

# Fullerene modified single-use electrodes as a convenient biosensor platform for electrochemical monitoring of drug-DNA interaction

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Received: 08 February 2022 / Revised: 09 May 2022 / Accepted: 12 May 2022

**ABSTRACT:** Fullerene enriched disposable electrodes were developed and used as a biosensor platform for electrochemical monitoring of drug-DNA interaction. The surface of pencil graphite electrode (PGE) was modified with fullerene in order to enhance electrode surface for efficient dsDNA immobilization. The surface of fullerene modified PGEs (f-PGEs) was characterized using scanning electron microscopy (SEM), and electrochemical impedance spectroscopy (EIS). The behavior of dsDNA layer onto f-PGE surface was investigated by EIS measurements in  $\text{Fe}(\text{CN})_6^{4-/3-}$  redox system. After optimization of several experimental parameters, the suitability of the constructed electrodes as a sensor platform for monitoring of drug-DNA interaction has been examined. The reproducibility of the biosensor was also tested in the presence of dsDNA immobilization. Consequently, the developed fullerene based biosensor offers suitable platform for the electrochemical analysis of drug-DNA interaction sensitively.

**KEYWORDS:** Fullerene; pencil graphite electrodes; electrochemical biosensor; electrochemical impedance spectroscopy; drug-DNA interaction.

## 1. INTRODUCTION

Fullerene is a unique carbon structure that brings a new level to nanomaterial applications. This nanostructure has unique physical and chemical properties and readily available with high purity [1,2]. Researchers have been investigating the prospect to use this third allotrope of carbon, which has many conjugated electrons, as a mediator in the design of various sensors. Fullerene-modified electrodes have been shown to be an excellent working electrode with great properties such as a large electroactive surface area, strong electrical conductivity, and biocompatibility [3-5]. The enormous surface area of the fullerene nanomaterial, which is due to its spherical shape, is highly desired characteristic in biosensors and sensor systems [6-12]. Due to the ability of lowering the potential of electro-reduction of redox substrates and increasing the reaction rates, fullerenes have been used to improve the sensitivity, selectivity, and reproducibility of electrochemical biosensors [13,14]. Thus, fullerenes have attracted great interest in recent years in the design of novel biosensing systems. For instance, Hernandez *et al.* [15] developed a low-cost electrochemical methodology for the quantification of ciprofloxacin in beef samples with nafion and fullerene modified carbon paste electrode (N-F/CPE) by cyclic voltammetry (CV) and differential pulse voltammetry (DPV) techniques. The analytical performance of the proposed methodology was resulted in LOD of 1.0  $\mu\text{M}$ , a LOQ of 3.0  $\mu\text{M}$  and repeatability of 5.38 %. Materon *et al.* [16] reported fullerene ( $\text{C}_{60}$ ), reduced graphene oxide (rGO) and Nafion (NF) ( $\text{C}_{60}$ -rGO-NF/SPE) modified screen printed electrodes to determine the antibiotic metronidazole (MTZ). Under optimized conditions, the  $\text{C}_{60}$ -rGO-NF/SPE sensor exhibited a linear response in square wave voltammetry for MTZ concentrations from  $2.5 \times 10^{-7}$  to  $34 \times 10^{-6}$  M, with a detection limit of  $2.1 \times 10^{-7}$  M. The developed sensor also applied to determine MTZ in serum and urine samples [16]. Kong *et al.* [17] developed an electrochemical sensor which was based on the delaminated titanium carbide nanosheet ( $\text{d-Ti}_3\text{C}_2\text{T}_x$ ) and fullerene composite modified glassy carbon electrode ( $\text{d-Ti}_3\text{C}_2\text{T}_x/\text{C}_{60}/\text{GCE}$ ). The prepared electrode showed electrocatalytic activity for the oxidation of baicalein which has a variety of

Eksin E, Erdem A. Fullerene modified single-use electrodes as a convenient biosensor platform for electrochemical monitoring of drug-DNA interaction. J Res Pharm. 2022; 26(4): 997-1006

beneficial pharmacological effects such as anti-inflammatory, antioxidant, anti-microbial, etc. The detection of baicalein showed a linear range of 0.015-4.0  $\mu\text{M}$  with a detection limit of 0.005  $\mu\text{M}$  [17]. For the selective determination of phenolic compounds, namely, catechol and hydroquinone, an electrochemical sensor that is based on platinum nanoparticles (Pt NPs) and fullerene composite was constructed by modifying Pt/fullerene composite on the surface of a pyrolytic graphite electrode by Zhu *et al.* [18]. The sensor exhibited high electrocatalytic activities and large peak-to-peak separation toward the oxidation of catechol and hydroquinone by DPV, as well as a wide linear concentration range, high sensitivity, and low limit of determination.

