Egypt. J. Chem. **Vol. 62,** No. 9, pp. 1739 - 1748 (2019)

Egyptian Journal of Chemistry
http://ejchem.journals.ekb.eg/

A Copper Oxide Nanoparticle Modified Screen-printed Electrode for Determination of Mirtazapine

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DEVELOPMENT of a disposable copper oxide nanoparticles modified screen-printed carbon electrode (CuONP/SPCE) as a quick and convenient method for determination of Mirtazapine (MZ) is studied. It was demonstrated that the nano-copper oxide (CuONP) on the SPCE could significantly enhance the electrochemical oxidation of MZ at pH7.0. The electrochemical response characteristics of MZ on the modified electrode were investigated by cyclic voltammetry (CV) and differential pulse voltammetry (DPV). Under the optimized experimental conditions, the analytical results showed linear responses over the range 66.6–662.3ng/mL. The detection and quantification limits, LOD and LOQ were 4.5, 13.4 ng/mL, respectively. The results indicate that the suggested sensor is highly suitable for clinical analysis, quality control determination of MZ in pharmaceutical formulations and spiked serum.

Keywords: Mirtazapine, Copper oxide nanoparticles, Screen-printed carbon electrode, and voltammetry.

Introduction:

Screen printing technology is a well-established technique for the fabrication of both chemical and biosensors[1]. Electrochemical biosensors based on screen printed carbon electrode (SPCE) have attracted intense attentions as diagnostic tools as they are disposable, portable, rapid and produce comparable results as conventional methods. SPCE based electrochemical biosensor system have a widely used to fabricate disposable and economical electrochemical sensors such as cancer biomarker detection [2], uric acid sensing [3], amyloid beta biomarker for Alzheimer's disease diagnosis [4]. SPCE have been utilized within many notable pieces of work without the additional pre-treatment. Modification of the electrodes may be used to achieve highly sensitive electrochemical responses and clear desirable potential. In such work, minimum costs and easy of production are essential [5-9].

The great versatility of screen-printed electrodes resides in their wide range of possible modifications. The variety of composition of ink in the printing process can be chosen as graphite particles, polymeric binder and other additives which are utilized for dispersion, printing and adhesion tasks. The ink formulation is regarded by the manufacturer as proprietary information and it has been shown that differences in ink composition e.g. type, size or loading of graphite particles and in the printing and curing conditions can strongly affect the electron transfer reactivity and the overall analytical performance of the resulting carbon sensors [10-12].

Metallic nanoparticles, such as copper oxide nanoparticles, are of great interest due to their important properties and their numerous possible applications. So, Application with screen printed electrochemical sensors provide excellent plat-forms for modification with a variety of nanoparticles [13] and structurally related materials requiring no pre-treatment such as electrode polishing or electrochemical pre-

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Received 27/2/2019; Accepted 8/4/2019
DOI: 10.21608/ejchem.2019.10062.1663

treatment via electro-deposition, as is common with other electrode materials.

Mirtazapine (MZ), IUPAC name (1, 2, 3,4, 10, 14b-hexahydro-2 -methylpyrazino [2,1-a] pyrido [2,3-c] benzazepine, is a tetracyclic antidepressant with different structure from any other antidepressant.MZ is available as film coated tablets and the initial dose is 15-30 mg/day. It is used for the treatment of depression by enhancing the central noradrenergic and specific serotonergic activity and blocking α2 receptors. It is metabolized in the liver via the P450 cytochrome oxidase pathway. Elimination occurs via urine (75%) and feces (15%). Clearance of the drug is decreased in the presence of renal or liver impairment. Therefore, a lower dosage is recommended in the elderly and patients with renal or liver disfunction [14-18].

MZ was analyzed in biological samples by using high performance liquid chromatography [19-21], gas chromatography [22], capillary electrophoresis [23], HPTLC [24] and spectrofluriomtry [25]. Ozkan et al. performed a voltammeric assay for MZ in pharmaceutical dosage form by using glassy (GC) carbon and boron dopped diamond (BDD) electrodes [26].

As a continuation of previous work in voltammetric field [27-29], in this work CuONP is used as a modifier in the ink of screen-printed carbon electrode and testing its performance for determination of electrochemical measurement of MZ. Nanomaterials [30] as CuONP, were expected to provide higher sensitivity in electrochemical detection of MZ since it provides high current density, high charge carrier mobility, very low resistivity, inert surface, and high thermal conductivity [31]. To our knowledge, there is no research report of using copper oxide nanoparticles to quantify MZ.

