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Electro-oxidation and Determination of Gabapentin at Copper Sulfide Nanostructures Modified Carbon Paste Electrode

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Abstract- For the first time, a carbon paste electrode modified with copper sulfide nanostructures for determination of gabapentin (GP) was described. In CV studies, no oxidation response of gabapentin can be seen at the unmodified electrode, but at the copper sulfide nanostructures modified carbon paste electrode (CSN-MCPE), a large anodic peak appears, indicating that the anodic oxidation of gabapentin could be catalyzed at CSN-MCPE. This proves that the copper sulfide nanostructures bear the main role in electrocatalytic oxidation of gabapentin. It has been shown that using the CSN-MCPE, gabapentin can be determined by DPV and amperometry with limit of detections 0.5 and 0.73 μmol L^{-1}, respectively. The electrode response towards gabapentin was quite reproducible and a long-term stability of the electrode (more than 45 day) was observed. Furthermore, the proposed modified electrode was successfully applied to the determination of gabapentin in real samples. High sensitivity, excellent selectivity and ease of preparation are acknowledges of this electrode.

Keywords- Copper sulfide nanostructures, gabapentin, Electrocatalytic oxidation, Amperometry

1. INTRODUCTION

New anticonvulsant drug gabapentin (1-(aminomethyl) cyclohexaneacetic acid) (Scheme 1), was originally developed as a structural analogue of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) to reduce the spinal reflex during the treatment of spasticity, and later found to have anticonvulsant activity in various seizure models [1]. Gabapentin (GP) is also effective in the prevention of frequent migraine headaches, neuropathic pain, and nystagmus and treatment of nerve pain caused by herpes virus or shingles [2]. The molecule incorporates a lipophilic cyclohexane ring into its structure, which allows gabapentin, unlike GABA, to cross the blood–brain barrier.

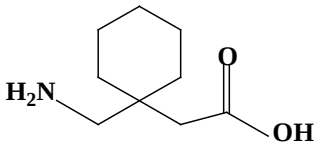
Several analytical methods have been reported for the determination of gabapentin. These methods are based on high-performance liquid chromatography (HPLC) with UV spectrophotometric and fluorescence detection systems [3–8]; capillary electrophoresis with UV/fluorescence detection [9]; gas chromatography (GC) with flame ionization and mass spectrometric (MS) detection [10–12]; voltammetry [13] and a potentiometric PVC membrane sensor [14]. The HPLC and CE methods require derivatization of gabapentin to produce a chromophore detectable by UV/F. The GC methods require derivatization of gabapentin to improve the volatility and avoid column interactions. Generally, for routine analysis of large series, the derivatisation step increases the time of sample preparation and the cost of the method. Despite wide use of gabapentin, a simple and reliable analytical technique is required for its assay in bulk drug and pharmaceutical formulations. Analysis of gabapentin in pharmaceutical formulations is also quite limited and includes spectrofluorometry [15] and colorimetric detection [16] and one HPLC [17] (all of them require derivatization or capillary electrophoresis).

Gabapentin is not electroactive at the surface of most unmodified electrodes; the only report is on gold electrode [13]. Chemically modified electrodes such as nanotubes of nickel oxide modified carbon paste electrode [18] and silver nanoparticle modified multiwalled carbon nanotubes (MWCNTs) paste electrode [19] were used for the voltammetric determination of gabapentin, through an electrocatalytic mechanism.

Electrochemical techniques have been proven to be very sensitive to the determination of drugs and related molecules. The advance in electrochemical techniques in the field of analysis of drugs is due to the simplicity, low cost and relatively short analysis time when compared to electrophoretic and chromatographic techniques. Moreover, the use of chemically modified electrodes in electrochemical methods is widely reported for sensitive and selective determination of various pharmaceuticals [20,21]. Carbon electrodes may be classified in two sections as homogeneous (glassy carbon, graphite, vitreous carbon, screen printed, fullerens, carbon nanotubes and diamond) and heterogeneous (carbon paste, modified carbon paste) [22]. The ease and speed of preparation and of obtaining a new reproducible surface, low residual current, porous surface, and low cost of carbon paste are some

advantages of CPE over all other carbon electrodes. Therefore, CPE can provide a suitable electrode substrate for preparation of modified electrodes [23]. Modification of the paste matrix with various transition metal complexes [24–26] were reported in recent years. These electrodes have been widely used in electroanalysis due to their ability to catalyze the redox processes of some molecules of interest, since they facilitate the electron transfer [13].

In the study described here, the electrooxidation and determination of gabapentin at copper sulfide nanostructures modified carbon paste electrode was investigated. To the best of our knowledge, there is no work reporting the preparation of such an electrode for gabapentin before.



