Original Research Article

A New Sensing Strategy for Determination of Tamoxifen Using Fe₃O₄/Graphene-Ionic Liquid Nanocomposite Amplified Paste Electrode

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KEYWORDS

ABSTRACT

Monitoring tamoxifen as an anticancer drug with high side effects is so important in the chemotropic process. In this regard, a fast and simple electrochemical sensor was fabricated using a carbon paste electrode (CPE) modified with 1-octyl-3-methylimidazolium chloride (OMIC) and Fe3O4/graphene nanocomposite and utilized for tamoxifen monitoring. Fe₃O₄/graphene nanocomposite (Fe₃O₄-GR) was synthesized by a one-pot synthesis approach, following by then characterized by FESEM and EDS methods. The Fe₃O₄-GR/OMIC/CPE offered catalytic activity on the redox reaction of tamoxifen and enhanced its oxidation current about 4.59 times. Moreover, the high electrical conductivity of mediators aided the reducing the oxidation potential of tamoxifen (about 80 mV) compared with the unmodified electrode. In addition, Fe₃O₄-GR/OMIC/CPE showed a linear dynamic range of 0.01 μM – 150 μM with a detection limit of 7.0 nM for sensing of tamoxifen using the square wave voltammetric method. Furthermore, Fe₃O₄-GR/OMIC/CPE displayed a superior ability for sensing tamoxifen in real samples with an acceptable recovery range. In brief, Fe₃O₄-GR/OMIC/CPE provided good selectivity for sensing f tamoxifen in an aqueous solution in the presence of organic and inorganic interferences.

GRAPHICAL ABSTRACT
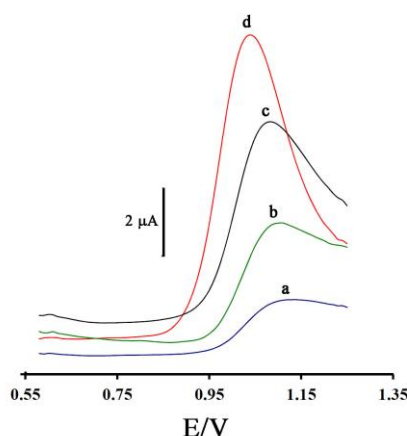
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Introduction

The growth of urbanization and the use of toxic substances in the preparation of food, as well as industrial waste, has led to the introduction of cancer as a major problem in human societies in the last century [1-4]. Today, cancer has been recognized as one of the leading causes of death and its various types have been identified [5, 6]. Accordingly, the need for chemotherapy and the use of anti-cancer drugs has increased in recent years and has become one of the main drugs used [7]. Nevertheless, the destructive effects of anti-cancer drugs are known to be one of the most important problems that make its use require more control [8]. Dose control of the drug which is used in the chemotherapy process is one of the main treatment processes for cancer patients, thereby it requires analytical sensors [9]. On the other hand, tamoxifen is one of the important anticancer drugs for treat breast cancer in women and men with many side effects [10, 11]. The sensing of tamoxifen in chemotherapy procedures is very important to control drug doses in the human body.

Accordingly, various analytical methods for measuring anticancer drugs and especially tamoxifen have been proposed [12-17]. Among these methods, scientists have paid more attention to electrochemical methods, and this is due to the important advantages of this method, such as high analysis speed and low cost [18-20]. On the other hand, the variety of electrochemical sensors, due to the ability to modify with different materials, has made selective measurement possible for a wide range of compounds [21-24].

Nanotechnology is a revolutionary approach to research that has transformed most fields in recent decades [25-30]. Nanomaterials' unique characteristics have made them a viable option in a wide range of technical fields [31-37]. Scientific reports have showed that high-conductivity nanomaterials have been used to design high-performance electrochemical sensors [38]. Scientific reports show that high-conductivity nanomaterials have been used to design electrochemical sensors [39-42]. Carbon-based nanomaterials, metal nanomaterials, and polymer nanofibers have enhanced the performance of electrochemical sensors and provided the ability to sensing trace amounts of pharmaceutical and biological compounds [43-46].

Bearing all in mind, in the present study, we developed Fe_3O_4-GR/OMIC/CPE as a new and highly-sensitive electrochemical sensor for the determination of tamoxifen in pharmaceutical and biological samples with acceptable recovery data. The Fe_3O_4-GR/OMIC/CPE improved oxidation signal of tamoxifen and was used as new analytical tool for monitoring of tamoxifen in different real samples.

