Electroanalytical Determination of Antiinflammatory Drug Tenoxicam in Pharmaceutical Dosage Forms

Antienflamatuvar İlaç Tenoksikamın Farmasötik Dozaj Formlarından Elektroanalitik Miktar Tayini

Electroanalytical Determination of Tenoksikam

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Abstract: The electro-oxidation behavior of nonsteroidal anti-inflammatory drug tenoxicam (TX) was studied on multiwalled carbon nanotubes (MWCNTs) modified glassy carbon electrode (GCE) by cyclic voltammetry (CV), differential pulse voltammetry (DPV) and square wave voltammetry (SWV). GCE was modified with MWCNTs for sensitive determination of TX with voltammetric methods. The current peaks for TX occurred at around 0.520 V for DPV and 0.570 V for SWV when the potential was scanned in the positive direction. The oxidation process of TX has shown irreversible and diffusion controlled behavior. The linear responses have been obtained in the range from 2×10^{-7} to 1×10^{-5} M with the limit of detection (LOD) 1.43×10^{-9} for DPV and from 8×10^{-9} to 8×10^{-6} with the LOD 9.97×10^{-10} for SWV in 1 M acetate buffer solution at pH 5.5. Fully validated DPV and SWV were successfully applied for the determination of TX from pharmaceutical dosage form and obtained satisfying results.

Key words: Glassy carbon electrode, multiwalled carbon nanotubes, tenoxicam, voltammetry.

Özet: Nonsteroidal antienflamatuvar ilaç etken maddesi tenoksikamın (TX) elektro-oksidasyon davranışı çok duvarlı karbon nanotüple (MWCNTs) modifiye edilmiş camsı karbon elektrot (GCE) ile dönüşümlü voltametri (CV), diferansiyel puls voltametri (DPV) ve kare dalga voltametri (SWV) ile çalışıldı. Camsı karbon elektrot, TX'in voltametrik metodlarla hassas tayini için MWCNTs ile modifiye edildi. Potansiyel pozitif yönde tarandığında TX'in pik akımı 0.520 V civarinda DPV ile, 0.570 V civarında SWV ile oluştu. TX'in oksidasyon prosesi tersinmez ve difüzyon kontrollü davranış gösterdi. DPV ve SWV için doğrusal cevaplar sırasıyla 2×10^{-7}- 1×10^{-5} M, 1.43×10^{-9} M yakalama alt sınırı (YAS) ile, 8×10^{-9} - 8×10^{-6} M, 9.97×10^{-10} M YAS ile 1 M asetat tamponu pH 5.5 içinde elde edildi. Tamamen valide edilmiş DPV ve SWV başarılı bir şekilde TX'in farmasötik dozaj formundan miktar tayini için uygulandı ve memnun edici sonuçlar elde edildi.

Anahtar kelimeler: Camsı karbon elektrot, çok duvarlı karbon nanotüp, tenoksikam, voltametri.

Introduction:

Tenoxicam (Figure 1) is a nonsteroidal anti-inflammatory drug (NSAID) and shows analgesic, antiinflammatory and antirheumatic properties. TX, a member of oxicams class, is widely used to swelling, relieve inflammation, stiffness, and pain associated with osteoarthritis, rheumatoid arthritis, arthrosis, ankylosing spondylitis, arthritic diseases such as tendinitis, bursitis, shoulder or hip periarthritis (shoulder-hand syndrome), sprains and injuries, acute gout. TX inhibits prostaglandin biosynthesis both in vitro and in vivo. It indicates strong inhibitory effect in vitro on human metalloproteinase (stromelysin and collagenase) enzymes that stimulate cartilage destruction.[1]

In literature, high performance liquid chromatography (HPLC),[2-7] thin layer chromatography (TLC),[8] flow injection spectrophotometric analysis,[9-11] spectrophotometric and spectrofluorimetric methods[12-15] are reported as the methods for determination of TX in pharmaceuticals and biological samples. These methods require mostly time-consuming sample preparation procedures such as extraction and costly instrumentation makes their usage inconvenient. Electrochemical methods are user friendly, no pretreatment is required for them, and they use low-cost instrumentation and minimum amount of organic solvent comparing to the reported analytical methods. Additionally, electrochemical methods supply high sensitivity, precision, accuracy and wider linear dynamic range. [16,17]

