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Electrochemical determination of carbamazepin in the presence of paracetamol using a carbon ionic liquid paste electrode modified with a three-dimensional graphene/MWCNT hybrid composite film

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ABSTRACT

In this research work, a carbon ionic liquid paste electrode (CILPE) based on butyl-3-methylimidazolium bis (trifluoromethylsulfonyl) imide ([bmim] NTF2) was fabricated and further modified with graphene/multiwall carbon nanotube (GR/MWCNT) hybrid composite. The modified electrode (GR/MWCNT/CILPE) was used for measurement of carbamazepine (CBZ) in the presence of paracetamol (PA) with an excellent electrochemical catalytic behavior. The application of the electrode was investigated by cyclic voltammetry and differential pulse voltammetry. The oxidation peak currents of CBZ and PA were linear at the ranges of 1–60 μM and 2–80 μM, respectively. Also, the detection limits for CBZ and PA were 0.233 μM and 0.262 μM, respectively. The proposed sensor was successfully applied for the determination of CBZ and PA in tablet and urine samples.

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1. Introduction

Carbamazepine (CBZ) (Fig. 1a), is an anticonvulsant, antiepileptic and mood stabilizing drug which is used primarily in the treatment of epilepsy and bipolar disorder. It can also be administered to patients who have other illnesses including schizophrenia, neuromyotonia, attention-deficit hyperactivity disorder (ADHD), and post-traumatic stress disorder [1,2]. As a result of its widespread use, CBZ determination in biological and pharmaceutical samples is of great importance. Several analytical methods have been used for determination of CBZ in pharmaceutical formulations and biological samples including capillary electrophoresis [3], liquid chromatography [4–6] and electrochemical methods [7,8]. Although liquid chromatography has been widely recommended for determination of CBZ, because of its high sensitivity and selectivity [9], but it is time consuming, solvent usage intensive and requires expensive devices and maintenance.

Paracetamol (PA), (Fig. 1b) has been used comprehensively all over the world as the reducer of fever and as a pain killer for the relief of moderate pain associated with backache, headache, arthritis and post-operative pain [10]. However, the overdose of PA can lead to the accumulation of toxic metabolites which may cause hepatotoxicity and nephrotoxicity [11]. Several analytical methods such as spectrophotometry [12], chromatography [13], capillary electrophoresis [14] and

electrochemical methods [15,16] have been developed for determination of paracetamol in solutions. Whereas, combination drugs consisting of paracetamol and carbamazepine are widely used as analgesic and antipyretic agents for treating the symptoms of different painful processes, thus a simple, rapid and reliable method that could be easily and widely used for the simultaneous quantitative estimation of these compounds is necessary.

Among the different analytical methods, electrochemical determination has proved to be sensitive and reliable for determination of numerous electroactive components [17–19]. On the other hand, the poor ability of the bare electrodes in direct electrochemical activity of different electroactive materials has led to interest in the use of mediators and modified electrodes to catalyze the electrochemical oxidation and/or reduction of them [20,21].

MWCNTs have been widely used in electrochemistry due to their unique one-dimensional (1D) structural, electronic, and physical properties. In the field of chemically modified electrode, one of the most important characteristics of MWCNTs is their reported ability to promote electron-transfer process [22–26].

Graphene (GR) a 2D carbon material comprised of a single sheet of hexagonally packed carbon atoms [27,28], has attracted tremendous attention because of its unique nanostructure and extraordinary electrocatalytic properties such as high surface area, excellent conductivity, and high mechanical strength [29]. Based on its properties, GR is considered as an ideal electrode material for electrochemical and biosensing [30]. However, the excellent properties of GR emerge only in a planar

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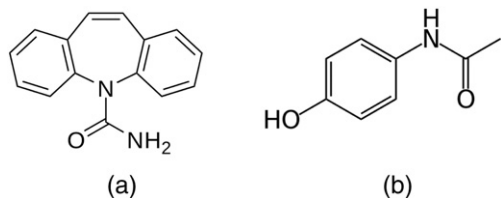
Fig. 1. Chemical structure of carbamazepine (a) and paracetamol (b).

direction. The properties of MWCNTs emerge in the axial direction while providing current density, high specific surface area, and thermal conductivity. Thus, a GR-MWCNT hybrid that combines the unique properties of the two carbon allotropes in all directions and provides a high surface area per unit volume for increased catalyst loading could be an ideal electrode material [31,32].

