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Electrochemical Determination of Thioridazine at Carbon Ionic Liquid Electrode

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ABSTRACT

In this manuscript a simple, rapid, and sensitive electrochemical method for the direct determination of thioridazine (TR) was developed. The electrochemical behavior of TR was studied at carbon ionic liquid electrode (CILE). The cyclic voltammetric results showed that CILE remarkably improved electrocatalytic activity towards the oxidation of TR in slightly acidic solutions. It led to a significant enhancement of the anodic peak current for TR with three anodic peaks at 0.59V, 0.78V and 0.93V, respectively and could effectively accumulate the drug at the electrode surface. The electrocatalytic performance was further exploited as a sensitive detection scheme for the determination of TR by differential-pulse voltammetry (DPV). Under optimized conditions, the calibration linear range and detection limit were 0.25 to 100 μM and 50 nM, respectively. The proposed method was successfully used to quantification of TR in pharmaceutical samples. Also the analytical performance of this sensor has been evaluated for detection of TR in human serum samples.

Keywords: Carbon ionic liquid electrode; Electrochemistry; Thioridazine

INTRODUCTION

More than 50 years ago the antipsychotic properties of some drugs were revealed [1]. Phenothiazines are common neuroleptic antipsychotics applied to medication of mental syndromes. Their derivatives are recognized by tricyclic rings with sulfur and nitrogen atoms at positions 5 and 10 [1,2]. They regularly act by blocking dopamine D_2 receptors [3]. Thioridazine (TR) which is chemically known as (10-[2-(1-methyl-2-piperidyl) ethyl]-2-methylthiophenothiazine) (Scheme 1) belongs to the antipsychotic phenothiazine group, and is applied as a tranquillizer and antidepressant in treating some psychotic disorders without potentiate anesthetics action and therapeutically significant anti-emetic or hypothermic effects. This drug is used generally for the medication of schizophrenia and the control of mania and agitation. It also may be prescribed for the management of anxiety states, a problematic behavior in children. A severe side effect of TR is the possibly deadly narcoleptics malignant syndrome [4,5].

The wide-spreading application of TR and the necessity for clinical and pharmacological investigation require fast and sensitive analytical techniques to determine the amount of TR in pharmaceutical formulations and

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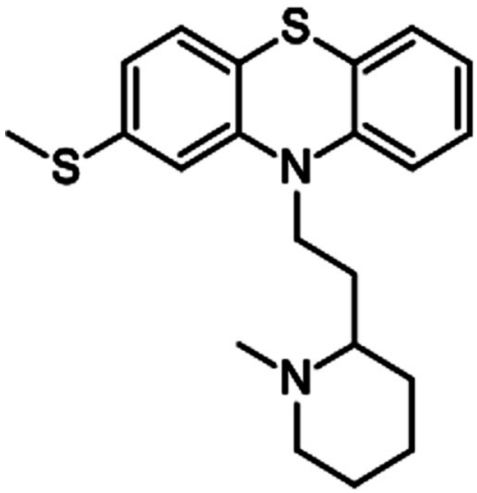
biological fluids. The most general techniques for the determination of TR in commercial dosage form were based on fluorometric [6], gas-liquid chromatographic [7], spectrophotometric [8,9] and high-performance liquid chromatographic (HPLC) methods [10,11]. Nevertheless these methods are time vesting, are solvent usage intensive, and require costly devices and instrumentation. The benefits of electroanalytical techniques in analysis of drugs are their simplicity, fast response and low cost equipment. However, only few electrochemical analysis of TR is reported [12,13].

For the first time carbon ionic liquid electrode (CILE) was introduced in 2006 as a new and high performance carbon composite electrode [14]. The basic idea for fabrication of this novel electrode was the replacement of classic nonconductive organic binders in carbon paste electrodes (CPEs) with a pyridinium-based ionic liquid. Some efficient behaviors of CILE comprise wide potential window in aqueous solutions, low background current, renewable surface, resistivity toward bio-molecules fouling and a rapid electron transfer [15]. Due to such exceptional behavior CILEs can be applied as proper sensors in electrochemical analysis of different biological compounds.

