Int. J. Electrochem. Sci., 14 **(2019)** 4508 – 4519, doi: 10.20964/2019.05.08

International Journal of
ELECTROCHEMICAL
SCIENCE
www.electrochemsci.org

Voltammetric Determination of Tenoxicam in Drug Formulation at Modified Glassy Carbon Electrode

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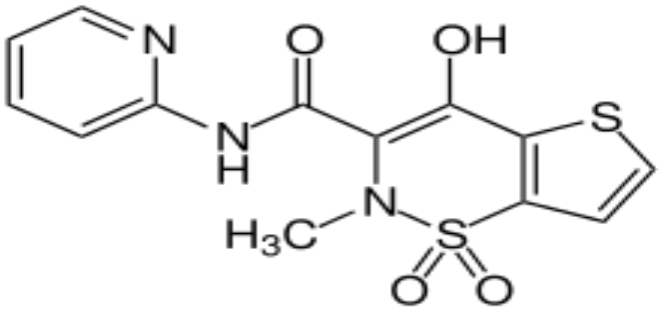
Received: 7 January 2019 / *Accepted:* 20 February 2019 / *Published:* 10 April 2019

In this study, the electrocatalytic reduction of tenoxicam (TNX) was studied on a 4-aminobenzene sulfonic acid (4-ABSA) modified glassy carbon (GC) electrode using cyclic voltammetry (CV) and differential pulse voltammetry (DPV) techniques. The modified glassy carbon electrode showed a significant catalytic effect on the reduction of TNX in a wide pH range of 3.0-8.0. The CV technique was used to investigate electrochemical behaviors of TNX and the effect of pH on the reduction reaction. 0.2 M acetate buffer (pH 5.0) was selected as support electrolyte. The voltammetric determination of TNX was performed using differential pulse voltammetry (DPV) technique. The limits of detection (LOD) and quantification (LOQ) were determined to be 2.82×10^{-7} M and 9.43×10^{-7} M. Also, the amount of TNX in the drug tablets was determined at the optimum conditions developed. It is observed that the modified GC electrode is sensitivity and selectivity for the determination of TNX in Oksamen tablets by DPV technique

Keywords: tenoxicam, voltammetric determination, electrochemical reduction, electrochemical polimerization, modified glassy carbon

1. INTRODUCTION

Tenoxicam (4-hydroxy-2-methyl-N-pyridyl-2H-thieno (2,3-e)-1,2-thiazine-3-carboxamide-1,1-dioxide) (Scheme 1), is a nonsteroidal anti-inflammatory drug active ingredient of the "oxicams" chemical class. The drug is commonly used in the treatment of chronic rheumatic diseases [1] and its daily dose is usually 20 mg [2, 3]. Furthermore, TNX showed a good analgesic and antiinflammatory effect in animal models. The mechanism of action is not known exactly such as non-steroidal anti-inflammatory drugs, but it is thought to be multifactorial [4].



Scheme 1. Chemical formula of tenoxicam

Up to now, TNX has been determined with the different methods such as flow injection spectrophotometric [5], high-performance liquid chromatography [6], TLC analysis [7], ultraviolet spectrophotometry [8], potentiometric ion-selective membrane electrodes [9], infrared spectrophotometry [10], electroanalytical [11].

The working electrodes such as a carbon paste electrode [12, 13], tast polarography (TP) [14], pulsed amperometric detection at bare glassy carbon electrode [15], a boron-doped diamond electrode [16], a novel carbon paste electrode modified [17], a carbon ceramic electrode modified [18] have been used to determine with electrochemical methods of TNX. However, a voltammetric technique, which is used the GC electrode modified with electrochemical polymerization of 4-aminobenzene sulfonic acid for determine of TNX, has not been recorded yet.

In this study, a sensitive, simple, rapid and economical voltammetric method was improved for the determination of TNX. The modified GC electrode, which is showed an electrocatalytic effect on the reduction of TNX, was used for determine the amount of TNX in the drug tablets.

2. MARERIALS AND METHODS

2.1 Instrumentation

A potentiostat meter (VersaSTAT^3, Princeton Applied Research, USA) was used for the voltammetric measurements. Glassy carbon electrode (GCE) (3.0 mm diameter) were used as a working electrode and purchased from BAS. Electrochemical cell consists of triple eletrot system. A platinum wire used as auxiliary electrode and a Ag/AgCl (NaCl 3 M, BAS) used as reference electrode are the other electrodes.