Scheme 1. The chemical structure of gabapentin

2. EXPERIMENTAL

2.1. Chemicals and reagents

All chemicals used in this work were of analytical grade, purchased from Merck (Darmstadt, Germany) and Sigma Aldrich and were used without further purification. Gabapentin was received from the Center of Quality Control of Drug, Tehran, Iran. The Gabapentin capsules were obtained from a local drugstore. Standard solutions of authentic drug were prepared by dissolving an accurate mass of the bulk drug in an appropriate volume of 0.1 mol L^{-1} NaOH solution (which was also used as the supporting electrolyte).

2.2. Apparatus

All electrochemical measurements were carried out in a three-electrode cell using an Autolab electrochemical system (Eco Chemie, Utrecht, the Netherlands) equipped with PGSTAT-12 and GPES software. A bare or modified carbon paste electrode was used as a working electrode, Ag/AgCl/saturated KCl and a Pt wire were used as reference electrode and counter electrode, respectively. All experiments were carried out at room temperature.

2.3. Preparation of copper sulfide nanostructures

The procedure for preparation of Cu_2S nanostructures was adapted from Ref. [27]. Self-mosaic flower-like Cu_2S nanostructure was prepared by a two-step hydrothermal process. The original self-assembled Cu_2S nano-flowers were obtained by the following first step.1 g

of $CuCl_2$.2 H_2O and 0.8 g of thiourea powders were added into 80 mL ethanol to form yellow–green slurry. The slurry was stirred for 30 min and then transferred into a 100 mL Teflon autoclave. The autoclave was maintained at 160 °C for 6h and then air-cooled to room temperature. The resulting dark precipitates were washed with distilled water and ethanol several times and then dried at 50 °C under vacuum for 10 h.

2.4. Preparation of copper sulfide nanostructures modified carbon paste electrode

The carbon paste electrode modified with copper sulfide nanostructures was prepared by hand mixing 68% graphite powder, 12% copper sulfide nanostructures and 20% paraffin oil in an agate mortar to get homogeneous carbon paste. Then a portion of the composite mixture was packed into the end of a polyethylene syringe (2 mm in diameter). Electrical contact was made by forcing a thin copper wire down into the syringe and into the back of the composite. Before each measurement, pushing an excess of paste out of the tube and then polishing the freshly exposed paste with weighing paper obtained a new surface. Also, unmodified carbon paste was prepared in the same way but without adding copper sulfide nanostructures to the mixture. Then, the modified electrode was placed in 0.1 mol L^{-1} NaOH and the electrode potential was cycled between -250 and 1000 mV (*vs.* Ag/AgCl) at a scan rate of 50 mVs^{-1} for 16 cycles in a cyclic voltammetry regime until a stable voltammogram was obtained. The electrode was rinsed with distilled water, and applied for electrochemical studies.

2.5. Gabapentin capsule assay procedure

In order to analyze the drug capsules, ten capsules were weighed and the contents emptied into a mortar. The empty capsule shells were weighed to determine the average fill weight in each capsule. The fill material was gently ground using a pestle for some minutes to break any aggregated or cemented material. Appropriate accurately weighed amounts of the homogenized powder were transferred into 100 mL calibrated flasks containing 50 mL of 0.1 mol L^{-1} NaOH solution. The contents of the flasks were sonicated for 30 min, and then the undissolved excipients were removed by filtration and diluted to volume with the supporting electrolyte. Appropriate solutions were prepared by taking suitable aliquots of the clear filtrate and diluting them with 0.1 mol L^{-1} NaOH solution. The gabapentin content was determined by DPVs technique using the modified electrode.

2.6. Analysis of spiked human serum sample

Human blood serum samples were obtained from healthy volunteers. They were centrifuged at 4,000 rpm for 30 min at room temperature to remove serum proteins. Then, 1.2 mL acetonitrile was added to remove serum protein. After vortexing for 1 min, the mixture

was centrifuged for 10 min at 6,000 rpm to remove the serum protein residues. Supernatant was taken carefully and appropriate volumes of this supernatant were transferred into the electrochemical cell and diluted up to the volume with the NaOH [28].

3. RESULTS AND DISCUSSION

3.1. Cyclic voltammetric studies

In order to reveal the electrocatalytic activity of CSN-MCPE toward the oxidation of gabapentin, the voltammetric experiments were carried out on both modified and unmodified CPEs in the presence of gabapentin. Fig. 1 shows the cyclic voltammograms of CSN-MCPE in the absence and presence of gabapentin in 0.1 mol L^{-1} NaOH solution. As shown, no oxidation response of gabapentin can be seen in the potential range from 0.1 to 0.8 V on unmodified CP electrode (curves a and b), indicating electroinactivity of gabapentin on carbon based surfaces in the swept potential range. But at the CSN-MCPE, a large anodic peak appears at 534 mV (curve d), indicating that the anodic oxidation of gabapentin could be catalyzed at CSN-MCPE. This proves that the copper sulfide nanostructures bear the main role in electro-catalytic oxidation of gabapentin. Regarding the reaction product(s) of the electrooxidation process on CSN-MCPE, gabapentin as a primary straight chain amine can be oxidized on copper-based electrodes to the corresponding imine, nitril, and/or aldehyde analogs [29–31], as shown in Scheme 2.