TX was determined using differential pulse polarographic method in pharmaceuticals and blood, with static mercury drop electrode.[18] El Maali *et al*. investigated the electro-reduction behaviour of TX and piroxicam at the static mercury drop electrode.[19]The electro-reduction of TX was also investigated by hanging mercury drop electrode.[20]

In recent years, working electrodes were modified with carbon nanotubes (CNTs) for electrochemical and bio-electrochemical studies.[21,22] CNTs can be used electrode materials with useful properties, through CNTs show excellent high chemical stability, high mechanical strength, and a wide range of electrical conductivity. CNTs supply a modifier to promote electron transfer reactions between many biological important species and the surface of the electrode. CNTs modified electrodes have been indicated to have excellent electroanalytical properties such as

low background current, wide potential window, high sensitivities and low detection limits.[23] The excellent properties of carbon nanotubes enable them to be extremely inviting to obtain chemical sensors and used for electrochemical detection.[24]

The aim of this study was to develop a MWCNTs modified GCE for electroanalytical determination of TX and to investigate electro-oxidative behavior of TX with voltammetric methods. The obtained MWCNTs modified GCE and fully validated voltammetric methods indicated low detection limit, high selectivity, sensitivity, and good recovery results in electroanalytical determination of TX.

EXPERIMENTAL

Figure 1

Instrumentation

All experiments were carried out using a three-electrode electrochemical cell with a GCE (Bioanalytical Systems, ϕ: 3 mm diameter) as working electrode, a platinum wire as the counter electrode (Bioanalytical Systems) and Ag/AgCl electrode (Bioanalytical Systems, 3.0 M KCl) as the reference electrode. All voltammetric measurements were performed using Autolab Pgstat128n potentiostat/galvanostat with Nova 10.0 software (Metrohm-Autolab, The Netherlands). The pH measurements were carried out using Hanna HI2211 pH meter (Romania) with an accuracy of ±0.05 pH at room temperature. All of the electrochemical measurements were performed at room temperature (25 ± 1 ^{o}C).

Reagents

Tenoxicam was supplied by Deva-Turkey and its pharmaceutical dosage form (Tilcotil® tablets, 20 mg TX contain per tablet) purchased from pharmacy and was used without further purification. TX stock solutions (1 × 10^{-3} M) were prepared in methanol and stored at +4 ^{o}C away from light. TX working solutions for voltammetric investigation were prepared by the direct dilution of the stock solution with the selected supporting electrolyte containing a constant amount of methanol (20% V/V). MWCNTs were purchased from NanoLab. U.S.A. with ~95% purity, 1-5 μm lengths and 30±10 nm diameter. *N,N*-Dimethylformamide (DMF) were from Fluka (Switzerland).

Britton-Robinson buffer solutions (0.04 M) were prepared at pH 3.0-8.0 from 0.04 M CH_3COOH (Merck, Germany), 0.04 M H_3BO_3 (Aldrich, U.S.A.) and 0.04 M H_3PO_4 (Merck, Germany). Acetate buffer solutions (1 M) at pH 3.5, 4.5 and 5.5 were prepared from 1 M CH_3COOH (Merck, Germany). Phosphate buffer solutions (0.1 M) were prepared from H_3PO_4 (Merck, Germany) for pH 2.0-4.0 and Na_2HPO_4 (Aldrich, U.S.A.), NaH_2PO_4 (Merck, Germany) for pH 5.0-8.0. The pH values were adjusted with 5 M NaOH (Aldrich, U.S.A.) solution.

Sartorius Arium proUV nanopure water (resistivity ≥18 MΩ cm), and analytical reagents were used for the preparation of solutions.

Preparation of MWCNTs modified GCE

The 0.2% and 0.5% (mg mL^{-1}) MWCNTs dispersion in DMF were sonicated for 4h to obtain a homogeneous mixture. GCE was polished with aqueous slurry of alumina powder (ϕ:0.01 μM) on a polishing pad (Bioanalytical Systems polishing pad) and then rinsed with nanopure water before coating it. Four different suspensions of MWCNTs in DMF 2.5 and 5 μL / 0.2% and 1 and 5 μL / 0.5% were dropped on the surface of GCE to select suspension of MWCNTs according to the optimum peak current obtained for TX. The selected dispersion of MWCNTs in DMF for voltammetric determination of TX was dropped on the surface of GCE. The resulting modified electrode was named as MWCNTs modified GCE. The MWCNTs modified GCE electrode dried for overnight at room temperature. After each measurement, the electrode surface was cleaned with cyclic voltammetry in the potential range between -0.4 V and +1.0 V (3 cyclic) in buffer solution.