Experimental

Materials and Reagents

Copper oxide nanoparticles, particle size<50 nm, was purchased from Sigma–Aldrich (analytical-reagent grade, Sigma–Aldrich, Germany). Mirtazapine, graphite (particle dimension 20 mm), cellulose acetate, acetone and cyclohexanone were kindly supplied from National Organization for Drug Control and Research NODCAR. REMERON® tablets (15 mg) from local Pharmacy market produced by MSD

Britton–Robinson buffers (BR) were used. A 0.04 M Britton–Robinson buffer solution for the *o*-boric, *o*-phosphoric and acetic acids was prepared using Merck analytical grade reagents. Solutions of different pH values were prepared from this by the addition of 0.2M sodium hydroxide. All chemical used was purchased from Merck (analytical-reagent grade). All solutions were prepared with Millipore Milli-Q nanopure water (resistivity >18 Ω/cm). Experiments were performed at room temperature, 25±1°C.

Apparatus

Voltammetric measurements were taken using AUTOLAB Metrohm electro analyzers model 797VA Computrace, Switzerl and using for recording Cyclic and differential wave voltammetric measurements. A HANNA 213 pH meter was used for adjust the pH.

Working screen-printed electrode preparation

Figure 1 shows hand-made screen-printed working electrode that used in the determination of MZ. 0.1 g cellulose acetate and 0.40 mg of graphite was well mixed with10.0mL of (1:1 acetone and cyclohexanone) [9]. A successive layer of the last ink mixture was printed onto a PVC strip substrate for the construction of the working screen-printed electrode (30 mm × 6 mm,1.0 mm thick). The working electrode was formed by grazing the ink over an etched stencil thickness 100.0 µm, finally an insulator layer (polystyrene) was printed over the sensor strip[15]. To describes an easy procedure to obtain nanoparticle-modified working SPCE. 5µL of Stock solution of 1mg/mL of CuONP, ZnONPor MWCNT was casted on the carbon working electrode of SPCE and waiting until the solvent was evaporated in room temperature. This step is repeated for three times. Careful transportation of the electrodes is necessary.

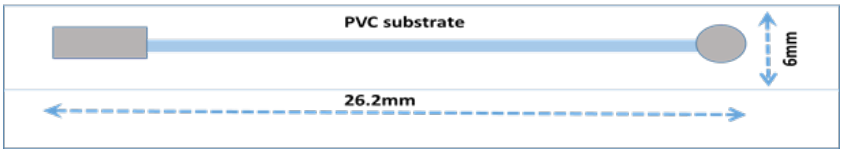

Fig. 1. Schematic diagram of the sensor preparation.

Application to pharmaceutical product

Five mitrazipine tablets (labeled 15 mg per tablet) were grinding. The tablet solution was prepared by dissolving an adequate portion weighed of this powder equivalent to 10 mg of MZ in 10mL double distilled water by ultra-sonication. The prepared solution was diluted to obtain a final concentration of 0.5 mg/mL Then, different volume of the diluted solution was transferred into a 10 mL volumetric flask and diluted to the mark with BR buffer (pH 7.0). The drug was determined using the standard addition method. The peak current at the working electrode was measured using the DPV method, and the concentration of the drug was calculated.

Application to spiked plasma

The spiked blood samples were centrifuged to separate the plasma (supernatant) from the solid portion. The plasma was kept frozen until assays. A stock solution of 0.5 mg/mL of MZ was prepared in deionized water. Then, 0.1 ml was transferred to a 10 mL volumetric flask and completed to the mark with BR buffer of pH 7.0. Quantitative volume was transferred to the electrolytic cell and 10 microliters of plasma were added followed by successive addition of stock solution containing MZ. DPVs were recorded according to the recommended procedure MZ. Values of the current (I) versus the corresponding concentration were plotted to obtain the calibration graph.

