ORIGINAL ARTICLE

Voltammetric determination of amitriptyline based on graphite screen printed electrode modified with a Copper Oxide nanoparticles

Hadi Beitollahi[1]; Fariba Garkani Nejad[2]; Somayeh Tajik[1]; Shohreh Jahani[1]; Pourya Biparva[3]*

[1]*Environment Department, Institute of Science and High Technology and Environmental Sciences, Graduate University of Advanced Technology, Kerman, Iran*
[2]*Department of Chemistry, Graduate University of Advanced Technology, Kerman, Iran*
[3]*Department of Basic Sciences, Sari Agricultural Sciences and Natural Resources University, Sari, Iran*

Abstract
A novel electrochemical sensor was proposed for the determination of amitriptyline based on the copper oxide (CuO) nanoparticles modified graphite screen-printed electrode. CuO nanoparticles were used to enhance the surface area of the electrode and then improve the sensitivity of the electrochemical sensor. Amitriptyline electrochemical response characteristics of the modified electrode in a phosphate buffer solution (PBS) of pH 7.0 were investigated by cyclic voltammetry, differential pulse voltammetry and chronoamperometry. The linear range for the detection of amitriptyline was changed from 1.0 μM to 200.0 μM with the detection limit of 0.4 μM (S/N=3). Finally, the proposed method was applied to measure amitriptyline in real samples. It was shown that the proposed sensor exhibited significant promise as a reliable technique for the detection of amitriptyline in real samples.

Keywords: *Amitriptyline; CuO nanoparticles; Electrochemical sensor; Graphite screen-printed electrode; Voltammetry.*

INTRODUCTION

Amitriptyline (AMT), 3(10, 11-dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)-*N,N*-dimethyl propane-1 amine hydrochloride, is a medicine used to treat a number of mental illnesses. It is one of the most commonly prescribed tricyclic antidepressants that inhibit the membrane pump mechanism responsible for the uptake of serotonin and norepinephrine in serotonergic and adrenergic neurons [1, 2]. A change in the concentration of amitriptyline in the body may influence its bioavailability and subsequently, its magnitude of action. Common side effects of amitriptyline include a dry mouth, sleepiness, trouble seeing, constipation and low blood pressure on standing. Serious side effects may include seizures, glaucoma, urinary retention and a number of heart issues. In view

of this, amitriptyline quantification is required to achieve better remedial effect and a lower toxicity [3-5]. A range of analytical methods such as gas chromatography/FID, gas chromatography-mass spectrometry, capillary electrophoresis, fluorimetry, HPLC and spectrophotometry are reported in the literature for amitriptyline quantification [6-13]. However, aforementioned methods suffer from some disadvantages with regard to time, cost, sensitivity and selectivity.

Electrochemical methods are promising analytical methods that have been used to measure directly the concentration of various drugs, in most instances, without separation of active pharmaceutical ingredients from the formulation matrix [14]. In addition electrochemical sensors are used in pharmaceutical analysis mainly due to their inexpensive, easy fabrication, fast response

* Corresponding Author Email: *h.beitollahi@yahoo.com*

and reduced time of analysis, adequate accuracy and selectivity [15-18]. Therefore the advantages of electrochemical techniques make them suitable for determination of amitriptyline.

Screen-printing technology, which has been adopted for microelectronics, is significantly used to fabricate electrodes for disposable electrochemical sensors. Screen-printed electrodes (SPEs) are highly-versatile, easy to use, cost-effective analytical tools, also suitable to miniaturization and applied widely in the electroanalytical chemistry field [19, 20]. In order to improve their electrochemical performance, SPEs have been modified with nanosized materials [21-26].

Recently non-precious transition metals and metal oxides are drawing increasing attention as modifier due to the ability to promote electron transfer reactions at low overpotential, their ease of synthesis, outstanding electrocatalytic activity, good stability and low cost [27-36]. Among them, copper oxide (CuO) is a p-type metal oxide semiconductor with a narrow band-gap stands as a good candidate in terms of its abundant reserves, low impact on the environment, cost-effectiveness, and fascinating electrochemical and catalytic properties [37-43].

According to the previous points, it is important to create suitable conditions for analysis of amitriptyline in biological fluids. In this study, CuO nanoparticles were used to improve the sensitivity of sensors for voltammetric determination of amitriptyline. The proposed sensor showed good electrocatalytic effect on amitriptyline. Eventually, we evaluate the analytical performance of the suggestion sensor for amitriptyline determination in real samples.

EXPERIMENTAL
Apparatus and chemicals

The electrochemical measurements were performed with an Autolab potentiostat/galvanostat (PGSTAT 302N, Eco Chemie, the Netherlands). The experimental conditions were controlled with General Purpose Electrochemical System (GPES) software. The screen-printed electrode (DropSens, DRP-110, Spain) consists of three main parts which are a graphite counter electrode, a silver pseudo-reference electrode and a graphite working electrode.