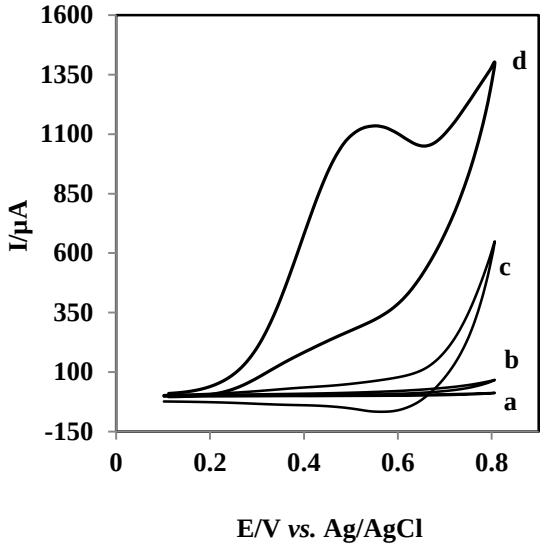
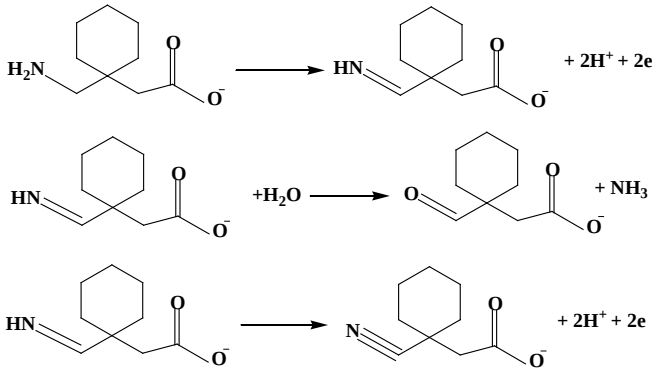


Fig. 1. Cyclic voltammograms of bare CPE (a, b) and CSN- MCP electrode (c, d) in 0.1 mol L^{-1} NaOH solution in the absence (a, c) and presence of 50 µmol L^{-1} gabapentin (b, d). Conditions: potential range 100 to 800 mV scan rate of 50 mV s^{-1}



Scheme 2. The proposed reaction mechanism for the electrooxidation of gabapentin

The voltammetric signals were affected by the composition of the paste. It was observed that the sensitivity of the sensor first rapidly increases with increasing the copper sulfide nanostructures content in the paste up to about 12%, and then started to level off and even slightly decreases with the higher loadings (not shown). This is because the sites for adsorption increased with the increase of copper sulfide nanostructures percentage in the modified electrode, while the excess of copper sulfide nanostructures increase the resistance of the electrode. Hence a copper sulfide nanostructures (12%, w/w) modified carbon paste electrode was used throughout this work.

With the increase of gabapentin concentration, the anodic peak current gradually increased (Fig. 2). The characteristic shape of cyclic voltammogram in this potential region indicates that the signal is due to the oxidation of gabapentin. The catalytic peak current is proportional to the concentration of gabapentin in the range of 5 μmol L^{-1} to 55 μmol L^{-1}.

The influence of scan rate was investigated in the range of 7-160 mVs^{-1} on the electrochemical behavior of CSN-MCP in the presence of gabapentin (Fig. 3A). A linear relationship was observed between anodic peak current with scan rate (Fig. 3B) indicates an adsorptive redox process, which may be due to the tendency of gabapentin to interact with copper ions at the electrode surface [32]. A linear relationship was also observed between log I_{pa} and log ν with a slope of 0.5269 (Fig. 3C) which shows the large contribution of adsorption of gabapentin to the current flow; in the case of diffusion currents, the slope approaches 0.5 [33].