Ionic liquids (ILs) have received great interests recently because of their unusual properties as liquids [33–35]. ILs are composed of only ions, they show very high ionic conductivity, nonvolatility, and chemical stability. As new green media, ILs have many unique electrochemical properties, such as higher ionic conductivity and wider electrochemical windows [36–39]. CILPE is a new type of working electrode that is prepared by using an ionic liquid as a binder and modifier in the traditional carbon paste electrode (CPE). Due to the presence of IL in the carbon paste, CILPE had shown the advantages such as increased conductivity,

easy preparation, good reversibility, high sensitivity and the ability to lower the over-potential of the electroactive compounds [40]. CILPE can also be further decorated to get the modified electrode. Different kinds of the modified CILPE had been prepared and used for electro-chemical sensing with excellent performance [41,42].

In this study, a three-dimensional graphene/MWCNT hybrid composite was fabricated and further modified on a 1-butyl-3-metylimidazolium bis (trifluoromethylsulfonyl) imide ([bmim]NTF2) based carbon ionic liquid paste electrode (CILPE). The modified electrode was further used for the detection of CBZ in the presence of PA. To the best of our knowledge, the electrochemical detection of CBZ by using CILE has not been reported in the literature. Based on the electrochemical response of CBZ and PA on GR/MWCNT/CILPE, a new electrochemical method was established for simultaneous determination of CBZ and PA with good electrocatalytic activity, high sensitivity, good reproducibility, long-term stability and low cost.

2. Experimental

2.1. Chemicals

CBZ was purchased from Alborz Bulk pharmaceutical Co. (Tehran Iran), PA was obtained from Borhan Darou Co. (Mashhad Iran). 1.0×10^{-2} M stock standard solutions of CBZ and PA were prepared and stored at 4 °C. Working standard solutions were prepared by
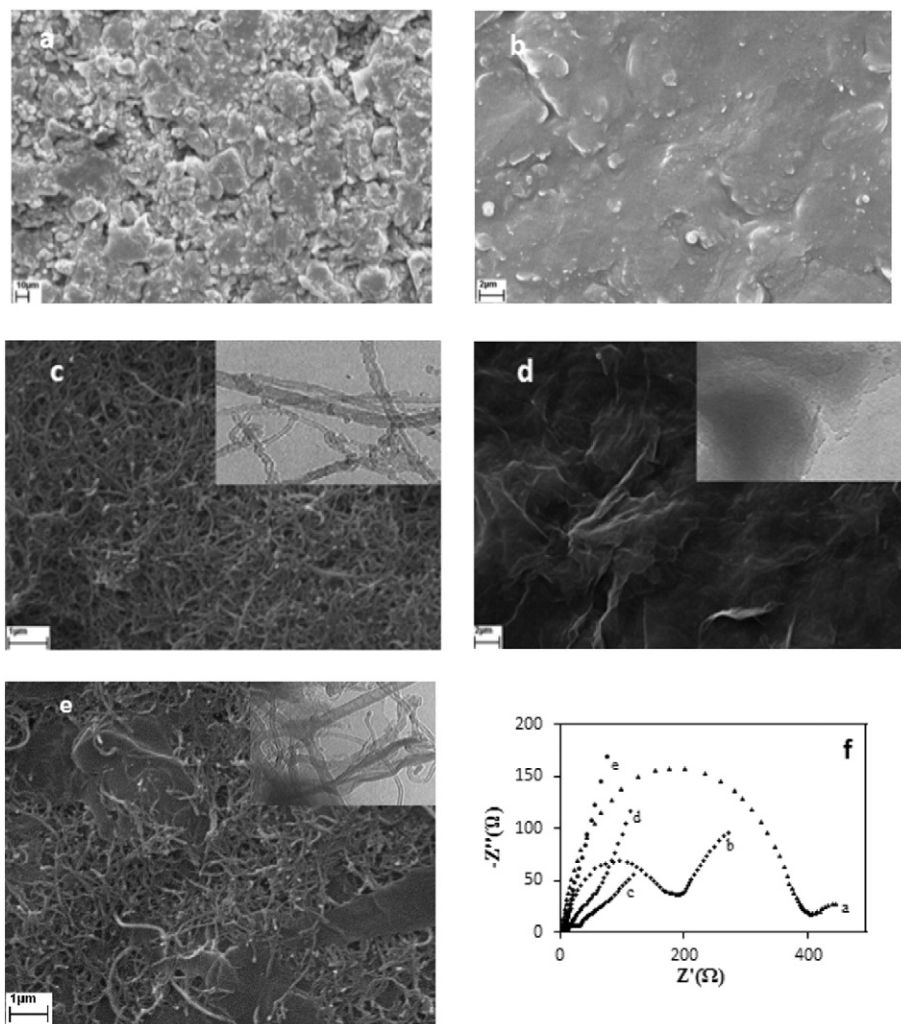

