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Research Article

ELECTROCHEMICAL DETERMINATION OF THE INTERACTION BETWEEN ANTICANCER DRUG CAPECITABINE AND DNA BY CARBON PASTE ELECTRODE

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ABSTRACT

In this study, the interaction of an anticancer drug, Capecitabine with DNA was investigated by electrochemical methods using carbon paste electrode (CPE). The interaction of Capecitabine with single-stranded Calf thymus DNA (ss DNA) and double-stranded Calf thymus DNA (ds DNA) at electrode surface, or in solution phase was investigated by monitoring the changes at the oxidation signal of guanin base of DNA measured by differential pulse voltammetry (DPV) technique. Impedimetric measurements were performed by electrochemical impedance spectroscopy technique that also confirmed that ds DNA was immobilized onto the electrode surface. The detection limit (DL) in the case of interaction of Capecitabine with dsDNA and ssDNA interaction was calculated and found to be 17.35µg/mL and 17.12µg/mL, respectively.

Keywords: *DNA Biosensors, Capecitabine, CPE*

INTRODUCTION

Biosensors are obtained by incorporating biological substances such as enzymes, cells, tissues, antibodies, nucleic acids into the structure of an electrochemical sensor (Özsöz., et al 2002; Wang, 2002). DNA biosensors are biosensors in which DNA is used as the biological material that recognizes it by interacting with the substance to be analyzed (Wang, 1997; Erdem, 2007) . DNA biosensors are used to elucidate the effects of certain DNA - targeted drugs or substances on DNA and to determine the interaction mechanisms of these substances (Wang, 1997; Nawaz, et al., 2006). Drug interaction with nucleic acids is one of the most important factors in the design of drugs and the development of related processes (Erdem, 2002). Many different techniques are used to examine drug - DNA interaction, which have several advantages and disadvantages. Therefore, the demand for new techniques for drug design and process development based on drug-DNA interaction is increasing (Özsöz, et al., 2002; Nawaz, et al., 2006).

Electrochemical DNA biosensors consist of a nucleic acid recognition layer immobilized to the electrochemical transducer (Rauf, et al., 2005; Erdem and Özsöz, 2001). The nucleic acid recognition layer detects changes in DNA structure or the specific sequence of DNA during the interaction of the binding molecules with DNA. DNA - drug interaction mechanism can be explained using the difference between pre - and post - interaction measured signals (Erdem and Özsöz., 2001). This interaction is also used to determine the quantity of the drugs analyzed or to design new drugs (Rauf, et al., 2005). During the design of many newly synthesized substances, drugs and especially DNA - targeted carcinogenic drugs, rapid and effective clarification of the interaction of these substances with DNA will enable these studies to progress more rapidly for their purposes. DNA - drug interactions can be detected successfully using DNA biosensors. This detection can be achieved by the guanine/adenine signal, which is the electroactive bases of the DNA, or by the electrochemical signal of the drug to be analyzed. DNA - drug interactions can be interpreted according to the changes in these signals (Wang, et al., 1998). Biosensors containing the nucleic acid (DNA) recognition surface are used for purposes such as elucidating or quantifying the interaction mechanism of the substance to be analyzed (carcinogenic substances, drugs, etc.) that interact with this surface, or monitoring hybridization events in certain regions of the base sequence in DNA (Wang, et al., 1998). Interaction of DNA with certain drug molecules (especially interaction with drug molecules with anticancer properties) and determination of this interaction with new methods developed is highly important for new product designs. The rapid detection of by - products that may occur in DNA after the interaction of a chemical substance or metabolite with DNA is very important for cancer research (Mikkelsen, 1996). There are many publications in the literature on DNA – drug interaction. In one of them, in the study of anticancer herbal medicine emodin with differential pulse voltammetry technique and using alternating voltammetry technique (L. Wang et al., 2006). found that emodine intercalated into DNA double helix structure and interacted with DNA. In another study; according to the study of (H. Nawaz et al, 2006) with ciprofloxacin having antibacterial effect of quinoline derivative, it showed that ciprofloxacin binds to DNA electrostatically and by intercalation (Niu, et al., 2008).