All pH measurements with an EZDO 5011 model digital pH-meter were performed. The deionized water was obtained from water purified with an aqua MAX^{TM}- ultra water purification system (young Lin Inst.) 18.2 MΩcm^{-1}.

2.2 Reagents and materials

TNX and Oksamen were supplied from Basel Kimyevi Maddeler ve Ilac. San. Tic. A.S. Istanbul-Turkey. A stock solution of 1.0x10^{-3} M of TNX was prepared in methanol. The other solutions

were obtained by dilution with 0.2 M acetate buffer (pH 5.0) of the stock solution. 0.2 M acetate buffer (pH 5.0) was selected as the supporting electrolyte solution to investigate the electrochemical behaviors of TNX. All chemical substances used for experimental work were reagent-grade commercial products.

2.3 Polishing and Cleaning of Glassy Carbon Electrode

The GC electrode was polished in 1 μm, 0.3 μm, 0.05 μm alumina slurries on Buehler polishing microcloth. The polished GC electrode was sonicated in a mixture of 1:1 (v/v) nitric acid/water (HNO_3+H_2O), in ethanol and in ultra pure water for 10 min, respectively. Finally, the polished and cleaned GC electrode was rinsed with water and dried under a stream of argon. The bare GC electrode was used for the derivatization.

2.4 Calibration graph for determination of TNX

The stock solution of $1x10^{-3}$ M TNX was prepared by dissolving in methanol of TNX. The different concentrations of the TNX solutions were obtained with diluting with 0.2 M acetate buffer solution (pH 5.0) of the stock solution. The DPV voltammograms of solutions of different concentrations of TNX were recorded. The calibration graph was constructed by using the data obtained under the optimum conditions described in the experimental section. The concentration range of the linear calibration curve for DPV is from $3x10^{-6}$ M to $1x10^{-5}$ M. the DPV technique was used to determine the amount of TNX in tablets.

2.5 Procedure for Oksamen tablets

In order to determine the amount of TNX in 20 mg Oksamen drug tablet, a drug tablet with a mass of 200 mg was taken and powdered. A solution of 10 mL of 1.20 mg from the powdered tablet form was prepared in methanol. The stock solution of 1 mL was diluted to 10 mL with 0.2 M acetate buffer (pH 5.0). The DPV voltammogram of the sample was recorded. The amount of TNX in the drug tablet was determined by using the drawn calibration graph.

3. RESULTS AND DISCUSSION

3.1 Derivatization of Glassy Carbon Electrode

The GC electrode surface was modified by the cyclic voltammogram of 10 cycles in the potential range from -1.5 V to +2.4 V of $2.0x10^{-3}$ M 4-ABSA in 0.10 M PBS (pH 7.0) (Fig. 2). The polymer film on the modified surface is blue polymer film [19]. Also, the modified GC electrode was activated with the CV voltammogram of 10 cycles at 100 mVs^{-1} scan rate in the potential range from -1.0 V to +1.0 V in 0.1 M phosphate buffer (pH 7.0) medium. After the activation process is

completed, the prepared modified and activated electrode has been used for voltammetric studies. The modified electrode was washed with ultra pure water and stored in 0.1 M PBS (pH 7.0) before use.

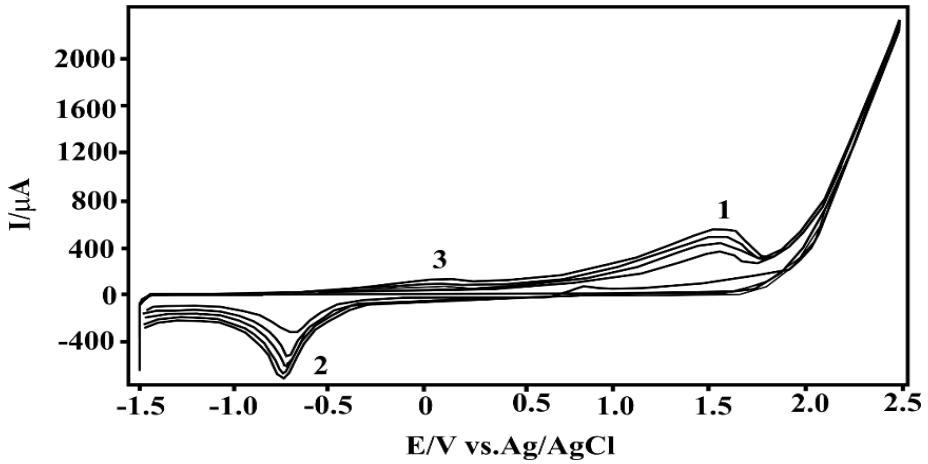


Figure 1. The cyclic voltammogram of 10 cycles in the potential range from -1.5 V to +2.4 V of $2.0x10^{-3}$ M 4-ABSA in 0.10 M PBS (pH 7.0) (Scan rate 100 mVs^{-1}).