All solutions were freshly prepared with double distilled water. Amitriptyline and all other reagents were of analytical grade and were obtained from Merck chemical company (Darmstadt, Germany).

The buffer solutions were prepared from orthophosphoric acid and its salts in the pH range of 2.0-9.0. Copper oxide nanoparticles were synthesized in our laboratory as reported previously [32]. A typical SEM (KYKY, SBC-12, China) for synthesized Copper oxide nanoparticles is shown in Fig. 1.

Preparation of modified electrode

The bare screen-printed electrode was coated with CuO nanoparticles as follows. A stock solution of CuO in 1 mL aqueous solution was prepared by dispersing 1 mg CuO with ultrasonication for 1 h, and a 5 µl aliquot of the CuO /H_2O suspension solution was casted on the carbon working electrodes, and waiting until the solvent was evaporated in room temperature.

Preparation of real samples

Five amitriptyline tablets (labeled 10 mg per tablet, Mahban Darou Distribution Company, Iran) were grinding. Then, the tablet solution was prepared by dissolving 50 mg of the powder in 25 mL water by ultrasonication. Then, different volume of the diluted solution was transferred into a 25 mL volumetric flask and diluted to the mark with PBS (pH 7.0). The amitriptyline content was analyzed by the proposed method using the standard addition method. Urine samples were stored in a refrigerator immediately after collection. 10 mL of the sample was centrifuged for 15 min at 2000 rpm. The supernatant was filtered out using a 0.45 µm filter. Then, different volume of the solution was transferred into a 25 mL volumetric flask and diluted to the mark with PBS (pH 7.0). The diluted urine sample was spiked with different amounts of amitriptyline.

RESULTS AND DISCUSSION
Electrocatalytic oxidation of amitriptyline at CuO/SPE

The electrochemical behavior of amitriptyline 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 amitriptyline. Thus the electrochemical behavior of amitriptyline was studied in 0.1 M PBS in different pH values (2.0 < pH < 9.0) at the surface of CuO/SPE by CV. It was found that the electro-oxidation of amitriptyline at the surface of CuO/SPE was more favored under neutral conditions than in acidic or basic medium. Thus, the pH 7.0 was chosen as the optimum pH for electrocatalysis of amitriptyline oxidation at the surface of CuO/SPE.

Fig. 2 depicts the cyclic voltammetric responses for the electrochemical oxidation of 40.0 μM amitriptyline at CuO/SPE (curve a) and bare SPE (curve b). The anodic peak potential for the oxidation of amitriptyline at CuO/SPE (curve a) is about 740 mV compared with 940 mV for that on the bare SPE (curve b). Similarly, when the oxidation of amitriptyline at the CuO/SPE (curve a) and bare SPE (curve b) are compared, an extensive

enhancement of the anodic peak current at CuO/SPE relative to the value obtained at the bare SPE (curve b) is observed. In other words, the results clearly indicate that the CuO nanoparticles improve the amitriptyline oxidation signal. Fig. 3 shows the Electro-oxidation mechanism of amitriptyline at CuO/SPE.

The effect of potential scan rates on the oxidation current of amitriptyline has been studied
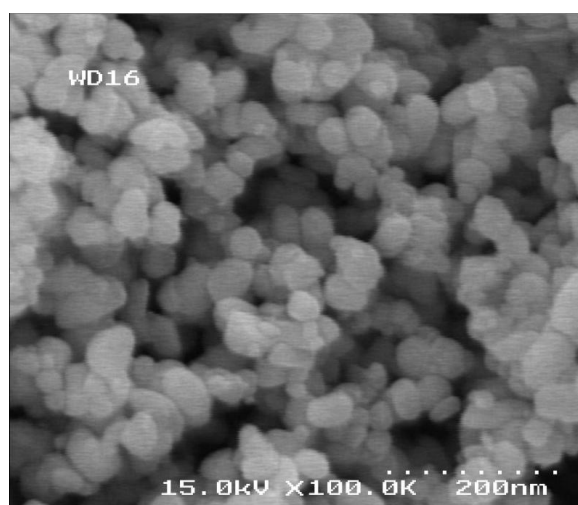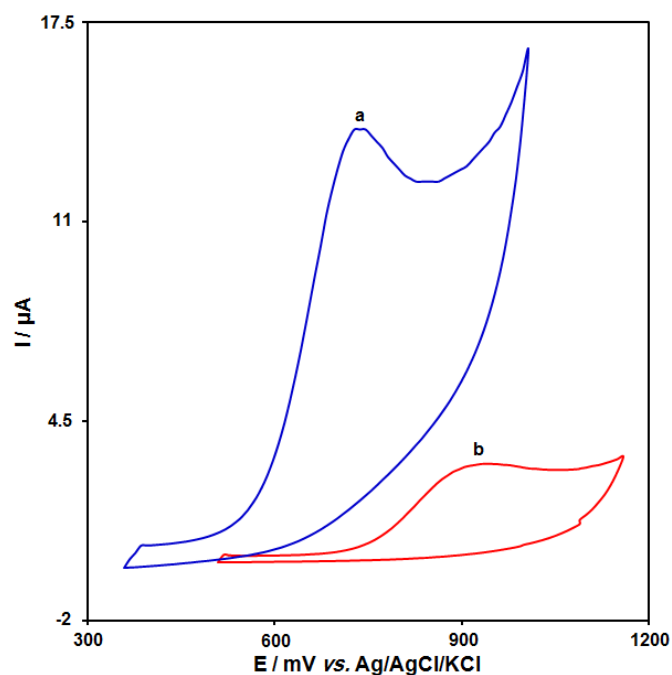

