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A Carbon Nanocomposite Ionic Liquid Electrode Based on Montmorillonite Nanoclay for Sensitive Voltammetric Determination of Thioridazine

P. Aberoomand Azar[1,*], *F. Farjami*[2], *M. Saber Tehrani*[1], *E. Eslami*[1]

[1] Department of Chemistry, Science and Research Branch, Islamic Azad University, P.O. Box 1415-775, Tehran, Iran
[2] Department of Chemistry, Science and Research Branch, Islamic Azad University, P.O. Box 73715-181, Fars, Iran
[*]E-mail: parvizaberoomand@gmail.com

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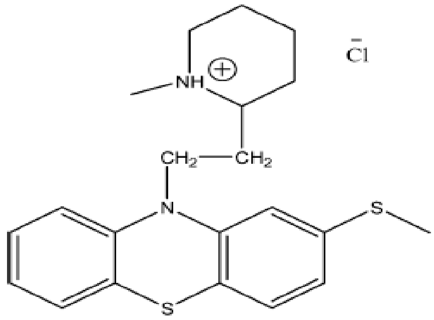
A carbon nanocomposite electrode has been designed by incorporation of montmorillonite nanoclay into the carbon ionic liquid electrode for the electrochemical determination of (10-[2-(1-methyl-2-piperidyl) ethyl]-2-methylthiophenothiazine) (thioridazine).The surface of the proposed electrode was characterized by scanning electron microscopy. Adsorptive stripping voltammetry was applied as a very sensitive analytical method for the determination of sub-micromolar amounts of thioridazine. A linear dynamic range of 0.1- 50 µM with a detection limit of 21 nM thioridazine was obtained. The prepared modified electrode shows several advantages such as simple preparation method, excellent activity in physiological conditions, low detection limit, long-term stability and remarkable voltammetric reproducibility. The modified electrode was employed for the determination of thioridazine in pharmaceutical formulations and blood serum samples.

Keywords: Carbon ionic liquid electrode, Electrochemistry, Nanoclay, Thioridazine ,voltammetry

1. INTRODUCTION

Thioridazine hydrochloride, (TR-HCl), (Scheme 1) a member of the antipsychotic phenothiazine group, used as a tranquillizer and antidepressant in managing some psychiatric disorders without potentiate anesthetics action and therapeutically significant anti-emetic or hypothermic effects. This drug is used mainly in the treatment of schizophrenia and the control of mania and agitation. It may be used in the management of anxiety states, a behavior problem in children [1]. A serious side effect of TR is the potentially fatal narcoleptics malignant syndrome [1]. Various methods such as chromatography [2,3], spectroscopy [4], titrimetry [5], chemiluminescence [6], capillary electrophoresis with amperometric detection [7], and electrochemical methods [1,8-15] have been reported for the determination of phenothiazine drugs in pharmaceutical preparations and body fluids. Electrochemical methods may be used for this purpose due to their excellent sensitivity, short analysis time, simplicity, and the low costs involved in the implementation of these powerful tools for measuring different analytes.



Scheme 1. Chemical structure of (TR-HCl)

The application of nanomaterials in various fields of science and technology has been extensively developed because of the unique properties of these materials [16-17]. Chemically modified electrodes (CMEs) have attracted much attention due to their significant advantages [18-20]. Various modifers reported for the voltammetric determination of different molecules/metal ions are viz., nanomaterials, [21-22] macrocycles, [23-24], inorganic complexes, [25-26] etc. Clays have attracted great attention due to their unique properties. Clays are stable aluminosilicates with high cation exchange capacity, and exfoliated clay particles have a platelet shape with nanoscopic size [27]. Despite their low electrical conductivity, some properties of the clays such as their ionic exchange capacity, good catalytic support, large surface area, mechanical stability and low cost make them suitable as electrode surface modifiers [28]. In green chemistry terms, environmentally friendly analytical protocols and devices, negligible waste, and nontoxic materials make clay minerals of considerable interest to the analytical community [29]. Clays are also mixed with carbon paste to enhance the adsorptive and ion-exchange properties of the electrode [30]. Montmorillonite nanoclay with its inherent layered inorganic nanostructure is a member in the smectite group of clays [31-33] and has a high affinity for several substances (e.g., heavy metals and organic molecules)[28, 33]. High performance carbon ionic liquid electrodes (CILE) has been proposed as a kind of chemically modified carbon paste electrode (CPE) and was used for different electrochemical applications [30,34]. Substituting the traditional liquid paraffin with ILs, CILE has exhibited advantages such as high sensitivity, stable electrochemical responses, good anti-fouling ability and inherent electrocatalytic activity [35]. Chemically modified CILE has also been prepared which can combine attractive properties (the advantages) of modifier and the CILE [36-38]. In the present work the nanocomposite electrode was applied for electrochemical detection of TR. The results illustrate that the electrode exhibits an excellent route to the sensitive determination of TR. The proposed electrode is simple to prepare, reproducible, easily renewable and cost effective.

