/2}\), the linear regression equation expressed as \(I_{pa}\) (\(\mu\)A) = 1.21966 \times 10\(^{-6}\) + 2.1588 \times 10\(^{-7}\) \(v^{1/2}\) (V s\(^{-1}\)). The above result indicates that the process is diffusion controlled.
The linear regression equation for log \( I_{pa} \) vs. log \( n \) was given by the equation: 
\[
\begin{align*}
\text{log } I_{pa} (\text{m}A) &= -6.00137 + 0.26711 \text{ log } n (V \text{ s}^{-1}) \\
\end{align*}
\]
(Fig. 3d). The slope value of 0.26 gives an ideal reaction condition for diffusion controlled process [29]. Thus the anodic behaviour of CPZ exhibits diffusion controlled process.

For an irreversible anodic reaction, the standard rate constant \((k^0)\) can be calculated by Laviron equation [30]:
\[
E_p = E^0 + \left( \frac{2.303RT}{nF} \right) \log \left( \frac{RTk^0}{anF} \right) + \left( \frac{2.303RT}{nF} \right) \log \nu
\]
where, \( E^0 \) refers to formal potential, \( R \) indicates the universal gas constant, \( T \) is the absolute temperature, \( a \) gives the electron transfer co-efficient, \( F \) indicates Faraday’s constant.

The ‘zn’ value has been calculated from the slope of \( E_p \) vs log \( \nu \). The linear regression equation is given as \( E_p (V) = 0.66374 + 0.04825 \text{ log } n (V \text{ s}^{-1}) \); \( r = 0.9955 \). In this experiment the slope value for peak a was found to be 0.0482. By substituting \( T = 298 \text{ K}, R = 8.314, \) and \( F = 96485 \), \( zn \) value was found to be 0.7156 and 0.9324. For irreversible electrode reaction, \( zn \) value is 0.5. Thus, the number of electrons involved in electro-chemical reaction was found to be 2 for both the peaks. The intercept of \( E_p \) vs log \( \nu \) curve is 0.66374 and the value of \( k^0 \) is found to be 15.03 \( \mu s^{-1} \).

### 3.5. Analytical application of CPZ

The quantitative estimation of CPZ was studied by using the DPV technique. DPV has got more prominence compared to CV due to its sensitivity and low background current [30–32]. In the linear concentration range from 0.01 \( \mu \text{M} \) to 0.08 \( \mu \text{M} \), the concentration of CPZ increases with increase in peak current as shown in the Fig. 4a. The linear regression equation is: 
\[
I_{pa} (\mu A) = 1.37127 \times 10^{-8} \text{ M} + 2.66543 \times 10^{-7} \; ; \; r^2 = 0.9955
\]

The limit of detection (LOD) value can be calculated using the formula, \( \text{LOD} = 3 \frac{S}{m} \) and found to be 3.002 nM. Table 1 gives the reported and experimentally determined LOD values of CPZ. Thus the

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![Scheme 1. Structure and possible mechanism of CPZ.](image-url)
proposed electrode has been proven to be better sensor compared to other carbon based electrodes.

3.6. Pharmaceutical analysis

The analysis of CPZ present in tablet sample (EMETIL-25) was studied by using differential pulse voltammetric method. Standard addition method was used to investigate CPZ in tablet samples. Suitable amount of CPZ tablets were grounded to get a fine powder and dissolved in phosphate buffer solution (0.1 M). The obtained solution was sonicated for about 10 min and filtered using whatman filter paper. Finally, the resultant filtrate was transferred into 50 ml volumetric flask and diluted upto the mark. Further, the required amount of sample solution was taken for analysis. Differential pulse voltammograms were recorded after the addition of known concentration of CPZ to tablet solutions as shown in Fig. 5. Table 2 shows the recovery result of CPZ in tablet samples which found in the range of 99%–100%. Hence, the obtained results show that PGE could be applied successfully for the detection of CPZ in pharmaceutical tablets.

4. Conclusion

The anodic behaviour of CPZ was successfully investigated by using PGE. PGE showed the good peak current enhancement in comparison with Alanine and Glycine modified PGE’s. Among CPE (carbon paste electrode), BDDE (Boron doped diamond electrode), GCE (glassy carbon electrode) and other modified electrodes, the PGE showed the good electrocatalytic activity towards the oxidation of CPZ. The developed PGE shows a low limit of detection, a wide potential range, selectivity, sensitivity and reliability. Thus, the proposed electrochemical method is simpler, less time consuming, and shows a good practical applicability in determination of CPZ with acceptable percentage recovery. This method can thus be applied for real samples analysis.

![Fig. 3. Voltammograms of 0.1 mM CPZ in 0.1 PBS (pH 7.0) at various scan rates. (a) Curve a to h gives the scan rates of 25 mV S$^{-1}$ to 200 mV S$^{-1}$; (b) Linear plot of anodic peak currents verses square root of scan rates; (c) Linear plot of anodic peak currents verses the scan rates; (d) Linear plot of logarithmic anodic peak currents verses the logarithmic scan rates.](image-url)

Table 1

<table>
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<tr>
<th>Electrode</th>
<th>Analytical technique</th>
<th>pH</th>
<th>Linear range (μM L⁻¹)</th>
<th>LOD (μM L⁻¹)</th>
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<td>MGE⁹</td>
<td>CV⁺</td>
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<td>DPV⁺</td>
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<td>0.006</td>
<td>[34]</td>
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<td>0.1–350</td>
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<td>[24]</td>
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<tr>
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<td>DPV⁺</td>
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<td>0.1–40</td>
<td>3</td>
<td>[35]</td>
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<tr>
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<td>DPV⁺</td>
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Acknowledgements

The authors are grateful to the University Grant Commission-Basic Scientific Research, New Delhi, India for providing financial assistance and DST (SERB) for providing the instrumental facility.

References

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