Understanding how drug molecules interact with DNA has become a hot topic of research in the fields of chemistry, molecular biology, and medicine. It is also an important aspect of pharmacology, as it aids in the understanding of drug action processes and the development of more efficient and specifically targeted drugs with fewer side effects [19]. Such interactions are studied using a variety of spectroscopic techniques, such as, UV-Visible, Infrared (IR), Raman spectroscopies or atomic force microscopy (AFM), electrophoresis, mass spectrometry etc. [20]. However, these techniques take time and require expensive instrumentation and long sample preparation times. Electrochemical methods have been proven to be a facile and convenient technique for the sensitive identification of biologically essential organic compounds that undergo oxidation and reduction reactions, such as drugs and related substances in pharmaceuticals and body fluids. Electroanalytical techniques are extremely useful in the field of drug analysis because of their low cost, fast analysis time, and excellent sensitivity and specificity. Impedimetric biosensors have been utilized for detection a number of biomolecules. In this regard, Katz and Willner [21] recently published a study of impedance spectroscopy for exploring biomolecular interactions at conductive and semi-conductive surfaces, as well as immunosensors, nucleic acid sensors, and enzyme based biosensors.

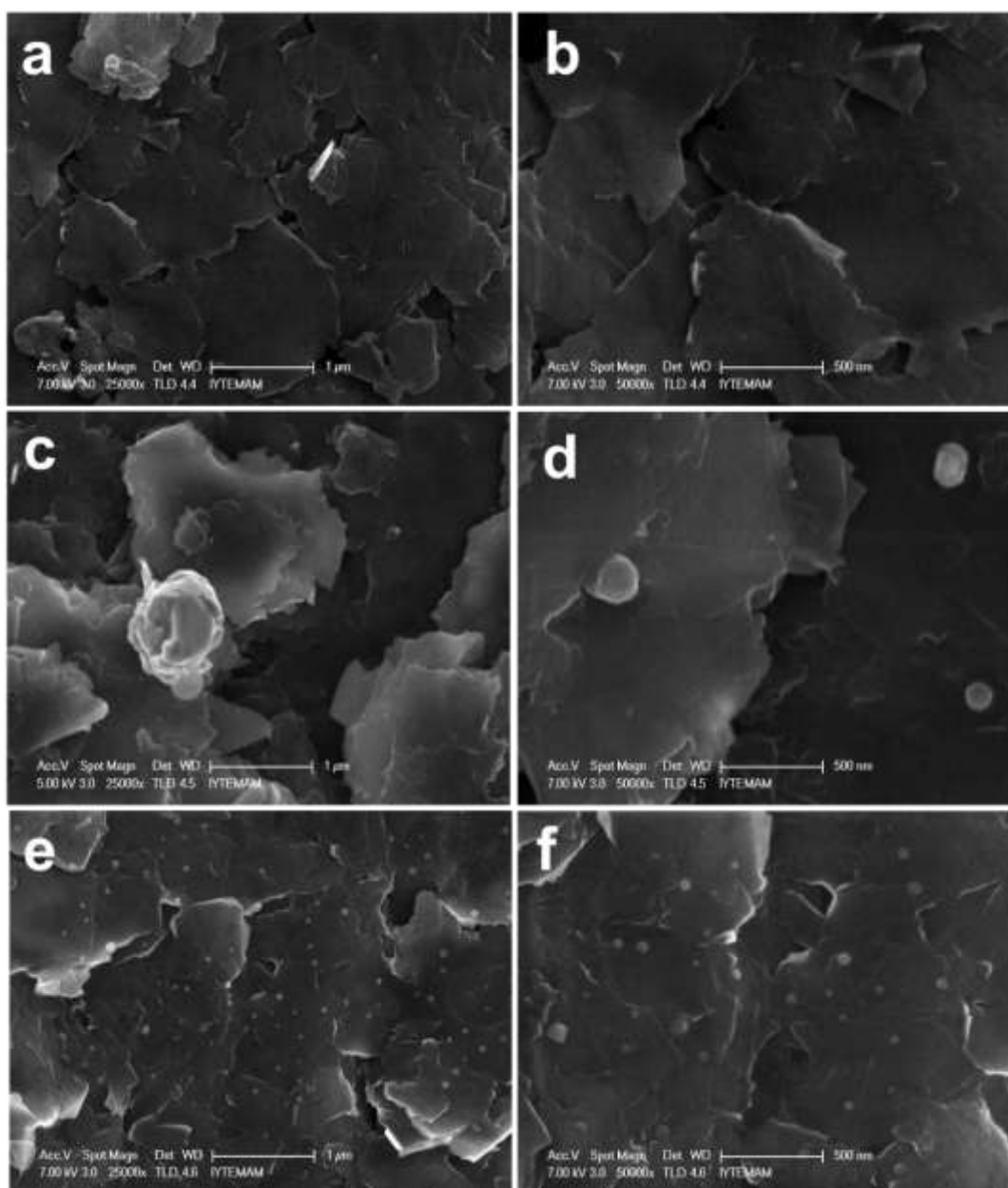
The objective of the current work is to develop a sensitive and convenient nucleic acid biosensor for electrochemical monitoring of drug-DNA interaction. Within our knowledge, fullerene modified single-use graphite electrode was developed for the first time herein as a sensing platform and applied for electrochemical monitoring of drug-DNA interaction through the measurement of impedance. For this purpose, double stranded DNA was immobilized onto the surface of fullerene modified single-use pencil graphite electrodes (f-PGEs) to obtain nanomaterial-based biosensor. Then, drug-DNA interaction was monitored with f-PGE biosensor by measuring charge transfer resistance ( $R_{ct}$ ) value via electrochemical impedance spectroscopy (EIS). Lumazine was chosen as a model drug for this assay. Analytical performance including reproducibility of the biosensor was tested and discussed.