2. MATERIALS AND METHODS

2.1. Reagents

Thioridazine hydrochloride (TR-HCl), pyridine, diethyl ether, were purchased from Merck. Montmorillonite nanoclay, graphite powder (particle size<100 μm) (Aldrich) and ammonium hexafluorophosphate, iodooctane (Fluka) were used as received. All other chemicals were of analytical grade from Merck. The ionic liquid, octylpyridinium iodide, was synthesized as described elsewhere [39]. $[OPy]^+ [PF_6]^-$ was obtained by anion exchange of octylpyridinium- iodide with ammonium hexafluorophosphate. Deionized distilled water was used to prepare all solutions. Briton-Robinson buffer solution (H_3PO_4+H_3BO_3+CH_3COOH) were used to study the effect of pH on the analytical signal. Phosphate buffer solution (PBS) 0.07 M, pH 7.0 was used as supporting electrolyte. The pharmaceutical samples were selected from TR-HCl (Minoo Pharmaceutical- Company (80 mg), Tehran, Iran). Before use, the tablets were ground into powder, dissolved in water, filtered and diluted to certain volume. Daily-based fresh frozen female blood donors, obtained from Central Blood Transfusion Organization (Shiraz, Iran).

2.2. Electrode preparation

Carbon ionic liquid electrode (CILE) was prepared by hand-mixing, in a mortar, the graphite powder and $[OPy]^+[PF_6]^-$ with a ratio of 50/50 (w/w). A portion of the resulting paste was packed firmly into the cavity (2.0 mm i.d.) of a Teflon holder. Note that in order to have better homogeneity in the composite and to lower background current, the electrode should be heated (e.g. by using a hair drier) to a temperature above the melting point of IL (m.p. ~ 65 ^oC) prior to use [30]. The electric contact was established with a copper wire contact to the carbon composite. A new surface was obtained by smoothing the electrode onto a smooth paper. Nanoclay modified carbon ionic liquid electrode (NC –CILE) was prepared the same as CILE with the weighed amounts of graphite powder, ionic liquid, and nanoclay (40%:50%:10%, wt %), respectively.

2.3. Apparatus

Electrochemical measurements were done with a galvano potentiostat Behpajooh Co. model BHP2063+. The electrochemical cell was assembled with a conventional three-electrode system; with a saturated calomel electrode as a reference electrode (SCE) and a platinum disk as a counter electrode. The cell was a one-compartment cell with an internal volume of 10 mL. All experiments were typically conducted at room temperature. Scanning electron microscopy (SEM) images were observed using

SEM (Philips XL 30 and S-4160) with gold coating equipped with energy dispersive X-ray spectroscopy (EDX).

2.4. Procedure

A certain volume of TR stock solution and 9.0 mL 0.07 M PBS pH 7.0 were added into an electrochemical cell and then the three-electrode system was installed on it. This solution (0.1mM) was applied for optimization of parameters. For TR, an accumulation potential of 0 V was applied to the NC –CILE for 240 s while the solution was stirred at 400 rpm with the magnetic stirrer. At the end of the accumulation period, the stirring was stopped, and a 5 s rest period was allowed for the solution to become quiescent. A new surface was readily obtained by smoothing the electrode for one minute onto a smooth paper. The elctrode was stored in air at ambient temperature between experminets. The voltammogram was then recorded by scanning the potential towards the positive direction from 0 to 0.9V versus SCE with scan rate of 50mVs^{-1}. The quantitative determination of TR was achieved by measuring its oxidation peak current after background subtraction.