This study describes the application of CILE as a suitable sensor for investigation of TR electrochemical reaction as well as the use of DPV for sensitive quantification of this antipsychotic drug. The oxidation of TR was specified with the well-defined anodic response compared to conventional CPE. This characteristic suggests that the CILE can be successfully used for both approaches including the study of electrochemical behavior and the up-growth of new analytical procedures to be applied for the determination of TR.



Scheme 1. Molecular structure of TR.

EXPERIMENTAL

Reagents and Solutions

Potassium dihydrogen phosphate, dipotassium hydrogen phosphate and graphite powder were purchased from Merck and were used as received. TR was kindly supplied by Darou Pakhsh Pharmaceutical Company (Tehran, Iran) and used without prior purification. The ionic liquid, 1-octylpyridinum hexafluorophosphate, was synthesized as described elsewhere [16]. The 1.00×10^{-2} M stock solution of drug was prepared by dissolving an appropriate amount of TR in double distilled water and stored at 4 °C. Phosphate buffer (PBS) 0.1 M, pH 7 was used as supporting electrolyte. All solutions were freshly prepared with double distilled water. Daily-based fresh frozen male blood donors, obtained from Central Blood Transfusion Organization (Shiraz, Iran).

Electrode Preparation

CILE was fabricated by thoroughly hand-mixing the graphite powder and OPFP with a ratio of 50/50 (w/w) in a mortar and pestle, followed by packing the resulting paste firmly into the electrode cavity (1.8 mm i.d.) of a Teflon holder. In order to

have better homogeneity in the composite and to lower background current, the electrode was heated for 2 min in oven, to a temperature above the melting point of IL (m.p. ~ 65 °C) prior to use [17]. A copper wire inserted into the carbon paste provided the electrical contact. CPE was prepared by hand-mixing paraffin oil and graphite powder with 70/30 graphite/paraffin oil (w/w).

Apparatus

Voltammetric measurements were done by an Autolab electrochemical system (Eco-Chemie, Utrecht, The Netherlands) equipped with Autolab PGSTAT-302N, GPES software (Eco-Chemie, Utrecht, The Netherlands). The electrochemical cell was assembled with a conventional three electrode system: an Ag/AgCl/ KCl (3 M) reference electrode (Metrohm) and a platinum disk as a counter electrode. The working electrodes used in this study were CPE and CILE. All experiments were normally conducted at 25 °C without removing the dissolved oxygen.

RESULTS AND DISCUSSION

Electrocatalytic Properties of CILE toward Oxidation of TR

The cyclic voltammograms of TR (100μM) at CPE (dashed line) and CILE (solid line) in PBS 0.1M (pH=7) were shown in Figure 1. Three oxidation peaks at 0.59V, 0.78V and 0.93V were observed for CILE. It can be seen that the oxidation peak at the CPE was weak and wide due to slow electron transfer, while the response was significantly amplified at the CILE.

This performance is due to the electrocatalytic effect prompted by the presence of IL applied as pasting binder instead of conventional mineral oils. A possible description for the electrocatalytic effect of IL (OPFP) towards TR oxidation is that the IL used in the fabrication of the electrodes have properties like polar organic solvents and thus can extract TR from aqueous solution during adsorptive accumulation time and thus caused peak current enhancement at CILE [4].

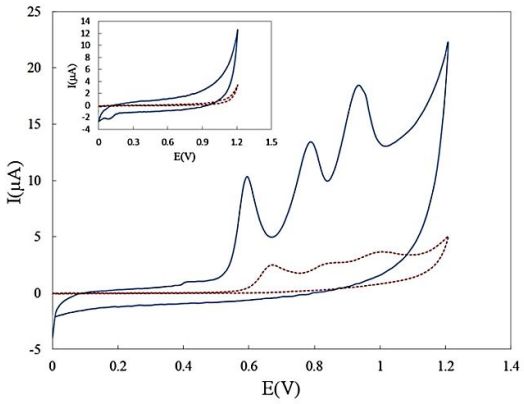


Fig. 1. Cyclic voltammograms of CPE (dashed line) and CILE (solid line) in PBS 0.1 M with pH 7 at a scan rate of 50mVs^{-1}; in the absence (inset) and presence of 100μM TR.

