Advances in Nanochemistry
ISSN: 2676-5462

Research

A sensitive electrochemical sensor based on multiwall carbon nanotube-ionic liquid/nickel oxide nanoparticles for simultaneous determination of the antipsychotic drugs clozapine and sertraline

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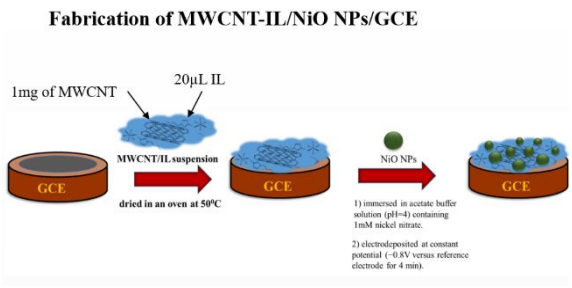
Received 16th June 2021,
Accepted 6th September 2021,
DOI: 10.22126/anc.2021.6588.1027

Abstract

In this report, a glassy carbon electrode (GCE) modified with multi-walled carbon nanotube (MWCNT), ionic liquid (IL) and nickel oxide nanoparticles NiO NPs has been introduced for the simultaneous determination of clozapine (CLOZ) and sertraline (SER) as antipsychotic drugs in biological fluids and pharmaceutical formulation using differential pulse adsorptive stripping voltammetric (DPAdSV) technique. The MWCNT-IL/NiONPs modifier catalyzed the oxidation of both drugs and enhanced the sensitivity of the resulted electrode for CLOZ and SER monitoring. The response of the electrode to CLOZ and SER oxidation were linear over the concentration ranges of 0.5 – 67 µM and 0.21 – 85 µM (R^2>0.99), respectively. The detection limits of 0.052 and 0.047 µM were obtained for CLOZ and SER, respectively. The proposed electrochemical sensor exhibited a high sensitivity, good selectivity, and was successfully used for simultaneous determination of CLOZ and SER in real samples.



Keywords: *Clozapine (CLOZ), Sertraline (SER); 1-Buthyl-3-Methylimidazolium Hexaflourophosphate ($BMIMPF_6$), Cyclic voltammetry (CV); Differential pulse adsorptive stripping voltammetry (DPAdSV).*

Introduction

Clozapine (CLOZ), as an atypical antipsychotic drug, is the most efficacious medication against both the negative and positive symptoms of schizophrenia and providing effective treatment for patients who are unresponsive to other antipsy-chotics. Despite its high efficacy, CLOZ has side effects such as agranulocytosis. Therefore, due to its importance, different analytical methods such as spectrometry and chromatography[1,2] have been used for determination of CLOZ. Sertraline (SER), is an active drug for depression treatment and it inhibits the reuptake of serotonin.[3] Sertraline is naphthalenamine-derivative and its structure differs from classic tricyclic antidepressants (TCAs), but has less side effects. The efficacy of SER for depression is similar to that of TCAs. In addition SER is used for obsessive-compulsive, panic, and social anxiety disorders in both adults and children. Spectrophotometry,[4] voltammetry,[5] high-performance liquid chromatography (HPLC),[6] and gas chromatography[7] have been used for SER determination.

Among the analytical methods for drug analysis, the electrochemical methods have attracted the attention of researchers that may be due to their sensitivity, selectivity, simplicity, and low cost. Sensitive and selective voltammetric determinant of organic compounds which are accompanied with high over potential at bare metallic electrodes, using chemically modified electrodes have open a new field in electrochemical techniques because they have notable advantages such as the catalytic capabilities, enrichment, and selectivity. Different techniques have been used for improving the electrochemical performance toward target analytes.[8-12] Due to the unique properties of nanoparticles they have been applied in various fields of science and technology. Owing to excellent physical and catalytic properties of metal oxide, they have found different applications in many areas of chemistry, physics, and materials science.[13-18] The oxide of metals such as nickel, manganese, zirconium, titanium, tungsten, iridium, iron, zinc, and copper are suitable matrixes for electrode modification,[19-26] because they have high electrical conductivity, wide electrochemical working window, high

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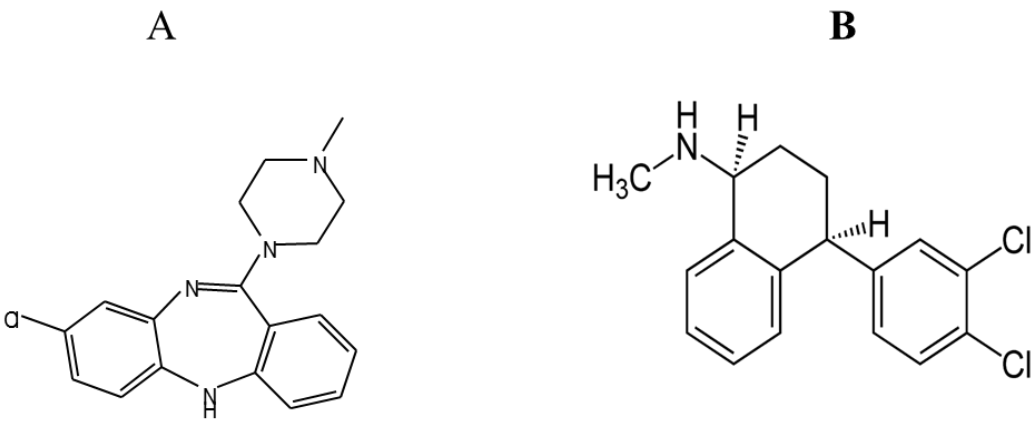
Cite this article: Ehzari, H., Gholivand, M.B., & Shamsipur, M. (2021). A sensitive electrochemical sensor based on multiwall carbon nanotube-ionic liquid/nickel oxide nanoparticles for simultaneous determination of the antipsychotic drugs clozapine and sertraline. *Advances in Nanochemistry*, 3(1), 23-33. DOI: 10.22126/anc.2021.6588.1027

Publisher: Razi University



Scheme 1. *Chemical structure of* ***(A)*** *Clozapine (CLOZ) and* ***(B)*** *Sertraline (SER).*

biocompatibility, large surface area, no toxicity, chemical and photochemical stability, electrochemical activity, and ease of preparation. Nickel oxide (NiO), as a p-type semiconductor with high chemical stability, electrocatalysis ability, electron transfer capability, and good biological compatibility has been used for electrode modification.[27,28] Many previous reports have shown that combining NiO with carbon materials that possess high specific surface areas, high chemical stability, and good conductivity can improve the electrochemical performance of NiO.[29-31]

Ionic liquids (ILs) as a class of ionic solvents which consisting of bulky asymmetric organic cation and organic/inorganic anion have chemical and thermal stability, relatively high ionic conductivity, negligible vapor pressure, and wide electrochemical window.[32] They have been used not only as solvent but also as the modified materials.[33,34]

In the present work a mixture of CNTs and IL was casted on the GCE surface and then a stable film of NiO was electrodeposited on its surface. This strategy combines the attractive mechanical and electrical characteristics of carbon nanotubes with the unique properties of IL and NiO. The catalytic activity of the NiO/MWCNTs/IL/GCE towards CLOZ and SER oxidation was studied and was used for their simultaneous determination in human serum and pharmaceutical formulation samples.