Fig. 1: SEM images of Copper Oxide nanoparticles.

Fig. 2: Cyclic voltammograms of (a) CuO/SPE and (b) bare SPE in 0.1 M PBS (pH 7.0) in the presence of 40.0 μM amitriptyline at the scan rate 50 mVs^{-1}.

(Fig. 4). The results showed that increasing in the potential scan rate induced an increase in the peak current. In addition, the oxidation process is diffusion controlled as deduced from the linear dependence of the anodic peak current (I_p) on the square root of the potential scan rate ($v^{1/2}$) over a wide range from 10 to 400 mV s^{-1}.

Fig. 5 shows a Tafel plot that was drawn from points of the Tafel region of the LSV. The Tafel slope of 0.1407 V obtained in this case agrees well with the involvement of one electron in the rate determining step of the electrode process, assuming a charge transfer coefficient of α=0.58 [44].

Chronoamperometric measurements

Chronoamperometric measurements of amitriptyline at CuO/SPE were carried out by setting the working electrode potential at 0.8 V for the various concentration of amitriptyline in PBS (pH 7.0) (Fig.5). For an electroactive material (amitriptyline in this case) with a diffusion coefficient of D, the current observed for the electrochemical reaction at the mass transport limited condition is described by the Cottrell equation [44].

$$I = nFAD^{1/2}C_b\pi^{-1/2}t^{-1/2}$$

Where, D and C_b are the diffusion coefficient (cm^2 s^{-1}) and the bulk concentration (mol cm^{-3}), respectively. Experimental plots of I vs. t$^{-1/2}$ were employed, with the best fits for different concentrations of amitriptyline (Fig. 6a). The slopes of the resulting straight lines were then plotted vs. amitriptyline concentration (Fig. 6b). From the resulting slope and Cottrell equation the mean value of the D was found to be 8.1 × 10^{-5} *cm^2/s*.
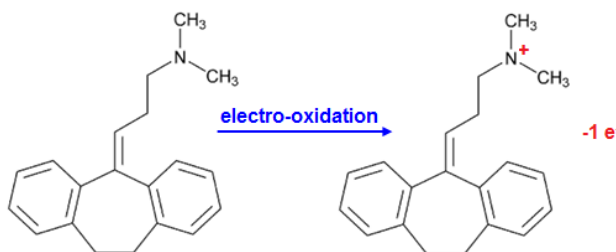

Fig. 3: Electro-oxidation mechanism of amitriptyline at CuO/SPE.
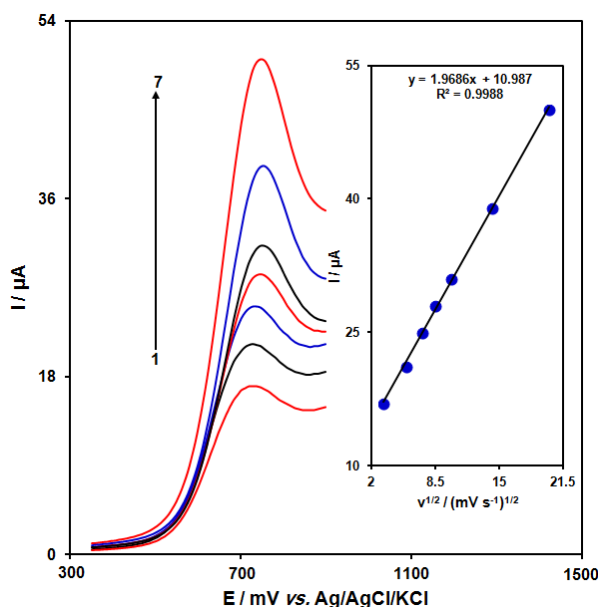