## 2. RESULTS and DISCUSSION

To develop an efficient electrochemical assay, selection of a proper electrode material is a crucial step. Thus, a variety of electrode types were used in conjunction with nanostructures for different sensing applications [1-18]. Due to their lower background currents, superior sensitivity, reproducibility, amendable electroactive surface area, cost effective and ease of disposability, pencil graphite electrode has gain considerable attention in recent years. Herein, the single-use pencil graphite electrode (PGE) surface was functionalized with fullerene which exhibited the superior improvement of the electrode properties compared with the bare pencil graphite electrode. The surface morphologies of bare PGE, f-PGE and dsDNA immobilized f-PGE were investigated by SEM. Figure 1 shows the topographies of each PGEs at different steps. As fullerenes can be clearly seen in Fig. 1-c,d,e,f, dsDNA molecules can also be distinguished as network structure at some parts of f-PGE in Fig. 1-e,f.

Since the concentration of fullerene is of great importance for the effectiveness of electrode surface modification, three different concentrations, 500, 700 and 900  $\mu\text{g/mL}$  were employed to test the optimal condition (Figure 2). The semicircle diameter ( $R_{ct}$ ) related to the electron-transfer-limited process was measured and evaluated. When fullerene was applied to PGE surface, a larger semicircle domain was observed, indicating a higher  $R_{ct}$  on the f-PGE. This was due to the fact that a thicker fullerene layer would increase the electron-transfer distance between the redox probe  $[\text{Fe}(\text{CN})_6]^{4-/3-}$  and the electrode, resulting in an increment at electron transfer resistances [22,23]. The  $R_{ct}$  values were recorded as  $78.5 \pm 10.6 \text{ Ohm}$  (RSD %, 13.5 %,  $n = 3$ ),  $146.5 \pm 16.2 \text{ Ohm}$  (RSD %, 11.1 %,  $n = 3$ ) and  $158 \pm 85.5 \text{ Ohm}$  (RSD %, 53.9 %,  $n = 3$ ), after modification of 500, 700 and 900  $\mu\text{g/mL}$  fullerene onto PGE, respectively. In the presence of 900  $\mu\text{g/mL}$  fullerene, the highest  $R_{ct}$  value was obtained (Figure 2d), nevertheless the relative standard deviation (RSD %) was too high (RSD %, 53.9 %), which makes these results statistically insecure. This may indicate that the