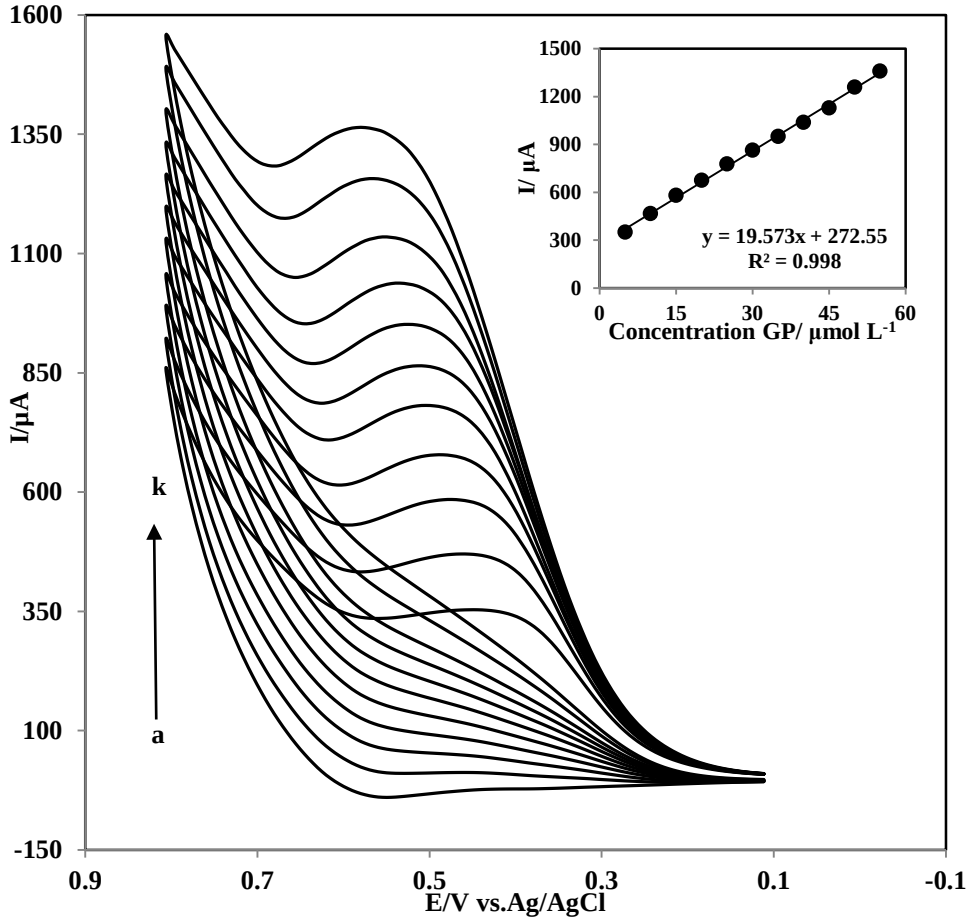


Fig. 2. Cyclic voltammograms of a CSN-MCPE in the presence of various gabapentin concentrations: (a)–(k): 5, 10, 15, 20, 25, 30, 35, 40, 45, 50 and 55 µmol L^{-1}, respectively, at a scan rate of 50 mV s^{-1}, in 0.1 molL^{-1} NaOH solution. Inset: Variation of anodic peak current *vs*. gabapentin concentration

At higher scan rates, the peak currents versus the scan rate plots deviated from linearity and the peak currents became proportional to the square root of the potential scan rate (Fig. 3D). The data indicated that the peak current was diffusion controlled. In addition, with increasing scan rates, the peak separations began to increase, indicating that the limitation arising from charge transfer kinetics. These results suggested that the anodic peak was governed by both adsorption and diffusion.

The E_p of the oxidation peak was also dependent on scan rate. The plot of E_p *vs.* log ν was linear having a correlation coefficient of 0.9919 (Fig. 3E) and the relation between E_p and ν can be expressed by the equation $E_p(V)=0.1542 \log \nu(V\ s^{-1})+0.2723$. Based on Laviron's theory for an irreversible electrode process [34], the E_p–ν relationship can be described by the following eq. (1):

$$E_p = E^{\circ'} + \left(\frac{2.303RT}{\alpha nF}\right) log \left(\frac{RTk_s}{\alpha nF}\right) + \left(\frac{2.303RT}{\alpha nF}\right) log\, v \quad (1)$$

where α is the transfer coefficient, k_s is the standard heterogeneous rate constant of the reaction, n the number of electrons transferred, ν the scan rate and $E^{\circ'}$ is the formal redox potential. Other symbols have their usual meaning. Thus the value of α_n can be easily calculated from the slope of E_p *vs*. log ν.