3.2 Electrochemical reduction of TNX on Modified Glassy Carbon Electrode

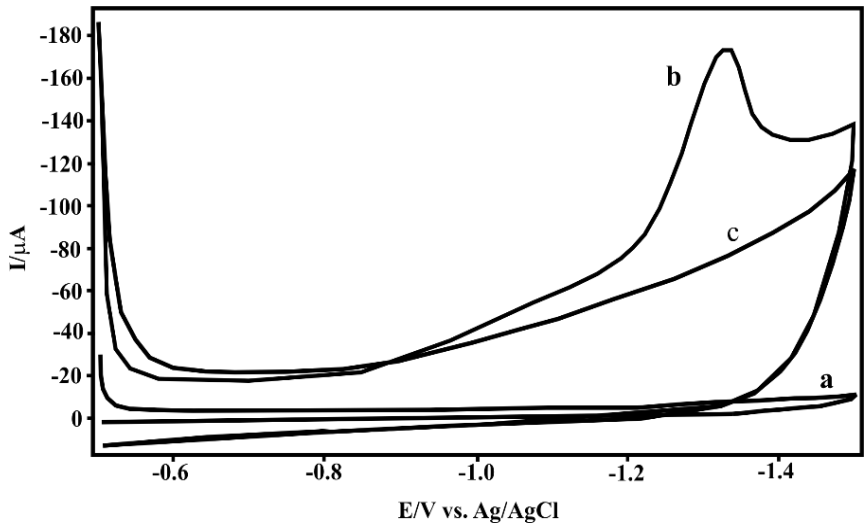


Figure 2. Cyclic voltammograms recorded at (a) bare GC (b) modified GC electrodes of $1x10^{-4}$ M TNX in 0.2 M acetate buffer (pH 5.0) (c) is the cyclic voltammogram of 0.2 M acetate buffer (pH 5.0) at the modified glassy carbon (Scan rate: 50 mVs^{-1}).

To investigate the electrochemical reductions of TNX on the bare GC and the modified GC electrodes was used the CV technique. The cyclic voltammograms recorded at the GC (a) and the modified GC (b) electrodes of $1x10^{-4}$ M TNX at 0.2 M acetate buffer (pH 5.0) at the scan rate of 50 mVs^{-1} is showed in Fig. 3.

Fig. 2a shows the cyclic voltammogram of TNX obtained by using the bare GC electrode. As can be seen in Fig. 2b, when modified GC electrode is used for reduction of TNX, it is understood that

there is an increase in reduction peak current observed at -1350 mV. Also, in comparison with the data at the bare GC electrode, a decrease in overpotential of TNX was recorded.

3.3 Effect of pH

The effect of pH on the reduction of the TNX was studied by using several buffer solutions in the range of pH from 3 to 8. The most electrochemical signal increase was observed at 0.2 M acetate buffer (pH 5.0). Also, the reduction peak potential of TNX shifted a less negative value with increasing pH up to 5.0. Therefore, all voltammetric works were performed in acetate buffer medium at pH 5.0. The peak current values of the reduction peaks obtained from cyclic voltammograms of $1x10^{-4}$ M TNX solutions diluted with several support electrolytes in the range changed from pH 3 to 8 are shown in Fig. 4.

