

## VOLTAMMETRIC ANALYSIS OF TAMOXIFEN RECOVERY AND ITS INTERACTION WITH DNA

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### ABSTRACT

The design of biosensors is one of the most important areas of analytical chemistry today, and interest in DNA-based bio (nano) sensors developed to examine applications related to compound-DNA interaction has been increasing in the last two decades. Changing in DNA structure, even for therapeutic purposes, can have serious effects on human health. The detection of any chemical substances in DNA structure is very important. In this study, an anticancer drug Tamoxifen (TAM) is used in the treatment of cancer since the early 1970s was identifying the possible DNA interaction during treatment by using differential pulse voltammetry (DPV) based on both TAM and guanine oxidation signals at the disposable pencil graphite electrode (PGE). The effect of TAM on single stranded (ss)-DNA and double stranded (ds)-DNA showed differences, depending on the double helix and single stranded structure. It was found that TAM interacting to ds-DNA more strongly than ss-DNA. Thus, Drug-DNA interaction analysis has been investigated for the first time under optimized conditions with the Tamoxifen which, gave an oxidation peak potential near the guanine oxidation area. These results presented that the developed DNA biosensor could be detected TAM-DNA interaction as a sensitive, rapid and cost effective way. Electrochemical detection Tamoxifen recovery from commercial tablets was also studied..

**Keywords:** Electrochemical DNA Biosensor, Tamoxifen, Differential Pulse Voltammetry (DPV), Commercial Drug Tablet, Recovery Work.

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## **1. INTRODUCTION**

Breast cancer is the most common cancer in women, accounting for 32% of all newly diagnosed cancers (Kelsey and Bernstein, 1996), because breast cancer is estrogen-dependent, reducing estrogen secretion by oophorectomy, hypophysectomy, or adrenalectomy can cause the cancer to regress. The need for these surgical procedures was reduced by the introduction of tamoxifen, which acts as an antiestrogen by inhibiting the binding of estrogen to estrogen receptors (Osborn, 1998).

Tamoxifen (TAM) is an oral antiestrogen, first used in metastatic breast cancer in the early 1970s. Large clinical trials were initiated in the late 1970s and early 1980s to test the drug's role as adjuvant therapy in early stage breast cancer (Hurtado et al., 2007). There are several analytical methods to determine the concentrations of TAM in biological fluids and pharmaceutical preparations. The developed methods for TAM analysis include capillary electrophoresis (Bagni et al., 2010) and chromatography (Yang et al., 1999). Electrochemical techniques, especially as a biosensor, have received significant attention in the analysis of pharmaceuticals, due to their low detection limits and rapid analysis time. It provides various benefits to the analyzer in the analysis of fast, simple and low-cost drugs (Ozkan et al., 2004).

It is well known that several drugs and chemicals have a damaging effect on DNA. These molecules are generally interacting with DNA non-covalent or covalent ways such as groove binding, electrostatic binding or intercalative mode (Gupta et al., 2011). Therefore, it is important to detect the interaction way of DNA with the drug. The most common approach is to use electrochemical DNA biosensors containing a nucleic acid element to be immobilized on an electrochemical transducer for recognition. This recognition features helps to selectively detect a specific DNA sequence or to monitor changes in DNA structure during interaction with the drug molecule. Studying and investigating the interactions of drugs and DNA as a biosensor has an important place during the treatment (Jahandari et al., 2019). So far there has been only one voltammetric biosensor based TAM-DNA interaction which carbon paste electrode modified with graphene reported for TAM determination (Moghaddam et al., 2017).

In this study, TAM -DNA interaction analysis was performed and at the same time with DNA under optimized conditions using the TAM that gave an oxidation peak close to an area of guanine oxidation signal at disposable pencil graphite electrode (PGEs) for the first time. The developed electrochemical method for the determination of TAM contains the DPV technique, Britton Robinson (B-R) Buffer (pH=4.50) media. Additionally, the amount of TAM in commercial tablets was also determined with the developed technique.