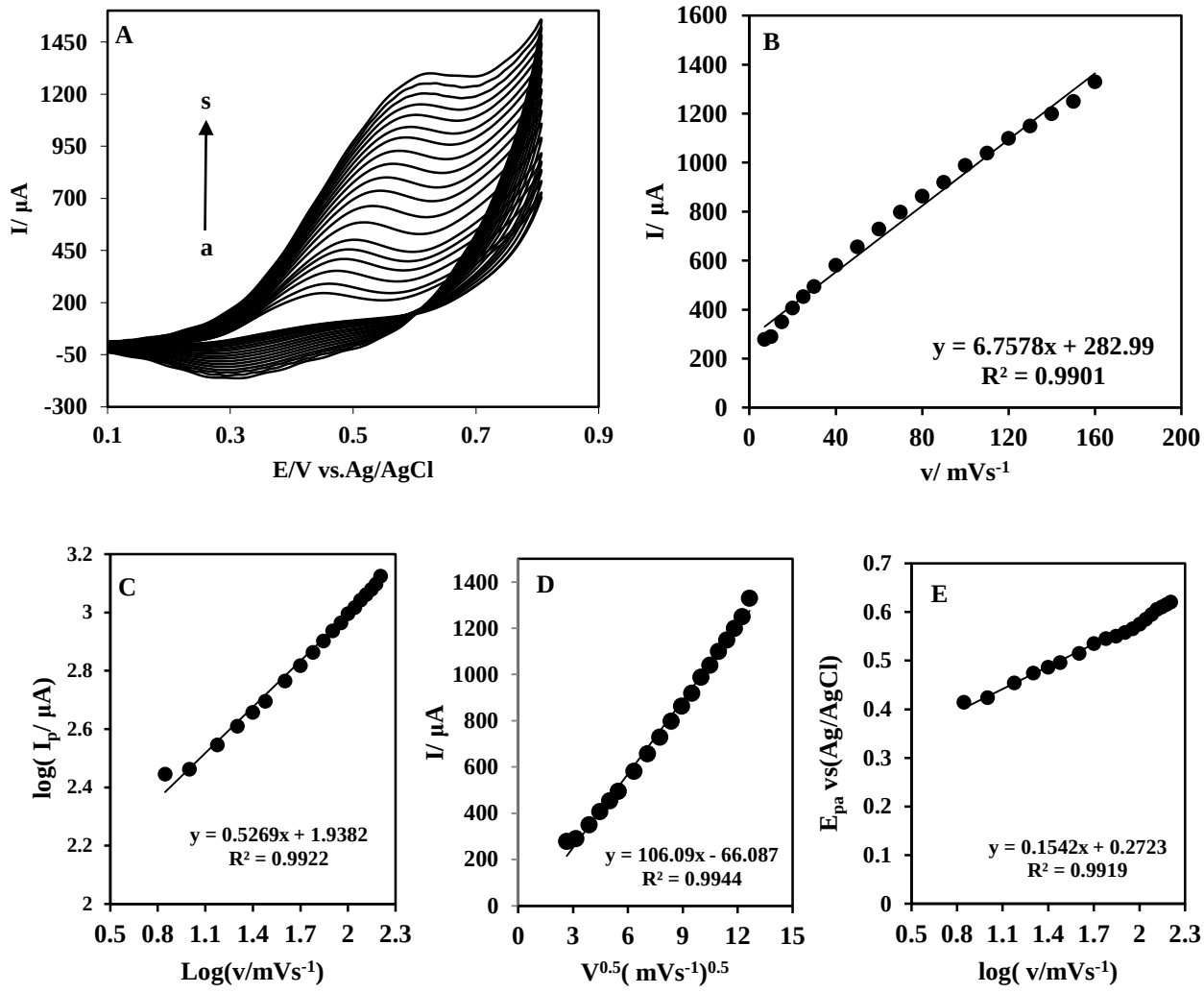


Fig. 3. A) CVs of CSN-MCPE in 0.1 mol L^{-1} NaOH solution containing 20 µmol L^{-1} gabapentin at various scan rates; from inner to outer scan rates of 7, 10, 15, 20,25, 30, 40,50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150 and 160 mV s^{-1}, respectively; B) Variation of anodic peak current *vs*. ν; C) plot of log I_{pa} *vs*. log ν; D) plot of anodic peak current *vs*. square roots of potential sweep rate; E) plot of peak potential *vs*. log ν

In this system, the slope is 0. 1542, taking T=298 K, R=8.314 J K^{-1} mol^{-1} and F=96480 C, αn was calculated to be 0.39. Generally, α is assumed [35] to be 0.5 in totally irreversible electrode process. Thus, n was calculated to be 0.8~1.0. The value of k_s can be determined from the intercept of the above plot if the value of $E^{\circ'}$ is known. The value of $E^{\circ'}$ in Eq. (1) can be obtained from the intercept of E_p *vs.* ν curve by extrapolating to the vertical axis at ν=0 [36]. In our system the intercept for E_p *vs.* log ν plot was 0.2723 and $E^{\circ'}$ was obtained to be 0.4478 V, the k_s was calculated to be 568.76 s^{-1}.

3.2. Chronoamperometric Study

In order to evaluate the reaction kinetics, the oxidation of gabapentin on CSN-MCPE was investigated by chronoamperometry. Fig. 4A shows the recorded chronoamperograms for the modified electrode in the absence and presence of different concentrations of gabapentin using a step potential to 0.51 V. As is obvious, the anodic current increased in the presence of the increasing amounts of the drug. The amount of catalytic current depends on the concentration of gabapentin as well as the catalytic rate constant, *k* [37]:

$$I_{catal}/I_L = \lambda^{1/2}\pi^{1/2}(KCt)^{1/2} \quad (2)$$

I_{catal} and I_L are limiting currents in the presence and absence of gabapentin, respectively. *C* is the molar concentration of gabapentin and *t* is the elapsed time (s). The value of *k* was calculated for different concentrations of gabapentin from the slope of I_{catal}/I_L versus $t^{1/2}$ plot (Fig. 4B). The average value for *k* was found to be 186.07×10^7 M^{-1} s^{-1}.