Fig. 4: LSVs of CuO/SPE in 0.1 M PBS (pH 7.0) containing 40.0 μM amitriptyline at various scan rates; numbers 1-7 correspond to 10, 30, 50, 70, 100, 200 and 400 mV s^{-1}, respectively. Inset: variation of anodic peak current vs. v$^{1/2}$.
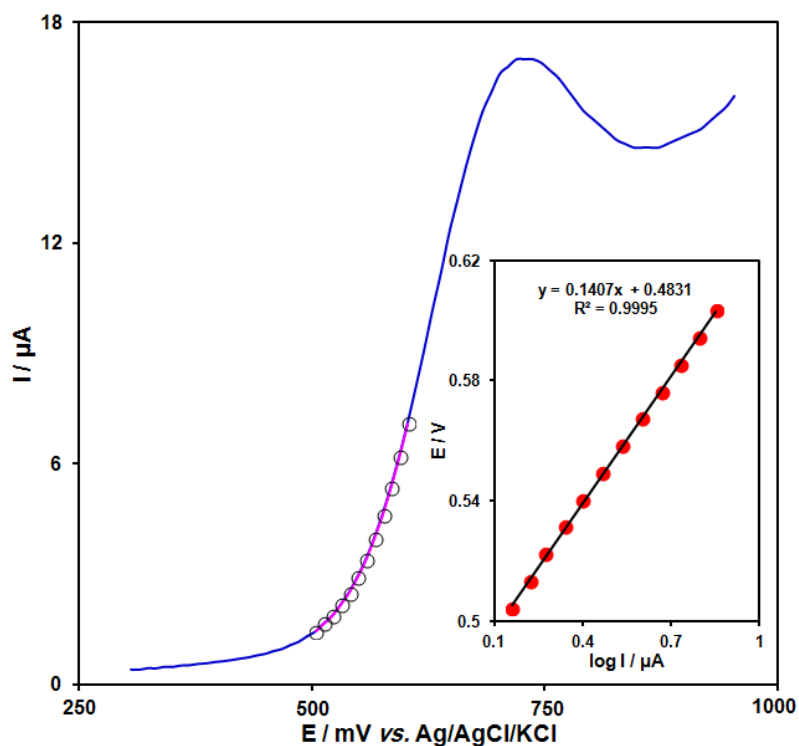
Fig. 5: LSV (at 10 mV s⁻¹) of electrode in 0.1 M PBS (pH 7.0) containing 100.0 μM amitripty-
line. The points are the data used in the Tafel plot. The inset shows the Tafel plot derived from
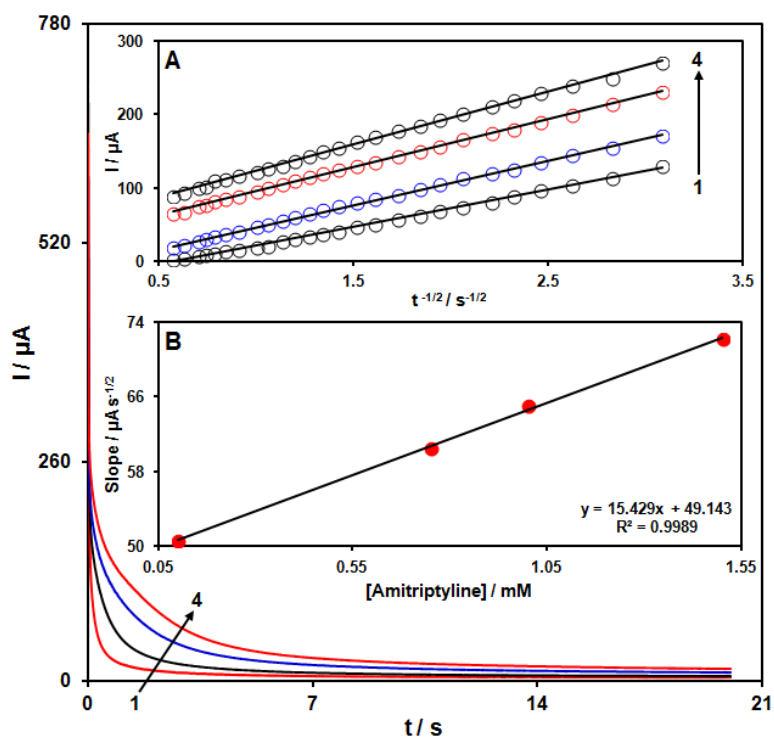the LSV.