## **2. MATERIAL AND METHOD**

### **2.1 Apparatus**

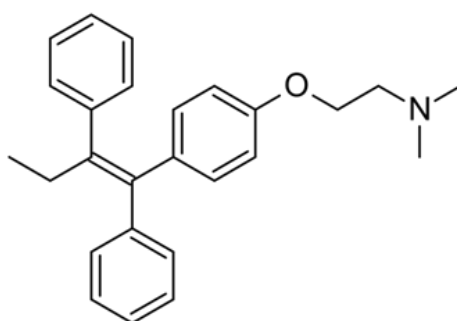
AUTOLAB 12 potentiostat/galvanostat device (Eco Chemie, Netherlands) was used for all electrochemical measurements and raw voltammograms were treated with a Savicky and Golay algorithm using GPES 4.9 software program by moving average method (peak width 0.01 V). The three electrode system was comprised of a pencil graphite electrode (PGE), Ag/AgCl/3M KCl reference electrode and a platinum wire as the auxiliary electrode. The Tombow 2B pencil lead of 0.5 mm diameter and length of 60 mm was used as PGE for the investigation. All experiments were performed at room temperature (22.0-25.0°C).

### **2.2 Reagents and materials**

In this study, CH<sub>3</sub>COOH (Riedel-de Haen, 99 %), CH<sub>3</sub>OH (Merck, 99.5 %), NaOH (Riedel-de Haen), NaCl (Sigma), K<sub>2</sub>HPO<sub>4</sub> (Merck), KH<sub>2</sub>PO<sub>4</sub> (Merck), H<sub>3</sub>BO<sub>3</sub> (Sigma), H<sub>3</sub>PO<sub>4</sub> (Sigma) were used. Double stranded calf thymus DNA and single stranded calf thymus DNA

were purchased from Sigma. The drug active ingredient tamoxifen which chemical formula stated in Figure-1 was obtained from Sigma. The stock solution of 5mM TAM was prepared by dissolving 46 mg TAM in 5 ml of methanol and stored at -20°C. The supporting electrolyte solution for the voltammetric investigations were prepared by dilution of the stock solution. Commercial form of TAM obtained from the AstraZeneca Company. All solutions were stored in the dark and were used within 24 hours to avoid decomposition. 0.067 M phosphate buffer (PBS, pH: 4.50-7.50), 0.2 M acetate buffer (ABS, pH: 3.50- 5.50) and 0.04 M B-R buffer (pH: 2.00-10.00) were selected as the support electrolyte solutions. The cyclic voltammetry (CV) and DPV voltammograms of TAM were recorded to determine the supporting electrolyte type and optimum conditions. Ultra-pure water (UPW) obtained from Sartorius Arium model Ultra-Pure Water Systems was used to prepare the supporting electrolyte solutions. All chemicals were of analytical reagent grade and were supplied from Sigma-Aldrich, Merck, and Riedel-de Haen.

**Figure-1.** The chemical formula of Tamoxifen



### 2.3 Calibration graph for the quantitative determination of TAM

The diluted TAM solutions were prepared by using diluting with B-R buffer solution from the stock solution. In B-R buffer (pH=4.50) medium, a linear calibration curve was performed. in the concentration range of TAM from 2.5  $\mu$ M to 70  $\mu$ M with DPV method.

### 2.4 Recovery works

Five tablets were weighed and powdered in a mortar to determine the amount of tamoxifen from Nolvadex tablets. Each tablet contains 30.4 mg of tamoxifen citrate which is equivalent to 20 mg of tamoxifen (TAM). A suitable amount of each sample was solubilized and sonicated for an hour, in order to prepare equivalent molar stock solutions. The recovery works were constructed by using proper aliquots, respecting the linear response of calibration graphs.

### 2.5 Sensor preparation

PGEs were activated in an electrochemical cell which contains 4 mL of an acetate buffer solution (ABS; pH=4.80). Their 1 cm surface has applied to the buffer solution for 30 seconds at a potential of +1.40 V (Subak and Ozkan-Ariksoysal, 2018). The activated PGE was modified with DNA and TAM by wet-adsorption technique.