Experimental

Reagents and chemicals

MWCNT with purity 95 % (10-20 nm diamaters and 1 µm length) was obtained from Nanolab (Brighton, MA). Clozapine (CLOZ), sertraline (SER), and 1-buthyl-3-methylimidazolium hexaflourphosphate were supplied from Sigma Aldrich (Madrid, Spain). All other chemicals were of analytical grade and were used without any purification. Britton–Robinson buffer (B-RB) solution was prepared from 0.1 M of acetic acid, phosphoric acid, and boric acid. Sodium hydroxide (0.2 M) was used for preparation of buffer solutions with different pH.

Apparatus

Electrochemical studies were carried out at room temperature using an Autolab potentiostat–galvanostat model PGSTAT30 (Utrecht, The Netherlands). A three electrode conventional cell with MWCNT/IL/NiONPs /GCE, Ag|AgCl|KCl (satd.), and a platinum wire as working, reference, and auxiliary electrodes, respectively was used. The output signal was acquired by NOVA 1.11 software. The modified electrodes morphology were investigated by a Philips instrument, Model X-30 scanning electron microscopy (SEM). The pH was adjusted by a Metrohm 691 pH meter.

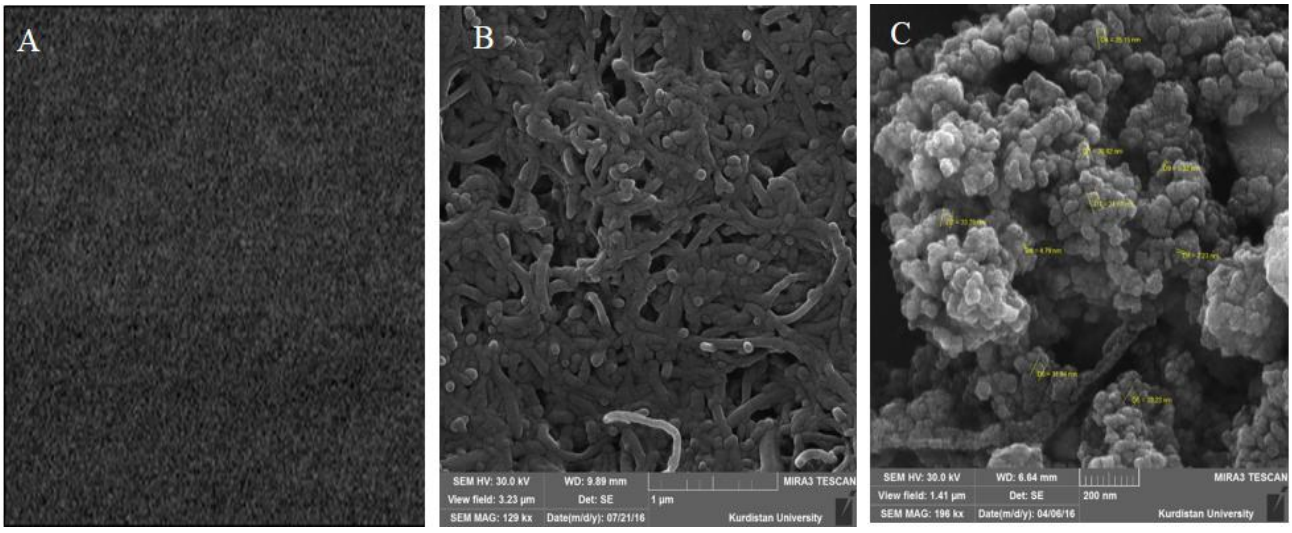


Figure 1. *SEM images of* ***(A)*** *GCE,* ***(B)*** *MWCNT-IL/GCE, and* ***(C)*** *MWCNT-IL/NiONPs/GCE.*

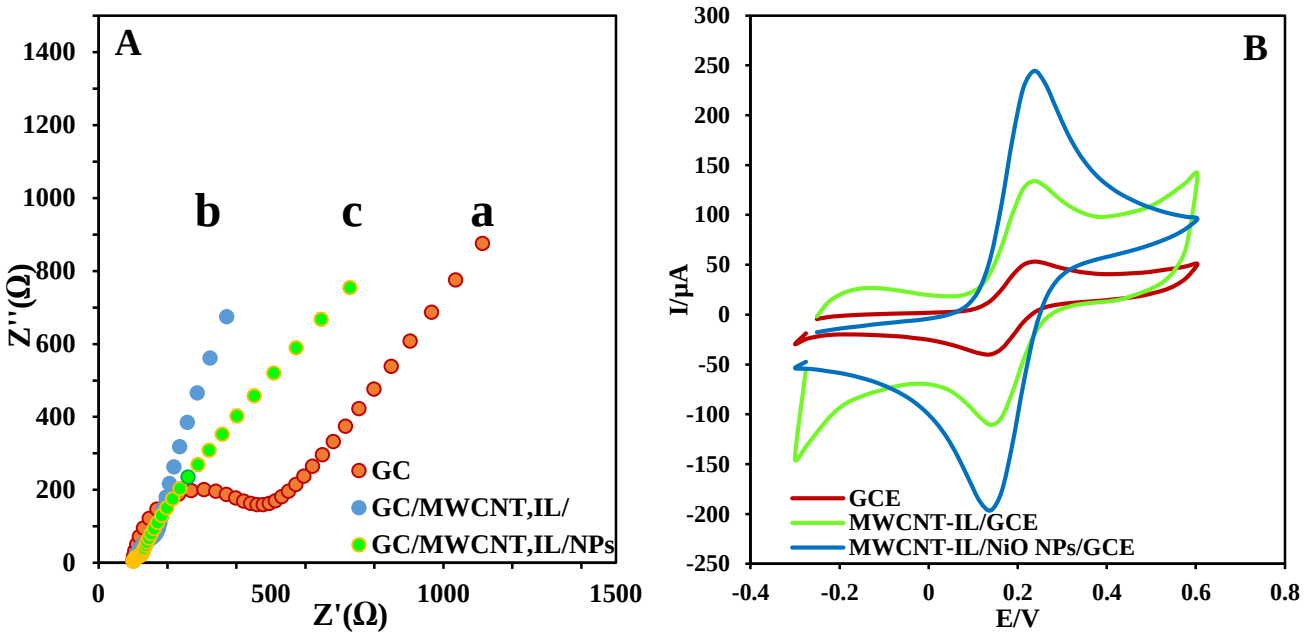


Figure 2. (A) *The Nyquist plots and* ***(B)*** *cyclic voltammograms of different modified electrodes in a solution containing 5.0 mM* $[Fe(CN)6]^{3-/4-}$ *and 0.1 M KCl at a scan rate of 100* mVs^{-1}.