Fig. 2. SEM images of (a) CPE, (b) CILPE, (c) MWCNT/CILPE, (d) GR/CILPE, (e) GR/MWCNT/CILPE (inset TEM image), (f) EISs of (a) CPE, (b) CILPE, (c)GR/CILPE, (d) MWCNT/CILPE, (e) GR/MWCNT/CILPE in 5.0×10^{-3} mol L^{-1} [Fe(CN)$_6$]$^{-3/-4}$ containing 0.1 mol L^{-1} KCl.
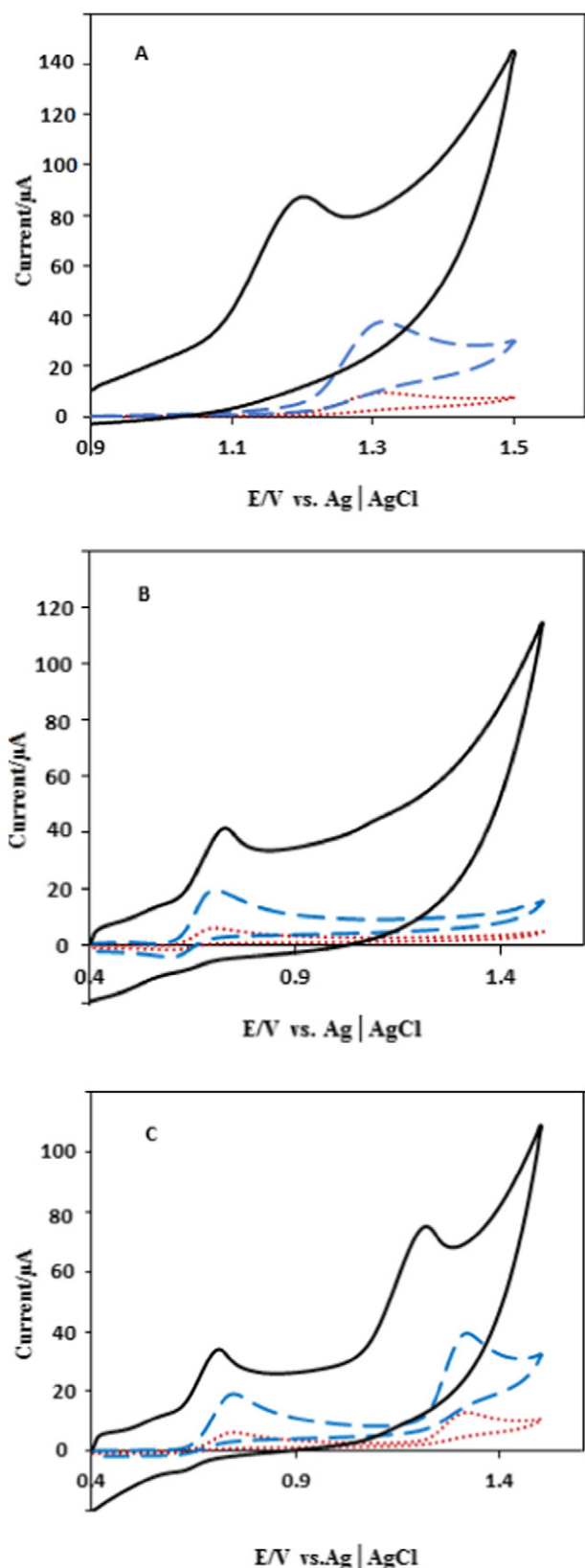
Fig. 3. Cyclic voltammograms of 100.0 µM of CBZ (A) 100.0 µM of PA (B) and 100 µM of CBZ + 100 µM of PA (C) at bare CPE (dotted line), CILPE (dashed line) and GR/MWCNT/CILPE (solid line) in 0.04 M BR (pH 2.0). In the all cases, the scan rate is 100 mV s^{-1}.