The experimental procedure for the surface and solution phase interaction process by using DPV. In the first step, the electrode surface was activated by using ABS (pH=4.80). Then for the solution phase interaction, the mixture of TAM and double stranded DNA (dsDNA) / TAM and single stranded DNA (ssDNA)/TAM was prepared at room temperature and waited for an hour. After this incubation step, electrode surfaces were covered with these solutions by adsorption technique for 20 minutes. dsDNA/ssDNA immobilized to the electrode surface by adsorption technique for the surface phase. The TAM interacted with DNA by adsorption

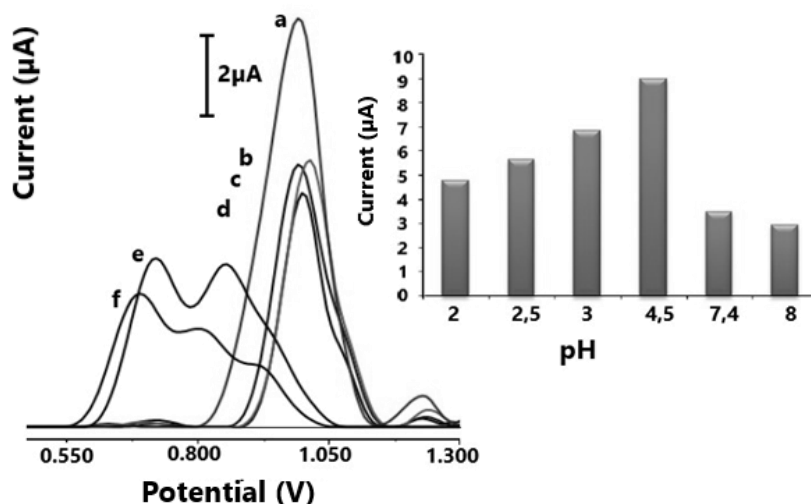
technique in different periods. The next step was to inhibition of nonspecific materials from the surface and then rinsed with ABS for 5 seconds to move unbound DNA from the electrode. The guanine oxidation signal and TAM signal were measured to determine the reaction process by DPV method after optimization of the immobilization time period of TAM/dsDNA/ssDNA for surface phase interaction.

### 3. RESULTS AND DISCUSSION

#### 3.1 Electrochemical oxidation of tamoxifen

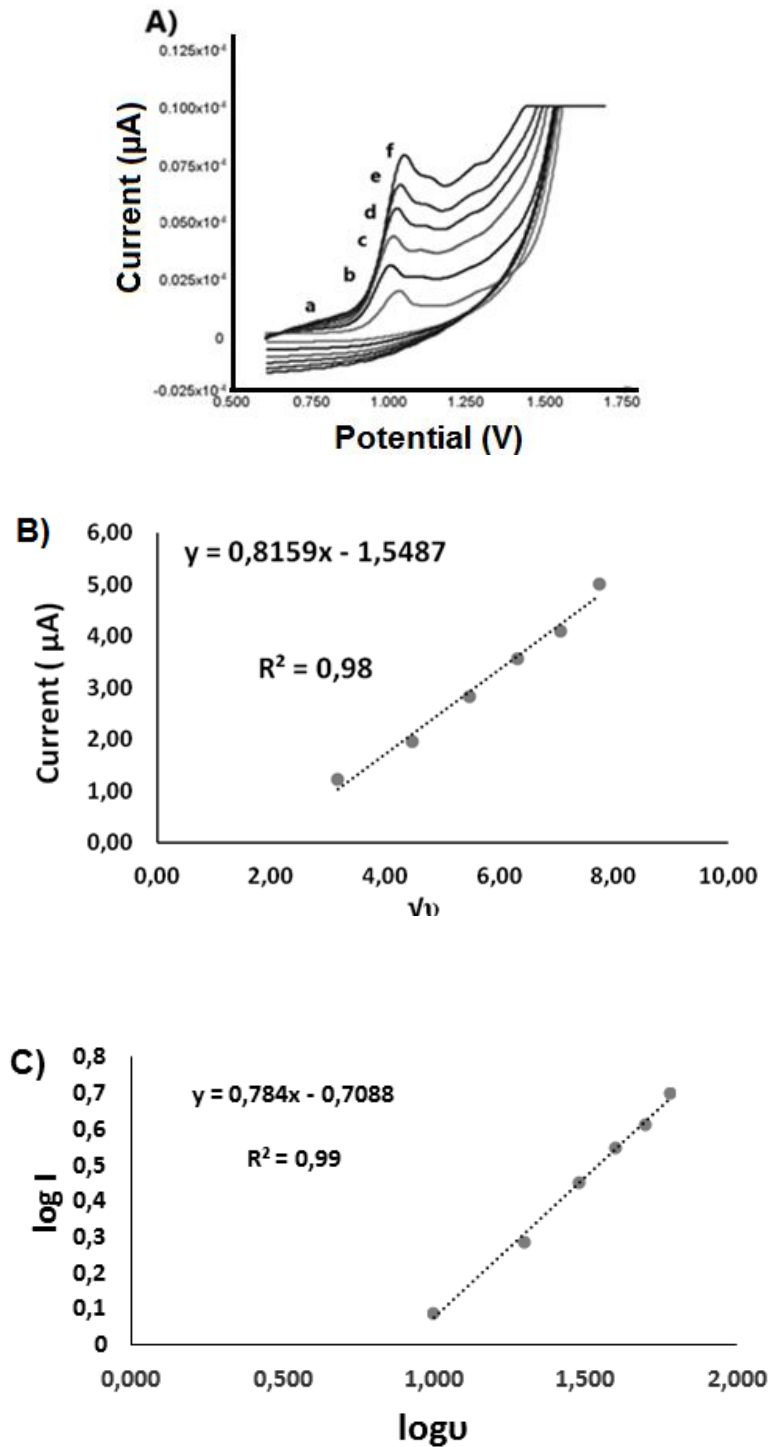
To determine optimal oxidation conditions of TAM, B-R buffers (pH: 2.00 to 8.00) were used as supporting electrolytes. DPV voltammograms of the 100 $\mu$ M TAM in B-R electrolytes at different pH were recorded. The highest current value related to the TAM oxidation was obtained in B-R buffer at pH=4.50 and this medium was chosen for further experiments. The oxidation peak current value of the 100  $\mu$ M TAM obtained with the buffer solutions at different pH in the range changed from pH: 2.00 to 8.00 as shown in Fig.2.