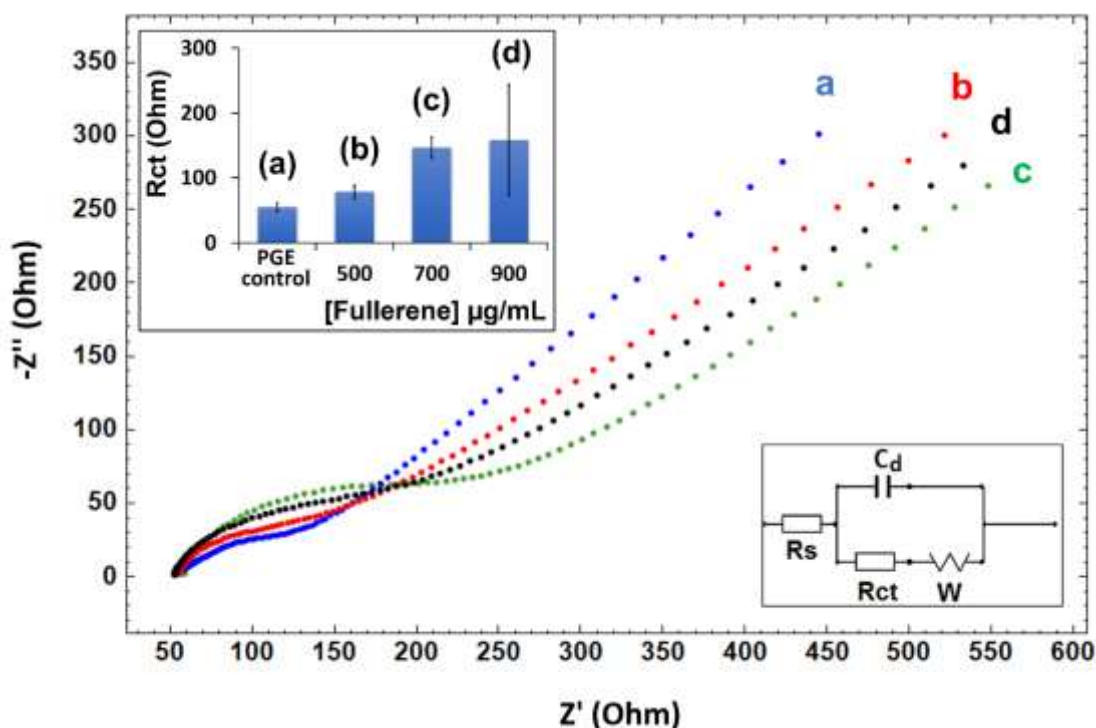
modification efficiency is low due to the presence of high amount (900  $\mu\text{g/mL}$ ) of fullerene on the surface. Since the most reproducible  $R_{ct}$  value was obtained with 700  $\mu\text{g/mL}$  fullerene (Figure 2c), it was chosen as optimum concentration for effective surface modification.



**Figure 1.** SEM images of PGE (a, b), f-PGE (c, d) and 50  $\mu\text{g/mL}$  dsDNA immobilized f-PGE (e, f) with resolutions of 1  $\mu\text{m}$  and 500 nm.

The Nyquist diagrams of bare PGE and f-PGE in the presence and absence of dsDNA immobilization are shown in Figure 3. The average  $R_{ct}$  value of PGE was measured as  $55.25 \pm 6.51$  Ohm (RSD %, 11.8 %,  $n=8$ ). After fullerene modification onto the PGE surface, 2.6-fold increase at the  $R_{ct}$  value was recorded and measured as  $146.50 \pm 16.27$  Ohm (RSD %, 11.1 %,  $n=8$ ). Due to the charge repulsion between negatively charged phosphate backbone of the DNA and  $[\text{Fe}(\text{CN})_6]^{3-/4-}$  the electron transfer ability was reduced at the electrode surface on the surface of dsDNA/f-PGE [24-29]. The  $R_{ct}$  was measured as  $3153 \pm 401.4$  Ohm (RSD %, 12.7 %,  $n=4$ ) after immobilization of dsDNA into the surface of f-PGE. Immobilization of dsDNA onto the surface of f-PGE resulted in a 21.5-fold increase in  $R_{ct}$  value, whereas immobilization of dsDNA onto the surface of bare PGE (dsDNA/PGE) resulted in a 14.9-fold increase. According to the method described by

Janeček *et al.* [30], the apparent fractional coverage values ( $\theta_R^{IS}$ ) were calculated for dsDNA/PGE and dsDNA/f-PGE as 0.934 and 0.954, respectively. The  $\theta_R^{IS}$  values were more than 0.9, indicating that the modification of fullerene was performed successfully. In comparison to PGE, the higher  $\theta_R^{IS}$  value with f-PGE demonstrated that more coverage was acquired at the surface of f-PGE.