appropriate dilution of a stock standard solution with BR buffer. A 0.04 M solution of Britton–Robinson buffer (BR) was prepared from H$_3$PO$_4$, CH$_3$COOH and H$_3$BO$_3$. MWCNTs with >95% purity, 20–30 nm

outer diameter, 10–30 µm length, inner diameter; 5–10 nm were purchased from US research nanomaterials, Inc. Graphene nanoplates were obtained from US research nanomaterials, Inc. (purity 99.5%, thickness 2–18 nm 32 layers). High viscosity paraffin (density: 0.88 g cm^{-3}) and butyl-3-methylimidazolium bis (trifluoromethylsulfonyl) imide from Fluka were used as the pasting liquid for the carbon paste electrode. Graphite powder (particle diameter: 0.10 mm) from Merck was used as the working electrode substrate. All other reagents were of analytical grade and used without further purification. Deionized distillated water was used throughout the work.

2.2. Apparatus

Voltammetric measurements were performed using a µAutolab electrochemical system (Metrohm) equipped with NOVA software. The electrochemical cell was assembled with a conventional three-electrode system; an Ag/AgCl/KCl (3.5 M) reference electrode and a platinum wire as a counter electrode (both from Azar electrode Co., Urmia Iran).Working electrode used in this study was a modified carbon paste electrode (MCPE) (2 mm diameter).

2.3. Preparation of modified electrode

A mixture of graphite powder and paraffin at a ratio of 70/30 (w/w) was blended by hand mixing with a mortar and pestle for preparation of CPE. The ionic liquid carbon paste electrode (ILCPE) was made of graphite powder, paraffin liquid and [bmim] NTF2 with a ratio of 70/20/10(w/w/w), respectively. Both unmodified and modified pastes were pressed into the end of a polyethylene tube (2 mm i.d.) with copper wire as conductor. Prior to use, a mirror-like surface can be obtained by polishing the electrode on a weighing paper. For further modification of CILE, 1.0 mg GR and 1.0 mg MWCNT were mixed completely in 2.0 mL DMF with ultrasonic agitation to form a homogenous mixture of MWCNT-GR. Then 12 µL of the mixture casting on the surface of CILPE. The solvent was then evaporated in air at room temperature.

3. Results and discussion

3.1. Electrode characterization

The surface morphologies of the constructed electrodes were investigated using scanning electron microscopy (SEM) and transmission electron microscopy (TEM), the results are shown in Fig 2. As is evident in Fig. 2a, irregularly shaped graphite flakes with separated layers are appeared at the surface of CPE, while at the surface of CILPE (Fig. 2b),a uniform and smooth film is observed, which is due to the high viscosity

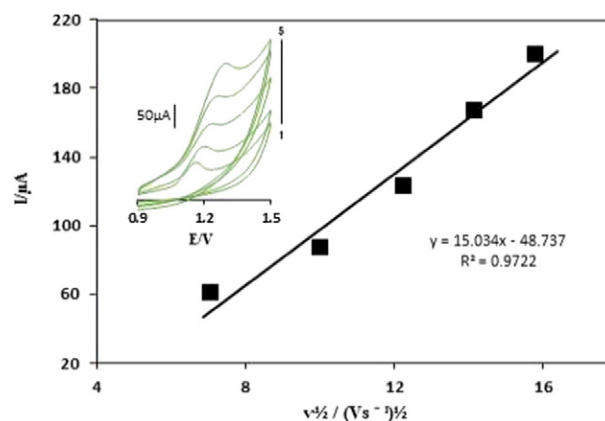**Fig. 4.** Plot of Ip versus v-1/2 for the oxidation of CBZ at GR/MWCNT/CILPE. Inset shows, cyclic voltammograms of CBZ (100 µM) at GR/MWCNT/CILPE at different scan rates of 50, 100, 150, 200 and 250 mV s^{-1} Electrolyte; 0.04 M BR buffer; pH 2.0.
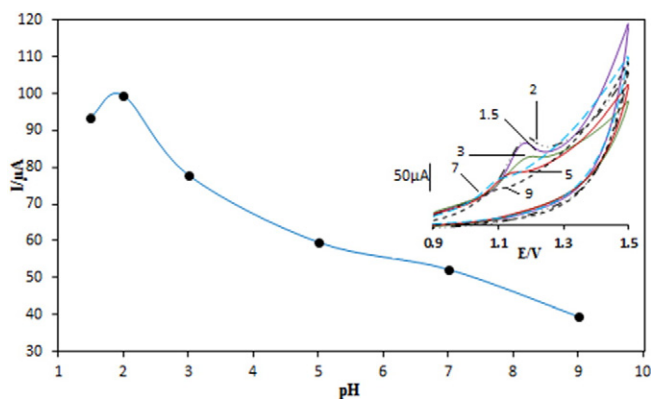
Fig. 5. Current–pH curve for electrooxidation of 100.0 μM CBZ at GR/MWCNT/CILPE with a scan rate of 100 mV s^{-1}. Inset; influence of pH on cyclic voltammograms of CBZ at the surface of the modified electrode (pH 1.5, 2, 3, 5, 7, and 9, respectively).