**Figure-2.** The oxidation peak current values obtained from DPV voltammograms of 100 $\mu$ M TAM in the range changed from pH: 2.00 to 8.00 in 0.04 M B-R buffers at PGE.



CV voltammograms of TAM in B-R buffer (pH=4.50) in scan rates between 10 to 60  $\text{mVs}^{-1}$  at PGE were recorded in Figure-3 (Potential range between +0.40 V and +1.4 V, pulse amplitude 50 mV and scan rate 16  $\text{mV/s}$ ). According to the results, the anodic peak at the voltammogram increase with the rising of the scan rate value. There was no peak in the cathodic region. Additionally, the positive shift was observed in the anodic peak potential of TAM.

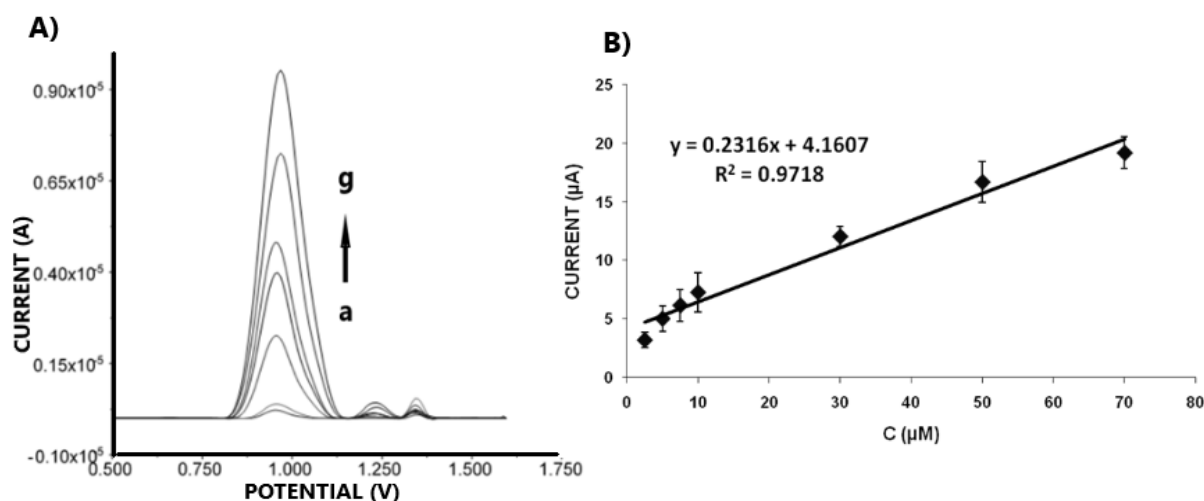
**Figure-3.** A) CV voltammograms of TAM in B-R buffer (pH=4.50) at PGE (Scan rates; 10, b) 20, c) 30, d) 40, e) 50, f) 60m Vs<sup>-1</sup>).  
B) The peak current values plotted against  $v^{1/2}$  obtained from the CV voltammograms of  $5 \times 10^{-5}$  M TAM in B-R buffer (pH=4.50) at PGE.  
C) The logarithm of peak current ( $\log I$ ) against the logarithm of scan rate ( $\log v$ ) obtained from the CV voltammograms of  $5 \times 10^{-5}$  M TAM in B-R buffer (pH=4.50) at PGE.).