Pharmaceutical Assay

Ten tablets taken from Tilcotil® (each tablet includes 20 mg TX) were first weighed and then powdered in a mortar. The needed amount of powder equivalent to 1×10^{-3} M of TX was diluted to 25 mL with methanol and sonicated for 10 min. The analyzed solutions were prepared by taking aliquots of the clear supernatant liquor and diluting with the selected supporting electrolyte TX working solutions for voltammetric inquiries were prepared by the direct dilution of the stock solution with 1 M acetate buffer solution at pH 5.5 containing a constant amount of methanol (20% V/V).

RESULTS AND DISCUSSION

The fabrication of MWCNTS modified GCE was optimized to obtain best MWCNTs suspension for TX oxidation. Effect of the volume of MWCNTs in DMF suspension on the peak current was investigated at four different loadings of MWCNT (2.5 and 5 µL / 0.2%, 1 and 5 µL / 0.5%) on the surface of GCE. The coated electrodes with 2.5 µL and 5 µL for 0.2%, 1 µL and 5 µL for 0.5% of MWCNTs suspension were performed 4 x 10^{-5} M TX by CV, DPV and SWV. As shown in Figure 2, DP voltammograms obtained from TX, the peak current reaches its maximum value (2.47 µA) when the amount of MWCNTs suspension (0.2%) is 2.5 µL. Thus, 2.5 µL for 0.2% MWCNTs suspension was chosen to modify the GCE and this electrode was used for all electrochemical studies. Also, Figure 2 shows response of TX obtained on bare GCE (0.040 µA). The peak current of TX on MWCNTs modified GCE (a) increased about 60 fold compared to peak current of TX on bare GCE (e).

Figure 2

Voltammetric Behavior of Tenoxicam at the MWCNTs modified GCE

Voltammetric responses of TX were checked out in detail by CV, DPV and SWV using MWCNTs modified GCE over the pH range of 2.0-8.0 in different buffer solutions. The cyclic voltammograms of 1 × 10^{-5} M TX solution exhibited irreversible electrochemical oxidation process on MWCNTs modified GCE in all working solutions (Figure 3). The cyclic voltammetry scan was carried out from -0.40 V to 1.0 V in the positive direction and anodic response of TX was observed at about +0.55 V at scan rate of 100 mV s^{-1}.

Figure 3

The influence of pH on the peak current and potential was inquired from pH 2.0 to 8.0 using CV, DPV and SWV methods. The results acquired from CV, DPV and SWV showed similarity. Therefore, only DPV results for the main oxidation step was showed as E_p-pH and I_p-pH plot in Figure 4. The peak potentials of the responses were shifted to more negative potentials by increased pH. This is based on the oxidation of conjugate base at less positive potentials compared to the corresponding acid form. The TX oxidation peak which corresponds to the

electroactive group in acid-base equilibrium with a pK_a of about 5.5[25] indicates pH dependence. Above pH 5.5, the peak potential about happens pH independent (Figure 4A). The linear relationship between E_p-pH can be clarified according to the following equation between 2.0 and 5.5 in all supporting electrolytes: E_p(mV) = -24.7pH+654.2 (r=0.9987). The slope value (-24.7) was about half of to -59.0 mV/pH, so, it was inferred that the number of protons is half of the number of electrons transferred in the TX reaction. This can be attributed to the oxidation of amide group in the structure of TX.

The impact of pH on the TX peak current on MWCNTs modified GCE indicated that the peak current of TX was maximum in the 1 M acetate buffer at pH 5.5 (Figure 4B). Thus, 1 M acetate buffer was selected as the supporting electrolyte for the quantitative determination of TX from pharmaceutical dosage forms.