of ionic liquid that embedded in carbon layers and connected them together. Fig. 2c shows the curved tubular structures of MWCNTs and Fig. 2d shows a paper-like structure of graphene sheets at the surface of CILPE. After addition the graphene/MWCNT hybrid composite to the CILPE (Fig. 2e inset), a three-dimensional network-like structure can be seen at the surface of the electrode, indicating that the hybrid composite has been successfully modified on the CILPE.

Electrochemical impedance spectroscopy (EIS) was used to characterize the electron transfer properties of different modified electrodes. EIS is an effective method to measure the impedance changes of an electrochemical system during the modification process. The EIS curve (Nyquist plot) consists of two parts: a semicircular part at higher frequencies corresponds to the electron transfer limited process and a linear part at lower frequencies corresponds to the diffusion process. The value of electron transfer resistance (Ret) can be estimated according to the diameter of the semicircle of the Nyquist plots at the high frequency region. Fig. 2f shows the Nyquist plots of the EIS of the (a) CPE, (b) CILPE, (c) GR/CILPE, (d) MWCNT/CILPE, (e) GR/MWCNT/CILPE. As is evident in Fig. 2f the electron transfer resistance decreases
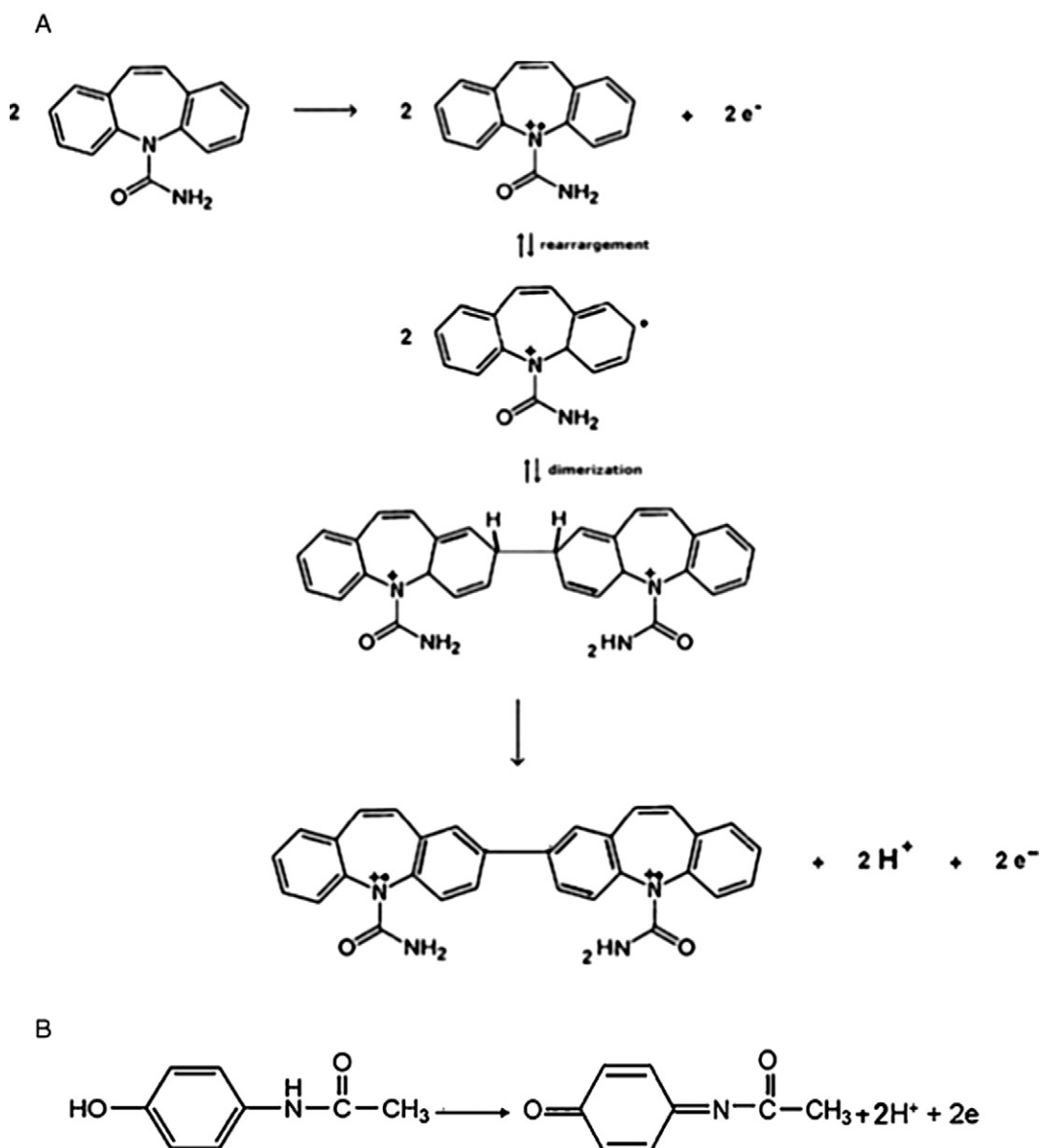
Scheme 1. Possible reaction pathways for electrooxidation of CBZ (a) and PA (b) at the surface of GR/MWCNT/CILPE. (Adapted from Ref. [8,44]).