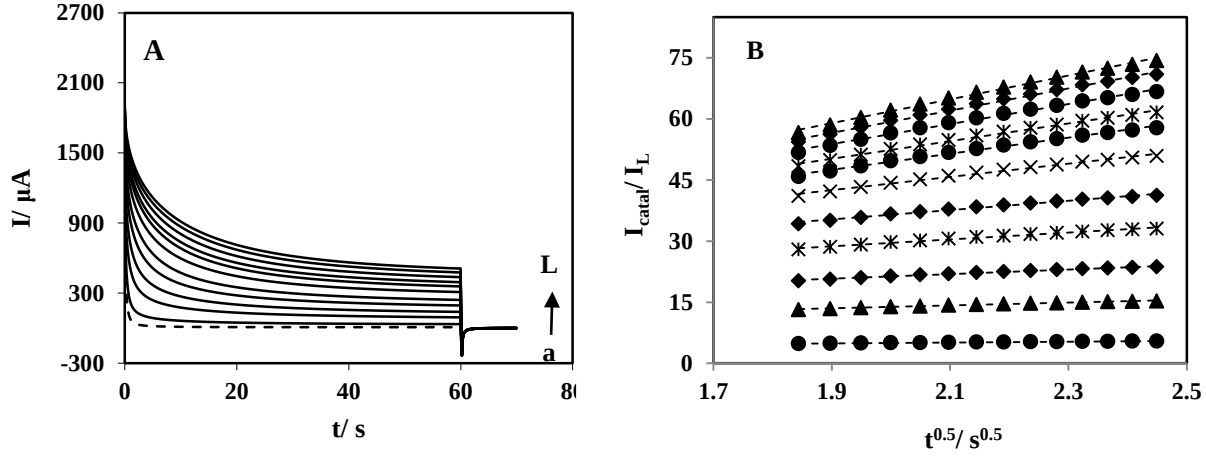


Fig. 4. A) Chronoamperograms obtained at CSN-MCPE in the presence of different concentrations of gabapentin; from bottom to top: 0.0, 5.0, 10.0, 15.0, 20.0, 25.0, 30.0, 35.0, 40.0, 45.0, 50.0, and 55.0 µmol L^{-1}; B) Dependence of I_{cat}/I_L on $t^{1/2}$

Analytical characteristics of CSN-MCPE for the amperometric determination of gabapentin were estimated. Fig. 5 shows the current-time responses of the modified electrode to gabapentin which was successively added to the electrochemical cell containing 0.1 molL^{-1} NaOH under hydrodynamic conditions, while the electrode potential was kept at 0.5. As shown in the figure a well-defined response was observed during the stepwise increasing of gabapentin concentration in the range of 2-24 µmol L^{-1}. It was observed that the sensor responds so rapidly to the substrate, as about 95% of the steady-state current appears within 30 s. The limits of detection (LOD) and quantization (LOQ) of the procedure were calculated according to the 3 SD/m and 10 SD/m criteria where SD is the standard deviation of the blank and m is the slope of the calibration curves [38]. The limits of detection and quantitation were found to be 0.73 µmolL^{-1}and 2.42 µmolL^{-1}for peak gabapentin.

The amperometric response of CSN-MCPE to gabapentin (4 µmol L^{-1}) was recorded over a continuous period of 1700 s (not shown), which showed nearly stable current with only 12% current diminutions after this long time. Thus, the electrode can be used as an excellent electrocatalytic material for sensitive and stable amperometric determination of gabapentin.

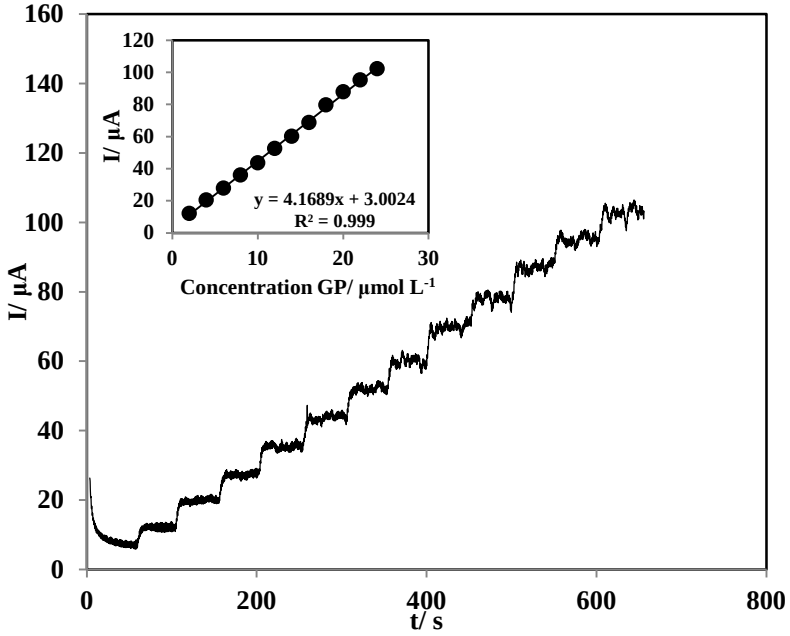


Fig. 5. The current time profiles recorded at the CSN-MCPE during the successive addition of gabapentin. Inset: Typical calibration graph derived from the current – time profile