The slope is between 0.50-0.75 indicates that the current is diffusion controlled and that it is 0.75-1.00 indicates that the current is adsorption controlled (Sadikoglu et al., 2016), (Moghaddam et al., 2017). The logarithm of peak current (log I) against the logarithm of scan rate (log v) was shown in (Fig. 3B). According to the results, the slope was found as 0.784 which is indicated that the current type of the TAM was adsorption controlled.

The calibration graph of Tamoxifen active ingredient which was determined to have adsorption controlled current type were measured by DPV with the PGE electrode at +0.75 V for 60 sec. in the range of +0.6 / +1.5 V. Calibration graph of Tamoxifen active ingredient was indicated in the Figure-4.

**Figure-4.** The plot of concentration versus current obtained from DPV voltammograms of TAM in the concentration range from 2.5 $\mu$ M to 70 $\mu$ M in B-R buffer (pH=4.50) at PGE. ((a) 2.5 $\mu$ M, (b) 5 $\mu$ M, (c) 7.5 $\mu$ M, (d) 10 $\mu$ M, (e) 30 $\mu$ M, (f) 50 $\mu$ M, (g)70 $\mu$ M TAM )



As shown in Fig. 4, the plot was obtained linear in the concentration range of 2.5 to 70 $\mu$ M TAM (AdsDPV technique for 60 sec at +0.75 V Potential range between +0.60 V and +1.5 V, pulse amplitude 50 mV and scan rate 16 mV/s). For the regression plot of the peak current versus TAM concentration, the slope was 0.2316 $\mu$ A/M, the intercept was 4.1607 $\mu$ A and the correlation coefficient was  $R^2=0.9718$ . Limit of detection (LOD) and limit of quantification (LOQ) values was calculated using the following equations (Can et al., 2015), (Sadikoglu et al., 2016).

$$\text{LOD} = 3 \text{ s/m}, \text{LOQ} = 10 \text{ s/m}$$

Where is the standard deviation of the peak currents (n=5) and m is the slope of the calibration curve. Accordingly, the standard deviation of the current values was found as  $4.46 \times 10^{-3}$  by taking the voltammogram at 5 $\mu$ M, which is the concentration above the lowest concentration in the calibration graph. The achieved LOD and LOQ were recorded  $8.66 \times 10^{-8}$  M and  $2.88 \times 10^{-7}$  M at PGE, respectively.

To investigate the effect of the additives contained in the commercial tablet on the optimized biosensor system, tablets containing the active ingredient on the market have been provided. Then, 5 mM TAM solution with the adequate amount of this powder was prepared and the DPV voltammogram of the sample was recorded. The equation of the calibration curve obtained from the DPV voltammograms. Different concentrations of TAM were recorded for the equation  $y = 0.2316x + 4.1607$ . According to this equation, the amount of TAM in one tablet

was determined to be 20.55 mg. Table.1, the recovery results obtained from the market tablets are listed. As seen on Table.1, the amount of pure active substances from commercial tablets calculated and compared with the value indicated on the tablets.

**Table.1** The assay of TAM in tablets by the DPV technique and recovery of TAM

Parameters	Results
TAM amount in commercial drug, mg	20.00
Amount found, mg	20.55
Relative Standard deviation( <i>RSD</i> / %)	3.99
Bias, %	1.04
Added TAM, mg	20.00
Found TAM, mg	21.15
Average recovery, %	105.74
The relative standard deviation of recovery ( <i>RSD</i> / %),	2.17
Bias, %	0.90

### 3.2 Investigating of TAM – DNA interaction

The selective analysis of cancer therapy drugs, especially TAM, could create the possibility to better control of the treatment process. Considering these, analytical sensors can be evaluated as an auxiliary device for such analysis in cancer patients (Teunissens et al., 2010).