Material and methods

Sensor preparation

Tamoxifen, graphite powder, 1-octyl-3-methylimidazolium chloride, ferric chloride, phosphoric acid, sodium hydroxide, iron (II) sulfate were purchased from Merck and Sigma-Aldrich Companies. The chemical precipitation approach was employed for the synthesis of Fe_3O_4/graphene nanocomposite according to our previous report.

Fe_3O_4-GR/OMIC/CPE was prepared by using a mixing of 940 mg graphite powder and 60 mg Fe_3O_4-GR. The powders were homogenized by the addition of 15 mL ethanol and hand mixing for 15 min. After evaporation of ethanol at 35 °C, Fe_3O_4-GR/OMIC/CPE was obtained by adding 10 drops of paraffin oil +2 drops of OMIC, and hand mixing of powders for 1 h in mortar and pestle.

Apparatus

An Ivium-Vertex Potentiostat/Galvanostat connected with the three-electrode electrochemical cell containing Pt wire (counter electrode), $Ag/AgCl/KCl_{sat}$ (Reference electrode) and Fe_3O_4-GR/OMIC/CPE (working electrode) was utilized for current-potential investigation. Fe_3O_4-GR nanocomposite was characterized by FE-SEM (TESCAN MIRA3).

Real sample

The dextrose saline and tamoxifen tablet (20.0 mg per tablet) were selected for real sample analysis. Four tablets of tamoxifen were selected, and then powdered in mortar and pestle.

Following, the powders were mixed together and dissolved in ethanol/water (1:1) solution under ultrasonication condition for 30 min. The as-obtained solution was filtered and diluted with 5 mL phosphate buffer solution pH=4.0. Subsequently, it was used for real sample analysis of tamoxifen.

Result and Dissection

Characterization of Fe₃O₄-GR nanocomposite
FESEM and EDS techniques were employed for characterization of Fe_3O_4-GR nanocomposite. EDS analysis data showed presence of 13.58% C, 42.81% O and 43.61% Fe that confirmed good purity of Fe_3O_4-GR nanocomposite in our synthesis procedure. FESEM image of Fe_3O_4-GR nanocomposite clearly showed decoration of

Fe_3O_4 nanoparticle at surface of 2D GR sheet (Figure 1).

Electrochemical behavior of tamoxifen
Oxidation signal of 50.0 µM tamoxifen was recorded at surface of Fe_3O_4-GR/OMIC/CPE in the pH range of 3.0-6.0. As can be seen, the maximum oxidation current tamoxifen was observed at pH=4.0 and this value was selected as optimum condition (Figure 2). In addition, oxidation potential of tamoxifen was shifted to negative value with increasing of pH=3.0 to pH=6.0, confirming the electro-oxidation of tamoxifen was dependent of proton concentration in the solution.
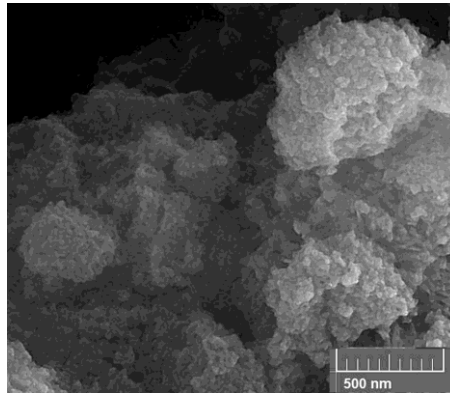

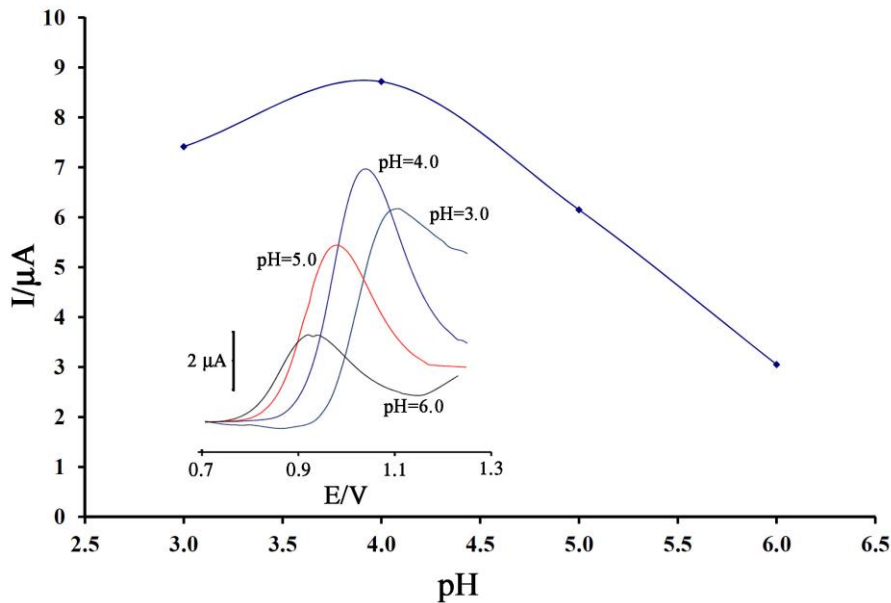**Figure 1:** FESEM of Fe_3O_4-GR nanocomposite