3. RESULTS AND DISCUSSION

3.1. Characterization of NC-CILE

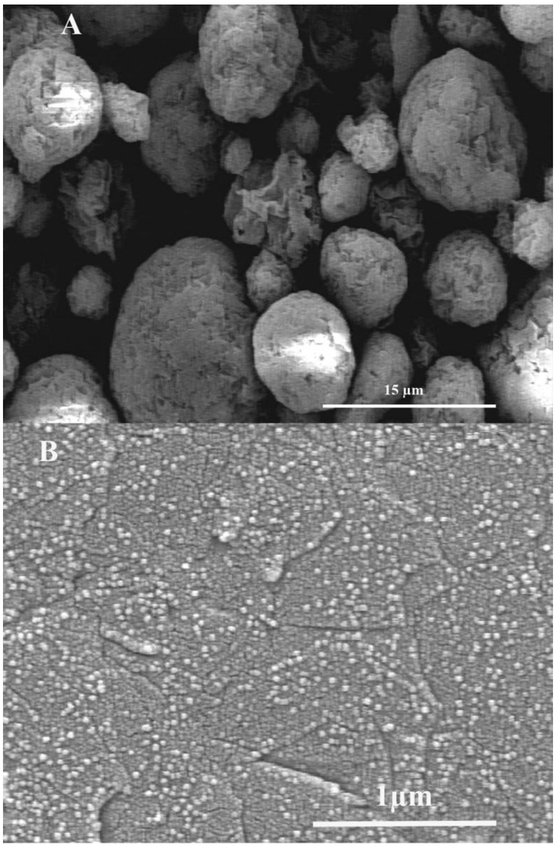


Figure 1. SEM micrographs of nanoclays as received (A), NC-CILE (B).

In this study, nanoclays are incorporated into the CILE (NC-CILE). Figure 1 shows SEM micrographs of nanoclays (as received) (A) and NC-CILE (B). As it can be seen, nanoclays are in the form of large and small aggregates. However, after the incorporation of nanoclays into the CILE, nanoclay particles are dispersed in the form of homogeneous nanostructures with a dimension about 30 nm. Certainly, the narrowly dispersed nanoparticles enhance the contact surface area of the clays with the solution.

3.2. Electrochemical characterization of TR on the surface of CILE and NC-CILE

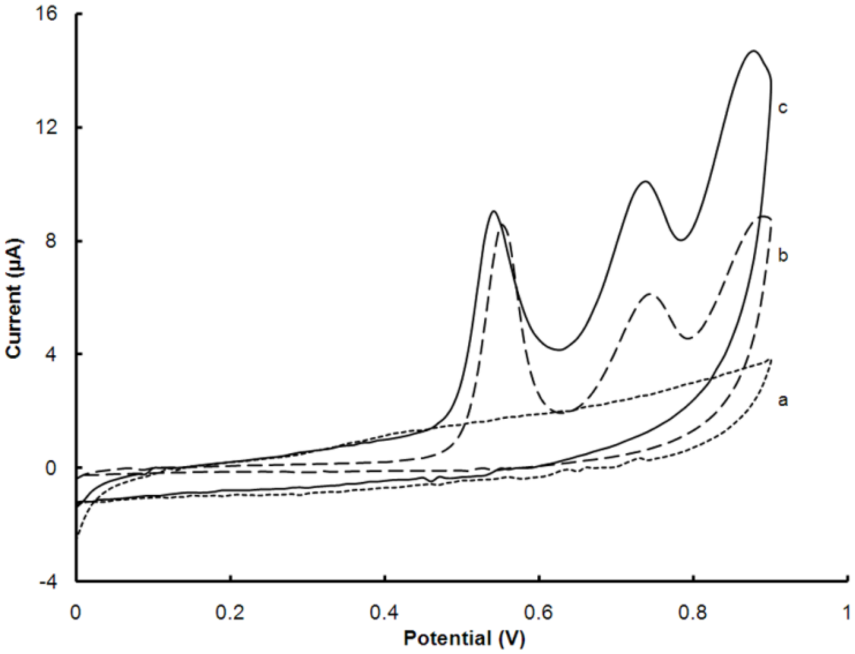


Figure 2. CVs of NC –CILE (a, c) and CILE (b) in 0.07M PBS (pH 7.0) in the presence (b, c) and in the absence (a) of 0.1mM TR at a scan rate of 50 mVs^{-1}.