Many antitumor drugs show their effect by binding to DNA (Wang, et al., 2006, Richardson and Springfield., 1981). This information provides an opportunity to examine whether many compounds have potential to be used as anticancer drugs. In similar studies based on drug - DNA interaction, electrochemical studies (Marin, et al., 1998) have shown that drugs that interact with DNA cause a decrease or increase in the electrochemical response (Wang, et al., 1996; Yan, et al., 2001). Changes in the signals of electroactive bases in DNA or changes in the electrochemical signal of the substance to be analyzed provide reliable interactions between the analyte and DNA. In this study, the interaction and electrochemical behavior of

the anticancer drug, capecitabine, with single - use CPE modified or unmodified by DNA were investigated. DNA – drug interactions can be classified in two ways as interaction in solution phase and interaction on the electrode surface (İnteraction on the DNA modified electrode surface, interaction on the surface of the drug modified electrode). In this study, the interactions in solution phase and DNA modified electrode surface will be examined. The amount of capecitabine will be calculated based on reductions in the signal of the electroactive guanine base of DNA. In addition, when the capecitabine concentration is changed, parameters such as the response of the guanine signal, duration of interactions, and reproducibility will be examined. Although there have been many studies on anticancer drugs in the literature, no studies have examined the capecitabine - DNA interaction with CPE. In this respect, our study will eliminate an important deficiency in the literature (Palecek, 1996).

MATERIALS and METHODS

Devices Used

Scales (Precisa XB 220A), Sound vibrating cleaner (Bandelin Sonorex), pH - meter (WTW series), Magnetic stirrer (AGE velp), Vortex (Velp scientifics), Potentiostat (AUTOLAB 302, GPRES 4.9 software, Eco Chemie), Ag/AgCl reference electrode, Platinum wire (used as auxiliary electrode).

Chemicals Used

Capecitabine (CPT) (Sigma), Acetic acid (99-100%) (Sigma-Aldrich), Hydrochloric acid (37%) (Sigma-Aldrich), Sodium Hydroxide (Sigma), Tris (hydroxymethyl) aminomethane hydrochloride (Sigma), Sodium chloride (Sigma), EDTA disodium salt (Sigma), *Calf thymus* ds-DNA (Sigma), *Calf thymus* ss-DNA (Sigma), 18 mega-ohm ultra-pure water was used in all studies. Experimental studies were performed at room temperature (25.0 ± 0.5 ° C).

Preparation of the solutions used

Preparation of buffer solutions:

Preparation of 0.05 M phosphate buffer solution (pH 7.4; PBS): The 0.05 M phosphate buffer solution used during the measurements contained 1.36g (0.01 mol) KH_2PO_4, 6.96 g (0.04 mol) KH_2PO_4 and 1.168 g NaCl (0.02 mol) per liter.

Preparation of 0.50 M acetate buffer solution (pH 4.81; ABS): The 0.5 M acetate buffer solution contains about 29 mL of concentrated acetic acid per L and 1.168 g NaCl. The pH of the buffer solution was adjusted to 4.81 with 0.1 M NaOH solution.

Preparation of 0.01 M Tris-HCl, 1 mM EDTA buffer solution (pH 8.0;Tris-EDTA): The 0.01 M Tris-HCl, 1 mM EDTA buffer solution used contains 1.576 g Tris HCl and 0.372 g EDTA per liter. The pH of the solution was adjusted to 8.0 by adding 0.1 N NaOH and/or 0.1 N HCl measured with the pH meter.

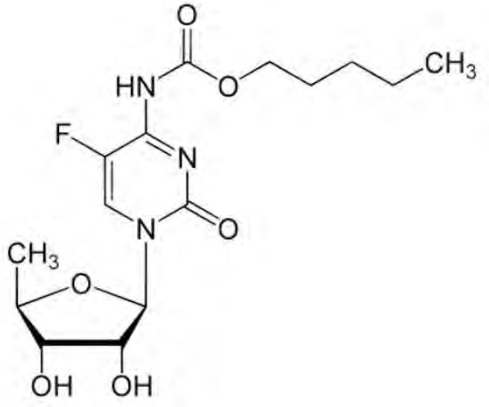
Preparation of the Capecitabine solution: The stock solutions of the purchased 100% pure Capecitabine with ABS buffer were prepared and stored at 4˚C by placing them in eppendorf tubes in volumes of 50µL for later use.

Preparation of DNA solutions: DNA from *Calf thymus* gland (= *Calf thymus* DNA); double-stranded DNA (ds DNA) stock solutions; 1000µg/mL was prepared with TE solution (10 mM Tris-HCl, 1 mM EDTA, pH 8.0) and stored below zero [21]. The Ct - ds DNA dilute solution was prepared with 0.5M Acetate buffer (pH 4.8). To minimize the exposure of the solution to light, it was stored in the refrigerator at -20˚C in a non-light box. The single stranded DNA (ss DNA) solution was also prepared as described above for ct - ds DNA and was stored

in the refrigerator at -20°C. The single-stranded DNA (ss DNA) solution was also prepared as described above for ct - ds DNA and stored in the refrigerator at -20 °C.