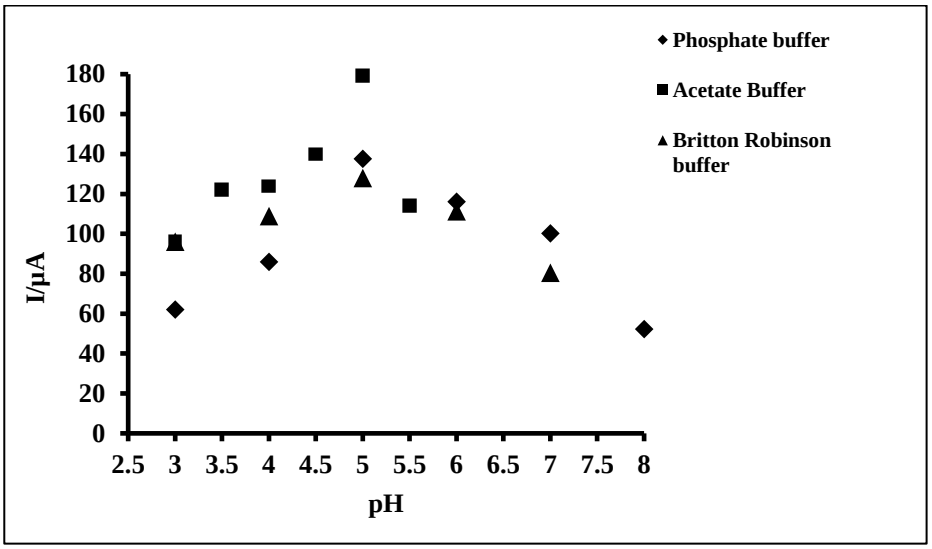


Figure 3. The reduction peak current values of $1x10^{-4}$ M TNX recorded in the range from pH 3.0 to 8.0 in 0.1 M phosphate, 0.2 M acetate and 0.04 M Britton-Robinson buffers at a scan rate of 50 mVs^{-1}.

As seen in Fig. 3, the reduction peak current of TNX in 0,2 M acetate buffer was reached to the maximum value at pH 5.0. Also, the anodic peak potential shifts toward a less negative values with increasing pH up to 5.0.

The CV voltamograms of $1x10^{-4}$ M TNX in 0.2 M acetate, 0.1 M phosphate and 0.04 M Britton-Robinson buffers in the potential range from -0.5 to -1.5 V is given in Fig 4.

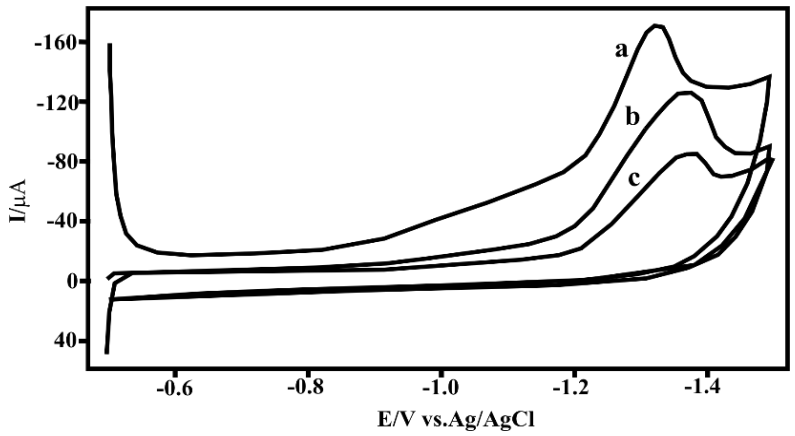


Figure 4. The CV voltamograms of $1x10^{-4}$ M TNX at the scan rate of 50 mVs^{-1} in the potential range from –0.5 to -1.5 V in 0.2 M acetate buffer (a), 0.04 M B-R buffer (b) and c) 0.1 M phosphate buffer (pH 5.0).

As shown in Figure 4, the peak current value of the reduction peak of TNX in 0.2 M acetate buffer (pH 5.0) is greater (-179.19 µA). In addition, the peak potential shifted a less negative value (-1,330 V). Therefore, all voltammetric studies were performed in 0.2 M acetate buffer (pH 5.0) medium.

3.4. The nature of the reducion peak of TNX

Fig. 5 shows the cyclic voltammograms of $1x10^{-4}$ M TNX in 0.2 M acetate buffer (pH 5.0) on the poly(4-ABSA/GC) electrode surface at the following scane rates: 10, 20, 30, 40, 50, 100, 200 and 300 mVs^{-1}.