The interaction time between DNA at solution phase interaction procedure was investigated at different times of periods such as 20min., 60min., 24 hrs. in Figure-5. To keep the analysis time short, it was decided to continue the experimental applications with 20 minutes interaction since there was no significant difference at the end of 60 minutes and 20 minutes interaction.

**Figure-5.** Voltamogram of the interaction time period TAM with dsDNA; (a) 10ppm dsDNA, (b) 5 $\mu$ M TAM (c) 20 min. interaction, (d) 60 min. interaction, (e) 24 hrs, voltamograms obtained after interaction in solution phase.

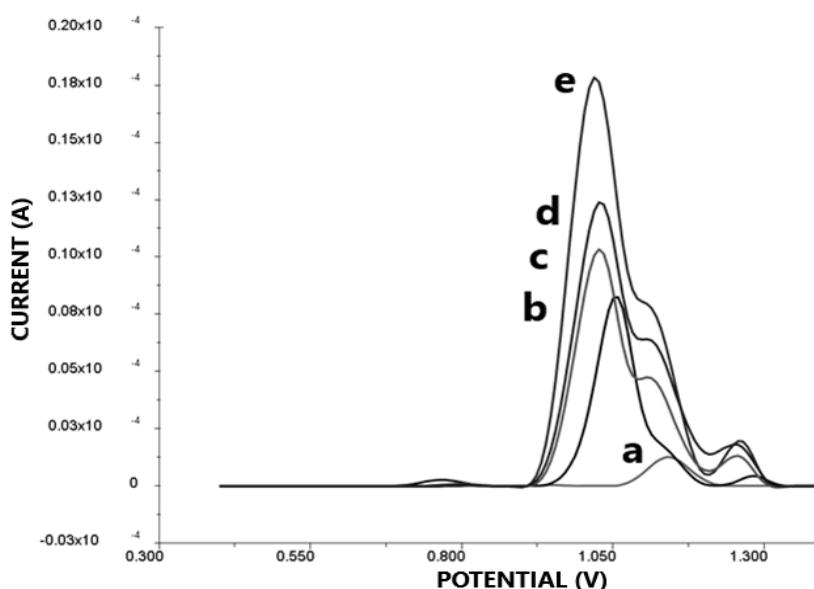
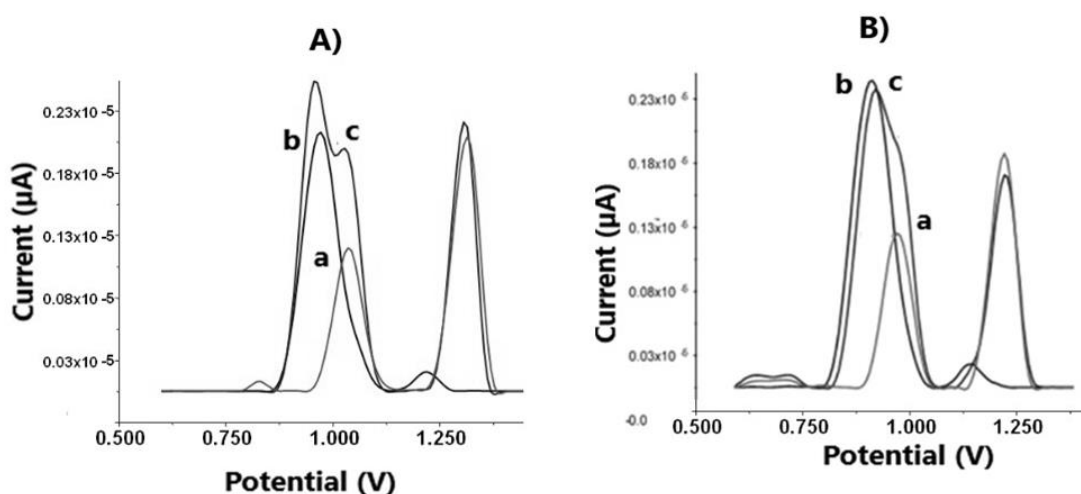
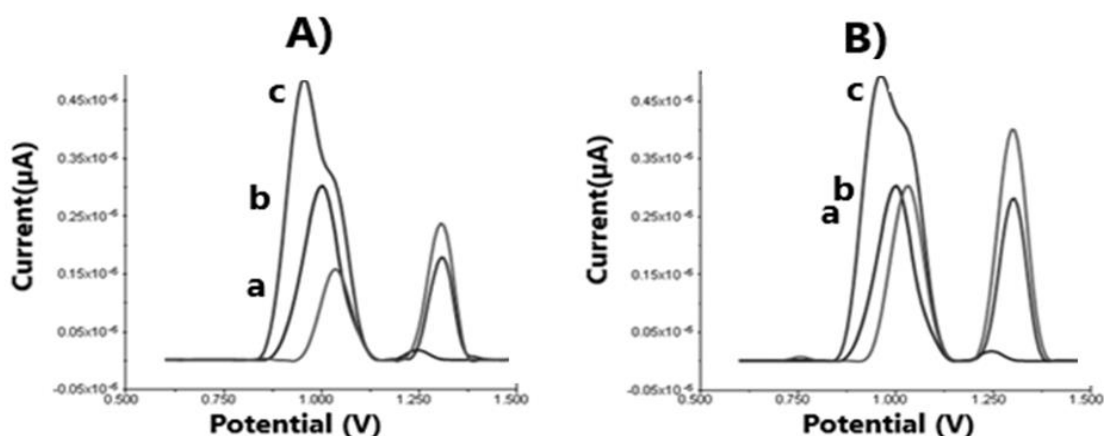