**Figure 2.** Nyquist diagrams of (a) bare PGE (in the absence of fullerene), (b) 500  $\mu\text{g/mL}$ , (c) 700  $\mu\text{g/mL}$ , (d) 900  $\mu\text{g/mL}$  fullerene modified PGE. Histograms representing the average  $R_{ct}$  values ( $n=3$ ) recorded by (a) base PGE, (b) 500  $\mu\text{g/mL}$ , (c) 700  $\mu\text{g/mL}$ , (d) 900  $\mu\text{g/mL}$  fullerene modified PGE.

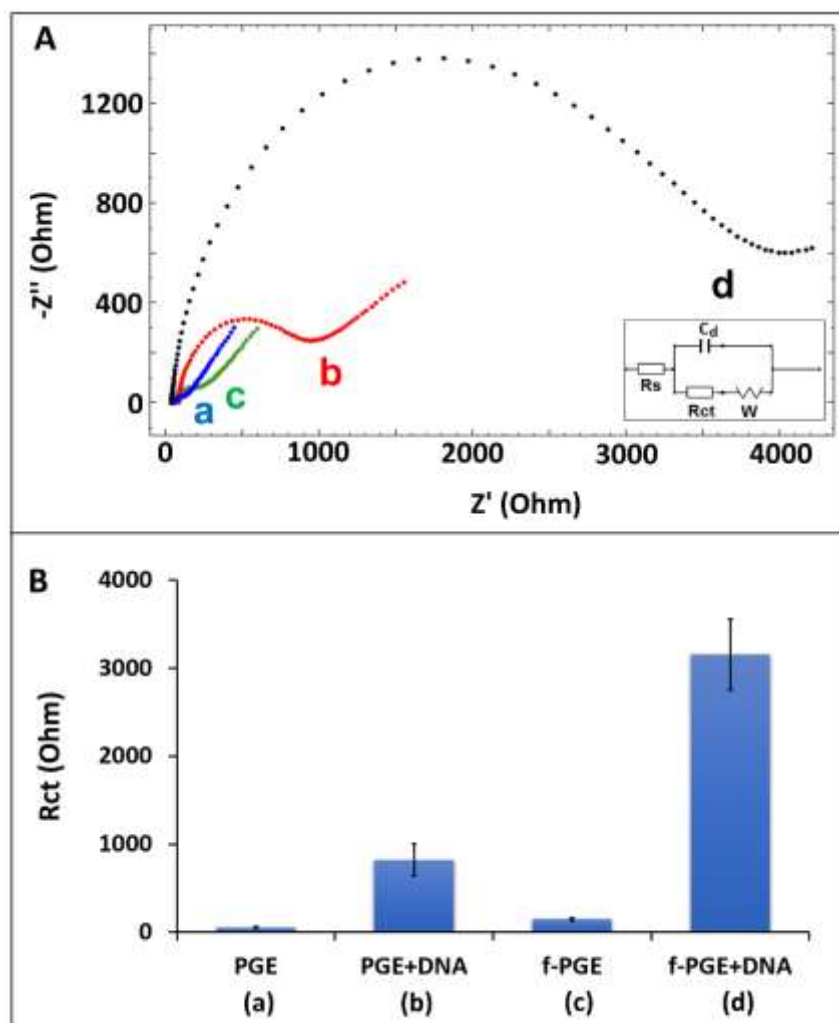
Since the highest and the most reproducible  $R_{ct}$  value as  $798 \pm 84$  Ohm (RSD %, 10.5 %,  $n=3$ ) was achieved in the presence of 10  $\mu\text{g/mL}$  dsDNA (Table 1), this concentration was chosen as the best dsDNA concentration for interaction study.

The limit of detection (LOD) was calculated as 1.09  $\mu\text{g/mL}$  in the linear concentration range between 2.5 and 10  $\mu\text{g/mL}$  dsDNA with the equation reported by Miller and Miller [31]. The equation was  $R_{ct} (\text{Ohm}) = 16.63 C_{dsDNA} (\mu\text{g/mL}) + 634$ , and the regression coefficient  $R^2$  of the linear curve was 0.99 as shown in Figure S1.