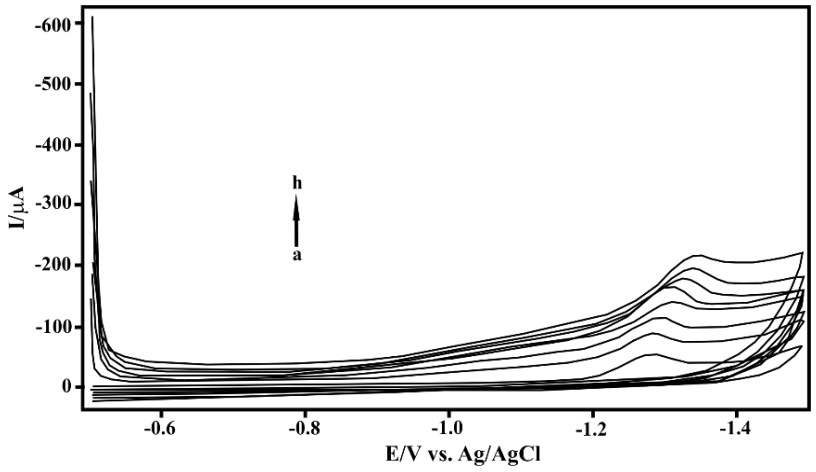


Figure 5. Cyclic voltammograms recorded of $1x10^{-4}$ M TNX in 0.2 M acetate buffer (pH 5.0) by using modified GC electrode at scan rates: a) 10, b) 20, c) 30, d) 40, e) 50, f) 100, g) 200 and h) 300 mVs^{-1}.

The reduction peak current values increase by increasing of the scan rate. In addition, the peak potential values shifted to more negative values by increasing of scan rate.

The peak current values plotted against $v^{1/2}$ and the logarithm of peak current (log *I*) against the logarithm of scan rate (log *v*) are shown in Fig. 6 and in Fig 7, respectively.

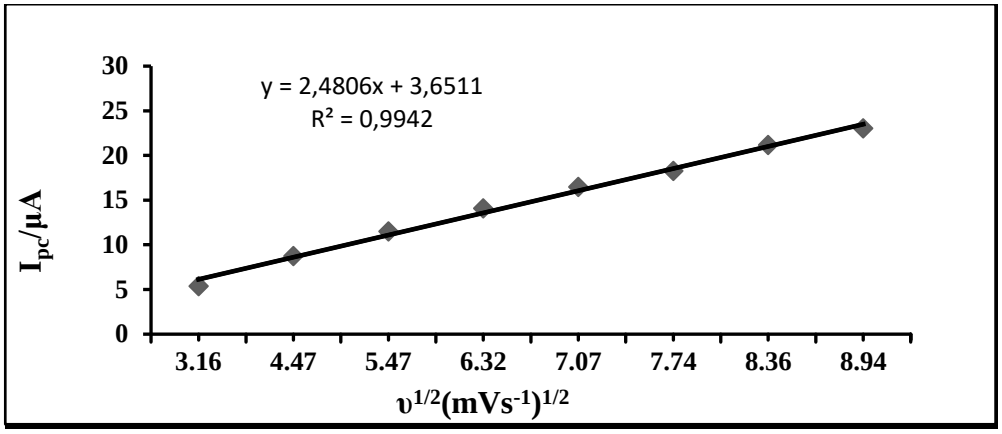


Figure 6. The peak current values plotted against $v^{1/2}$ obtained from cyclic voltammograms recorded at modified GC electrode of $1x10^{-4}$ M TNX in 0.2 M acetate buffer (pH 5.0). Scan rates: a) 10, b) 20, c) 30, d) 40, e) 50 f) 60, g) 70, h) 80 mVs^{-1}.

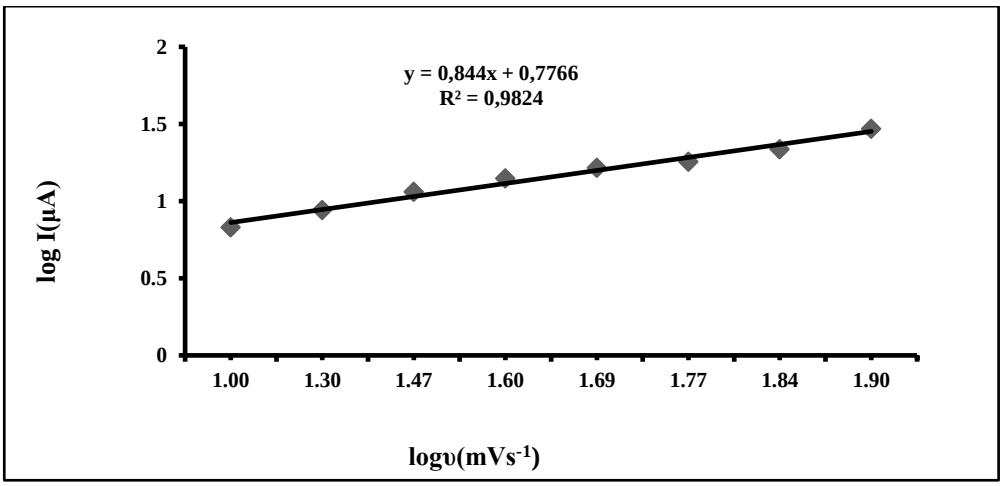


Figure 7. The logarithm of peak current (log *I*) against the logarithm of scan rate (log *v*) obtained from cyclic voltammograms recorded at modified GC electrode of $1x10^{-4}$ M TNX in 0.2 M acetate buffer (pH 5.0). (Scan rates: a) 10, b) 20, c) 30, d) 40, e) 50 f) 60, g) 70, h) 80 mVs^{-1}).