Effect of the Solution pH

The electrode reaction can be affected by the pH of the electrolyte. The electrooxidation of 1mM TR was studied over the pH range 2.0–8.0 in phosphate buffer solution by cyclic voltammetry (Figure 2a). Within the range of pH 2.0 to 8.0, peak current increased. Above pH 7, the peak current decreased dramatically. The highest anodic peak current was obtained in phosphate buffer with pH 7.0 (Figure 2b). Hence, pH 7.0 was selected as an optimum pH for remaining studies. A plot of peak potential versus pH has been illustrated (Figure 2c). A linear portion was observed in the range of pH from 2.0 to 8.0, with the slope of 0.0283 V/pH which indicates that unequal number of electrons and protons involved in redox process according to the following equation [18].

$$0.0592(h/n)\text{V/pH} \quad (1)$$

where *h* and *n* are the number of protons and electrons involved in the electrode process, respectively. It seems acceptable that the mechanism of TR oxidation includes the participation of one proton and two electrons [4] (scheme 2).

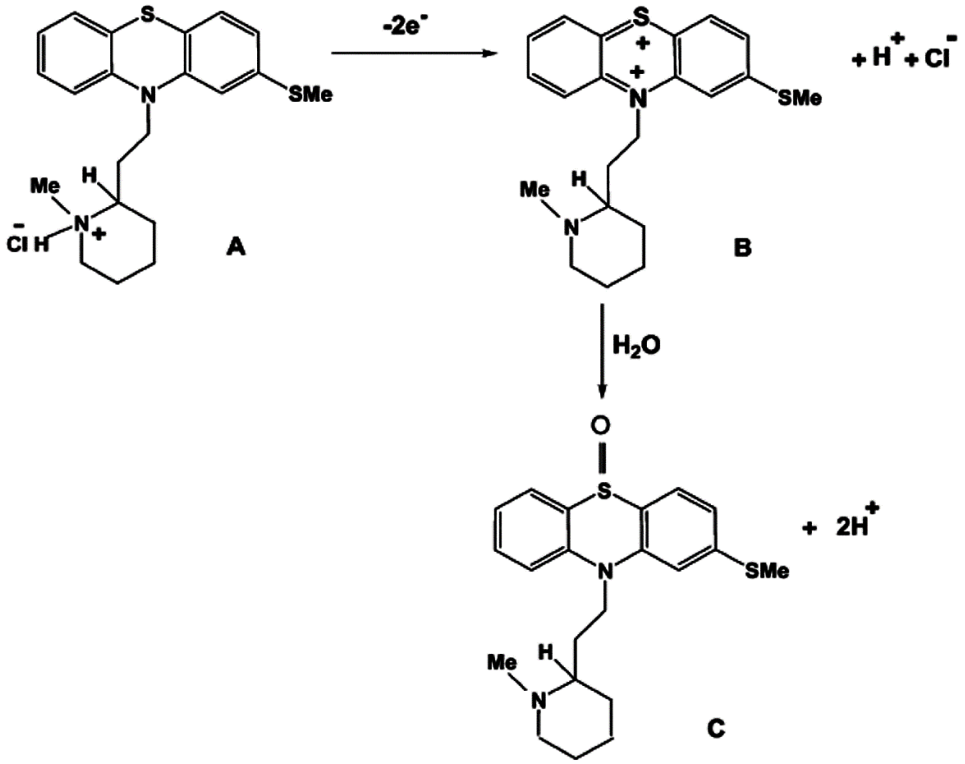
Scan Rate Effect Studies

To examine the predominant type of mass transport, effect of scan rates on the electrooxidation of TR was investigated using cyclic voltammetry over the range of 1-100 mVs^{-1} (Figure 3). The linear relation between anodic peak current and scan rate specifies that the oxidation is adsorption controlled (Figure 3 inset). Moreover, Plot of log anodic peak current vs. log scan rate (Figure 4b) was also linear over the range of (1-100mVs^{-1}). For an ideal reaction of surface species, a slope of 1.00 is acceptable and the slope of 0.85 is close to the expected value corroborates that the TR electrooxidation reaction is an adsorption-controlled process.