Figure 4

Scan rate studies were performed to understand the electrochemical process for TX at the surface of MWCNTs modified GCE. The electrochemical behavior of 8×10^{-5} M TX in 1 M acetate buffer at pH 5.5 was investigated at different scan rates ranging from 5 to 200 mV s^{-1} by CV. The peak potential of TX solution is shifted to the anodic direction when the scan rate is increased (Figure 5). A plot of peak current versus the scan rate showed a straight line with a slope of 0.0118 (equation 1). This indicated that the electrochemical reaction is checked by the diffusion of the electroactive species to the MWCNTs modified GCE surface.[26,27] Related equations are noted below:

$I_p = 0.0118\upsilon+0.15$; r = 0.997 (n=8) (equation 1)

Figure 5

It was also observed that the anodic peak current of TX shifted to a higher positive value when the scan rate was increased. This approves the irreversibility of the oxidation reaction of TX on the MWCNTs modified GCE.[28]

Calibration curve and method validation

Quantitative analysis of TX for validation studies were performed using DPV and SWV. The calibration curves for DPV and SWV were drawn by plotting the peak

current versus the TX concentration. TX responses were linear between the ranges of 2×10^{-7} - 1×10^{-5} M for DPV and 8×10^{-9} - 8×10^{-6} M for SWV. Equations obtained from the calibration data were given as follows:

$I_p(\mu A) = 52349\mu M - 0.0209$; r = 0.997 (n=10) for DPV (equation 2)

$I_p(\mu A) = 25472\mu M + 0.0039$; r = 0.997 (n=14) for SWV (equation 3)

DP and SW voltammograms for various concentrations of TX were demonstrated in Figure 6A and 6B, respectively.

Figure 6

LOD and LOQ values were figured out according to the 3s/m and 10s/m, respectively (s is the standard deviation of the peak currents obtained from three sequential measurements and m is the slope of the related calibration graph).[29-32] The characteristics of the calibration curve results for DPV and SWV are shown in Table 1.

Table 1

We have determined the precision of the improved methods by the repeatability and reproducibility studies. 6×10^{-6} M TX solution in 1 M acetate buffer at pH 5.5 was used for the experiments. To calculate relative standard deviation (RSD %) values for DPV and SWV, five measurements were taken from different solutions with the same TX concentrations in a day for repeatability and in different days of a week for reproducibility. These results (Table 1) demonstrated that the developed methods with MWCNTs modified GCE were good in precision, accuracy, repeatability and reproducibility.

Stability studies of the MWCNTs modified GCE were performed as a function time. For the purpose of the peak current 4×10^{-5} M TX was examined with DPV for 1 M acetate buffer solution at pH 5.5 on the same MWCNTs modified GCE stored at room temperature two months. After four and eight weeks, the modified electrode kept 99.65% and 98.41% of the peak current of TX, respectively. Following after two weeks the peak current value kept only 95.12%. Consequently, the MWCNTs modified GCE demonstrated long term stability.

In literature, electroanalytical determination of TX has been achieved by various electrodes. In Table 2, results obtained in this study and from other voltammetric studies in the literature were compared in the way of electrode, linearity range and LOD. El-Maali *et al.'s* study demonstrated wider linearity range and lower LOD value. However, the use of mercury electrode provides a disadvantage to work because of the highly toxic nature of the mercury. In this study, MWCNTs modified GCE provided a good linear range and detection limit with SWV and the MWCNTs modified GCE. Additionally, it has some advantages such as easy preparation, user friendly and long term stability. As a result, the MWCNTs modified GCE can be used more safely and sensitively in electroanalytical determination of TX.

Table 2

Tablet analysis

DPV and SWV methods which were developed using MWCNTs modified GCE were applied for the determination of TX the pharmaceutical dosage forms (Tilcotil® tablets). Each tablet in pharmaceutical dosage form contains 20 mg TX. The DPV and SWV methods were applied in direct determination TX in pharmaceutical dosage form without pretreatment such as extraction, evaporation steps. Furthermore recovery studies proposed methods and modified electrode were also carried out via adding known amounts of pure TX to pharmaceutical form. Five repetitive experiments were done using the related calibration curve which is a straight line and the obtained results were demonstrated in Table 3. As shown in Table 3, the results were satisfactory and indicated the validity of the methods and modified electrode for the determination TX in pharmaceutical.