The linearity between the square root of scan rate and peak current was obtained in the range of scan rate of 10-80 mVs^{-1}. The linear regression equation was $Ip(\mu A)= 2.48\upsilon^{1/2}+3.65$ with correlation coefficient (r=0.994). The correlation coefficient is very close to 1.0. Therefore, it is understood that the oxidation process is diffusion controlled. The plot of logarithm of peak current (log *I*) versus logarithm of scan rate (log *v*) has a slope of 0.844 which is greater than the theoretical value of 0.75.

Since the slope is at about 0.844, it can be considered that the electrochemical reduction reaction of TNX is the diffusion-controlled but adsorption is also effective. Also, the cyclic voltammogram of three cycles of $1x10^{-4}$ M TNX in 0.2 M acetate buffer at modified GC electrode was recorded to evaluate the nature of the reduction peak of TNX (Fig. 8).

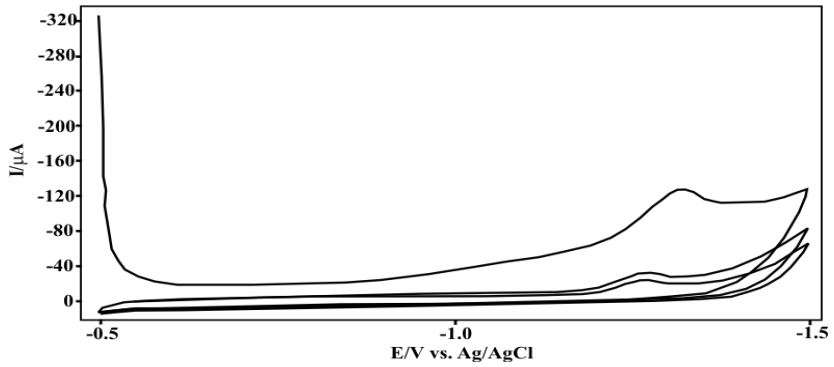


Figure 8. The cyclic voltammogram of the three cycles recorded in the potential range from -0.5 V to -1.5 V of $1x10^{-4}$ M TNX in 0.2 M acetate buffer (pH 5.0) at the modified GC electrode (scan rate: 50 mVs^{-1}).

As seen in Fig. 8, the reduction peak of TNX appeared in the first cycle. However, the current of this peak decreased in second and third cycles. It is estimated that the reduction peak current decreased in the second and third cycles due to the adsorption on the surface of the modified glassy carbon electrode of TNX molecules or the ones of reduction products. This observation can be shown as another piece of evidence that the electrochemical reduction reaction of TNX is diffusion controlled but adsorption is also effective. Therefore, the modified glassy carbon electrodes were only used for one measurement. Consequently, the glassy carbon electrode surface was again cleaned and modified before each new experiment.

3.5. Determination of the analytical concentration range of TNX by DPV technique

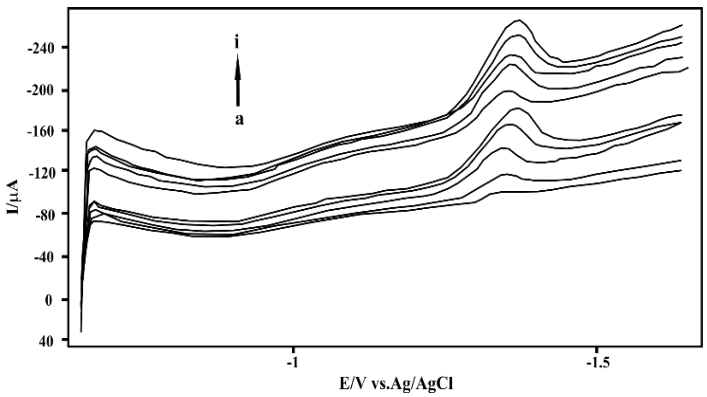


Figure 9. DPV voltammograms recorded at modified GC electrode for increasing concentrations of TNX in 0.2 M acetate buffer (pH 5.0). a) $3x10^{-6}$ M; b) $5x10^{-6}$ M; c) $7x10^{-6}$ M; d) $9x10^{-6}$ M; e) $1x10^{-5}$ M; f) $3x10^{-5}$ M; g) $5x10^{-5}$ M; h) $7x10^{-5}$ M and i) $9x10^{-5}$ M TNX

The assay of TNX at modified GC electrode was performed by using DPV technique in 0.2 M acetate buffer (pH 5.0). The DPV voltammograms recorded in the potential range from -0.2 to -1.7 V for the different concentrations of TNX are shown in Fig 9.