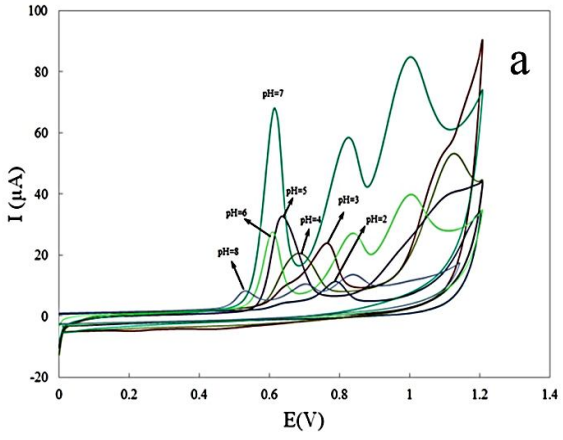
In addition with increasing scan rate, the oxidation peak potentials shift to more positive values, this also verifies the irreversible electrooxidation process.

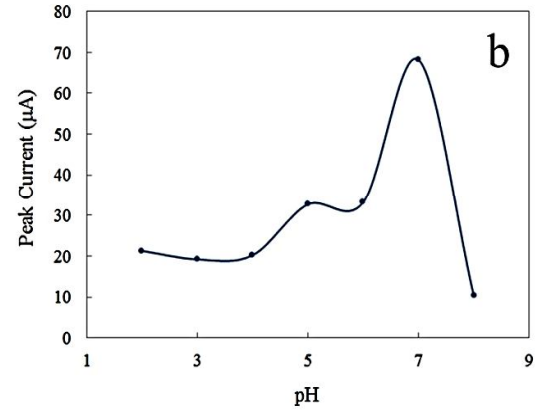
There was also a linear relation between the peak potential and log of scan rate with a correlation coefficient of 0.9911 by the following equation: E_{pa}= 0.0223 log ν + 0.5101. (Figure 4a) The Tafel slope (b) can be obtained from the slope of anodic peak potential versus log of sweep rate using Equation 1[19]:

E_{pa}= b/2 log v + constant. (3)



Scheme 2. The proposed mechanism for electrooxidation of TR.





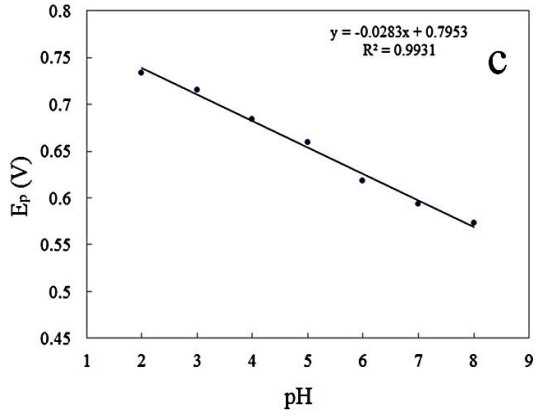


Fig. 2. (a) Effect of pH on the cyclic voltammograms recorded for a TR solution of 1 mM and scan rate of 0.1 Vs^{-1}. pH values: 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0. (b) Plot of anodic peak current versus pH and (c) plot of anodic peak potentials versus pH.