Recommended Experimental Procedure

Appropriate aliquots of MZ drug working solution (0.5 mg/mL) transferred into a 25 mL volumetric flask, filled to the mark with 0.04 M BR buffer pH 7.0 to cover the final concentration 66.6– 662.3 ng/mL. The solution transferred to the voltammetric cell. The sterile time was 10 s with continuous stirring at speed of 1000 rpm at room temperature. Then stop the stirrer and the solution was allowed to rest for 10 s, then voltammograms were carried out using the modified electrode at scan rate 100 mV/s and 10 mV/s, applying CV and DPV, respectively. The scan carried out over a range from +600 to +1400 mV. The mean of triplicate measurements of content in the sample was calculated using the obtained regression equations.

Results and Discussion

Electrochemical oxidation of mitrazipine at CuONP/SPCE

Typical cyclic voltammograms of bare CPE, CuONP, ZnONP or MWCNT/ SPCE towards the electrochemical sensing of mirtazapine are shown in Fig. 2 (A and B). The cyclic voltammetric responses for the electrochemical oxidation of 65.0 µg/mL of MZ was documented, in the range of 600 to 1400 mV (Fig. 2A), in BR buffer pH 7.0, at a scan rate of 100 mV/s for the tested electrodes. bare SPCE exhibited a peak current of 0.5 µA at 940 mV, which corresponded to the electrochemical oxidation of MZ. It seems that the electrochemical reaction kinetics were improved by CuONP/SPCE, which clearly enhanced the peak currents of MZ at 1050 mV with a value of 1.85 µA. The increase in current was due to the larger surface area of the modified electrode, which improved the electrode kinetics. In other words, the results clearly indicate that the CuONP improve the MZ oxidation signal.

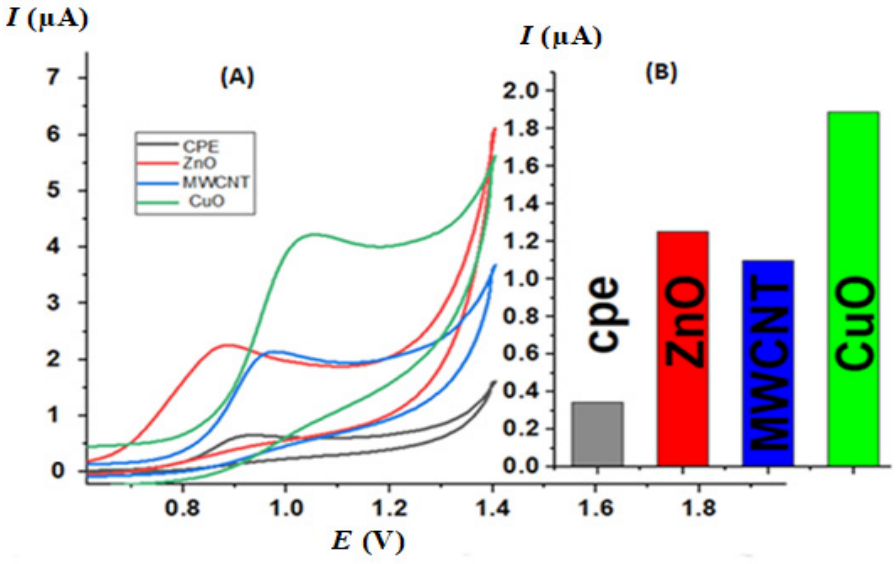

Fig. 2. Cyclic voltammograms of (1) bare (2) ZnO (3) MWCNT (4) CuONP/SPCE and in 0.1 M BR buffer (pH 7.0) in the presence of 10µg/mL mirtazapine at the scan rate 100 mV/s.

Effect of pH

The electrochemical behavior of MZ is dependent on the pH value of the aqueous solution. Therefore, pH optimization of the solution seems to be necessary in order to obtain the electrocatalytic oxidation of MZ. Thus the electrochemical behavior of mitrazipine was studied in 0.1 M BR buffer in different pH values (3.0 < pH < 11.0) at the surface of CuONP/SPCE by CV. It was found that the electrooxidation of mirtazapine at the surface of CuONP/SPCE was more favored under neutral conditions than in acidic or basic medium. The intersection of the Ep-pH curve of MZ and the is located around 7.0, close to the pKa of the piperazine moiety, while the slope of the Ep-pH curve of was found to be 55.30 mV/pH. This slope was close to the expected theoretical value of 59 mV/pH, indicating that the number of protons and electrons involved in the oxidation of MIR is equal. Thus, to attain higher sensitivity the pH 7.0 was chosen as the optimum pH for electrocatalysis of mitrazipine oxidation at the surface of CuONP/SPCE.