Cyclic voltammograms (CVs) of CILE and NC –CILE were obtained at a potential sweep rate of 50 mV s^{-1} in PBS (0.07M pH 7) containing 0.1 mM TR and given in Figure 2. With both CILE (curve b) and NC-CILE (curve c) three oxidation peaks were obtained at about 0.54, 0.75, 0.87 V. Similar behavior has been observed for TR oxidation and other phenothiazine drugs such as chlorpromazine on a GCE [40], CPE [12] and Au electrode [41] and the details of the oxidation mechanism were reported previously [12, 40-41]. Under the same conditions and in the absence of TR, no peak was observed on bare NC –CILE (curve a) and CILE (not shown) in the working potential range. The first oxidation peak potential of TR on both CILE and NC-CILE are slightly lower than those reported on a carbon paste electrode modified with ZnS nanoparticles (~0.65 V) [12], a GC electrode modified with Nitrogen-doped carbon nanotubes /gold composites (~ 0.58 V) [13], a GC electrode (~ 0.59 V) [14], a carbon paste electrode modified with β-cyclodextrin (0.56V) [15].

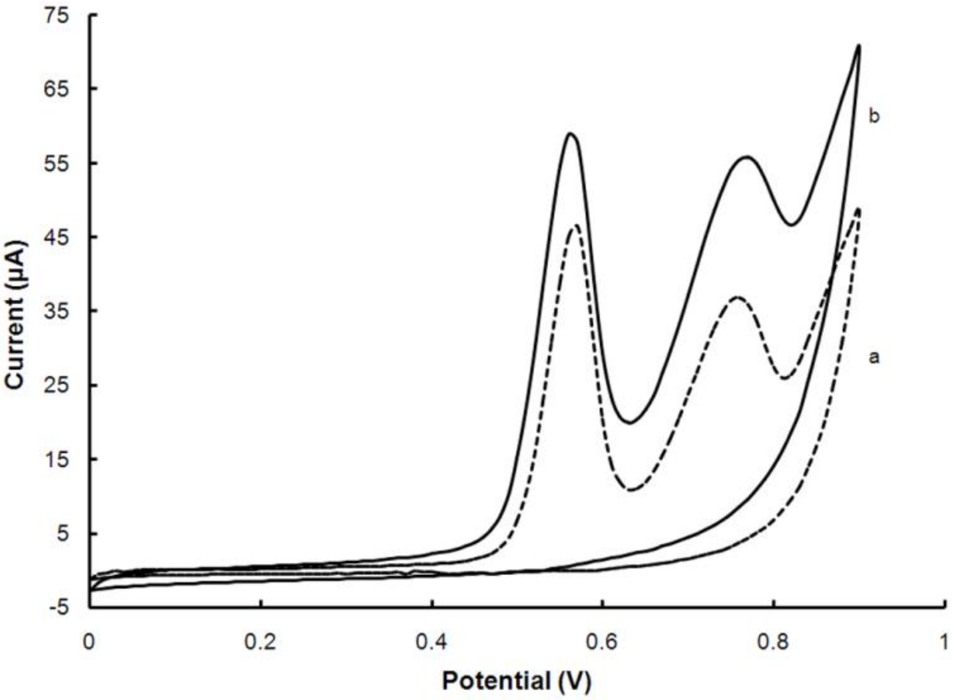


Figure 3. CVs of 0.1mM TR in 0.07M PBS (pH 7.0)at a scan rate of 50 mVs^{-1} (a) CILE , (b) NC – CILE after 240 s preconcentration time (accumulation potential 0 V).

The currents of the oxidation peak at about 0.54 V (the first oxidation peak) were almost equal at both CILE and NC-CILE, but the peak currents increased after a certain accumulation time. Figure 3 shows CVs for 0.1 mM TR following 240s adsorptive accumulation at both electrodes. The use of accumulation period results in peak current enhancements for both CILE and NC- CILE. However the enhancement is larger for NC-CILE. The reasons for which are as follows; 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 both CILE and NC-CILE. On the other hand, the structural characteristic of montmorillonite nanoclay incorporated into NC-CILE should be considered. It possesses a physical structure consisting of sheets of aluminosilicates [42], which is neutralized by the intercalation of compensating, exchangeable Na^+. The Na^+ ion can be exchanged with a wide variety of hydrated inorganic cations or organic cations [43]. Exchange of Na^+ with the cations of the ILs has been reported in the literature [42]. Several other researchers also applied the cation exchange property of montomorillonit for the adsorption of some cationic electroactive compounds on the surface of electrode [44-45]. Since TR are protonated and have positive charge in the working solution (0.07 M PBS, pH7.0), their interactions with montomorillonite nanoclays are similar to the other organic cationic species in this matrix. It can be concluded that the synergistic effect of both nanoclays and IL can effectually increase the rates of drug preconcentration from aqueous solution to the electrode surface by ion exchange and adsorption. Therefore, NC-CILE provides higher currents and thus higher sensitivity for the same concentration of TR. Therefore, NC-CILE was selected for further studies.