after modification of the electrode and the GR/MWCNT/CILPE modified electrode shows the smallest diameter of the semicircle. The obtained results indicate that the presence of high conductive ionic liquid in the paste, effectively improves the interfacial electron transfer and when GR/MWCNT hybrid immobilized on the CILPE surface, the electron can transfer in 3D direction and the efficiency of electron transfer significantly improves.

3.2. Cyclic voltammetric study of CBZ and PA

The electrochemical behaviors of CBZ and PA at different fabricated electrodes were characterized by cyclic voltammetry. The cyclic voltammograms of CBZ and PB obtained at bare CPE, CILPE and GR/MWCNT/CILPE are shown in Fig. 3. As is evident in Fig. 3A (dotted line) for 100 μM solution of CBZ an irreversible behavior with a broad and weak oxidation peak, around 1.317 V with 10.7 μA peak current is observed at bare CPE. But in the case of CILPE, the oxidation peak is located at 1.305 V with the peak current (Ip) at 37.7 μA, Fig. 3A (dashed line). As is seen in Fig. 3A (solid line), in the case of GR/MWCNT/CILPE, the oxidation peak is appeared at 1.252 V with the peak current as 87.2 μA. Similar behavior was observed for 100 μM solution of PA on different modified electrodes. As is shown in Fig. 3B, the oxidation peak currents on CPE (dotted line), CILPE (dashed line) and GR/MWCNT obtained in this study, show that CBZ and PA have the highest peak currents at GR/MWCNT/CILPE modify electrode with respect to the other constructed electrodes. This improvement in electron transfer kinetics may be attributed to the following factors. First, [bmim] NTF2 could improve the electrical conductivity and chemical stability, thus enhancing
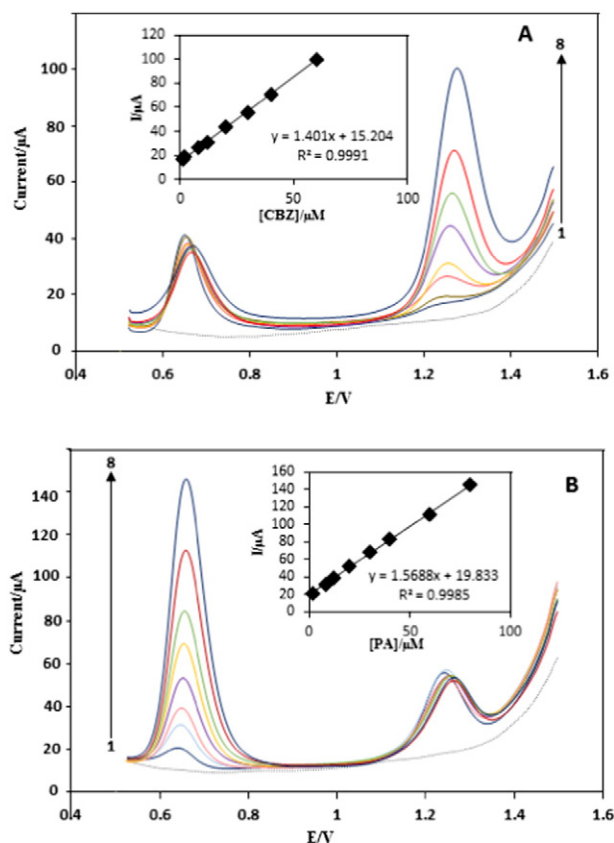
the electrochemical performance of the modified electrode. Second, the small size, high loading, large surface area, and high electrocatalytic activity of both GR and MWCNT could enhance the performance of the electrode and reduce the charge transfer resistance which greatly enhanced the peak currents. Third, the 1D MWCNT and 2D GR form a 3D hierarchical structure. Thus, GR-MWCNT hybrid combines the unique properties of the two carbon allotropes in all directions and provides a high surface area per unit volume for increasing the catalyst loading.