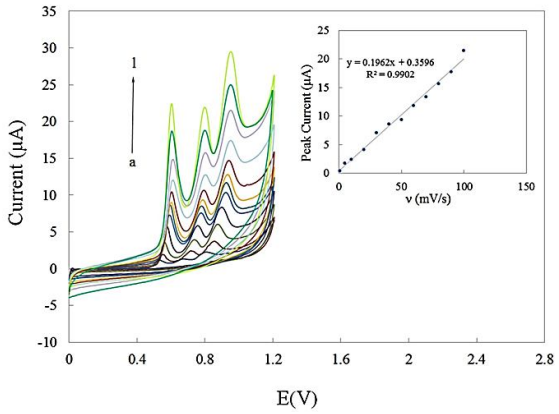
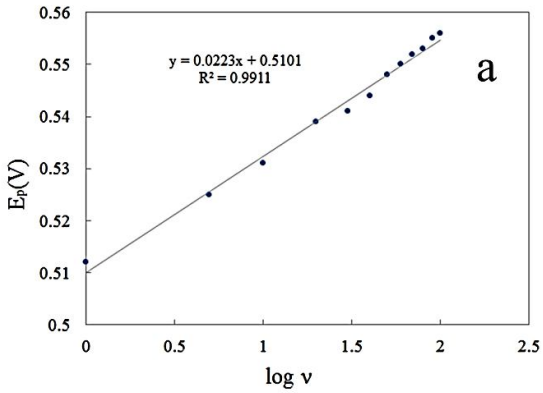


Fig. 3 Cyclic voltammograms of 100μM TR in PBS 0.1 M with pH 7.0 at different scan rates 1-100 mVs^{-1}.



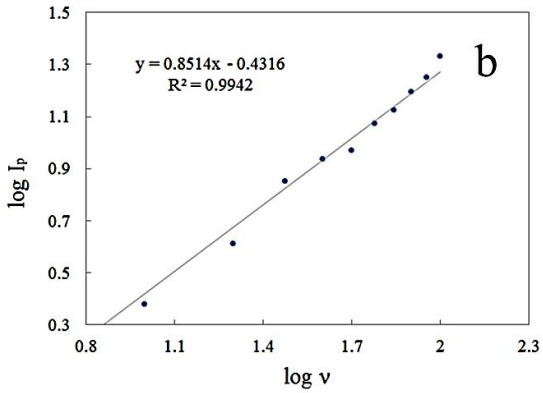


Fig. 4. (a) linear dependence of log peak current to scan rate in the range of 1-100 mVs^{-1} and (b) the plot of peak potential versus log scan rate for 100μM TR in PBS 0.1 M with pH 7.0.

Tafel slope was found to be 45 mV. By using the number of electrons that involved during TR oxidation (n=2) and the Tafel slope, the value of transfer coefficient was calculated according to following equation [20]:

$b = (2.303RT)/[(1-\alpha)nF]$ (4)

the value of α was found to be 0.34.

Effect of Accumulation Potential, and Accumulation Time

The influence of accumulation potential and accumulation time on the peak current of TR oxidation was investigated. The accumulation potential was studied in the range of 0.1 to 0.5 V and best anodic response was achieved for accumulation potential of 0.3 V. The accumulation time was studied in the range of 0 to 420s. The peak current was increased with increasing the accumulation time up to 270s and then decreased. This could be due to the adsorption of TR on CILE became saturated.

Differential Pulse Voltammetry of TR at CILE

In order to develop a voltammetric method for quantitative determination TR, differential pulse voltammetry technique was used as a sensitive analytical procedure. The phosphate buffer solution of pH 7.0 was selected as supporting electrolyte. Figure 4 illustrates the differential pulse voltammograms obtained for a series of TR solution with different concentrations and the respective calibration curve (inset). Good linearity was found in the concentration ranges of 2.5×10^{-6} to 1.0×10^{-4} M, which is represented by the line equation:

$$i_p\,(\mu A) = 1.0891\ C_{TR}\ (\mu M) + 0.6021 \quad (R^2=0.9965)$$

The limit of detection (LOD) was calculated by the parameters obtained from the analytical curve, using LOD = $3S_b/m$, where S_b is the standard deviation of blank (n=7) and m is the slope of calibration curve. Under the given conditions, the calculated LOD was found to be 5.0×10^{-8}. The relative standard deviation (RSD) of the five times repeated measurement of 30μM TR with the same electrode was 4.21%, whereas the RSD was 4.70% for 5 different electrodes.