As shown in figure 9, the increase in the concentration of TNX causes to increase of the peak current values of reduction peak. Linear calibration curve was constructed in the concentration range from $3x10^{-6}$ to $1x10^{-5}$ M from current and concentration date obtained for TNX (Fig. 10).

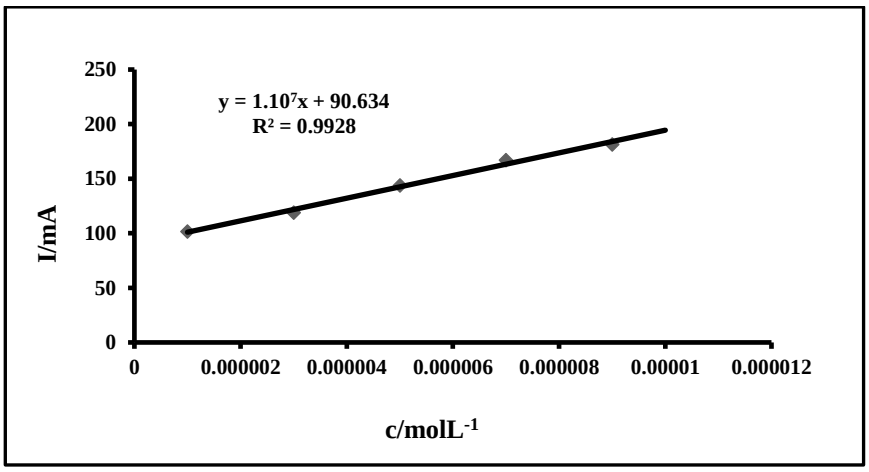


Figure 10. Calibration curve of concentration versus current obtained from DPV voltammograms of TNX in the concentration range from $3x10^{-6}$ M to $1x10^{-5}$ M in 0.2 M acetate buffer (pH 4.50) at modified GC electrode.

The plot was obtained linear in the concentration range of $3x10^{-6}$ to $1x10^{-5}$ M TNX. For the regression plot of the peak current versus TNX concentration, the slope was $1x10^{7}$ μA/M, the intercept was 90.634 μA and the correlation coefficient was $R^2 = 0.993$. Limit of detection (LOD) and limit of quantification (LOQ) values were calculated using the following equations [19]:

LOD = 3 s/m, LOQ = 10 s/m

Where, s is the standard deviation of the peak currents (for five runs) and m is the slope of the calibration curve. To determine LOD and LOQ values, the standard deviation of peak currents for five measurements recorded at $3x10^{-6}$ M, which is the concentration above the lowest concentration in the calibration graph, was determined to be 0.943. The achieved LOD and LOQ were $2.82x10^{-7}$ M and $9.43x10^{-7}$ M at modified GC electrode, respectively.

The different detection limits, pH, linear range and potential values for determination with several electrochemical methods of TNX were recorded in the literature. The results obtained in this study and the other references for the determination of TNX are given in Table 1 with different parameters.

Table 1 The reported electrodes for determination of TNX, voltammetric technique and analytical parameters.

Working electrode	Voltammetric technique	E_p (V)	pH	linear range (μg L^{-1})	LOD (M)	References
1 Static mercury drop electrode	Differential pulse polarography	-1.33	5.3	25-20000	-	11
2 A bare carbon paste rotating disk electrode	Cyclic voltammetry	0.74	0.4	-	-	13
3 Dropping mercury electrode	Tast polarography and differential pulse polarography	-1.1 -1.1	4.5 4.0	33.6-3360	$3.00x10^{-8}$	14
4 Glassy carbon electrode	Pulsed amperometric detection	1.5	7.5	3360-33600	$3.00x10^{-7}$	15
5 Boron-doped diamond electrode	Differential pulse voltammetry	1.4	-	168-16800	$3.00x10^{-8}$	16
6 A modified carbon paste electrode	Square wave voltammetry	0.85	7.0	235-269000	1.20×10^{-7}	17
7 Modified carbon ceramic electrode	Differential pulse voltammetry	0.75	7.0	269-33637	$1.25x10^{-7}$	18
8 Modified glassy carbon electrode	Differential pulse voltammetry	-1.33	4.5	1009-3363	$2.82x10^{-7}$	This work

As can be seen Table 1, the quantitative determination based the reduction or oxidation of NAP using the several working electrode was performed with different voltammetric techniques.