3.3. DPV analysis of Gabapentin

Since DPV has a much higher current sensitivity than cyclic voltammetry, we used DPV method (with a pulse height of 50 mV and a pulse width of 1.0 mV) for the determination of gabapentin. Fig. 6 shows DPVs of different concentrations of gabapentin and the obtained calibration curves. The results showed a linear segment for gabapentin concentration from 2

to 22 μmol L^{-1} gabapentin. The detection limit was estimated to be 0.5 μmol L^{-1} (S/N=3). The determined parameters for calibration curves of drug, accuracy and precision, LOD and LOQ, and the slope of calibration curves are reported in Table 1. Comparison of the analytical figures of CSN- MCPE for gabapentin determination with similar reports is shown in Table 2. The linear range and LOD of the proposed method is comparable with of the previous works.

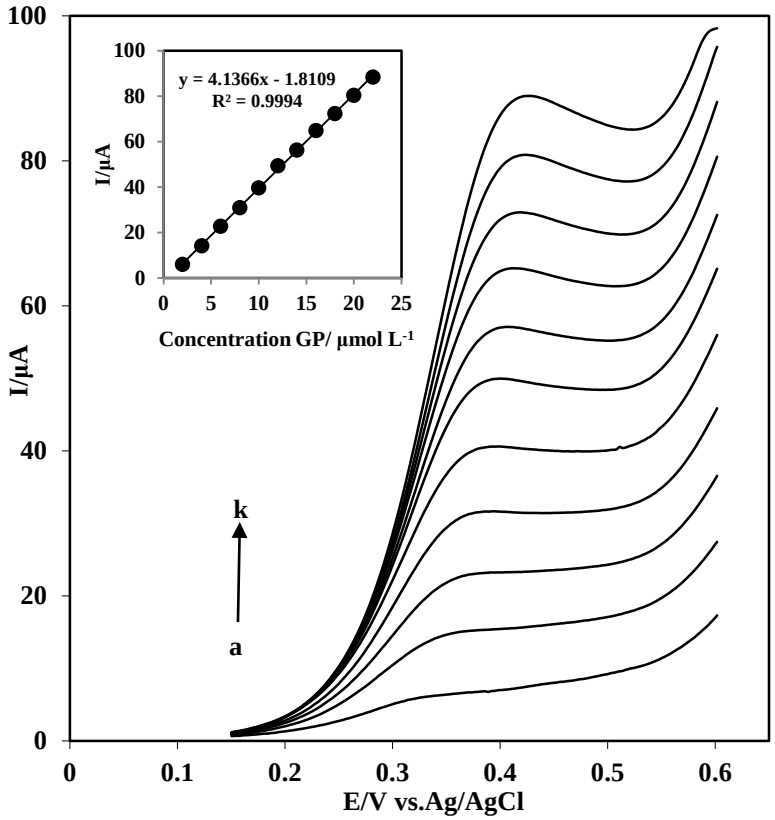


Fig. 6. DP voltammograms of CSN-MCPE in 0.1 mol L^{-1} NaOH solution containing different concentrations of gabapentin. 2–22 corresponds to 2.0, 4.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, 18.0, 20.0, and 22.0 μmol L^{-1} gabapentin. Inset: Plots of electrocatalytic peak current as a function of gabapentin concentration

Table 1. The determined parameters for calibration curve, accuracy and precision (n=3) for oxidation of gabapentin on CSN-MCPE

Linear range (μM)	2–22
Slope (A M^{-1})	(4.1366±0.006)
Intercept (A)	(-1.18109±0.009)×10^{-6}
LOD (μM)	0.5
LOQ (μM)	1.67
RSD (%)	5.78%

Table 2. Comparison of analytical characteristics of CSN-MCPE for the determination of gabapentin with other electrodes

Electrode	Technique	Linear range (µM)	Sensitivity	LOD (µM)	Ref.
Nickel oxide nanotube-modified carbon paste electrode	Amperometry	2.4-50	0.0163 µA µmol^{-1} L	0.3	[18]
AgNPa/MWCNT-paste Electrode	SWV	0.003-2.9×10^{4}	10.52 µA log (mol^{-1} L)	0.00056	[19]
Gold electrode	DPV	0.3-15	0.2729 µA µmol^{-1} L	0.13	[20]
CSN-MCPE	Amperometry	2-24	4.1689 µA µmol^{-1} L	0.5	This work
CSN-MCPE	DPV	2-22	4.1366 µA µmol^{-1} L	0.73	This work