**Table 1.** The average  $R_{ct}$  values ( $n=3$ ) with RSD % measured after immobilization of dsDNA in its various concentrations on f-PGE.

[dsDNA] $\mu\text{g/mL}$	The average $R_{ct}$	RSD %
2.5	$671.5 \pm 95.4$	14.2
5	$778.6 \pm 180.7$	23.2
7.5	$687 \pm 45$	6.58
10	$798 \pm 84$	10.5
15	$664 \pm 164$	24.7

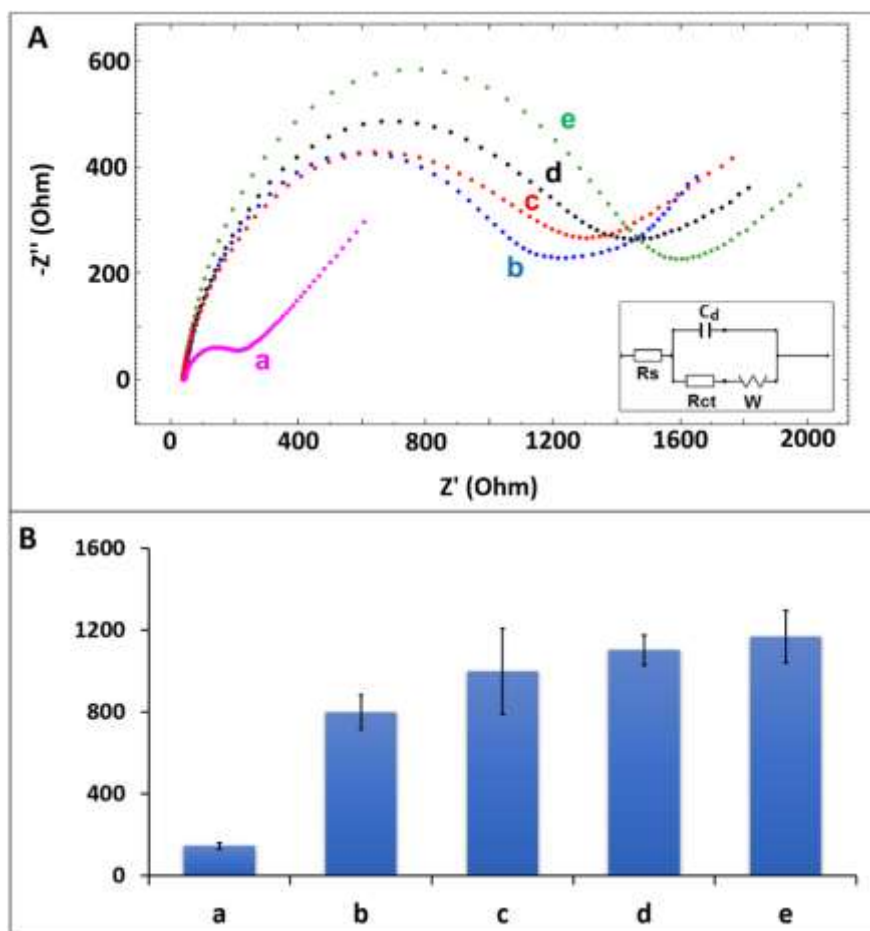




**Figure 3. A.** Nyquist diagrams of (a) PGE, (b) dsDNA/PGE, (c) f-PGE, (d) dsDNA/f-PGE. **B.** Histograms representing the average  $R_{ct}$  value (n=3) recorded by PGE, dsDNA/PGE, f-PGE, and dsDNA/f-PGE.

Prior to drug-DNA interaction studies, the reproducibility of the fullerene-based biosensor was tested. 10  $\mu\text{g/mL}$  dsDNA was immobilized onto the surfaces of five different f-PGEs and measurements were carried out under the same conditions. Similar  $R_{ct}$  values, 760 Ohm, 715 Ohm, 921 Ohm, 831 Ohm, 855 Ohm were recorded with each f-PGEs and relative standard deviation (RSD %) was 9.8 %. These tests revealed that the proposed biosensor had a high level of reproducibility.