The effect of electrolyte pH on the oxidation of mirtazapine at CuONP/SPCE was represented in Fig. 3(A,B) as discrepancy pulse voltammograms in BR buffer (pH = 3-11). The anodic peak potentials go negatively with pH indicating that MZ oxidation is a pH-reliant reaction corresponding to the linear regression formula

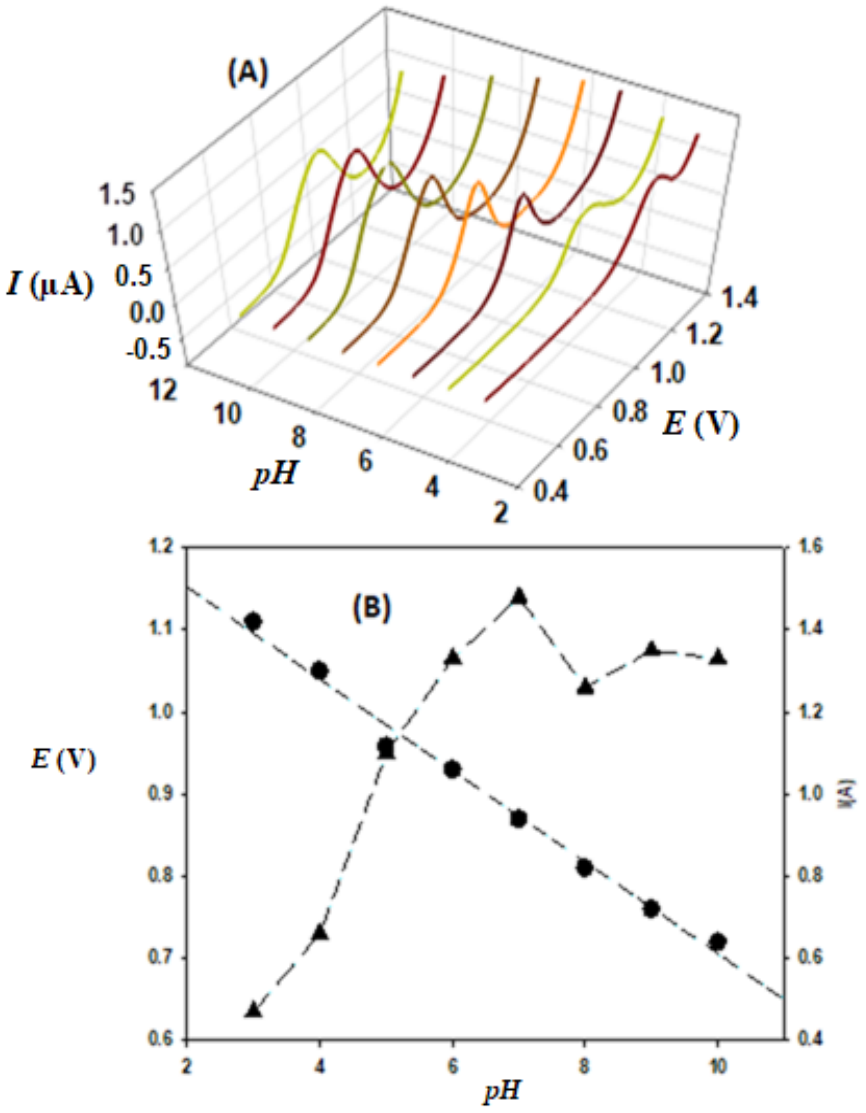

Fig. 3. A) differential voltammetric response of 10µg/mL MZ at CuONP/SPCE in 0.04 M BR buffers of different pH values. B) Contrast among the anodic peak current and potential at various pH values.

Effect of scan rate

The effect of varying scan rate upon the electrocatalytic oxidation of MZ at the CuONP/SPCE was investigated via CV, Figure 4. The electrochemical oxidation peak potential shifted to more positive potentials with increasing scan rate, confirming the kinetic limitation in the electrochemical reaction [32-33]. Also, a plot of peak height (Ip) vs. the square root of scan rate ($v^{1/2}$) was found to be linear in the wide range of 20–300 mV/s. As depicted in Figure 4, a plot of log peak current with log scan rate gives a linear relationship with a slope of 0.437; This value close to the theoretical value of 0.5, indicates that the electrochemical oxidation of mirtazapine is controlled by diffusion processes [34].