General information about Capecitabine (CPT)

Figure 1: Structural formula of Capecitabine ($C_{15}H_{22}FN_3O_6$).



Pharmacological Properties: Capecitabine is a cancer (chemotherapeutic) drug. It prevents the prolifereation of cancer cells. Slows down their development. And slows down their spread in the body. Capecitabine is a non-cytotoxic fluoropyrimidine carbamate that acts as an orally administered prodrug of the cytotoxic 5-fluorouracil (5-FU). Capecitabine is activated through several enzymatic steps. In the last step, thymidine phosphorylase (ThyPase), an enzyme involved in its conversion to 5-FU, is found in tumor tissues; this enzyme is also found in normal tissues but is usually at lower levels. In human cancer xenograft models, capecitabine showed a synergistic effect in combination with docetaxel; this effect may be due to the increase in thymidine phosphorylase functions by docetaxel. There is evidence that the metabolism of 5- FU in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidilic acid, thereby inhibiting deoxyribonucleic acid (DNA) synthesis. 5-FU formation also results in inhibition of RNA and protein synthesis. Since DNA and RNA are essential for cell division and growth, the effect of 5-FU may be to produce a thymidine insufficiency that causes cell unstable growth and death. The effects of blocking DNA and RNA synthesis are evident on cells that proliferate and metabolize 5-FU faster. Studies have supported the use of Xeloda as a first-line treatment for metastatic colorectal cancer. Data from a multicentered, randomized, controlled phase III trial support the use of Xeloda in combination with docetaxel after the failure of anthracycline-containing cytotoxic chemotherapy to treat patients with locally advanced or metastatic breast cancer. In addition, data from multicentered two-phase II studies support the use of Xeloda monotherapy for the treatment of patients after failure of the taxanes and anthracycline-containing chemotherapy regimen, or for whom further anthracycline treatment is not indicated (Karadeniz, et al., 2007).

Method Used

For the steps regarding the activation of the electrodes used and attachment of ct - ds DNA and ct - ss DNA to the electrode surface, interaction of DNA material with the material examined on the electrode surface, the path reported in the current literature (Erdem, et al., 1999; Kuralay, et al., 2009; Wang, et al., 2001) was followed. The electrode was renewed each time and repeated 5 times in succession and current values were measured.

Preparation of electrodes used

In this study, using the differential pulse voltammetry technique, μ-AUTOLAB III (Eco Chemie, Netherlands) was used as the potentiostat device and GPES 4,9 was used as the software program. As the triple electrode system, carbon paste electrode was used as working electrode, Ag/AgCl was used as reference electrode and platinum wire was used as counter electrode. Each electrode was connected to the system by metal connections and this triple electrode was adjusted to a volume of 6 mL of the measuring solution into which the system was immersed.

Carbon Paste Electrode (CPE) Preparation: The working electrode is made of 3 mm diameter glass tube and contains carbon paste inside, and electrical conductivity is provided by copper wire. The carbon paste was prepared by homogeneous mixing of graphite powder and mineral oil at a ratio of 70: 30. After the electrode (CPE) was prepared, the electrode surface was turned into a homogeneous surface with parchment paper (Wang, 1997; Erdem and Özsöz, 2001; Wang, et al., 1996).

Electrochemical Impedance Spectroscopy (EIS) Measurements: After the DNA (ct - ds DNA and ct – ss DNA) immobilization optimization and DNA - CPT interaction optimization for the working electrode, necessary solutions were prepared and measurements were taken for EIS experiments. Solutions were prepared containing 164.5mg $K_3Fe(CN)_6$ (molecular mass: 329.243 g) and 208.13 mg $K_4Fe(CN)_6.3H_2O$ (molecular mass: 422,38 g) redox probes in which measurement would be made with different pH values. To the prepared redox solution probe [Fe $(CN)_6^{3-/4-}$1.49 g of KCl was added (for 200 mL) to keep the ionic strength constant. The redox pair probe was adjusted in this way in all experiments. In electrochemical impedance spectroscopy experiments, Ag/AgCl was used as reference electrode and Pt wire as auxiliary electrode. Using the Frequency Analyzer (FRA) software, the impedance of the solutions was obtained by electrochemical impedance spectroscopy technique. The impedance measurements were fixed at a wave height of 10 mV in the prepared redox solution so that the system properties were kept in equilibrium. In order to obtain Nyquist curves, the applied frequency was adjusted between 0.1 Hz and 100 kHz. As with all previous studies, the surface of the electrodes was refreshed each time, repeated 5 times in succession, and the surface resistance of the electrode was measured.