Fig.5 shows the result of the interaction time study between TAM and dsDNA in solution phase (Potential range between +0.60 V and +1.5 V, pulse amplitude 50 mV and scan rate 16 mV/s). According to the data obtained, as the interaction time increases, the signal increases in the guanine oxidation region and the oxidation signal of TAM. To our best knowledge, the increase of DNA signal overtime was interpreted as the possibility of opening of the double helix with the TAM effect. ssDNA and dsDNA were measured respectively to investigate the interaction mechanism of the TAM with DNA. Two different methodologies are surface phase and solution phase interaction also compared to the clarification of the reaction mechanism. Figure-6 shows solution phase interaction and Figure-7 shows the surface phase interaction results.

**Figure-6.** DPV voltammograms of solution phase interactions results; A) dsDNA interaction; a: dsDNA, b: TAM, c: Interaction, and B) ssDNA interaction; a: ssDNA, b: TAM, c: Interaction (other conditions are as in Fig. 5).



**Figure-7.** DPV voltammograms of surface phase interactions results; A) dsDNA interaction; a: dsDNA, b: TAM, c: Interaction; B) ssDNA interaction; a: ssDNA, b: TAM, c: Interaction (other conditions are as in Fig. 5).



In Fig.6 and Fig.7, the interaction of the A) dsDNA- TAM and B) ssDNA-TAM were showed the solution phase interaction results (Fig.6) and surface phase interaction results (Fig.7) respectively.



In Fig.6-A DPV voltammograms of solution phase interactions results for dsDNA interaction respectively a: dsDNA= 1.30 $\mu$ A, b: TAM=2.11 $\mu$ A, c: Interaction=2.05  $\mu$ A (n=5).

In Fig.6-B interaction results for ssDNA is a: dsDNA= 1.16 $\mu$ A, b: TAM=2.33 $\mu$ A, c: Interaction=2.08  $\mu$ A (n=5).

In Fig.7-A DPV voltammograms of surface phase interactions results for dsDNA interaction respectively a: dsDNA= 1.90 $\mu$ A, b: TAM=2.72 $\mu$ A, c: Interaction=3.18  $\mu$ A (n=5).

In Fig.7-B interaction results for ssDNA is a: dsDNA= 2.80  $\mu$ A, b: TAM=3.15  $\mu$ A, c: Interaction=3.40  $\mu$ A (n=5).

In the solution interaction phase, the dsDNA signal in Fig-6A-a about 1.34 $\mu$ A and ssDNA Fig-6B-a is 1.16  $\mu$ A. Similarly in surface phase reaction signal in dsDNA Fig-6A-a is 1.90 $\mu$ A and ssDNA Fig-7B-a is 2.80  $\mu$ A. In Figures, 6A/B and 7A/B concluded that the individual ssDNA signal and the individual dsDNA signal were compared, that the ssDNA gave higher signal because of its open helix structure.