3.3. Effect of pH

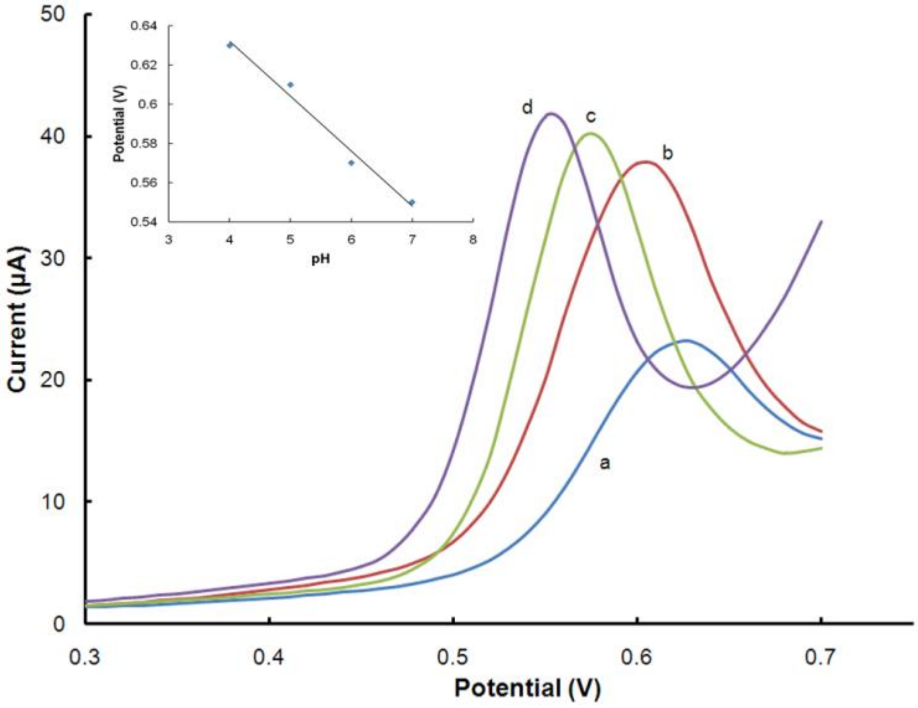
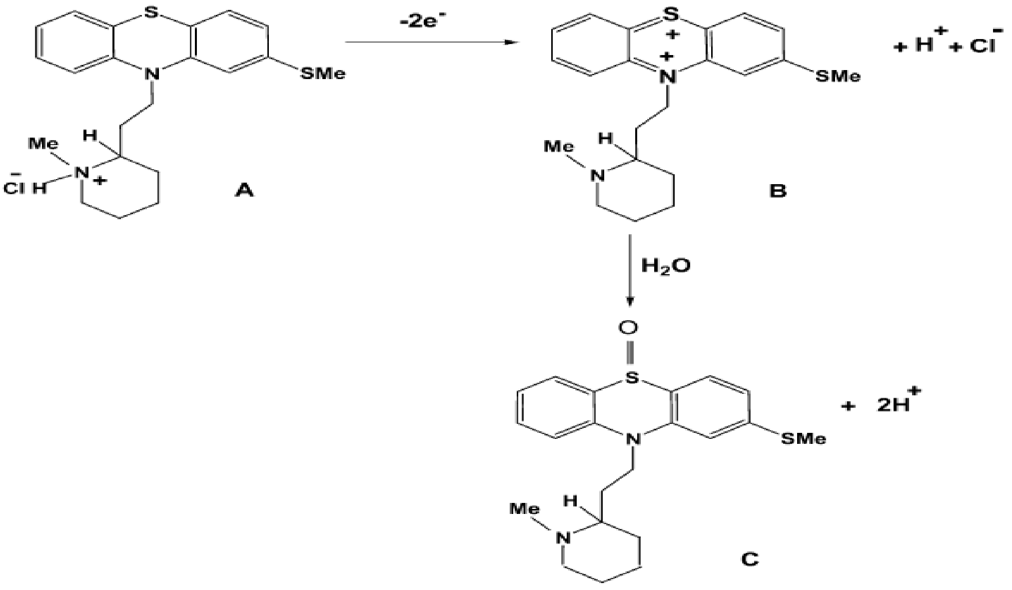


Figure 4. CVs of 0.1mM TR at the NC –CILE. pH: (a) 4.0; (b) 5.0; (c) 6.0 ; (d) 7.0; at 50mVs^{-1}. Inset: plot of oxidation peak potential vs. pH.