RESULTS AND DISCUSSION

DNA Immobilization on Activated CPE elektrod

Passive adsorption was selected for CPE as the immobilization technique. Separate experiments were performed for ct - ds DNA and ct - ss DNA with activated carbon paste electrodes. Firstly, the optimal time of immobilization (**Figure 2**) and then the optimal DNA concentration for that time were optimized (**Figure 3**) by keeping the concentrations of DNA to be immobilized constant. Guanine peak current values obtained from DPV measurements were used to optimize both time and DNA concentration. To do this, the triple electrode system was immersed into the electrochemical cell and then voltammetric measurement was performed. The oxidation signals of guanine were measured in ABS (pH 4.8) by DPV (Differential Pulse Voltammetry) technique with a scanning speed of 50 mV/s and pulse amplitude of 50 mV between 0.2 V and 1.4 V.

Figure 2: Voltamograms (A) and histograms (B) showing guanine signals measured by DPV technique after interaction of ct - ds DNAs immobilized on CPE surface at different times: (a) 1 (b) 3 (c) 5 (d) 7 (e) 9 (f) 11 min

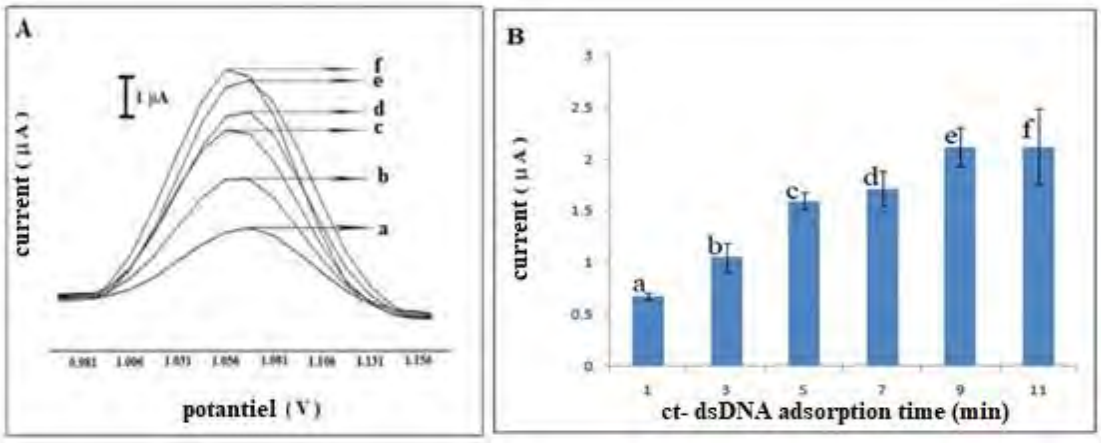
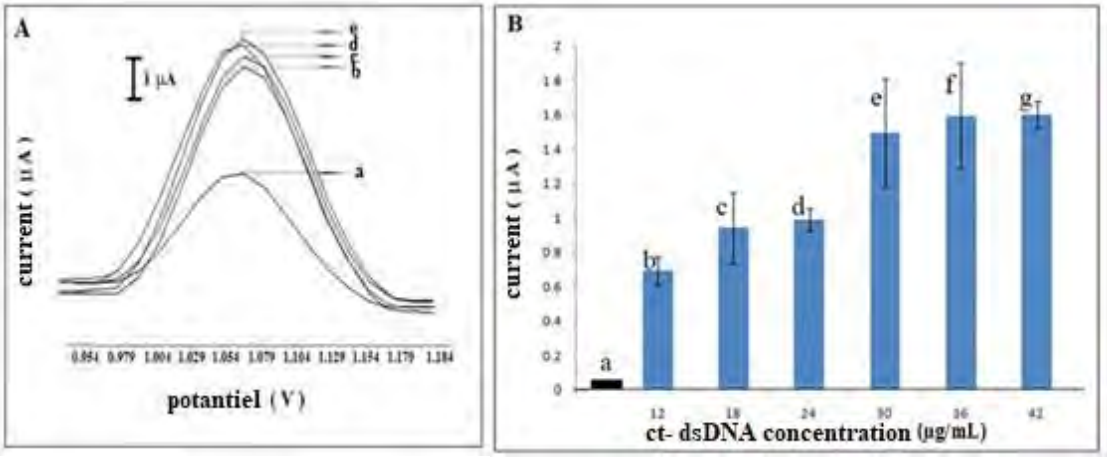