Fabrication of MWCNT-IL/NiONPs/GCE

The surface of a GCE was polished successively with 1.0 and 0.05 µm alumina and washed thoroughly with twice distilled water and then cleaned in ethanol and water under ultrasonication to remove the adsorbed particles. 1 mg of MWCNT and 20 µL IL were dispersed in 1 mL of N, N- dimethylformamide (DMF) by an ultrasonic bath for an hour, and then 4 µL of the prepared MWCNT/IL suspension was placed on the surface of a GCE and after spinning it was dried in an oven at 50 °C. At the surface of MWCNT/IL/GCE which immersed in acetate buffer solution (pH=4) containing 1 mM nickel nitrate, metallic nickel was electrodeposited at constant potential (−0.8 V versus reference electrode for 4 minutes) in pH 4. The electrodissolution and passivation of a nickel oxide layer at a MWCNT/IL/NiONPs/GC electrode was carried out by immersing the electrode (MWCNT/IL/NiONPs/GCE) into a fresh B-RB (pH 7) using cyclic voltammetric method in potential range of -0.50 to 1.0 V (30 scans) and at a scan rate of 100 mVs^{-1}.[35]

The obtained MWCNT/IL/NiONPs/GCE was washed carefully with twice distilled water and then dried at room temperature.

Finally, in order to obtain a stable response, the resulted electrode (MWCNT/IL/NiONPs/GCE) in 0.1 M of B-RB solution (pH=7), was subjected to CV at the potential windows of 0 to 1 V and scan rate of 100 mV s^{-1}.

Real samples preparation

Blood serum samples were collected from healthy volunteers. 2 mL methanol was added to 1.5 mL serum sample, after 10 minutes vortexing of the sample, centrifugation at 1500 rpm for 20 minutes was used for separation of the precipitated proteins. The clear supernatant layer was passed through a 0.45 mm filter to obtain free protein human serum sample and then it was spiked with known concentrations of CLOZ and SER and diluted to 10 mL.

A portion of homogenized powder of five tablets of CLOZ (100 mg per tablet, from Tehran chemie, Iran) and or SER (50 mg per tablet, Bakhtar Bioshimi Kermanshah, Iran) equivalent to a stock solution of a concentration of about 1.0×10^{-3} M were accurately weighed and dissolved in 100 mL of water/methanol mixture (80: 20) via ultrasonication (10 minutes). Appropriate solutions were prepared by taking suitable aliquots of the clear supernatant liquid and diluting them with the B-RB solutions. Each solution was transferred to the voltammetric cell and analyzed by standard addition method.

Results and discussion

Morphological studies of MWCNT-IL/NiONPs/GCE

The morphologies of GCE, MWCNT-IL/GCE, and MWCNT-IL/NiONPs/GCE were investigated with SEM (Figure1). The SEM image of the MWCNT-IL/GCE (Figure 1B) showed that the GCE surface was covered with homogenous MWCNT-IL and a net structure without aggregation was appeared. However, when NiO NPs was electrodeposited on the MWCNT-IL/GCE its image showed the presence of NiO as nanoparticles (from 20 to less than 100 nm) which are distributed uniformly over the MWCNT-IL/GCE surface (Figure 1C). The results confirmed the successful preparation of MWCNT-IL/NiONPs electrode, which could be applied to further uses.

The features of surface modification were also studied by electrochemical impedance spectroscopy (EIS) which its spectra were taken in 0.1 M KCl containing 5.0 mM $[Fe(CN)_6]^{3-/4-}$ in the frequency range of 0.1 Hz to 10 kHz and the results are showed in Figure 2A which its semicircle portion at high frequencies, and linear part at low frequencies corresponding to the electron transfer limiting process, and the diffusion limiting step of the electrochemical process, respectively.[36] The diameter of the semicircle represents the electron transfer resistance (R_{et}). The values of R_{et} were varied from 477 Ω to 120 Ω when the electrodes surface were modified with different modifiers. On the other hand, R_{et} of GCE (477 Ω, curve a) was decreased to 158 Ω, when it was modified MWCNT/IL (curve b) which revealed the role of MWCNT and IL in facilitating of the electron transfer at the electrode surface. Modification of GCE with MWCNT/IL/NiONPs was accompanied by further decreasing in the R_{et} (120 Ω, curve c), which indicates that NiONPs are effectively attached to the surface of the

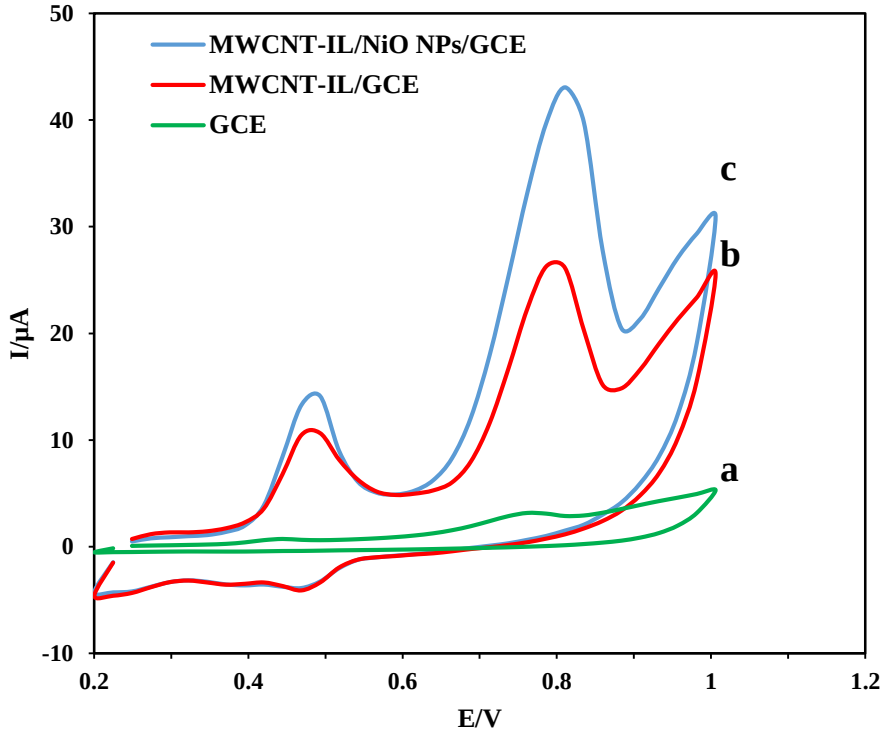


Figure 3. *Cyclic voltammograms of 30 µM of clozapine (CLOZ) and 45 µM of sertraline (SER) at (a) bare GCE, (b) MWCNT-IL/GCE, (c) MWCNT-IL/NiONPs/GCE. Measurement conditions: 0.1M B-RB (pH 7) at scan rate = 50 mVs^{-1}.*

MWCNT/IL/GCE and thus this modifier MWCNT-IL/NiONPs enhances the electrode conductivity.