3.6. Determination of TNX in pharmaceutical preparation

A drug tablet of 200 mg was taken to determine the amount of TNX in Oksamen 20 mg drug tablet and powdered. The solution of 10 mL of 1.20 mg of the drug form powdered was prepared in methanol. The volume of 1.00 mL of the stock solution prepared was diluted to 10 mL with 0.2 M acetate buffer (pH 5.0). The DPV voltammogram of the drug tablet dosage form containing TNX is shown in Fig. 11.

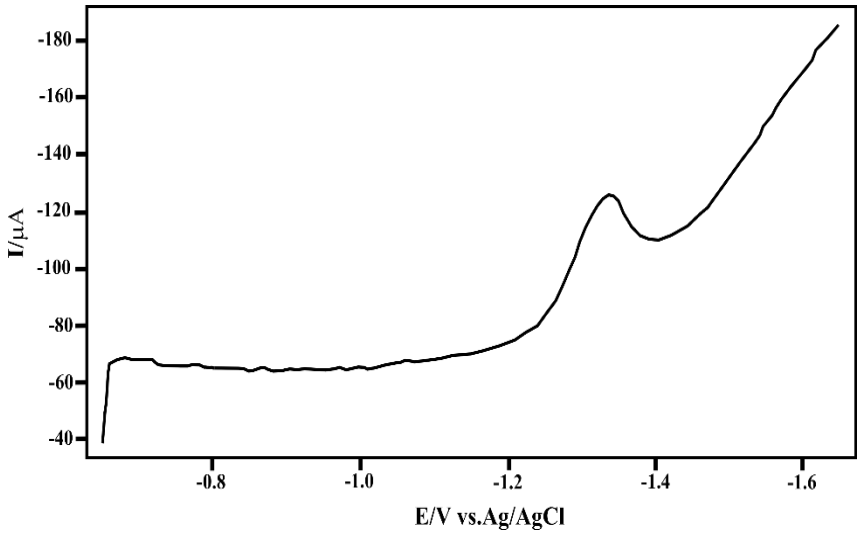


Figure 11. The DPV voltammogram of the drug tablet sample containing TNX in 0.2 M acetate buffer (pH 5.0) in the potential range from -0.7 to -1.6 V at modified GC electrode.

As shown in Fig. 11, when recorded the DPV voltammogram of the drug tablet dosage form sample containing TNX, its characteristic reduction peak has been found to be at about -1.33 V and the peak current is -125,630 µA. Consequently, it is understood that there is no interference on reduction of the TNX in the drug tablet dosage form at modified GC electrode.

The amount of TNX in Oksamen tablets was calculated by reference of calibration curve of concentration versus current obtained from DPV voltammograms. The results recorded are given in Table 2.

Table 2 Application of the DPV technique for the assay of TNX in Pharmaceutical Preparations

Parameters	Results
Labeled TNX , mg	20
Amount found, mg	19.6
Number of measurements, N	5
Relative Standard deviation (*RSD* / %)	0.24
Bias %	2.0

The drug dosage form contains auxiliary substances such as mannitol, sodium hydroxide, trometamol, sodium metabisulfite, sodium E.D.T.A., too.

The amount of TNX in the sample was calculated using of the equation the $y=1x10^7x+90.634$ obtained from the calibration graph of the DPV technique. According to the calculations made for the sample of 1.20 mg, the drug tablet dosage form contains TNX at the rate 9.8 % (w/w).

4. CONCLUSION

In this work, the modified glassy carbon electrode was used for electrocatalytic determination of TNX and showed a significant electrocatalytic effect on the reduction of TNX. TNX in drug tablet dosage form was determined as sensitivity and selectivity by using modified GC electrode in optimum conditions improved.

The DPV technique was used to the determination of TNX at the modified GC electrode in 0.2 M acetate buffer (pH=5.0) medium.

ACKNOWLEDGEMENTS
This work was supported by Tokat Gaziosmanpasa University Scientific Research Fund with a grant number 2016/76.

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