According to the obtained slope values of plots of Ep versus log scan rate, the number of electrons was found to be 1.89 for the CuONP/SPCE. These values were close to 2, indicating that two electrons and two protons are involved in the rate determining steps. The Tafel plot that was drawn, The Tafel slope of 0.0771 V obtained in this case agrees well with the involvement of two electrons in the rate determining step of the electrode process, assuming a charge transfer coefficient of α=0.61 [33].

Even though the exact oxidation mechanism of mirtazapine has not been determined. The author may assume that the first oxidation step of MZ is located on the piperazine moiety. This can be explained by the similarities of oxidation some compounds containing piperazine in terms of changes in the protonation of acid-base functions in the molecule [35, 36]. The oxidation occurred on the nitrogen atom of the piperazine ring of the molecule [37]. Fig. 5 shows the sugessted Electro-oxidation mechanism of mirtazapine at CuONP/SPCE.

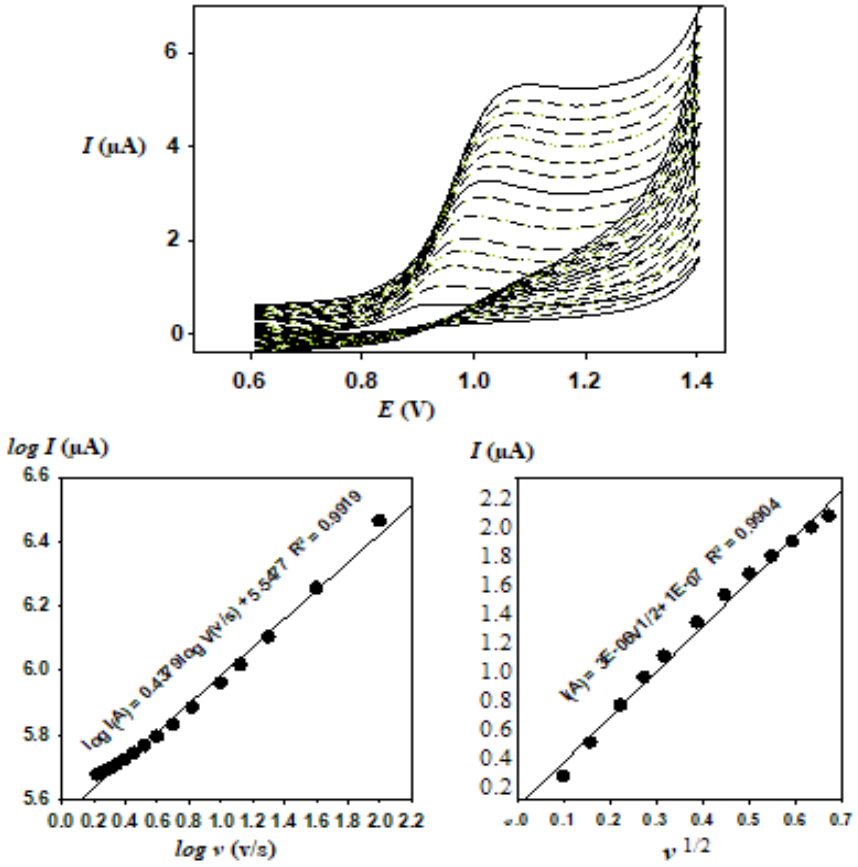

Fig. 4. Effect of varying the scan rate on 1.0x10^{-5}M (MZ) at CuONP/SPCE in BR buffer pH 7.0 using cyclic voltammetry. (A): Plot of log peak current versus log the scan rate. (B): Plot peak current versus square root of scan rate.