Cyclic voltammetry (CV) as the other technique was used for further investigation of the modified electrodes. The CV of above solution (KCl-probe solution) at the GCE, MWCNT-IL/GCE, and MWCNT-IL/NiONPs/GCE were recorded. At the bare GCE (Figure 2B, curve a) a redox peak with a peak-to-peak potential separation (ΔEp) of 98 mV was observed (Figure 2B, curve a). At the MWCNT-IL/GCE the anodic and cathodic peaks current were increased, and their ΔEp decreased to 86 mV (Figure 2B curve b). The presence of MWCNT-IL at the surface of GCE dramatically increases the electron transfer rate at the MWCNT-IL/GCE and also process reversibility. Further increase in peaks current and decrease in ΔEp (75 mV) were observed when MWCNT-IL/NiONPs/GCE was used as working electrode (Figure 2B, curve c). This modifier, improved the performance of the resulted electrode. On the other hand, the porous interfacial layer of the nano-NiO increases the surface area of the modified electrode and its conductivity, leading to a higher redox response.

Optimization of NiONPs amount

Modification of MWCNT-IL/GCE surface with NiONPs was carried out by electrodeposition of nickel ions in form of metalic nickel at constant potential (-0.08 V) and then followed by electrodissolution and passivation of Ni into NiO using CV in acetate buffer solution (pH 4) containing 1 mM nickel nitrate. Therefore, the electrodeposition time and the number of scans during both processes were optimized in the ranges of 60-300 s and 10-40 cycles, respectively. In each case the resulted modified electrode was used for determination of 30 µM CLOZ and 45 µM SER solution in 0.1 M B-RB (pH 7). Maximum response for both drugs were obtained when the electrodeposition time and number of scans were 240 s and 30 cycles respectively, which were chosen as optimal parameters for subsequent uses.

Surface area study

The apparent surface area (A) of the bare GCE, MWCNT/IL/GCE, and MWCNT/IL/NiONPs/GCE was estimated using CV. The CV experiments were performed in 0.1 M KCl solution containing 5 mM K_3 [Fe $(CN)_6$] at various scan rates using all electrodes. The slope of linear line of plot of peak currents versus square root of scan rates (I_p $=2.69\times10^5 n^{2/3} A D^{1/2} v^{1/2} C_o$)[37] was used for surface area determination. The estimated values of A, for the bare GCE, MWCNT/IL/GCE, and MWCNT/IL/NiONPs/GCE were 0.071, 0.268 cm^2, and 0.594 cm^2, respectively. The obtained maximum surface area for MWCNT/IL/NiONPs/GCE reveals the synergic effect of MWCNTs, IL, and NiONPs in improving the electrode's response.

Electrochemical behavior of CLOZ and SER on MWCNT-IL/NiONPs/GCE

Cyclic voltammetric technique was used to investigate the electrochemical behavior of 30 µM CLOZ and 45 µM SER at the bare GCE, MWCNT/IL/NiONPs/GCE, and MWCNT/IL/NiONPs/GCE in 0.1 M B-RB (pH 7) as supporting electrolyte at a scan rate of 50 mVs^{-1}. At the GCE two weak anodic peaks were appeared at about 0.4 and 0.8 V that are due to oxidation of CLOZ and SER, respectively. Modification of the GCE with MWCNTs not only enhanced the oxidation peaks current of CLOZ and SER but in the reversed scan showed two new cathodic peaks which the first one is due to the reduction of the oxidation product, while the second peak represents the reduction of a new compound. The same behavior has been reported for CLOZ.[38] In the case of SER only one anodic peak without any counterpart cathodic peak was obtained which shows the irreversibility of the SER oxidation process. The similar pattern but with remarkably enhances in anodic peaks current was observed at final modified electrode (MWCNT/IL/NiONPs/GCE)