Figure 2: I-pH curve for electro-oxidation of 50.0 µM tamoxifen recorded at surface of Fe_3O_4-GR/OMIC/CPE. Inset) SWV50.0 µM tamoxifen recorded at surface of Fe_3O_4-GR/OMIC/CPE in the pH range 3.0-6.0

Square wave voltammogram of 50.0 μM tamoxifen was recorded at the surface of CPE (Figure 3 curve a), Fe_3O_4-GR/CPE (Figure 3 curve b), OMIC/CPE (Figure 3 curve c) and Fe_3O_4-GR/OMIC/CPE (Figure 3 curve d), respectively. The oxidation currents of tamoxifen at the surface of each electrodes were detected about 2.13 μA, 4.36 μA, 7.29 μA and 9.79 μA, respectively. The comparison of the oxidation current of tamoxifen at the surface of CPE and Fe_3O_4-GR/OMIC/CPE showed that the sensitivity was enhanced 4.59 times, attributed to the presence of Fe_3O_4-GR and OMIC as the conductive mediators at the surface of the fabricated sensor.
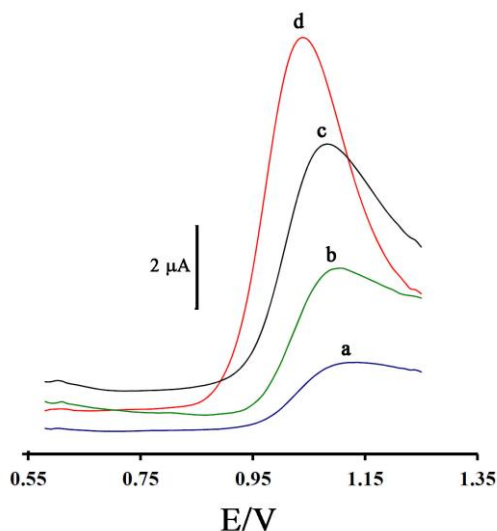

Figure 3: SW voltammograms of 50.0 μM tamoxifen at surface of a) CPE; b) Fe_3O_4-GR/CPE; c) OMIC/CPE and d) Fe_3O_4-GR/OMIC/CPE

Linear sweep voltammograms of 500.0 μM tamoxifen at surface of Fe_3O_4-GR/OMIC/CPE are displayed in Figure 4 inset. A linear relation between oxidation current of tamoxifen and $v^{1/2}$ was observed with the equation of $I = 0.6335 v^{1/2} – 0.7104$ ($R^2 = 0.9944$) that confirmed diffusion process of tamoxifen at surface of Fe_3O_4-GR/OMIC/CPE.

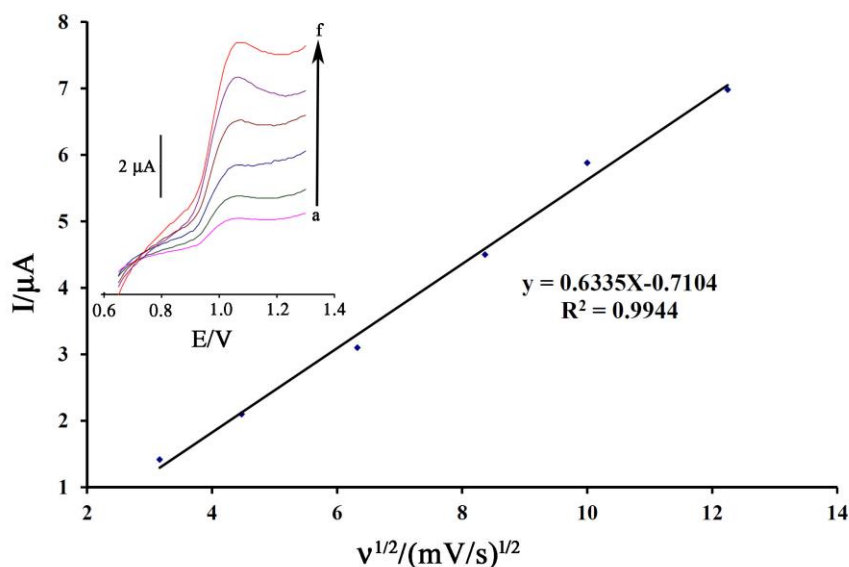**Figure 4:** I-$v^{1/2}$ curve for electro-oxidation of 500.0 μM tamoxifen at surface of Fe_3O_4-GR/OMIC/CPE. Inset) LSV 500.0 μM tamoxifen at scan rates a) 10; b) 20; c) 40; d) 70; e) 100 and f) 150 mV/s