Figure 3: In the absence of (a) ct - ds DNA immobilized on the CPE surface, voltamograms (A) and histograms (B) showing guanine signals measured by DPV technique of ct - ds DNA at different concentrations: (b) 12, (c) 18, (d) 24, (e) 30, (f) 36, (g) 42 µg/mL



Time and concentration optimization in DNA immobilization was performed separately for both ct - ds DNA and ct - ss DNA. As shown in **Figure 2** and **Figure 3**, while the optimum interaction time for ct - ds DNA was found to be 9 minutes most favorable for reproducibility and 42µg/mL for ct - ds DNA concentration, this time was determined as 9 minutes for ct - ss DNA and 36 µg/mL for ct ss-DNA (not shown).

Optimization studies of CPT (Capecitabine) interaction with immobilized DNA (ct-dsDNA and ct- ssDNA) on CPE surface

Ct - ds DNA and ct - ss DNA immobilized CPEs were incubated at 110 ’µL of solutions containing Capecitabine at various concentrations for various periods of time, and the optimal time for DNA-drug interaction (**Figure 4**) and then the optimal drug concentration for this time (Figure 5) was determined. Reductions in guanine peak currents after DNA - drug interaction were utilized in the optimization processes. The oxidation signals of guanine were measured in ABS (pH 4.8) by DPV technique with a scanning speed of 50 mV/s and pulse amplitude of 50 mV between 0.2 V and 1.4 V.

Figure 4: Response effect of CPT immobilization time: Voltamogram (A) and histogram (B) showing guanine signals measured by DPV technique by immersing at different times: (a) without CPT , with ct - ds DNA, (b) 1, (c) 2, (d) 3, (e) 4 ,(f) 5 min interacting whit ct - ds DNA immobilized CPEs in CPT solution

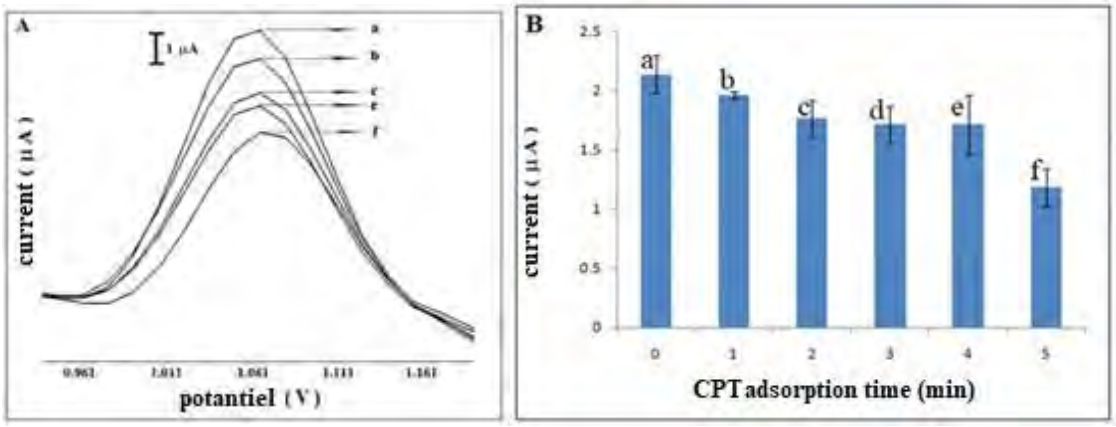
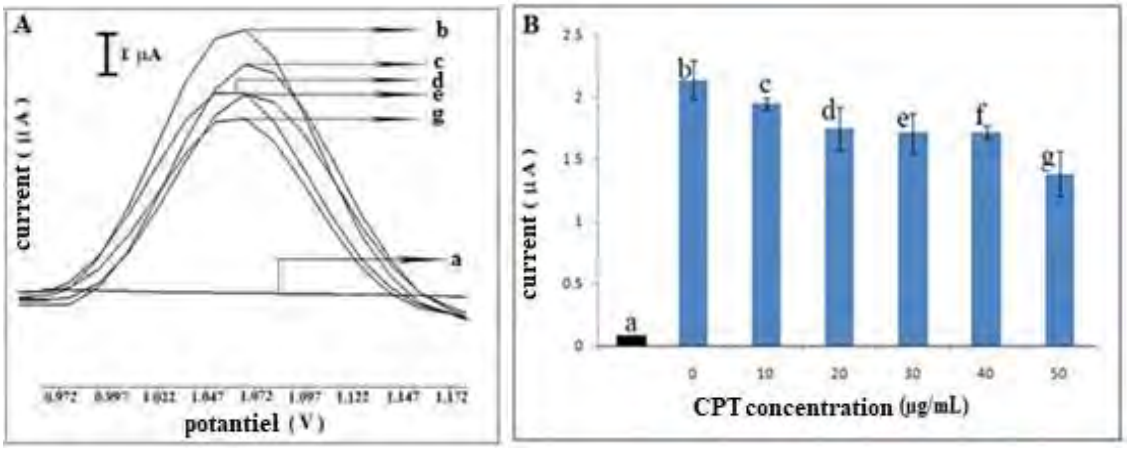