The determination of CBZ in the presence of PA in solution was also carried out on GR/MWCNT/CILPE. Fig. 3C shows the cyclic voltammograms for a mixture of 100 μM CBZ and 100 μM PA in 0.04 M solution of BR (pH 2) using different modified electrodes. The two oxidation peaks which are appear at 0.722 V and 1.227 V, could be attributed to the oxidation of CBZ and PA, respectively.

The effect of scan rate on the redox behavior of CBZ at the GR/MWCNT/CILPE was investigated by cyclic voltammetry. As is evident in Fig. 4, there is a linear relationship between the peak current and the square root of the scan rate which indicates the kinetics of the oxidation of CBZ at the surface of the modified electrode is controlled by diffusion process [43].

Fig. 5 shows the cyclic voltammetric response of 100 μM solution of CBZ at the modified electrode in the pH range 1.5–9. As shown in this figure, maximum performance of the electrode response is obtained at pH 2, therefore all of the experiments carried out in BR buffer solution at pH 2.

The possible reaction pathways for electrooxidation of CBZ and PA on GR/MWCNT/CILPE modified electrode in 0.04 M solution of BR (pH 2) can be proposed as shown in Scheme 1. Based on the previous reports about the anodic behavior of the CBZ molecule, the electrochemical process under discussion, can be related with the oxidation of the nitrogen atom in the central ring, which results in formation of cation radicals Scheme 1a [8]. As illustrated in Scheme 1a, due to the complexity of the oxidation process we, believe that the loss of electrons in two steps occur simultaneously and cannot be distinguished in the voltammogram or probably the last step cannot be occur in acidic media. The possible mechanism for electro-oxidation of PA is shown in Scheme 1b. PA oxidizes to N-acetyl-p-quinoneimine in a mechanism involving two protons and two electrons in the oxidation reaction [44].

3.3. Calibration plots and limits of detection

The determination of CBZ and PA at GR/MWCNT/CILPE was carried out in 0.04 M solution of BR (pH 2.0) by differential pulse voltammetry (DPV), where the concentration of the one species was changed while the another species remained constant. The results show the peak currents increase linearly upon increasing the concentration of CBZ and PA in solution. The calibration curves (inset of Fig. 6) was constructed

Table 1
Analytical parameters for simultaneous determination of CBZ and PA in BR at pH 2.0 using proposed method.

Analyte	Linear rang (μM)	Linear regression equation (I: μA, C: μM)	R^2	LOD (μM)
CBZ	1–60	I CBZ = 1.401C CBZ + 15.204	0.999	0.233
PA	2–80	I PA = 1.568 C PA + 19.833	0.998	0.262

Fig. 6. (A) Differential pulse voltammograms of GR/MWCNT/CILPE in 0.04 M BR (pH 2.0) containing 20.0 μM PA and different concentrations of CBZ: (1) 1.0, (2) 2.0, (3) 8.0, (4) 12.0, (5) 20.0 (6) 30.0 (7)40.0 (8)60.0 μM. Inset: plot of the electrocatalytic peak current as a function of CBZ concentrations. (B) Differential pulse voltammograms of GR/MWCNT/CILPE in 0.04 M of BR (pH 2.0) containing 20.0 μM CBZ and different concentrations of PA: (1) 2.0, (2) 8.0, (3) 12.0, (4) 20.0, (5) 30.0, (6) 40.0 (7) 60.0 (8)80 μM. Inset: plot of the electrocatalytic peak current as a function of PA concentrations.