The square wave voltammogram (SWV) of tamoxifen was recorded on concentration range of 0.01-150 μM (Figure 5 inset). Current-concentration curve for this investigation offered an equation of $I = 0.1549 C + 1.3720$ ($R^2 = 0.9952$) with detection limit of 7.0 nM that confirmed the high-sensitivity (0.1549 μA/μM) for sensing trace level of tamoxifen (Figure 5).
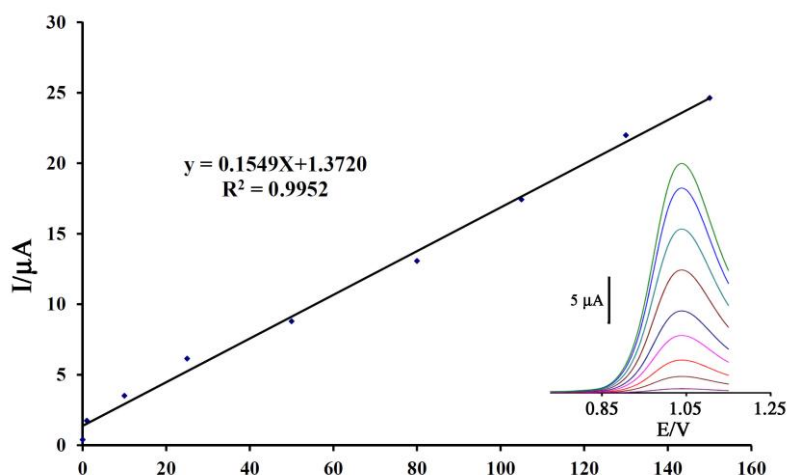
Figure 5: Current-concentration curve for electrooxidation of tamoxifen on concentration range 0.01-150 μM. Inset) Relative SW voltammograms for electrooxidation of tamoxifen on concentration range 0.01-150 μM

The selectivity of Fe3O4-GR/OMIC/CPE to sensing of 10.0 μM tamoxifen was examined by the SW method and results tabulated in Table 1.

Table 1: Selectivity data for sensing of 10.0 μM tamoxifen

Species	Tolerant limits ($W_{interference}/W_{tamoxifen}$)
Br^-, Na^+, Li^+ and Mg^{2+}	1000
Glucose	800
Glycine	600
Ascorbic acid	500
Vitamin B_9	150

Results confirmed the high-selectivity of Fe_3O_4-GR/OMIC/CPE to sensing of 10.0 μM tamoxifen at the optimum condition. The stability of Fe_3O_4-GR/OMIC/CPE to sensing of tamoxifen was checked by the SW voltammetric method at a period time of 70 days. The results showed the oxidation current of 10.0 μM tamoxifen was decreased by 90% of the initial current after 70 days that proved high stability of Fe_3O_4-GR/OMIC/CPE for sensing of tamoxifen.

Finally, the capability of Fe_3O_4-GR/OMIC/CPE was assessed for sensing of tamoxifen in the tablet and dextrose saline samples and obtained data were displayed in Table 2. According to the obtained data, Fe_3O_4-GR/OMIC/CPE showed satisfactory recovery data for determination of tamoxifen.

Table 2: Determination of tamoxifen in real samples (n=4)

Sample	Added (μM)	Expected (μM)	Founded (μM)	Recovery %
Tablet	---	2.00	2.09±0.23	104.5
	10.0	12.00	11.65±0.56	97.08
Dextrose saline	---	---	<LOD	---
	20.00	20.00	12.45±0.76	103.75

Conclusion

In this study, a powerful and stable electrochemical sensor was fabricated to be utilized as an analytical tool for sensing of tamoxifen in pharmaceutical samples. For this goal, Fe_3O_4-GR was synthesized by a simple and one pot chemical precipitation strategy. The Fe_3O_4-GR/OMIC/CPE offered a good catalytic activity on the redox reaction of tamoxifen with 4.59 times enhancement in the sensitivity. In addition, Fe_3O_4-GR/OMIC/CPE showed good ability for sensing tamoxifen in the real samples.

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Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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