Table 3

CONCLUSION

In this study, MWCNTs modified GCE was prepared for sensitive determination of TX. The fully validated DPV and SWV results demonstrated high sensitivity and reproducibility and repetitively via the developed sensor. The developed sensor was used for the determination of TX in the pharmaceutical form by DPV and SWV without any pretreatment. The results were recovered at high percentage. In addition to these, the prepared electrode in this study is very useful in

the voltammetric studies of tenoxicam due to its high accuracy, sensitivity, stability, repeatability and also its practical preparation. The sensor and method for determining accurate TX concentrations can be used in biological sample for pharmacokinetic studies and quality control laboratories.

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Table 1. Validation data of calibration lines for the quantitative determination of TX by DPV and SWV on MWCNTs modified GCE in 1 M acetate buffer at pH 5.5.

	MWCNTs modified GCE	
	DPV	**SWV**
Peak potential (V)	0.520	0.570
Linearity range (M)	2.0×10^{-7} -1.0×10^{-5}	8.0×10^{-9} -8.0×10^{-6}
Slope (μA μM^{-1})	52349	25472
Intercept (μA)	-0.0209	+0.0039
Correlation coefficient	0.997	0.997
Limit of detection (M)	1.43×10^{-9}	9.97×10^{-10}
Limit of quantification (M)	4.33×10^{-9}	3.02×10^{-9}
Repeatability of peak current (Relative standard deviation %)*	0.675	0.411
Repeatability of peak potential (Relative standard deviation %)*	0.044	0.319
Reproducibility of peak current (Relative standard deviation %)*	0.704	0.896
Reproducibility of peak potential (Relative standard deviation %)*	0.961	0.538

*Obtained from five experiments

Table 2. Compared parameters obtained using different electrodes for the determination of TX.

Electrode	Method	Linear range (M)	Limit of detection (M)	Ref.
Static mercury drop electrode	Differential pulse polarography	7.41×10^{-8}-5.90×10^{-5}	7.41×10^{-8}	18
Static mercury drop electrode	Square wave adsorptive stripping voltammetry	8.0×10^{-10}-10.0×10^{-5}	1×10^{-10}	19
Hanging mercury drop electrode	Differential pulse polarography	1.24×10^{-6}-9.79×10^{-6}	-	20
MWCNTs modified GCE	Differential pulse voltammetry	2.0×10^{-7}-1.0×10^{-5}	1.43×10^{-9}	This work
	Square wave voltammetry	8.0×10^{-9}- 8.0×10^{-6}	9.97×10^{-10}	

Table 3. The results for the determination of TX from tablet dosage forms and recovery experiments in 1 M acetate buffer at pH 5.5 by DPV and SWV on MWCNTs modified GCE.

	Tablet (mg)	
	Differential pulse voltammetry	**Square wave voltammetry**
Labeled claim (mg)	20	20
Amount found (mg)*	19.871	20.260
Relative standard deviation %	0.714	0.638
Bias %	0.645	-1.3
Added (mg)	20.00	20.00
Found (mg)*	20.035	20.018
Average recovered (%)	100.865	100.307
Relative standard deviation % of recovery	0.799	0.704
Bias %	-0.865	-0.307