Figure 5: Response effect of CPT concentration: Voltamogram (A) and histogram (B) showing guanine signals measured by DPV technique by immersing in CPT solutions of different concentrations such as ct - ds DNA immobilized CPE's (a) without ct - ds DNA (b) without CPT, with ct - ds DNA (c) 10 (d) 20 (e) 30 (f) 40 (g) 50 mg/ml.



Time and concentration optimization in DNA - CPT interaction was performed separately for both ct - ds DNA and ct - ss DNA. As shown in **Figure 4** and **Figure 5**, the optimal interaction time for ct - ds DNA with CPT was found to be optimal 3 minutes for reproducibility and the CPT concentration was 40 µg/mL, while this time was 3 minutes and the CPT concentration was 30 µg/mL for for ct - ss DNA-CPT interaction (not shown). Calibration curves for both ct - ds DNA - CPT and ct - ss DNA - CPT interactions using the data obtained are shown in **Figure 6** and **Figure 7**.

Figure 6: Calibration curve of CPT concentration change in CPT interaction with ct - ds DNA immobilized on CPE surface.

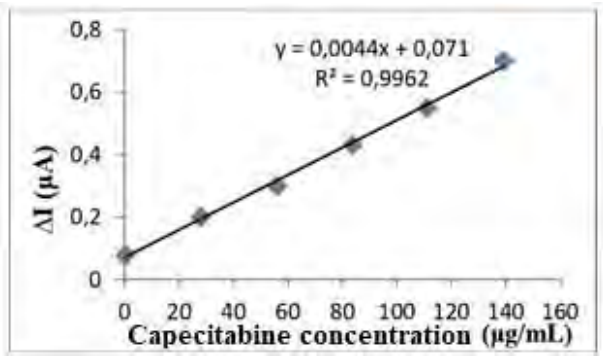
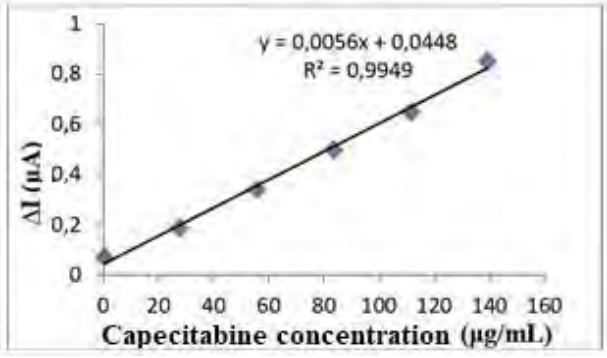


Figure 7: Calibration curve of CPT concentration change in CPT interaction with ct - ss DNA immobilized on CPE surface.