Fig. 6: Chronoamperograms obtained at CuO/SPE in 0.1 M PBS (pH 7.0) for different concentrations of amitriptyline.
The numbers 1–4 correspond to 0.1, 0.75, 1.0, and 1.5 mM of amitriptyline. Insets: (A) Plots of I vs. t$^{-1/2}$ obtained from
chronoamperograms 1–4. (B) Plot of the slope of the straight lines against amitriptyline concentration.

Calibration plot and limit of detection

The peak current of amitriptyline oxidation at the surface of the modified electrode can be used for determination of amitriptyline in solution. Therefore, differential pulse voltammetry (DPV) experiments were done for different concentrations of amitriptyline (Fig. 7). The oxidation peak currents of amitriptyline at the surface of a modified electrode were proportional to the concentration of the amitriptyline within the ranges 1.0 to 200.0 μM. The detection limit (3σ) of amitriptyline was found to be 4.0×10^{-7}M. These values are comparable with values reported by other research groups for electro-oxidation of amitriptyline at the surface of chemically modified electrodes (see Table 1).

Real sample analysis

In order to evaluate the analytical applicability of the proposed method, also it was applied to the determination of amitriptyline in amitriptyline tablet and urine samples. The results for determination of the amitriptyline in real samples are given in Table 2. Satisfactory recovery of the experimental results was found for amitriptyline. The reproducibility of the method was demonstrated by the mean relative standard deviation (R.S.D.).

Table 1: Comparison of the efficiency of electrochemical methods used in detection of amitiptyline.

| Method	Modifier	LOD	LDR	Ref.
Voltammetry	$SiO_2/Al_2O_3/Nb_2O_5/DNA$	0.12 μM	10.0-80.0 μM	3
Voltammetry	AuNPs@Polyethyleneimine-derived carbon hollow spheres	0.034 μM	0.1-700.0 μM	45
Voltammetry	Carbon nanotube	1.16 μM	0.0-30.0 μM	46
Voltammetry	poly(*N*-vinylimidazole)	-	10.0-100.0 μM	47
Voltammetry	Montmorillonite nanoclay and ionic liquid	24 nM	0.1-40.0 μM	48
Voltammetry	CuO nanoparticles	0.4 μM	1.0-200.0 μM	This work
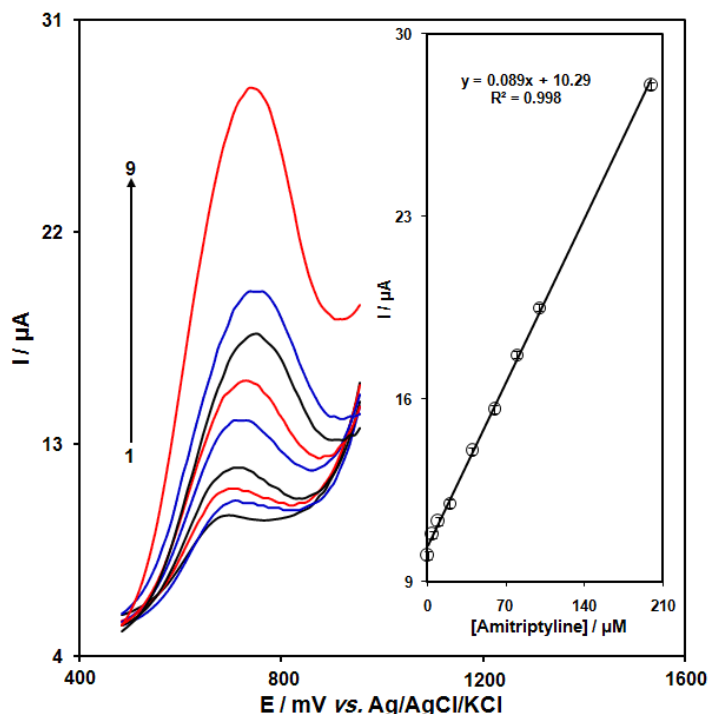
Fig. 7: DPVs of CuO/SPE in 0.1 M (pH 7.0) containing different concentrations of amitriptyline. Numbers 1–9 correspond to 1.0, 5.0, 10.0, 20.0, 40.0, 60.0, 80.0, 100.0 and 200.0 μM of amitriptyline. Inset: Plot of the electrocatalytic peak current as a function of amitriptyline concentration in the range of 1.0-200.0 μM.

Table 2: The application of CuO/SPE for determination of amitriptyline in amitriptyline
tablet and urine samples (n=5). All concentrations are in μM.