CVs of 0.1 mM TR were obtained in the pH range 4–7 employing the Britton–Robinson (B. R.) buffer and the results were presented in Figure 4.



Scheme 2. Proposed mechanism for electrooxidation of TR.

At pH values higher than 8, the solubility of the drugs is somewhat lowered due to the hydrophobic character of deprotonated molecule of TR [46]. Therefore, the range of pH selected was from 4 to 7. As seen, with solution pH raising the peak current increased and reached to the maximum value at pH 7. Since the pH 7 PBS gave the same response in terms of the peak current and the peak shape for TR, PBS with pH 7 was used as the supporting electrolyte in all voltammetric determinations. The plot of oxidation peak potential (E_p) vs. pH indicates that the E_p of TR (Figure 4, inset) varies linearly with pH. E_p is shifted toward negative values with increasing pH between 4 and 7 by the slopes of -0.028 V/pH. The linear regression equation is $E_p(V)=0.744–0.028$ pH. The slope of -0.028V/pH for TR oxidation indicating that a mechanism comprising two electrons and two protons (Scheme 2) in the electrochemical reaction. This is consistent with the previously proposed mechanism for the TR oxidation [12,41].

3.4. Effect of modifier

The amount of modifier can change the properties and functions of the electrode surface. The influence of the amounts of nanoclay on the voltammetric response of the NC –CILE was evaluated. Four electrodes containing different amounts of nanoclay (2.5, 5, 10 and 15, % weight percent ratio) were prepared and examined for their voltammetric signals under identical conditions. Maximum peak current for TR was obtained for 10% modifier in the CILE. The results indicated that by increasing the amount of modifier up to 10% the anodic peak current increased, whereas higher content of the modifier caused a decrease in the peak current. This is because the sites for adsorption increased with the increase of nanoclay percentage in the modified electrode, while the excess of nanoclay increases the resistance of the electrode which results in enhanced resistance to the electron transfer. Consequently a NC –CILE (10%, w/w) was used in further studies.

3.5. Effect of accumulation potential and accumulation time

The accumulation potential is also a major factor which affects the response sensitivity. The effect of accumulation potential on the peak current of TR was examined over the range of −0.5 to 1 V keeping the accumulation time 240s. The oxidation peak current increased up to 0 V. Therefore, an optimal accumulation potential of 0 V was used for further studies. An increase in the accumulation time improves the sensitivity of the determination. The accumulation time was changed from 0 to 300 s employing optimized accumulation potential value. It was observed that the peak current increased with accumulation time, the more TR was adsorbed and thus the peak currents became larger, and reached to a constant value after a certain accumulation period. Therefore, An accumulation time of 240 s was chosen for further experiments.