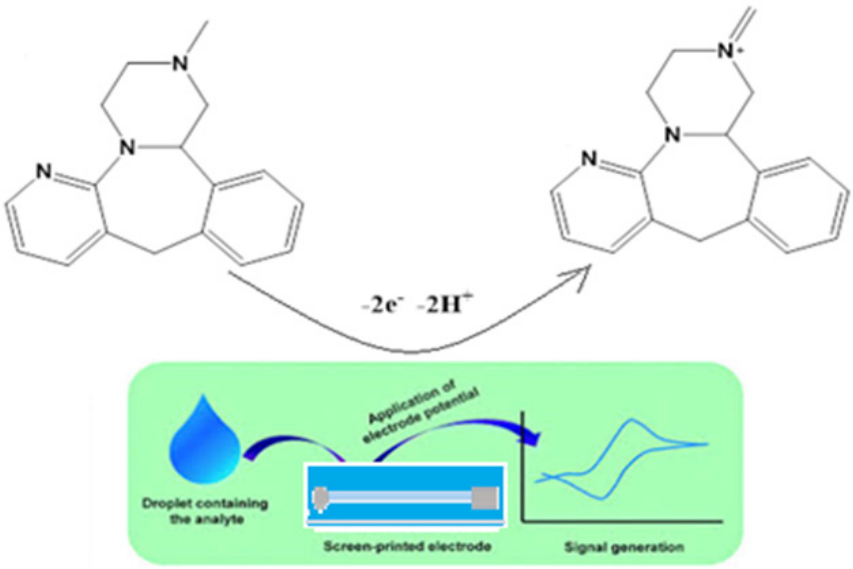

Fig. 5. shows the Electro-oxidation mechanism of mirtazapine at CuONP/SPCE.

Analytical Features of the Sensor

The concentration of mirtazapine was determined using DPV method, Figure 6. The plot of peak current vs. MZ concentration was linear over the range: 66.6– 662.3 ng/mL and the regression equation was : I (μA) = 0.00235C + 0.0291 (r^2=0.9966). The equation LOD=3S/x was used to estimate. The limit of detection, LOD where S is the standard deviation of the oxidation peak current (n=5) and x is the slope of the calibration curve. The calculated LOD was found to be 4.5 ng/mL. The limit of quantitation (LOQ) was calculated by the equation LOQ=10S/x, where S is the standard deviation of the intercept and x is the slope of the regression line [38-39]. The calculated LOQ was found to be 13.4 ng/mL. These values were compared with other reported research work [26], Table 1. The intraday and interday precisions of the proposed method were in the range 0.71–1.23% and 0.75–1.35%, respectively. The stability of the modified SPCEin dry place at temperature 4℃ has been tested. The modified electrode retained 95% of its initial response up to 1 month. This fact demonstrates the stability of SPCE at good storage conditions avoiding any surface contamination that can decrease the electrochemical activity of the working electrode. Comparing the proposed work value with values reported by other research groups for electrocatalytic oxidation of MZ at the surface of GC and BDD electrodes by, Table 1. However, those prior methods have not detection limit as low as the proposed method.

Application

In order to demonstrate the analytical applicability of the proposed electrode, also it was applied to the determination of MZ in tablets and spiked plasma samples. The results for applied determination of the MZ are assessed in Table 2. Satisfactory recovery of the experimental results was found for MZ. The reproducibility of the method was evaluated by the mean relative standard deviation RSD (%). Recovery ranged from 98.5% to 103.5% and RSD ranged from 1 to 3 were obtained. It is very clear that this sensor has significant potential for the determination of trace amounts of MZ in biological fluids.

Conclusion

Screen printed electrodes represent one of the most interesting and cost-effective alternatives in the design of electrochemical sensors for biomedical, environmental and industrial analyses. This work represents an easy method for the fabrication of CuONP/SPCE. The method has important advantages that include high degree of sensitivity, selectivity, and Environmental friendly in the determination of MZ. Comparing with other reported methods, the proposed method has distinct advantages over other existing methods in linear rang, detectability and durability, moreover, it can be applied to the determination of drug in spiked plasma without prior treatment. The proposed modified sensor provided a simple and reliable technique for mirtazapine detection in biological samples and routine work.