Sample	Spiked	Found	Recovery (%)	R.S.D. (%)
	0	2.5	-	2.9
	2.5	4.9	98.0	3.4
Amitriptyline tablet	5.0	7.7	102.7	1.9
	7.5	10.1	103.0	2.4
	10.0	12.4	99.2	2.7
	0	-	-	-
	5.0	5.1	102.0	2.6
Urine	10.0	9.7	97.0	3.4
	15.0	15.5	103.3	1.9
	20.0	19.8	99.0	2.2

CONCLUSIONS

Copper oxide (CuO) nanoparticles were used to construct an electrochemical sensor for amitriptyline sensing. CuO nanoparticles could effectively enhance the surface area and then improve the sensitivity of sensor. Under the optimized condition, the linear range was changed from 1.0 μM to 200.0 μM, and the detection limit was obtained 0.4 μM. In a word, the proposed sensor provided a simple and reliable technique for amitriptyline detection in biological samples and a notion to perfect the CuO-based sensor for trace detection.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

REFERENCES

[1] Leucht C., Huhn M., Leucht S., (2012), Amitriptyline versus placebo for major depressive disorder. *Cochrane. Database. Syst. Rev.* 12: CD009138.

[2] Furlanetto S., Orlandini S., Pasquini B., Del-Bubba M., Pinzauti S., (2013), Quality by design approach in the development of a solvent-modified micellar electrokinetic chromatography method: Finding the design space for the determination of amitriptyline and its impurities. *Anal. Chim. Acta.* 802: 113-124.

[3] Marco J. P., Borges K. B., Tarley C. R. T., Ribeiro E. S., Pereira A. C., (2013), Development and application of an electrochemical biosensor based on carbon paste and silica modified with niobium oxide, alumina and DNA ($SiO_2/Al_2O_3/Nb_2O_5/DNA$) for amitriptyline determination. *J. Electroanal. Chem.* 704: 159-168.

[4] Sanna M. D., Ghelardini C., Galeotti N., (2017), Effect of amitriptyline treatment on neurofilament-H protein in an experimental model of depression. *Brain. Res. Bull.* 128: 1-6.

[5] Farag R. S., Darwish M. Z., Fathy W. M., Hammad H. A., (2014), New HPLC method to detect amitriptyline in the blood of rats on combination treatment. *Int. J. Chem. Anal. Sci.* 4: 120-124.

[6] Joanna Karpinska J., Szostak J., (2005), Determination of chlorprothixene and amitryptyline hydrochlorides by UV-derivative spectrophotometry and UV-solid-phase spectrophotometry. *Spectrochim. Acta*. 61: 975-981.

[7] Bhatt M., Shah S., (2010), Development and validation of amitriptyline and its metabolite in human plasma by ultra performance liquid chromatography–tandem mass spectrometry and its application to a bioequivalence study. *Biomed. Chromatogr.* 24: 1247-1254.

[8] Turkmen Z., Mercan S., Bavunoglu I., Cengiz S., (2013), Development and validation of a densitometric-high-performance thin-layer chromatographic method for quantitative Analysis of amitriptyline in gastric lavage. *J. Planar. Chromatogr.* 26: 496-501.

[9] Papoutsis I., Khraiwesh A., Nikolaou P., Pistos C., Spiliopoulou C., Athanaselis S., (2012), A fully validated method for the simultaneous determination of 11 antidepressant drugs in whole blood by gas chromatography-mass spectrometry. *J. Pharm. Biomed. Anal.* 70: 557-562.

[10] Acedo-Valenzuela M. I., Mora-Diez N., Galeano-Diaz T., Silva-Rodriguez A., (2010), Determination of tricyclic antidepressants in human breast milk by capillary electrophoresis. *Anal. Sci.* 26: 699-702.

[11] Osorio A. C. P., Da Cunha A. L. M. C., Khan S., Franco C. J., Pereira-Netto A. D., Aucelio R. Q., (2014), Photochemical derivatization of amitriptyline using a green chemistry approach: Fluorimetric determination and photochemical reaction mechanism. *Anal. Methods.* 6: 4022-4028.

[12] Jakaria M., Zaman R., Parvez M., Hasanat A., (2015), *In Vitro* comparative degradation study between two brands of amytriptyline hydrochloride tablet using UV spectrophotometer. *Int. J. Pharm. Sci. Res.* 6: 209-212.

[13] Deepakumari H. N., Prashanth M. K., Kumar B. C. V., Revanasiddappa H. D., (2015), Highly sensitive and validated spectrophotometric technique for the assay of some antidepressant drugs. *J. Appl. Spect.* 81: 1004-1011.

[14] Beitollahi H., Raoof J. B., Hosseinzadeh R., (2011), Application of a carbon-paste electrode modified with 2, 7-bis(ferrocenyl ethyl)fluoren-9-one and carbon nanotubes for voltammetric determination of levodopa in the presence of uric acid and folic acid. *Electroanalysis*. 23: 1934-1940.