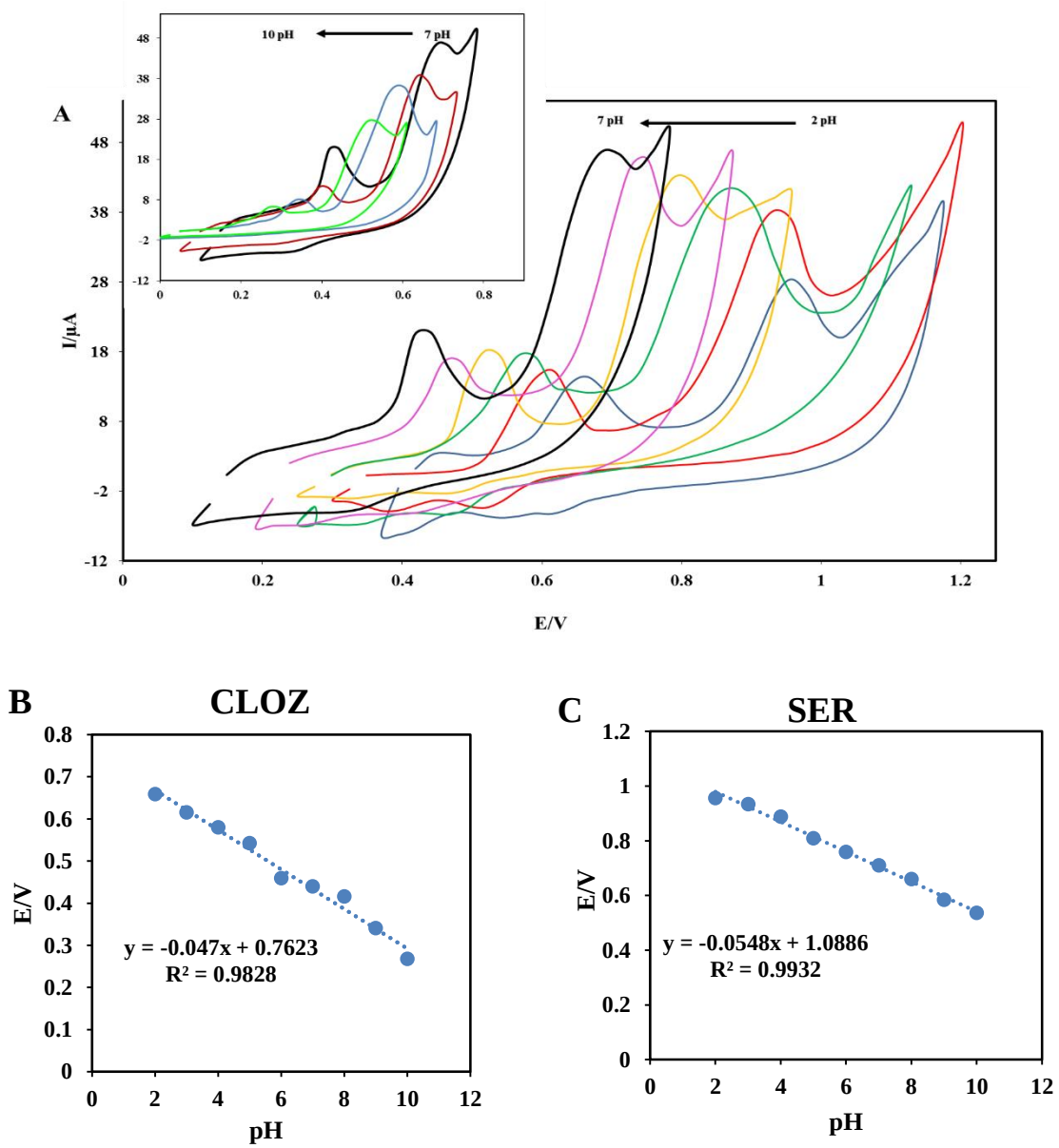


Figure 4. (A) *Effect of pH on the peak currents of 30 µM of clozapine (CLOZ) and 45 µM of sertraline (SER) on MWCNT-IL/NiONPs/GCE in solution 0.1 M B-RB (pH 7) at scan rate = 50 mVs^{-1}.* ***(B)*** *and* ***(C)*** *are the variation of peak potential (E_{pa}) of 30µM of CLOZ and 45 µM of SER vs. pH.*

revealed the catalytic activity of NiONPs in improving the sensitivity of the resulted electrode. However, excellent electrical conductivity of the MWCNT and IL and catalytic activity of the NiONPs improves the kinetic of electron transfer and leads to increase the electrochemical oxidation peaks current for CLOZ and SER.

pH effect

It is obvious that the electrochemical oxidation of organic compounds such as drugs are almost pH dependence. Therefore, the cyclic voltammetric response of MWCNT-IL/NiONPs/GCE to CLOZ and SER in 0.1 M B-RB was investigated in pH values ranging from 2.0 to 10. As shown in Figure 4 the peaks current and peaks potential are pH dependent. The maximum anodic peak current for CLOZ and SER was obtained at pH 7.0 and then it was used as the optimal pH value. It was also found that the anodic peaks potential of CLOZ and SER were shifted negatively with pH raising and linear proportionality of the anodic peak potential (E_{pa}) and pH for both drugs are presented in the following equations:

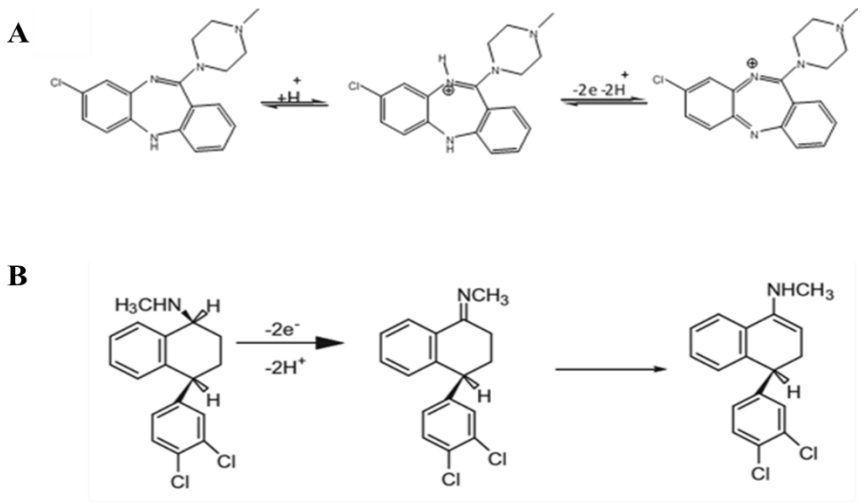
E_{pa} (mV) = −47.0 pH + 76.23 R^2=0.9828 for CLOZ (1)

E_{pa} (mV) = −54.8 pH + 108.86 R^2=0.9932 for SER (2)

From the slope of E_{pa} vs. pH plots, it was suggested that, the number of protons and electrons which involved in the anodic reaction of CLOZ and SER are equal and confirmed the previous reported oxidation mechanisms.[38,39]

Effect of scan rates

The influence of scan rate on oxidation peaks potential and peaks current of CLOZ (30 µM) and SER (45 µM) by recording their cyclic voltammograms in the range of 30-200 mVs^{-1} utilizing MWCNT/IL/NiONPs/GCE at pH 7 were investigated (Figure 5). The obtained results showed that, the peaks current of both tested compounds increase linearly with the scan rate.[37] These results



Scheme 2. *Oxidation mechanism of* ***(A)*** *Clozapine*[38,39] *and* ***(B)*** *Sertraline*[38,39].