In order to demonstrate the measurement of gabapentin in pharmaceutical preparations, we examined this ability in the voltammetric determination of gabapentin in capsule (nominal each capsule contains 100mg gabapentin). The results of three samples replicates taken by DPV method were averaged to be 98.22±1.63 mg gabapentin per tablet with the RSD of 3.2%, which is in satisfactory agreement with the claimed label. The values of experimentally determined drugs and declared values in capsules are tabulated in Table 3.

The applicability of the proposed DPVs method for the determination of gabapentin in biological fluids of human serum blood was attempted. The high sensitivity of the method allows the determination of gabapentin in spiked human serum samples (Table 4). The recovery of the analytes was measured by spiked drug into diluted serum samples. The DPVs were recorded after the serum was spiked with various amounts of the gabapentin within the working concentration range. Recoveries were found to lie in range of 101.6–106.25%. Good recoveries of gabapentin were achieved from this method, meaning that application of proposed sensor to the analysis of gabapentin in biological fluids could be easily assessed. Besides, the recovery studies of the spiked gabapentin in well water sample showed average values in the range from 97.92 to 103.14% (Table 5) show the satisfactory results for analytical determination of gabapentin in real sample.

In order to evaluate the selectivity of the proposed method in the determination of gabapentin the influence of various foreign species (inorganic ions and organic compounds commonly existed in pharmaceuticals and biological samples) on the determination of gabapentin (20 µmol L^{-1}) was studied at optimum conditions. The results showed that in the presence of 1000-fold of Ca^{2+}, Br^{-}, NH_4^{+}, SO_4^{2-}, citric acid, starch, oxalic acid and glucose

the current change was less than ±7%. Examination of glycine showed their tolerance limit about 8-fold compared to gabapentin.

The intra-assay precision of the sensor (repeatability) was evaluated by determination of gabapentin at two concentration levels (4.0 and 10.0 μmol L^{-1}) by the proposed method. The coefficients of variation (s^2) were 3.21% and 3.81% (five replicate measurements) for the above concentrations, respectively, showing a good repeatability. Inter-assay variation coefficients (reproducibility) on five sensors (made independently) were 3.9% and 2.83%, respectively, indicating acceptable fabrication reproducibility.

Table 3. Determination of gabapentin in tablets[a] by the proposed method (n=3)

No.	Amount Added (mg)	Amount Expected (mg)	Amount Found (mg)	Recovery (%)
1	0	100	98.6	98/6
2	100	200	198.1	99.05
3	200	300	291.2	97.07
4	300	400	394.1	98.52

[a] Each tablet contains 100 mg Gabapentin

Table 4. Gabapentin concentrations in spiked human serum samples

No.	Amount added (μM)	Amount found (μM)	Absolute recovery (%)	RSD (%)
1	0	Not detected	-	-
2	4	4.2	105	5.18
3	12	12.2	101.6	4.46
4	16	17	106.25	5.98

Table 5. Gabapentin concentrations in spiked water samples

No.	Amount added (μM)	Amount found (μM)	Absolute recovery (%)	RSD (%)
1	0	Not detected	-	-
2	12	13.4	110.30	4.8
3	24	25.1	104.58	4.44
4	35	35.8	102.29	4.67
5	40	42.8	101.20	5.1

Another advantage of the proposed modified electrode was that the resulting modified electrode showed good long term stability. Stability of the proposed electrode was tested by measuring the decrease in voltammetric current during repetitive DPV measurements of gabapentin with CSN-MCPE stored in solution or air. For example, this electrode, within 24

h, is used for the determination of 15 μmol dm^{-3} gabapentin in 0.1 mol L^{-1} NaOH solutions. Obtained results show that this electrode has remarkable stability and any significant change in the voltammetric currents was not shown. When the electrode was stored in the atmosphere, the current response remained almost unchanged for 45 days. RSD of repeated peak currents was (2.3.0%). The high stability of the CS- MCPE could be related to the strong affinity of CSN-MCPE and the insolubility of the CSN-MCPE in water.

4. CONCLUSION

A carbon paste electrode modified with copper sulfide nanostructures was prepared with carbon microparticles, Nujol and copper sulfide nanostructures. It was employed, for the first time, for electrooxidation and determination of gabapentin. The prepared electrode showed good catalytic activity in the oxidation of gabapentin. The electrode had a long lifetime and shelf storage advantages, so can be used as the detector of gabapentin in flow system. This CSN-MCPE electrode provides a new way to construct some other similar electrodes for successful analysis of pharmaceutical or biological samples.

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