Table 2
Comparison of some electrochemical methods for determination of CBZ.

Electrode	Method	LOD (μM)	Ref.
Ag/TiO$_2$ nanocomposite/CPE	DPV	0.86	[45]
MWCNTs/GCE	SWV	0.04	[46]
Graphene oxide/SWCNTs/GCE	Amperometry	0.029	[47]
Graphene-gold nanoparticle/AuE	EIS	0.303	[48]
Fullerene-C60/GCE	DPV	0.0162	[49]
GR/MWCNT/CILPE	DPV	0.233	This work

Table 3
Interference study for the determination of CBZ and PA under the optimized conditions.

Species	Tolerance limits ($W_{Substance}/W_{drug}$)	
	CBZ	PA
Glucose, fructose, lactose, sucrose	700	700
Ascorbic acid, urea, uric acid	200	100
K^+, Na^+, Cl^-, NO_3^-, SO_4^-	1000	800

in the concentration ranges of 1 to 60 μM for CBZ and 2 to 80 μM for PA. The detection limits ($3\,S_b/m$) were found to be 0.233 and 0.262 μM for CBZ and PA, respectively. The analytical parameters for simultaneous determination of CBZ and PA using proposed electrode are listed in Table 1. Table 2 shows the detection limits which are reported by other research groups for CBZ determination at different modified electrodes.

The relative standard deviation (RSD) for five replicate measurements was found to be 3.9% for 50 μM solution of CBZ. When the electrode was not in use, it was stored at 4 °C. No apparent change in peak current was observed after storage for 15 days. After storing for 1 month the responses maintained 98% compared with the initials. These results indicate that the proposed electrode has acceptable reproducibility and stability.

The main goal of this study was to measure CBZ and PA in solution simultaneously. As shown in Fig. 6. (A, B), the two anodic peaks, corresponding to the oxidation of CBZ and PA, indicate that the simultaneous determination of CBZ and PB is possible at the GR/MWCNT/CILPE electrochemical sensor.

3.4. Interference studies

The influence of potential interferences existing in biological fluids was also studied by analyzing a standard solution of 5 μM CBZ and PA under the optimum conditions. The tolerance limit was defined as the maximum concentration of the interfering substance. The results are shown in Table 3. Those results showed that these substances did not interfere with simultaneous determination of CBZ and PA and the peak current variation caused by them was less than 5%. It confirms that, GR/MWCNT/CILPE is highly selective for recognition of CBZ and PA in solution.

3.5. Analysis of real sample

In order to evaluate the feasibility of the proposed electrode, the determination of CBZ and PA in tablet and urine samples were performed by standard addition method. The obtained results are listed in Table 4. The good recovery results which are given in this table, demonstrate the capability of GR/MWCNT/CILPE modified chemical sensor for effective determination of CBZ and PA in both pharmaceutical and urine samples.

4. Conclusions

In the present paper a novel voltammetric sensor, butyl-3-methylimidazolium bis (trifluoromethylsulfonyl) imide ([bmim] NTF2) based carbon ionic liquid paste electrode (CILPE) with graphene/multiwall carbon nanotube (GR/MWCNT) hybrid composite as a modifier was fabricated and it was used for simultaneous determination of carbamazepine (CBZ) and paracetamol (PA) for the first time. The modified electrode showed 8.2-fold increment in the oxidation peak current of CBZ compared with traditional carbon paste electrode.GR/MWCNT/CILPE exhibited two well-defined redox peaks for oxidation of CBZ and PA with the potential difference of 0.53 V which was large enough for individually and simultaneously detection of these two compounds. The proposed electrode showed a high current sensitivity, low detection limit and high selectivity with high stability and good reproducibility which proved its potential sensing for measurement of these two drugs in solution. Furthermore, the electrode successfully applied for determination of CBZ and PA in pharmaceutical and urine samples with good recovery results.

Acknowledgments

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Table 4
Voltammetric determination of CBZ and PA in tablet and urine samples.

Sample	Spiked (μM)		Found (μM)		Recovery (%)	
	CBZ	PA	CBZ	PA	CBZ	PA
Tablet[a]	40	40	38.2	39.4	95.5	98.5
Urine	10	10	10.4	10.1	104	101
	30	30	29.4	30.8	98	102.6

The RSD for the determination of CBZ and PA in tablet and urine samples was less than 5% for n = 5.

[a] 200 mg tablet of CBZ and 500 mg tablet of PA, Sobhan Darou Co. Iran.

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