3.6. Effect of scan rate

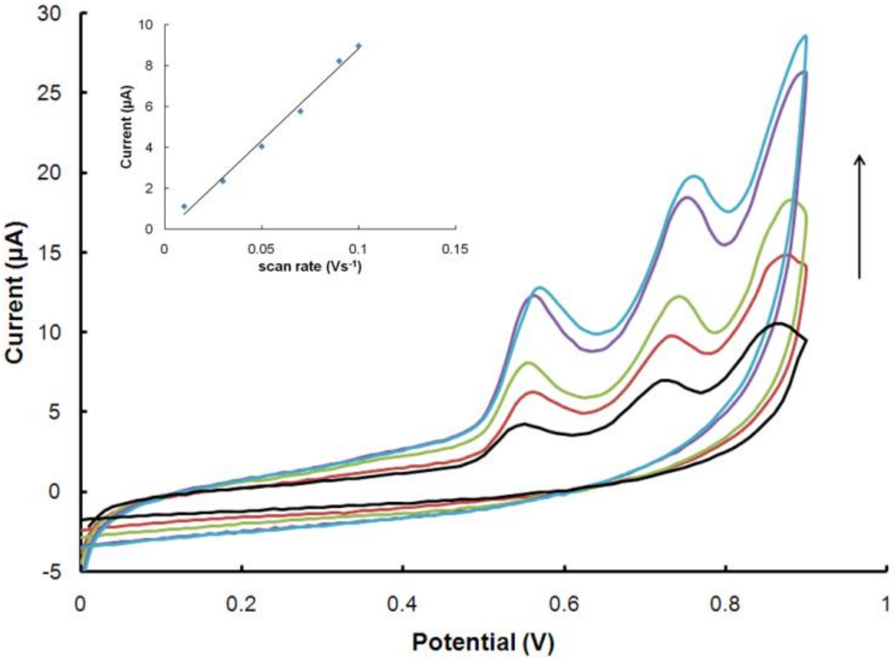


Figure 5. CVs of NC –CILE in0.07M PBS (pH 7.0) containing 0.1 mM TR at various scan rates. Inset: plot of peak current vs. scan rate.

To examine the predominant type of mass transport, a study was carried out using cyclic voltammetry. Figure 5 shows CVs of 0.1 mM TR at the modified electrode in buffered solution of pH 7.0 at different scan rates from10 to 100mVs^{-1}. With scan rate increasing, the anodic peak grew and the oxidation peak potential shifted to more positive potentials confirming the kinetic limitation in the electrochemical reaction [12]. The peak current is linearly proportional to scan rates (Figure 5, the inset). Plot of log (peak current) vs. log (scan rate) for the surface-adsorbed TR, was also linear (i_p=0.92ν+1.84(R^2 =0.990)) over the 10-100 mVs^{-1} range. A slope of 1.00 is expected for an ideal reaction of surface species and the slope of 0.92 is close to the expected value indicating the TR electrooxidation reaction is an adsorption controlled process.

3.7. Linear range and limit of detection

Under optimum conditions, the electrochemical reactions of different concentration of TR after 240s accumulation time have been studied and the CVs are shown in Figure 6. The calibration graph of current versus TR concentration in the range of 0.1–50 µM was linear (Figure 6, the inset) and equation can be described as follows:

$$Ip\ (\mu A)=0.845+1.380C\ (\mu M)(\ R^2=0.991)\,,$$

The detection limit for TR was found to be 21 nM. The responses of NC-CILE in terms of linear range, sensitivity and detection limit were compared to the other modified electrodes reported in the literature (Table 1) [1, 40, 12-15].

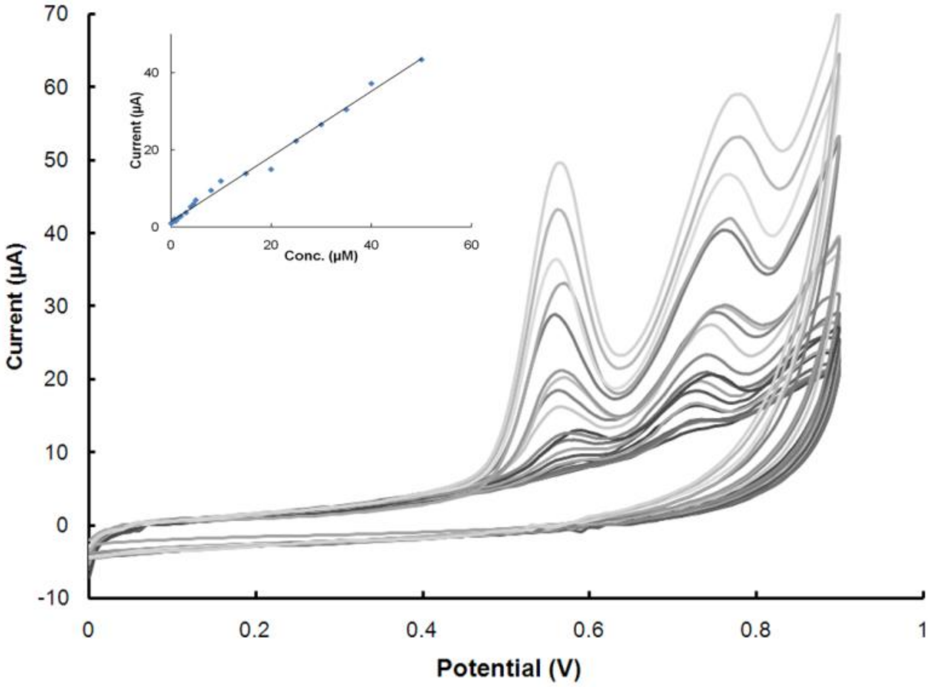


Figure 6. CVs of NC-CILE for different concentrations of TR in 0.07M PBS (pH 7.0), accumulation time 240 s and accumulation potential 0 V. Inset shows the calibration curve of peak current vs. TR concentration.