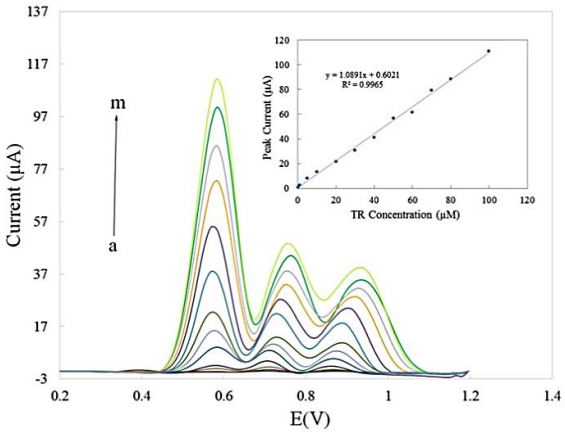


Fig. 5 Differential pulse voltammograms for various concentrations of TR (a) 0.25, (b) 0.7, (c) 1, (d) 5, (e) 10, (f) 20, (g) 30, (h) 40, (i) 50, (j) 60, (k) 70, (l) 80, (m) 100 μM, at CILE in 0.1M PBS (pH=7.0) accumulation potential of 0.3 V and accumulation time of 270s. Inset: Dependence of peak currents on the concentration of TR.

Interference Studies

To investigate the interference influence, some biological coexistents frequently exist in the body fluids such as glucose, ascorbic acid, and uric acid; were evaluated. The tolerance limit was defined as the maximum concentration of the interfering substance that caused an error less than ±5% for determination of TR. Under the optimum experimental conditions, the effect of interference on the voltammetric response of 30 μM was examined. The results showed that 10-fold excess of glucose; 5-fold excess of

ascorbic acid and 5-fold excess of uric acid; did not interfere with the analysis of TR.

Real Sample Analysis

The proposed method was used for the quantification of TR content in pharmaceutical preparations (nominal contain 10 mg TR/tablet). Five tablets of TR (Pars Daru Company, Tehran, Iran) were accurately weighed and triturated to fine powder in a mortar. Then, precise amount of the powdered sample corresponding to a solution of 1×10^{-4} M TR was dissolved in methanol by sonication for 10 min filtered into a 50 mL volume calibrated flask and diluted with double distilled water. A known volume of this solution was spiked into a 25 mL aliquot of the supporting electrolyte in the volumetric flask, followed by spikes of the standard TR solution. The standard addition method was applied in these experiments. The amounts of TR obtained in pharmaceutical formulations agree well with the label contents (Table 1).

In addition, to evaluate the competency of the proposed method for the analysis of real samples, it was applied for the analysis of the human blood plasma sample. A 10 ml human plasma sample was deproteinized by adding 2 ml of 10% (w/w) trichloroacetic acid. Then the solution was centrifuged and diluted 10 times with 0.1M PBS with pH 7.0. The proper amount of this diluted sample was transferred to the electrochemical cell for determination of TR. The DPV measurements were done as mentioned before. The results are presented in Table 2. The results demonstrated good quantitative recoveries which show suitability of proposed method for real sample analysis.

Table 1. Determination of TR in pharmaceutical formulations

No.	TR added (μM)	TR found[a] (μM)	Recovery (%)
1	0	4.57(±0.12)	-
2	2	6.38(±0.11)	90.05
3	4	8.33(±0.13)	93.51
4	6	10.60(±0.15)	100.4

[a] Average of three determination

Table 2. Recovery study of TR in human blood plasma sample.

No.	TR added (μM)	TR found (μM)	Recovery (%)
1	0	ND[a]	-
2	2	1.93(±0.17)	96.5
3	4	4.05(±0.13)	101.2
4	6	5.68(±0.16)	94.7

[a] Not detected

CONCLUSIONS

Carbon ionic liquid electrode can be used as a sensitive analytical sensor for electrochemical quantification of TR. The electrode displayed admirable response compared with conventional electrodes. We have also offered an appropriate analytical methodology for quantitative determination of TR, based on differential pulse voltammetry which exhibited excellent performance due to electrocatalytic effect of the proposed electrode.

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