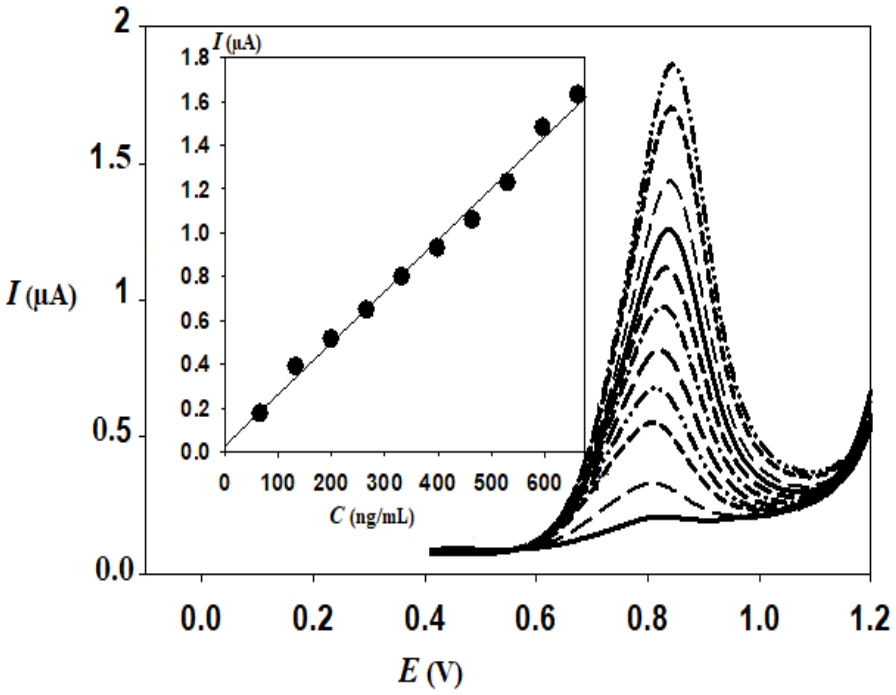

Fig. 6. DPVs of MZ in BR buffer at a scan rate of 10 mV/s solution (pH 7.0) containing different concentrations of MZ. Insets: the plot of the peak current as a function of MZ in concentration range 66.6– 662.3 ng/mL.

TABLE 1. Comparison of the efficiency of prior reported electrodes used in the electrocatalysis of MZ (Method: Voltammetry).

	Proposed CuONP/SPCE	Reportedmethod[26]	
		GCE	BDDE
Measured potential (V)	0.850	0.692	0.828
Scan rate (mV/s)	10	10	10
pH	7.0	7.0	8.0
Linearity range (ng/mL)	66.6– 662.3	212–2654	212–2654
RSD (%)	2.55		
r^2	0.9966	0.999	0.998
LOD (ng/mL)	4.5	31	60
LOQ (ng/mL)	13.4	92	183

a=intercept; b=slope; LOD=limit of detection; LOQ=limit of quantification; r^2= correlation coefficient.

TABLE 2. Application of standard addition method for the determination of MZ in tablets and serum samples.

	Taken ng/mL	Found ng/mL	Recovery (%)	% Mean ± % RSD[a]
MZ tablets	100	100.50	100.50	100.02±0.04
	200	199.80	99.93	
	300	302	10.07	
human plasma	150	155	103.30	101.15 ± 2.05
	200	198	99	

[a] Percentage relative standard deviation for five determinations.

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جزيء نانوي أكسيد النحاس كمعدّل لقطب الشاشة المطبوع لتقدير الميرتازابين

منال عبدالحميد الشال
الهيئة القومية للرقابة والبحوث الدوائية ص.ب ٩٢ مصر.

تمت دراسة تطوير جسيمات متناهية الصغر من أكسيد النحاس لتعديل قطب كهربائي مطبوع على الشاشة (CuONP / SPCE) كطريقة سريعة ومريحة لتقدير الميرتازيبين وقد ثبت أن اضافة أكسيد جزئ النحاس النانوى (CuONP) على القطب المعدليمكن أن يعزز بشكل كبير الأكسدة الكهروكيميائية للميرتازيبين عند درجة الحموضة ٧,٠. تم التحقيق في خصائص استجابة الكهروكيميائية من الميرتازيبين على القطب المعدلة بواسطة قياس الجهد دوري (CV) والفولتميتر النبض التفاضلي (DPV) في ظل الظروف التجريبية المُحسَّنة، أظهرت النتائج التحليلية استجابات خطية على مدى ٦٦,٦ - ٦٦٢,٣ نانوغرام / مل. كانت حدود التقدير الكشفى والكمي، ٤,٥، ١٣,٤نانوغرام / مل، على التوالي. تشير النتائج إلى أن المستشعر المقترح مناسب للغاية للتحليل السريري وتحديد تراكيز الميرتازيبين في المستحضرات الصيدلانية وبعض السوائل الحيوية.