Table1. Electrochemical detection of TR reported at various electrodes

Modified electrodes	Linear range (µM)	Detection Limit (nM)	References
GCE	100-1000	NR*	[40]
CoNP/MWCNT/GCE	0. 1-100	50	[1]
ZnS/CPE	0.1-36	65	[12]
N-CNTs/ gold-modified GCE	12-850	1300	[13]
GCE	3.2-750	205	[14]
β-CD-CPE	0.01-0.1	7	[15]
NC-CILE	0.1-50	21	This work
• Not reported			

Except for one case [15], the detection limit of this work is the best among the works have ever been published for the electrochemical determination of TR. The linear range of calibration curve was also better than most of the previously reported works [12,15].

3.8. Stability, repeatability and reproducibility of the electrode

The stability of the proposed nanocomposite electrode was checked by recording the response of the electrode in 2 µM of TR after every few days. The NC-CILE shows high stability for TR detection and retains 89% of its original response to TR after 30 days of storage. The repeatability was estimated through the relative standard deviation of 7 replicate measurements of a 0.07 M PBS (pH7.0) containing 2 µM of TR. The relative standards deviation (RSDs) of 2.24% revealed good repeatability. The responses of four similar electrodes were separately measured toward 2 µM TR, and RSDs of 2.7% was obtained confirming high reproducibility of the fabrication method.

The response of the proposed composite electrode was evaluated toward some common species found in biological fluids such as glucose, ascorbic acid, uric acid. The tolerance limit was defined as the maximum concentration ratio of interfere/TR causing an error less than ±5.0% for the determination of TR. In the presence of 10 µM TR the results showed that 120-fold excess of glucose; 100- fold excess of ascorbic acid and 50-fold excess of uric acid; did not interfere with the analysis of TR. .The results demonstrated good selectivity for the proposed electrode.

3.9. Real sample analysis

To evaluate the applicability of the proposed method, the NC –CILE was used for the measurement of TR content in pharmaceutical preparations. Five tablets of TR were accurately weighed and ground to fine powder. Then, definite amount of the powdered samples corresponding to a solution of 1×10^{-4} M TR was dissolved in double distilled water by sonication for 10 min, filtered into a 50.0 mL volume calibrated flask and diluted with double distilled water. A known volume of this solution was spiked into a 10-mL aliquot of the supporting electrolyte in the volumetric flask, followed by spikes of the standard TR solution.

Table 2. Determination of TR in pharmaceutical formulations and body fluids using the proposed method (n=3).

Sample	Added(µM)	Found (µM)	Recovery (%)
Tablet	0	0.43(±0.02)	-
	0.5	0.96(±0.04)	106.0
	1.0	1.47(±0.03)	104.0
	1.5	1.89(±0.01)	97.33
Blood serum	0	N.D.*	-
	0.5	0.49(±0.03)	98.0
	1.0	1.02(±0.04)	102
	1.5	1.49(±0.06)	99.3

- Not detected

The amounts of TR obtained in pharmaceutical formulations agree well with the label contents (Table 2). The NC –CILE was also used for the analysis of the blood serum sample using the standard addition method. The Blood serum sample was deproteinized by adding 2 ml of 10% (w/w) trichloroacetic acid solution to 10 ml sample and the solution was centrifuged then the sample was diluted 10 times with 0.07M PBS with pH 7.0. then appropriate amounts of this diluted sample was transferred to the electrochemical cell for the determination of TR. The results are presented in Table 2. The results show good quantitative recoveries which imply successful applicability of this method for real sample analysis.

4.CONCLUSION

In this work, CILE modified with montomorillonite nanoclay (NC –CILE) was demonstrated as a new and effective electrode for sensitive determination of TR. An effective accumulation of the drug molecules has been found on the electrode due to synergistic effect of nanoclays and IL. High stability and reproducibility as well as the ease of preparation, low cost and surface renewal made this electrode ideal for the determination of TR in pharmaceutical formulations and blood sample.

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