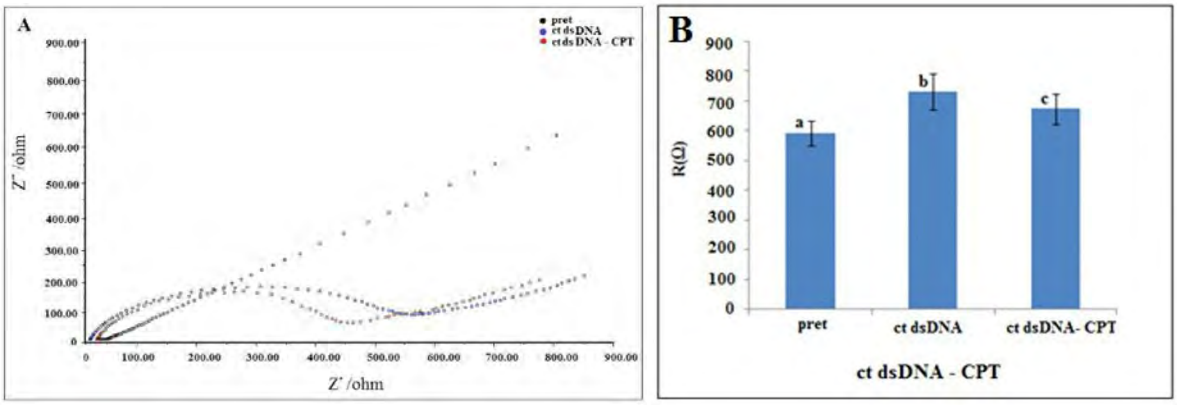


Determination limits were calculated according to the regression equation (y=0,044x + 0.071) of the calibration plot plotted for ct - ds DNA - CPT interaction with DL = yB + 3 sB correlation (yB: blind signal; sB: blind standard deviation; n = 4) and the regression equation (y=0.0056x + 0.0448) of the calibration plot plotted for ct - ss DNA - CPT interaction. The minimum detection limit for ct - ds DNA - CPT interaction was 17.35 μg/mL and the lowest detection limit for ct – ss DNA - CPT interaction was 17.12 mg/mL.

Results of Electrochemical Impedance (EIS) Tests

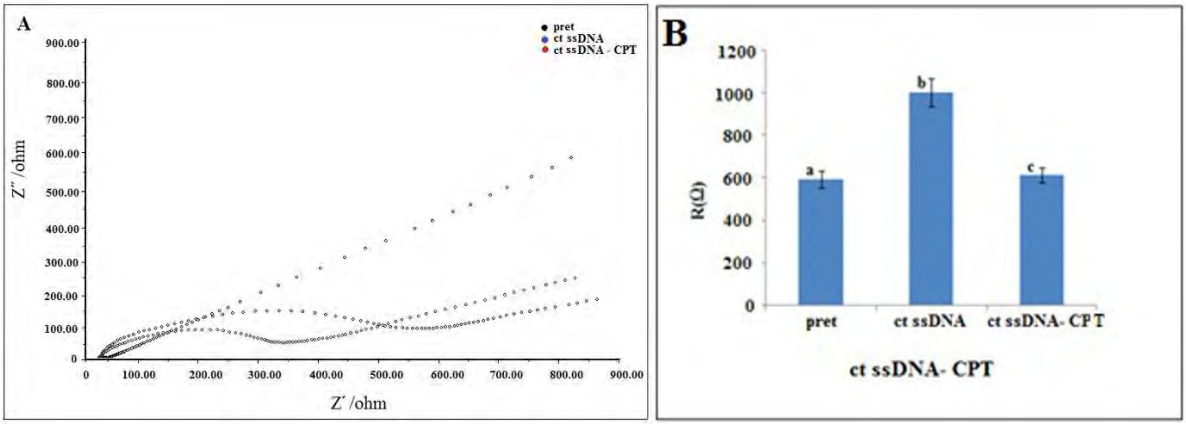
In this method, CPEs were activated by 1.4 V 60 seconds activation process applied in other studies. The only different step is the step where measurements are taken for EIS experiments using Frequency Analyzer (FRA) software instead of differential pulse voltammetry. After ct - ds DNA immobilization to the CPE surface at optimum conditions (42 μg / mL, 9 minutes), EIS experiments were performed in redox solution. Ct - ds DNA - CPE interaction on the surface of the CPE after immersion of ct - ds DNA immobilized on the surface of the CPE was again measured for its resistance to the transferred current in the redox solution and shown in **Figure 8** with the Nyquist curve generated from values close to the mean values.

Figure 8: (A) Niquist curve (B) Resistance of ct - ds DNA - CPT interaction to the transferred current load on the surface of the CPE; (a) resistance of activated CPEs, (b) resistance of ct - ds DNA immobilized CPEs, (c) resistance of ct - ds DNA - CPT interaction immobilized on CPE surface



After ct – ss DNA was immobilized to the CPE surface at optimum conditions (36 µg/mL, 9 minutes), all experiments on ct – ds DNA were repeated for ct – ss DNA. The resistance of the Ct - ss DNA - CPT interaction to the transferred current was measured and is shown in **Figure 9** with the Nyquist curve generated from values close to the mean values.