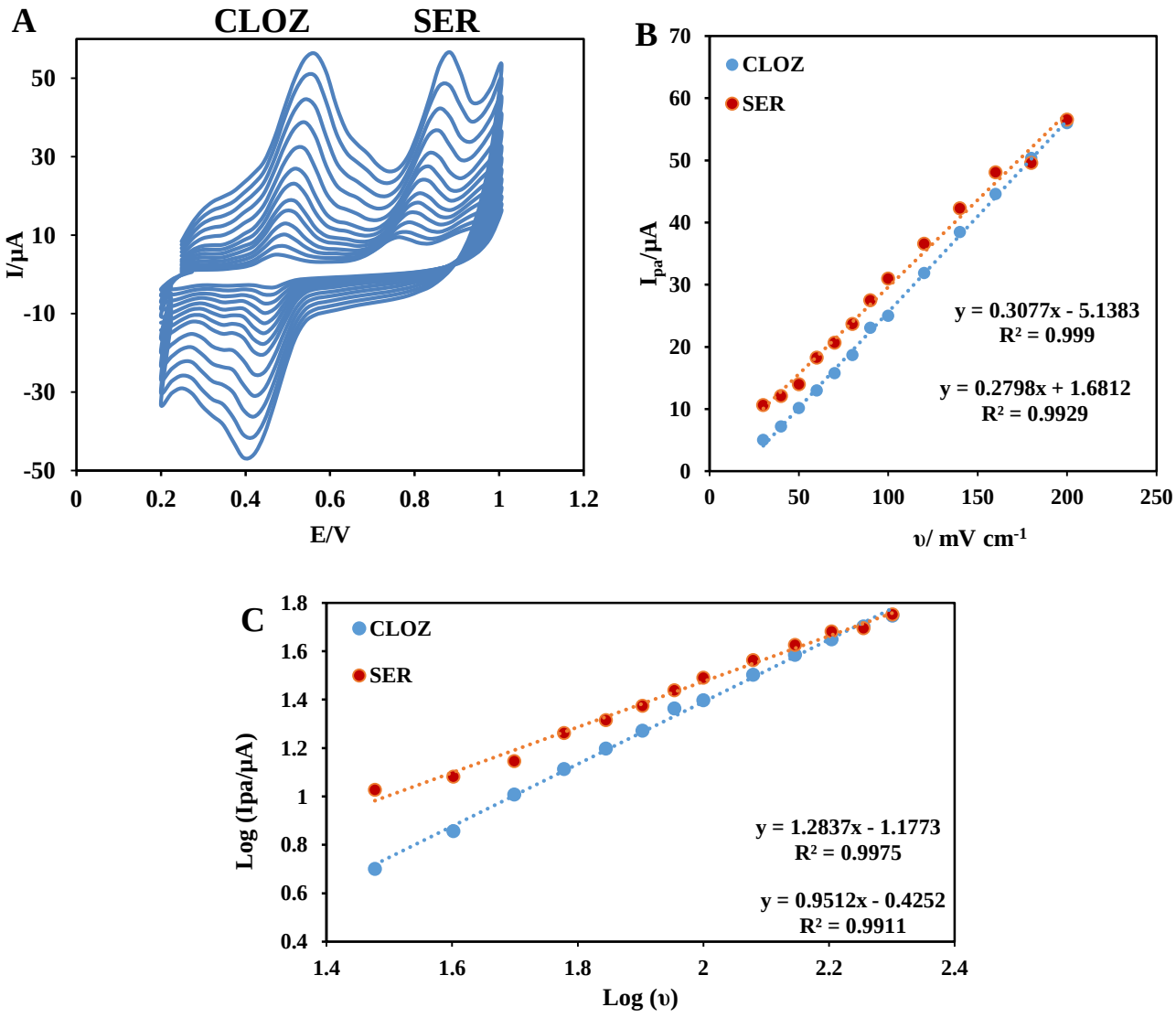


Figure 5. (A) *Cyclic voltammograms of 0.1 M B-RB (pH 7) containing 30 µM of clozapine (CLOZ) and 45 µM of sertraline (SER) at MWCNT-IL/NiONPs/GCE at different scan rates from 30 to 200 mV* s^{-1}. ***(B)*** *is the plot of peak current vs. Scan rate and* ***(C)*** *is the plot of log* I_P *vs. Logυ.*

indicate that the electron transfer reactions are controlled by the adsorption of CLOZ and SER at MWCNT/IL/NiONPs/GCE, which make this modified electrode suitable for the quantitative determinations of both drugs by stripping voltammetric technique.

Effect of accumulation parameters

The influence of accumulation potential as an important parameter for stripping techniques on the electrode response to 30 µM CLOZ and 45 µM SER was investigated. The examined potentials were in the range of -0.5 to 0.3 V. The anodic peaks current for CLOZ and SER were increased up to 0.2 V, and then decreased. Thus, an accumulation potential (E_{acc}) of 0.2 V was used as optimal E_{acc}. Figure 6 shows the dependency of the anodic peaks current with accumulation time (t_{acc}) for 30 µM CLOZ and 45 µM SER which, obtained by differential pulse adsorptive stripping voltammetry (DPAdSV). As it is seen the oxidation peaks current were increased with t_{acc} raising up to 120s, and then further increasing have no effect on the electrode responses. The accumulation time of 120s was applied as an optimal time for further uses.

CLOZ and SER determination

DPASV as a most sensitive method was chosen for simultaneous determination of CLOZ and SER. The DPAS voltammogram showed two anodic peaks at 390 and 700 mV for CLOZ and SER respectively which their currents were increased linearly by increasing the concentration of both compounds (Figure 7). The obtained dynamic ranges were 0.5-67 µM (R^2=0.9904) and 0.21-85 µM (R^2=0.9904) for CLOZ and SER, respectively. The linear regression equations are:

I_{pa} (µA) = 0.5146C (µM) + 0.9667 (r^2 = 0.9904) for CLOZ (3)

I_{pa} (µA) = 0.5306C (µM) + 2.6371 (r^2 = 0.9904) for SER (4)

By using the standard deviation of six parallel determination of peak current of the blank (s) and the slope of the calibration curve (m) the limit of detection (LOD) of both drugs were calculated from the equation LOD=3s/m. The calculated LODs for CLOZ and SER were 0.052 and 0.047 µM, respectively. Furthermore, the interfering effect of each drug on the other was checked by varying the concentration of one of them in the presence of fixed amount of the others. The analytical characteristic of this electrode was compared with those of other reported papers which were summarized in Table 1.

Repeatability and stability study

0.1 M B-R buffered solution (pH 7) containing 30 µM of clozapine (CLOZ) and 45 µM of sertraline (SER) was used for repeatability, reproducibility, and long-term stability investigation. The repeatability of the electrochemical signal at the MWCNT-IL/NiONPs/GCE was tested. After each experiment, the electrode was washed with double distilled water and the B-RB solution pH=7 and double distilled water. The relative standard deviations (RSD) for six measurements were 1.07% and 1.65%, respectively which shows the acceptable repeatability of the electrode. For reproducibility testing, six individual modified electrodes were fabricated, and the relative standard deviations (RSD) of the voltammograms of the above solution were calculated. The RSD of 2.16% and 3.29% were obtained for CLOZ and SER respectively, these results showed the acceptable reproducibility of the electrode. Furthermore, the long-term stability of the proposed modified electrode was studied by recording its response to the drugs. The electrode responses in the first week were encountered with no change in peaks current of drugs and after two months the electrode signals were associated with 8% decreasing in the peaks current which shows the stability of the modified electrode.