In the solution interaction phase, the TAM signal in Fig-6A-a about 2,11  $\mu$ A and ssDNA Fig-6B-a is 2,33 $\mu$ A. Similarly in surface phase reaction signal in dsDNA Fig-7A-a is 2,72  $\mu$ A and ssDNA Fig-7B-a is 3,15  $\mu$ A. In the solution phase, TAM interacted with ssDNA and dsDNA for an hour and immobilized to the electrode surface for 20 minutes. On the other hand, ssDNA and dsDNA immobilized to the electrodes selectively and interacted with TAM for an hour. The difference between the time of the period resulted in the signal difference.

After the interaction, there was an increase in guanine oxidation peak currents 65% in dsDNA Fig-6A-c and ssDNA Fig-6B-c signal about 55% in the solution phase. Also, there was an increase in guanine oxidation peak currents about 60% in dsDNA Fig-7A-c and ssDNA Fig-7B-c signal about 82% in surface phase interaction. TAM does not interact with the adenine base even though it has made signal changes with guanine.

As a result, the signals of dsDNA and ssDNA in the surface and solution phase gave parallel results. In the surface phase, procedure DNA materials selectively immobilized to the electrode surface and then rinsed with buffer solution to remove unbound materials in all the stages. In the solution phase, there is only one stage to remove unbound materials.

The interaction of TAM with dsDNA might be attributed to its intercalation into the base stacking domain of DNA double helix. The interaction of TAM with ssDNA indicated that the backbone of ssDNA is negatively charged phosphate on the exterior and can easily attract to the investigated cationic TAM via electrostatic attraction.

As a result, the interaction of the TAM molecule with both ssDNA and dsDNA was determined by the newly developed biosensor.

#### **4. CONCLUSIONS**

Tamoxifen, an anticancer drug, has been developed by using voltammetric techniques and new and sensitive methods can be used to quantify this drug. Besides, CV and DPV techniques were used to elucidate the mechanism of interaction of the molecule with the double stranded DNA (dsDNA) and single strand DNA (ssDNA).

Electrochemical reactions of TAM were investigated using a pencil graphite electrode. Measurements at various pH values show that TAM has adsorption controlled process. The peak of TAM was recorded using the DPV technique using PGE. To understand the adsorption controlled properties of the current type, various buffer solutions were tested and B-R Buffer pH=4.50 was found to be the most suitable buffer solution. The equations between log  $i_p$  and log  $v$  are examined. Scan rate values of 10-60mV/s at 5ppm concentration at pH=4.50 B-R

buffer were examined and it was concluded that TAM active ingredient was adsorption controlled.

Oxidation signals of the active ingredient in the range of +0.6/+1.5 V were obtained by depositing the active ingredient TAM by AdsDPV technique for 60 sec at +0.75 V. Linearity was obtained in the pencil graphite electrode in the concentration range of 2.50-70 $\mu$ M. The obtained validation parameters are given in Table1.

The interaction mechanism of the TAM was evaluated by using PGEs transducers with the DPV method. Reference articles and results show that TAM and DNA interact electrostatically and/or intercalatively (Synder and Brown, 2002). The findings of these studies suggest that the TAM does not interact with the adenine base even though it has make signal changes with guanine.

TAM tablet was obtained from a local commercial source and prepared in the same amount as the active ingredient. The tablet solution was taken and analyzed directly after preparation. Recovery studies were carried out by adding a known amount of pure active ingredient to a known amount of the analyzed solution. As a result, the % recovery value indicates that tablet TAM additives do not significantly affect our results. Interaction studies with DNA materials were performed and the behavior of tamoxifen active ingredient was investigated electrochemically on PGE. The interaction path in the solution phase and then the interaction path on the electrode surface are examined respectively. The interaction between the active ingredient and DNA materials was evaluated by using guanine oxidation peak current. The intra-day and inter-day reproducibility of guanine signals was 0.98% and 1.58% respectively.

In this article, the interaction of tamoxifen with dsDNA/ssDNA was investigated by voltammetric studies. The study of the interaction between the anticancer drug Tamoxifen and dsDNA/ssDNA is crucial to identify possible DNA damage during treatment. The research will also be valuable in the design of the molecule-specific electrochemical biosensor to be applied in diagnostic tests and the development of drugs for cancer treatment patients. A simple, fast and precise DPV method is recommended for the determination of Tamoxifen in pharmaceutical formulations. In conclusion, these studies in a new biosensor may play an important role in the development of unknown drug-DNA interaction mechanisms.

#### **ACKNOWLEDGEMENTS**

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