Next, the interaction of LMZ and dsDNA at f-PGEs in case of different interaction times was explored by EIS. The LMZ concentration was chosen as 2  $\mu\text{g/mL}$  which was used in our previous work [24]. After 10  $\mu\text{g/mL}$  dsDNA immobilization on f-PGE,  $R_{ct}$  value was measured as  $798.66 \pm 84.3$  Ohm (RSD %, 10.5 %, n =3) (Fig. 4b), which was 5.4-fold higher than the one measured by f-PGE (Fig. 4a). This increase at  $R_{ct}$  could be due to increment of negative charges of dsDNA on the electrode. After interaction 2  $\mu\text{g/mL}$  LMZ with 10  $\mu\text{g/mL}$  dsDNA during 5, 15 and 30 min, the increase ratios were calculated as, 25.3 %, 36.1 % and 46.5 %, respectively. An increase in the negativity of electrode surface may occur due to the charge repulsion between LMZ and dsDNA following the intercalation. As a result of the increase in negative charges at the electrode surface, the resistance increased, as previously observed in the studies related to nucleic acid ligands [22-29, 32, 35].



**Figure 4.** (A) Nyquist diagrams recorded with (a) f-PGE, (b) 10  $\mu\text{g/mL}$  dsDNA immobilized f-PGE before interaction, after interaction with 2  $\mu\text{g/mL}$  LMZ during (c) 5 min, (d) 15 min, (e) 30 min. (B) Histograms related to the average  $R_{ct}$  values (n=3) measured with (a) f-PGE, (b) 10  $\mu\text{g/mL}$  dsDNA immobilized f-PGE before interaction, after interaction with 2  $\mu\text{g/mL}$  LMZ during (c) 5 min, (d) 15 min, (e) 30 min.

### 3. CONCLUSION

Herein, fullerene modified single-use graphite electrode was used for the first time as a sensing platform and applied for monitoring of drug-DNA interaction through the measurement of impedance. This fullerene-based biosensor platform showed a good analytical performance in terms of low detection limit, good reproducibility and rapid response time. Additionally, the use of fullerene provided a great enhancement at  $R_{ct}$  value and thus led to a significant improvement in sensitivity of fullerene modified electrode. Easy preparation and rapid response are the main features of our biosensor. Moreover, the single-use fullerene modified PGE based biosensor bring herein the following important advantages: easy to use, cost effective per measurement, reproducible results, able to be prepared in a short time (i.e. 65 min; 30 min fullerene modification, 5 min air drying, 30 min dsDNA immobilization) compared to earlier works [25,27,32,35-38]. Therefore, the presented biosensor can be considered as a potential working electrode for the fast and sensitive impedimetric assay that could be applied for monitoring of interaction between pharmaceutical formulations and DNA. Besides, the proposed assay based on single-use biosensor technology, can be used as a very practical alternative to existing classical methods for monitoring not only drug-DNA interactions, but also to analyze various biomolecular interactions. In the near future, fullerene-based biosensors will appear as effective devices in electrochemical biosensing and be available commercial POC devices.

## 4. MATERIALS AND METHODS

### 4.1. Instrument

All electrochemical measurements were carried out in a Faraday cage using a three-electrode system and AUTOLAB-30 with NOVA 1.11 software (Eco Chemie, The Netherlands). Three electrode system was constructed with pencil graphite electrode, Ag/AgCl/3M KCl and Pt wire, as working, reference and counter electrode, respectively.

### 4.2. Chemicals

Fullerene ((1,2-Methanofullerene C<sub>60</sub>)-61-carboxylic acid), calf thymus double stranded DNA (dsDNA), Lumazine and all other chemicals were acquired from Sigma-Aldrich.

The stock solution of dsDNA was prepared as 1 mg/mL with Tris-EDTA buffer (10 mM Tris-HCl and 1 mM EDTA, pH 8.00). dsDNA aliquots stored at -20°C. Acetate buffer (0.50 M acetic acid and 20 mM NaCl, ABS, pH 4.80) was used for the preparation of the diluted dsDNA samples. The LMZ stock solution was prepared with Tris buffer (TBS; 50 mM Tris-HCl, 20 mM NaCl, pH 7.00) as reported in our previous work [16].