*Obtained from five experiments

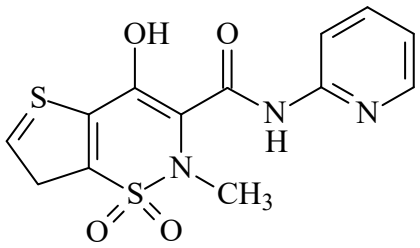


Figure 1. Chemical structure of TX

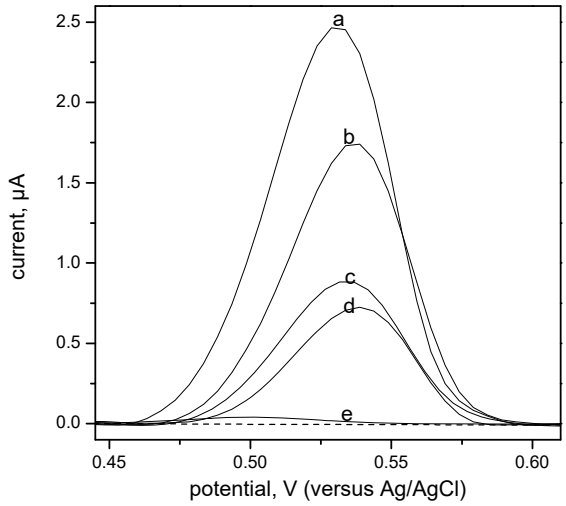


Figure 2. Differential pulse voltammograms 4×10^{-5} M of TX in 0.04 M Britton-Robinson buffer at pH 5.0 **a.** 0.2% 2.5 µL, **b.** 0.2% 5 µL, **c.** 0.5% 1 µL, **d.** 0.5% 2.5 µL of MWCNTs modified GCE, **e.** bare GCE. Dash line; 0.04 M Britton-Robinson buffer solution on 0.2% 2.5 µL of MWCNTs modified GCE.

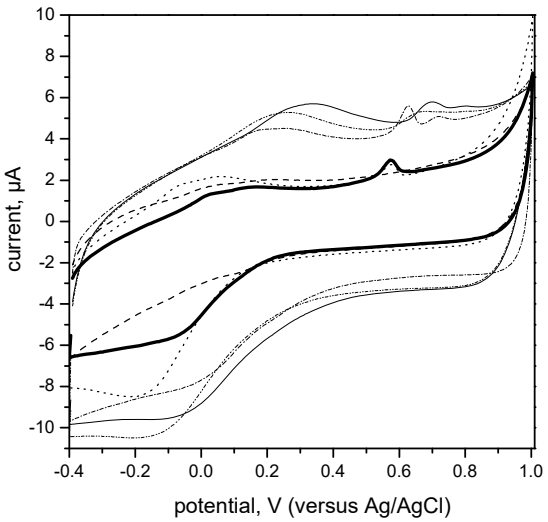


Figure 3. Cyclic voltammograms of 1.0×10^{-5} M TX in 1 M acetate buffer at pH 3.5 (−·−·), pH 5.5 (▬), 0.04 M Britton-Robinson buffer pH 3.0 (—), pH 4.0 (−··−), 0.1 M phosphate buffer at pH 7.0 (····) with MWCNTs modified GCE. 1 M acetate buffer at pH 5.5 (---); scan rate 100 mV s^{-1}.