Interference studies

The selectivity of the proposed sensor to some organic and inorganic species was investigated by analyzing the 0.1 M B-R buffered solution (pH 7) containing 30 µM of clozapine (CLOZ) and 45 µM of sertraline (SER) and different amounts of interfering compounds under optimum conditions. An error less than 5% was applied as tolerance limit for the determination of CLOZ and SER. The obtained results are given in the Table 2, which indicates that the foreign species had no significant influences on the intensity of the peak currents for CLOZ and SER. Thus, the selectivity of the proposed modified electrode is satisfactory and can be applied for simultaneous monitoring of CLOZ and SER in their tablets and human serum sample.

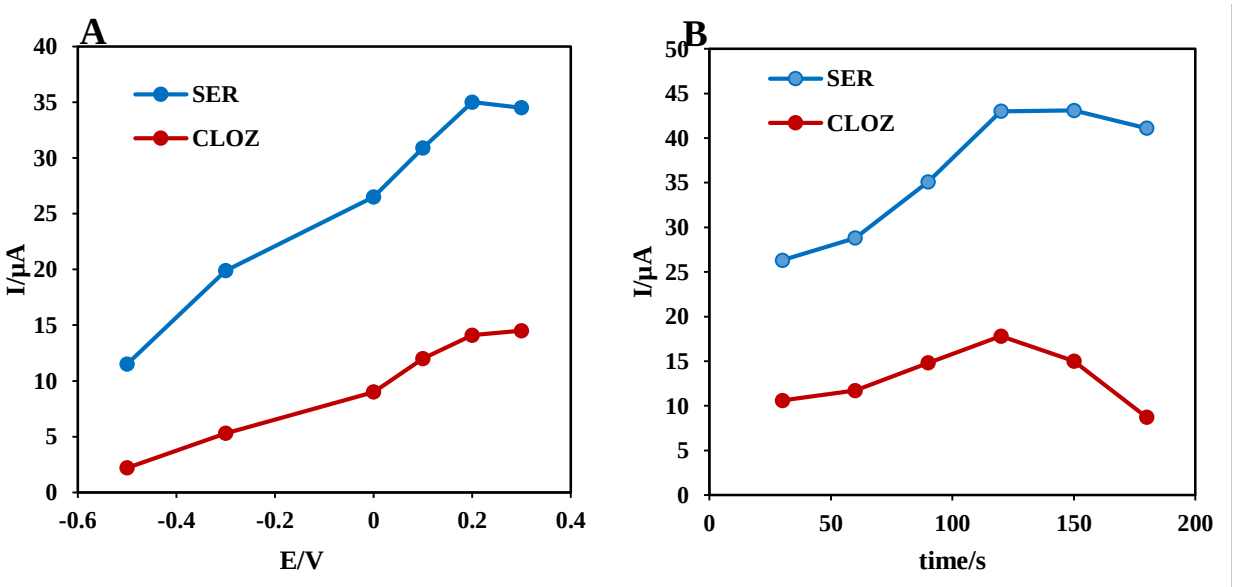


Figure 6. (A) *Effect of accumulation time (t_{acc}) and* ***(B)*** *Effect of accumulation potential (E_{acc}) on peak current of 0.1 M B-RB (pH 7) containing 30 µM of clozapine (CLOZ) and 45 µM of sertraline (SER) at MWCNT-IL/NiONPs/GCE.*

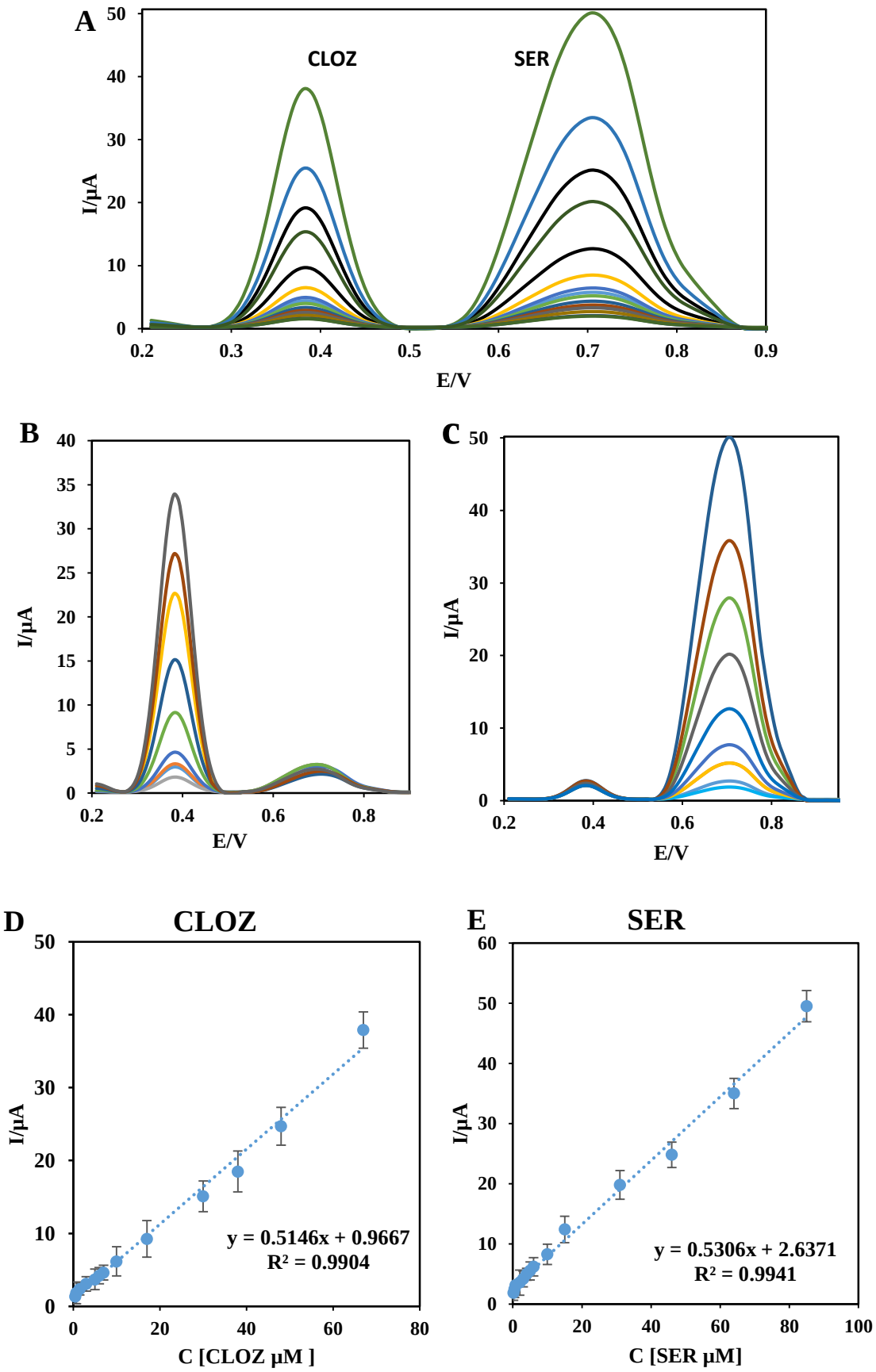


Figure 7. *DPVs for* ***(A)*** *Differential pulse voltammograms for different concentrations of CLOZ and SER mixture.* ***(B)*** *Solutions containing 45 µM SER and various concentrations of CLOZ.* ***(C)*** *Solutions containing 30 µM CLOZ and various concentrations of SER, respectively,* ***(D)*** *Plot of peak currents as a function of CLOZ concentration.* ***(E)*** *Plot of the peak currents as a function of SER concentration in 0.1 M B-RB (pH 7), accumulation time 120s and potential 0.2 V.*