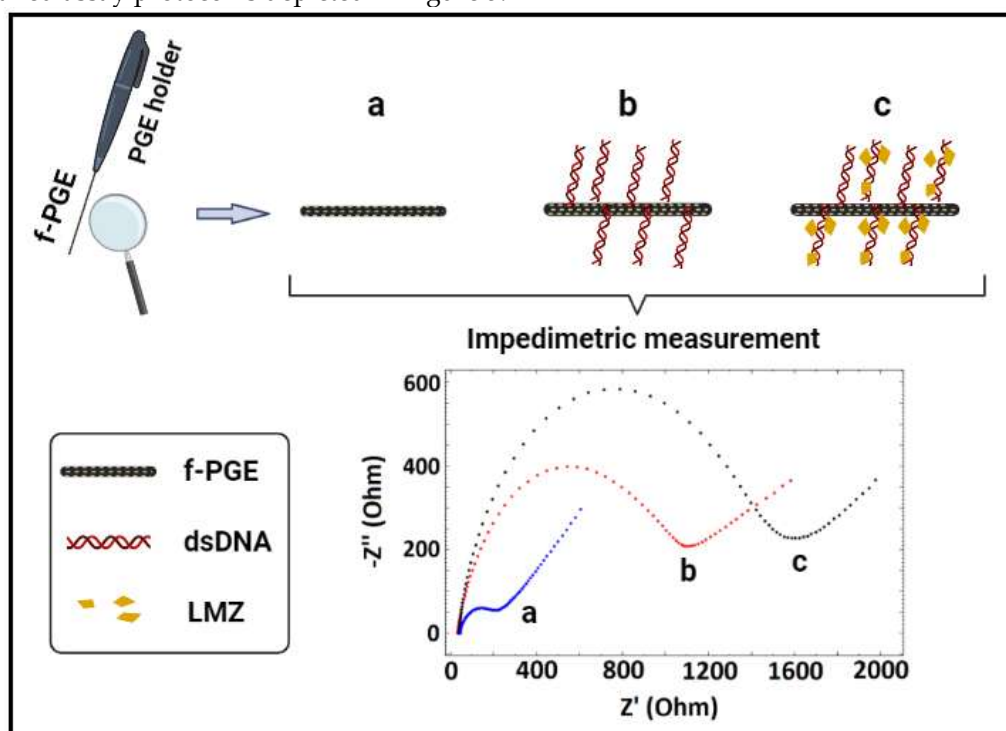
### 4.3. Preparation of nanomaterial-based biosensor

Fullerene was prepared in dimethyl sulfoxide (DMSO) by ultrasonication during 1h. PGEs were electrochemically activated by applying +1.40 V for 30s in ABS (pH 4.80) with differential pulse voltammetry (DPV). These PGEs were dipped into 40 µL of fullerene solution and kept for 30 min to achieve the surface modification. Then, f-PGEs were air dried for 5 min. For the immobilization of the dsDNA onto electrode surface, f-PGEs were dipped into 100 µL of 10 µg/mL dsDNA during 30 min. Then, each electrode treated with washing buffer ABS (pH 4.80) for 5s.

### 4.4. Drug-DNA interaction

To test the suitability of the constructed biosensors as a sensing platform for drug-DNA interaction, lumazine was chosen as a model drug molecule. dsDNA immobilized f-PGEs were dipped in 100 µL of 2 µg/mL LMZ solution at various concentrations and let to interact during various interaction time (15, 30, 60 min). Then, each electrode treated with washing buffer TBS (pH, 7.00) for 5s.

The detailed assay protocol is depicted in Figure 5.



**Figure 5.** The schematic view of experimental procedure followed for monitoring of drug-DNA interaction by f-PGEs.

#### 4.5. Impedimetric measurement

2.5mM  $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$  (1:1) that prepared in 0.1M KCl was used as redox probe in EIS measurements as reported in previous works [24-27,32,35,39,40]. The frequency range was 100 mHz to 1 kHz at an open circuit potential of +0.23 V vs Ag/AgCl/3M KCl with a 10 mV amplitude. The semicircle diameter of the Nyquist diagram corresponded to the charge-transfer resistance ( $R_{ct}$ ). The  $R_{ct}$  values were determined using the AUTOLAB-30, NOVA 1.11 fitting tool. All impedimetric measurements were performed in a Faraday cage.

**Acknowledgements:** A.E. would like to express her gratitude to the Turkish Academy of Sciences (TUBA) as a Principal member for its partial support.

**Author contributions:** Concept – E.E., A.E.; Design – E.E., A.E.; Supervision – A.E.; Resources A.E.; Materials –A.E.; Data Collection and/or Processing – E.E., A.E.; Analysis and/or Interpretation – E.E., Literature Search – E.E., A.E.; Writing – E.E., A.E.; Critical Reviews – E.E., A.E.

**Conflict of interest statement:** The authors declared no conflict of interest.

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