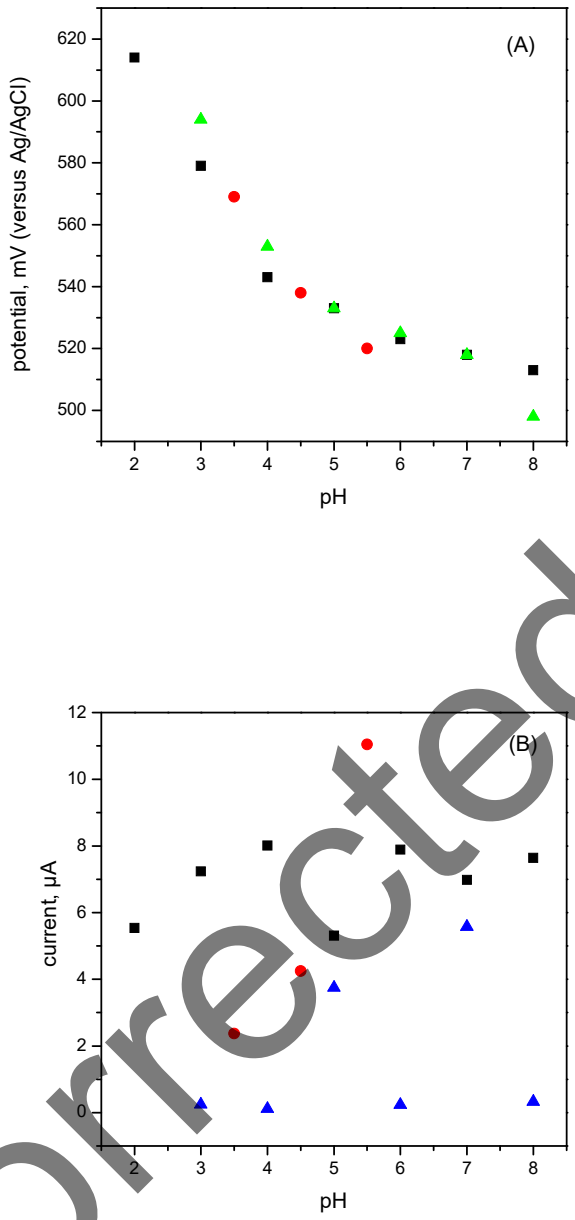


Figure 4. Plots of peak potential (E_p), versus pH (A) and peak current (I_p), versus pH (B) from differential pulse voltammograms of 1.0 × 10^{-5} M TX with MWCNTs modified GCE. Squares indicate 0.1 M phosphate buffer solution, tringle 0.04 M Britton-Robinson buffer solution and circles 1 M acetate buffer solution.

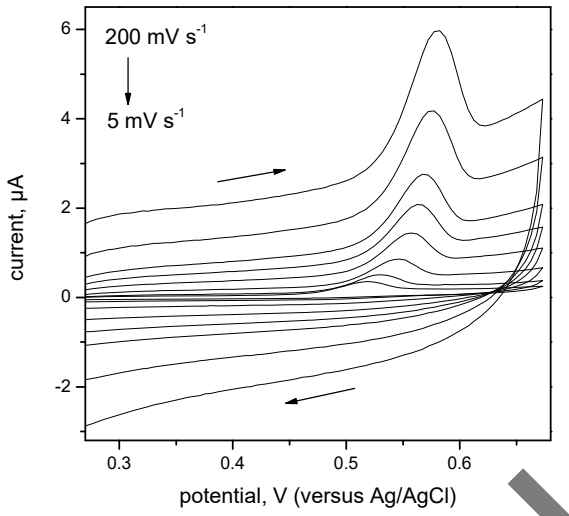
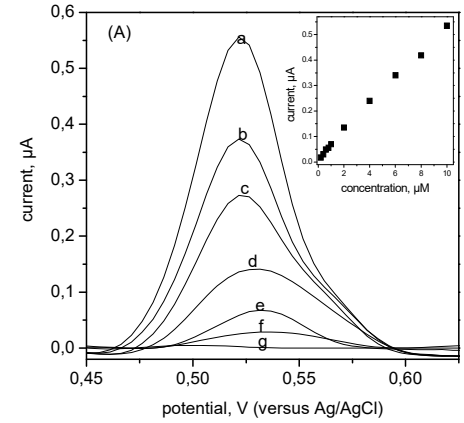


Figure 5. Cyclic voltammograms of 8.0 × 10^{-5} M of TX in 1 M acetate buffer solution at pH 5.5 at scan rates of 5, 10, 25, 50, 75, 100, 150 and 200 mV s^{-1} with MWCNTs modified GCE.



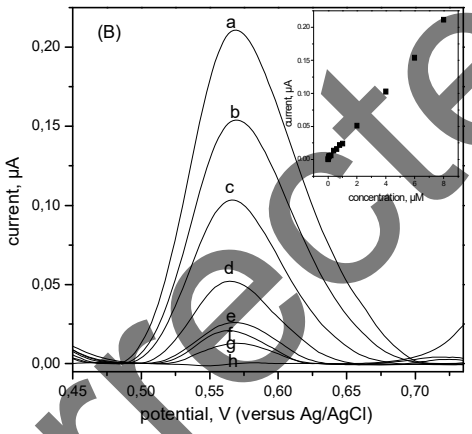


Figure 6. A. Differential pulse voltammograms **a**.1 × 10^{-5} M, **b**. 6 × 10^{-6} M, **c.** 4 × 10^{-6} M, **d.** 2 × 10^{-6} M, **e.** 1 × 10^{-6} M, **f.** 4 × 10^{-7} M TX in 1 M acetate buffer solution at pH 5.5, **g.** 1 M acetate buffer solution at pH 5.5 with MWCNTs modified GCE **B.** Square wave voltammograms **a.** 8 × 10^{-6} M, **b.** 6 × 10^{-6} M, **c.** 4 × 10^{-6} M, **d.** 2 × 10^{-6} M, **e.** 1 × 10^{-6} M, **f.** 6 × 10^{-7} M, **g.** 4 × 10^{-7} M TX in 1 M acetate buffer solution at pH 5.5, **h.** 1 M acetate buffer solution at pH 5.5 with MWCNTs modified GCE.