Figure 9: (A) Niquist curve **(B)** The resistance of the ct - ss DNA - CPT interaction to the transferred current load on the surface of the CPE; (a) resistance of activated CPEs, (b) resistance of ct - ss DNA immobilized CPEs, (c) Ct - ss DNA - CPT interaction immobilized on CPE surface



According to electrochemical impedance measurements in DNA immobilization or after DNA - CPT interactions, electrode surface differentiated and load transfer resistances increased.

CONCLUSION

In our study for sensor-based DNA analysis, activation of carbon paste electrodes (CPE), optimization for double stranded DNA (ct – ds DNA) and single stranded DNA (ct – ss DNA) analysis and its interaction with capecitabine (CPT), an anticancer drug, were investigated with electrochemical methods. In this study, where carbon paste electrodes were used as working electrodes, electrochemical behavior was investigated by differential pulse voltammetry (DPV) technique. Electrochemical determination of DNA immobilized on the

CPE surface was performed by measuring the oxidation signal of guanine, the electroactive base of DNA by DPV technique. Moreover, the effect of CPT concentration, change in DNA concentration and surface activation on the response was investigated and highly good results were obtained in terms of reproducibility and sensitivity. Before examining the interaction of anti-cancer drug CPT with DNA, electrochemical behavior of the drug in the studied potential range was examined and no electroactive species was observed in this range. After the interaction of CPT with DNA, it was observed that the oxidation signal of the guanine base, an electroactive group of DNA, decreased due to increased drug concentration in DNA - drug interaction. This reduction in guanine signals is a result of the interaction of CPT with double - stranded DNA, in alignment with the results of similar studies in the literature (Nawaz, et al., 2006), and may be explained by the fact that groups suitable for oxidation in the structure of this molecule are partly present for the redox reaction after interaction.

For immobilization of ct – ds DNA and ct – ss DNA on CPT surface, the optimized interaction time was 9 minutes for ct – ds DNA and 9 minutes for ct – ss DNA, the optimized amount of interaction was found to be 42 µg/mL for ct – ds DNA and 36 µg/mL for ct – ss DNA. In the examination of CPT - DNA interaction with DNA immobilized CPTs, the optimized interaction time was 3 minutes for ct – ds DNA and ct – ss DNA, the optimized amount of interaction was found to be 40 µg/mL for ct – ds DNA and 30 µg/mL for ct – ss DNA. In the examination of pH effect on CPE surface interactions, the pH of ct – ds DNA and ct – ss DNA was 4.8 and the guanine signal of ABS buffer was the highest.

For immobilization of ct – ds DNA to the activated CPE surface, after the optimum concentration of ct – ds DNA was determined as 42 µg/mL and the optimum interaction time was determined as 9 minutes and ct – ds DNA - CPT interaction at the activated CPE surface was determined to have an optimal CPT concentration of 40 µg/mL and an optimum interaction time of 3 minutes, EIS measurements were taken for activated CPE, ct ds-DNA immobilized CPE and CPE after ct ds-DNA - CPE interaction. After ct – ds DNA immobilization, an increase in the resistance of the CPE surface compared to the previous state was observed and a decrease in the resistance after ct–ds DNA - CPT interaction was observed. As is known, the resistance and conductivity are inversely proportional, that is to say, the higher the resistance, the lower the conductivity. When the histogram is examined with this in mind, we can say that the activated CPE conductivity is higher than the CPE after ct – dsDNA immobilized CPE and ct – dsDNA - CPT interaction. In the immobilization of ct–ssDNA to the activated CPE surface, the optimum concentration of ct – ss DNA was determined as 36 µg/mL and the optimum interaction time was determined as 9 minutes. And after ct – ss DNA - CPT interaction at the activated CPE surface was determined as 30 µg/mL of optimum CPT concentration and 3 minutes of optimum interaction time, EIS measurements were taken for activated CPE, ct – ss DNA immobilized CPE and CPE after ct – ssDNA - CPT interaction. After ct – ssDNA immobilization, it was observed that there was an increase in the resistance of the CPE surface compared to the previous state and a decrease in the resistance after ct – ss DNA - CPT interaction. Activated CPE conductivity was found to be higher than the CPE after ct – ss DNA immobilized CPE and ct – ss DNA - CPT interaction.

As a result, it is seen that electrochemical sensors developed using designed DNA biosensors can provide more sensitive, reliable and selective results in the determination of drug - DNA interactions. It is important to investigate whether Capecitabine, a commonly used anticancer drug, has an interaction with DNA and to develop an inexpensive and inexpensive electrochemical method for the determination of such drugs in biological samples.

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