[15] Ponvel K. M., Narayanaraja T., Prabakaran J., (2015), Biosynthesis of silver nanoparticles using root extract of the medicinal plant Justicia adhatoda: Characterization, electrochemical behavior and applications. *Int. J. Nano Dimens.* 6: 339-349.

[16] Beitollahi H., Ebadinejad F., Shojaie F., Torkzadeh-Mahani M., (2016), A magnetic core–shell $Fe_3O_4@SiO_2/MWCNT$ nanocomposite modified carbon paste electrode for amplified electrochemical sensing of amlodipine and hydrochlorothiazide. *Anal. Methods*. 8: 6185-6193.

[17] Ramezani Azghandi O., Farahbakhsh A., (2015), The obtain optimum production conditions for glucose oxidase biosensor using software Qualtek-4. *Int. J. Nano Dimens.* 6: 23-30.

[18] Radhika D., Samson Nesaraj A., (2014), Chemical precipitation and characterization of multicomponent Perovskite oxide nanoparticles – possible cathode materials for low temperature solid oxide fuel cell. *Int. J. Nano Dimens.* 5: 1-10.

[19] Jahani Sh., Beitollahi H., (2016), Selective Detection of dopamine in the presence of uric acid using NiO nanoparticles decorated on graphene nanosheets modified screen-printed electrodes. *Electroanalysis.* 28: 2022-2028.

[20] Patris S., Vandeput M., Kenfack G. M., Mertens D., Dejaegher B., Kauffmann J. M., (2016), An experimental design approach to optimize an amperometric immunoassay on a screen-printed electrode for Clostridium tetani antibody determination. *Biosens. Bioelectron.* 77: 457-463.

[21] Mahmoudi Moghaddam H., Beitollahi H., Tajik S., Soltani H., (2015), Fabrication of a nanostructure based electrochemical sensor for voltammetric determination of epinephrine, uric acid and folic acid. *Electroanalysis.* 27: 2620-2628.

[22] Filik H., Cetintas G., Koc S. N.,Gulce H., Boz I., (2014), Nafion-graphene composite film modified glassy carbon electrode for voltammetric determination of *p*-aminophenol. *Russ. J. Electrochem.* 50: 243-252.

[23] Beitollahi H., Garkani Nejad F., (2016), Graphene Oxide/ZnO Nano Composite for sensitive and selective electrochemical sensing of levodopa and tyrosine using modified graphite screen-printed electrode. *Electroanalysis* 9: 2237-2244.

[24] Hu C., Deng J., Xiao X., Zhan X., Huang K., Xiao N., Ju S., (2015), Determination of dimetridazole using carbon paste electrode modified with aluminum doped surface molecularly imprinted siloxane. *Electrochim. Acta* 158: 298-301.

[25] Beitollahi H., Gholami A., Ganjali M. R., (2015), Preparation, characterization and electrochemical application of Ag-ZnO nanoplates for voltammetric determination of glutathione and tryptophan using modified carbon paste electrode. *Mater. Sci. Eng. C.* 57: 107-112.

[26] Beitollahi H., Tajik S., Jahani Sh., (2016), Electrocatalytic determination of hydrazine and phenol using a carbon paste electrode modified with ionic liquids and Mmagnetic core-shell $Fe_3O_4@SiO_2$/MWCNT nanocomposite. *Electroanalysis.* 28: 1093-1099.

[27] Wang Y., Wang S., Tao L., Min Q., Xiang J., Wang Q., Xie J., Yue Y., Wu S., Li X., Ding H., (2015), A disposable electrochemical sensor for simultaneous determination of norepinephrine and serotonin in rat cerebrospinal fluid based on MWNTs-ZnO/chitosan composites modified screen-printed electrode. *Biosens. Bioelectron.* 65: 31-38.

[28] Molaakbari E., Mostafavi A., Beitollahi H., Alizadeh R., (2014), Synthesis of ZnO nanorods and their application in the construction of a nanostructure-based electrochemical sensor for determination of levodopa in the presence of carbidopa. *Analyst.* 139: 4356-4364.

[29] Li X., Xu H., Yan W., (2016), Electrochemical oxidation of aniline by a novel Ti/TiO$_{xHy/Sb-SnO2}$ electrode. *Chin. J. Catal.* 37: 1860-1870.

[30] Beitollahi H., Karimi-Maleh H., Khabazzadeh H., (2008), Nanomolar and selective determination of epinephrine in the presence of norepinephrine using carbon paste electrode modified with carbon nanotubes and novel 2-(4-oxo-3-phenyl-3,4-dihydro-quinazolinyl)-N'-phenyl-hydrazinecarbothioamide. *Anal. Chem.* 80: 9848-9851.