Table 1. *Comparison of analytical characteristic of the proposed sensor with others.*

drug	Electrode	Methods	Limit of detection (µM)	Linear range (µM)	References
CLOZ	TiO_2NP-MCPE[a]	DPASV[b]	0.006	0.5-45	[40]
	SNTs[c]/GC	CV[d]	0.03	0.3 -50	[41]
	PPY/CNT/GCE[e]	LSV[f]	0.003	0.01-5.00	[42]
	MHA[g]/AuE	DPV	0.007	1-50	[43]
	HMDE[h]	SWAdCS[i]	0.00045		[44]
	ISS-CILE[j]	CILE	0.0002	0.001–10	[45]
	ILCPE[b]	DPASV	0.2–1 &1–10	0.0009	[46]
	Bi–Sn NPs decorated on carbon aerogels	CV & DPV	0.5–2092	0.097	[47]
	TA/MWCNTs/GCE	SWV	0.0016	0.05- 0.375	[48]
	Go/Fe_3O_4/SiO_2	DPV	0.03	0.1-700	[49]
	MWCNT/IL/NiONPs/GCE	DPASV	0.052	0.5 - 67	**This work**
SER	R/GCE[k]	DPV	1.0	3.0-90.0	[50]
	GCE	OSWV[l]	10.4	40-800	[5]
	HMDE[h]	DPV	0.198	0.233 - 3.15	[51]
	HMDE[h]	ASSWV[m]	0.15	0.20- 1.20	[52]
	PVC/ PEDOT-C14[n]/pencil lead electrode	ITSV[o]	0.0045	0.01 -0.1	[53]
	CPE	SWV	0.0223	0.199-13.8	[54]
	MIP/Gr-SPCE	SWV	0.0019	0.005 -0.75	[55]
	$ZnFe_2O_4$ NPs modified SPE	DPV	0.02	0.07–300	[56]
	MWCNT/IL/NiONPs/GCE	DPASV	0.047	0.21-85	**This work**

a: Carbon Paste Electrode Modified with TiO_2 nanoparticles, b: ionic liquid-based carbon paste electrode (ILCPE), c: Novel silicate nanotubes, d: Cyclic Voltammetry, e: multiwalled carbon nanotubes (MWCNTs)/ polypyrrole (PPY)/ Glassy carbon, f: Liner sweep voltammetry, g: 16-mercaptohexadecanoic acid, h: Hanging Mercury Drop Electrode, i: square-wave adsorptive cathodic stripping, j: in situ surfactant- modified carbon ionic liquid electrode (ISS-CILE), k: Rutin-Modified Glassy Carbon Electrode, l: OsteryoungSquareWaveVoltammetry, m: Adsorptive Stripping Square Wave Voltammetry, n: poly(vinyl chloride)/ 3, 4-ethylenedioxythiophene, o: ion transfer stripping voltammetry.

Table 2. *Interference of organic and inorganic species in the presence of 30 µM CLOZ and 45 µM SER.*

Interference	($C_{species}$ /C_{CLOZ})	($C_{species}$ /C_{SER})
Mg^{2+}, Ca^{2+}, Na^{+}, K^{+}	950	1000
NH_4^{+},HCO_3^{-}, NO_3	300	300
Lactose, sucrose, glucose,	1000	850
Sorbitol, citric acid, urea	500	550

Table 3. *Recovery test of CLOZ and SER content of tablets (n = 3).*

Added (µM)		Found (µM)		Recovery (%)		R.S.D. (%)	
CLOZ	SER	CLOZ	SER	CLOZ	SER	CLOZ	SER
1.5	2.5	1.54	2.49	97.33	99.6	1.41	2.45
4	2	4.04	1.98	101	99	4.49	2.16

Table 4. *Determination of CLOZ and SER in Human serum (n = 3).*

Added (µM)		Found (µM)		Recovery (%)		R.S.D. (%)	
CLOZ	SER	CLOZ	SER	CLOZ	SER	CLOZ	SER
3	0	2.98	-	99.33	-	2.05	-
0	6	-	6.05	-	100.83	-	2.05
3	6	3.056	5.95	101.86	99.16	1.24	1.69

Real samples analysis

The application of the proposed electrode as an electrochemical sensor in real samples, was tested by analyzing of both drugs in pharmaceutical formulation and human serum. The standard addition method was applied to measure the CLOZ and SER content using DPAdSV method. Recovery studies were done after addition of known amounts of the drug to various pre-analyzed formulations of both drugs. The results are presented in Table 3. As it is obvious, the recovery of drugs was found to be between 97 –101%. Also the sensor was also applied for monitoring of CLOZ and SER in serum sample. The average of three replicate measurements of spiked drugs in serum sample are summarized in Table 4. The resulted recoveries were between 99 and 102%. Also the RSD of the proposed method is less than 5%, which shows the good precision of the method for drugs monitoring using the MWCNT-IL/NiONPs/GCE. This means that this electrochemical sensor should be applied for the simultaneous analysis of CLOZ and SER in real samples with different matrices.

Conclusion

In this study, a new sensor was introduced for detection of the antipsychotic drugs in neutral solution by DPAdSV. GCE was modified by MWCNT-IL (1-Buthyl-3-Methylimidazolium Hexaflourophosphate) and nickel oxide. The surface area of the GCE was enhanced and its catalytic activity improved, when MWCNT-IL/NiONPs was immobilized on the GCE and thus, leading to increase the sensitivity of the sensor for simultaneous determination of clozapine and sertraline. The suitable repeatability and stability are the other advantages of the proposed sensor. The linear range of the proposed sensor is wider than others and has a comparable detection of limit. In addition, the proposed electrochemical sensor was successfully used for determination of the antipsychotic drugs in serum and pharmaceutical samples.

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