[31] Gao Y. S., Wu L. P., Zhang K. X., Xu J. K., Lu L. M., Zhu X. F., Wu Y., (2015), Electroanalytical method for determination of shikonin based on the enhancement effect of cyclodextrin functionalized carbon nanotubes. *Chin. Chem. Lett.* 26: 613-618.

[32] Beitollahi H., Nekooei S., (2016), Application of a modified CuO nanoparticles carbon paste electrode for simultaneous determination of isoperenaline, acetaminophen and N-acetyl-L-cysteine. *Electroanalysis.* 28: 645-653.

[33] Zhang G. R., Xu B. Q., (2013), Nano-size effect of Au catalyst for electrochemical reduction of oxygen in alkaline electrolyte. *Chin. J. Catal. 34: 942-948.*

[34] Beitollahi H., Ghofrani Ivari S., Torkzadeh-Mahani M., (2016), Voltammetric determination of 6-thioguanine and folic acid using a carbon paste electrode modified with ZnO-CuO nanoplates and modifier. *Mater. Sci. Eng. C.* 69: 128-133.

[35] Keyvan Sh., Zobairi E. D., Islamnezhad A., (2012), Construction of Cu^{2+}-selective electrode and thermodynamic study of the ternary aqueous mixed electrolyte system ($CuCl_2$, KCl, H_2O) using nanocomposite-based potentiometric sensor. *Int. J. Nano Dimens.* 3: 115-119.

[36] Alizadeh T., Ganjali M. R., Akhoundian M., Norouzi P., (2016), Voltammetric determination of ultratrace levels of cerium(III) using a carbon paste electrode modified with nano-sized cerium-imprinted polymer and multiwalled carbon nanotubes. *Microchim. Acta* 183: 1123-1130.

[37] Song H., Ma C., You L., Cheng Z., Zhang X., Yin B., Ni Y., Zhang K., (2015), Electrochemical hydrogen peroxide sensor based on a glassy carbon electrode modified with nanosheets of copper-doped copper(II) oxide. *Microchim. Acta* 182: 1543-1549.

[38] Suramwar N. V., Thakare S. R., Khaty *N. T., (2012),* Synthesis and catalytic properties of nano CuO prepared by soft chemical method. *Int. J. Nano Dimens.* 3: 75-80.

[39] Pourahmad A., (2016), Green chemistry approach for the synthesis of CuO nanostructure. *Int. J. Nano Dimens.* 7: 121-126.

[40] Zhang X., Sun S., Lv J., Tang L., Kong C., Song X., Yang Z., (2014), Nanoparticle-aggregated CuO nanoellipsoids for high-performance non-enzymatic glucose detection. *J. Mater. Chem. A.* 2: 10073-10080.

[41] Noorizadeh H., Zeraatkish Y., (2015), Simple chemical method for synthesis of CuO/CuI nanocomposite. *Int. J. Nano Dimens.* 6: 211-216.

[42] Li C., Yamahara H., Lee Y., Tabata H., Delaunay J. J., (2015), CuO nanowire/microflower/nanowire modified Cu electrode with enhanced electrochemical performance for non-enzymatic glucose sensing. *Nanotechnology.* 26: 305503-305507.

[43] Dehno Khalaji A. A., Malekan F., (2014), Tetranuclear Copper (II) schiff base complexes as new precursor for synthesis of CuO nanoparticles by solid-state thermal decomposition. *Int. J. Nano Dimens.* 5: 583-586.

[44] Bard A. J., Faulkner L. R., (2001), Electrochemical methods fundamentals and applications, second ed, New York: Wiley.

[45] Rezayati Zad Z., Saeed Hosseiny Davarani S., Taheri A.R., Bide Y., (2016), Highly selective determination of amitriptyline

using Nafion-AuNPs@branched polyethyleneimine-derived carbon hollow spheres in pharmaceutical drugs and biological fluids. *Biosens. Bioelectron.* 86: 616-622.

[46] Duarte E. H., Dos Santos W. P., Hudari F. F., Bott Neto J. L., Sartori E. R., Dall'Antonia L. H., Pereira A. C., Teixeira Tarley C. R., (2014), A highly improved method for sensitive determination of amitriptyline in pharmaceutical formulations using an unmodified carbon nanotube electrode in the presence of sulfuric acid. *Talanta.* 127: 26-32.

[47] Biryol I., Uslu B., Küçükyavuz Z., (1996), Voltammetric determination of imipramine hydrochloride and amitriptyline hydrochloride using a polymer-modified carbon paste electrode. *J. Pharm. Biomed. Anal.* 15: 371-381.

[48] Eslami E., Farjami F., (2014), Electrochemical determination of amitriptyline using a nanocomposite carbon paste electrode in human body fluids. *J. Phys. Chem. Electrochem.* 2: 111-117.