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Short Communication

Electrochemical Detection of Tadalafil at Glassy Carbon Electrodes Modified with Ruthenium(II) Complex

Eyad S. M. Abu-Nameh[1,2,], Naela Al Absi[1], Mohammad A. Al-Wahish[3], Hamdallah A. Hodali[3], and Mohammad F. Khanfar[4]*

[1] Department of Chemistry, Faculty of Science, Al-Balqa Applied University, Al-Salt 19117, Jordan.
[2] Department of Pharmacy, Faculty of Pharmacy, Amman Arab University, Jordan.
[3] Department of Chemistry, Faculty of Science, The University of Jordan, Amman 11942, Jordan.
[4] Pharmaceutical-Chemical Engineering Department, School of Applied Medical Sciences, German Jordanian University, P.O.Box 35247 Amman 11180 Jordan.
[*]E-mail: abunameh@bau.edu.jo

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Ruthenium complexes are well known for their electrochemical activity, which could be attributed to the presence of stable ruthenium complexes with divalent ruthenium center, Ru^{2+}. In this work, dichlorobis[8-(diphenylphosphino)quinoline]ruthenium(II) was employed for the detection of tadalafil, a medication for erectile dysfunction, as pure standard or as an ingredient in a pharmaceutical dosage form. A linear range between 30.0 and 80.0 µM was reported with a correlation coefficient equals to 0.9661. The corresponding limit of detection (LOD) and limit of quantitation (LOQ) reported values obtained were 3.85 µM and 11.7 µM, respectively.

Keyword: Tadalafil, Ruthenium (II) Complexes, Diphenylphosphino quinoline, Oxidation

1. INTRODUCTION

Tadalafil (TAD) is a medication usually taken to overcome erectile dysfunction problems. It is commercially available as tablets with 5-20 mg ingredient content. Detection of TAD is of significant importance for quality assurance purposes, as well as for counterfeiting drug prevention. The structure of tadalafil is presented in Fig. 1.TAD content in different media such as blood plasma, bulk, and pharmaceutical dosage forms has been determined by the key instrumental techniques; photometry, high performance liquid chromatography (HPLC) [1-4], and electrochemistry [5-8]. Tadalafil absorbs UV light in the 280-300 nm range so when HPLC is coupled with UV detectors, different chromatographic methods could be optimized and utilized for the detection purposes. The

chromatographic detection of TAD by sensitive, simple, selective, and robust HPLC methods has been reported.

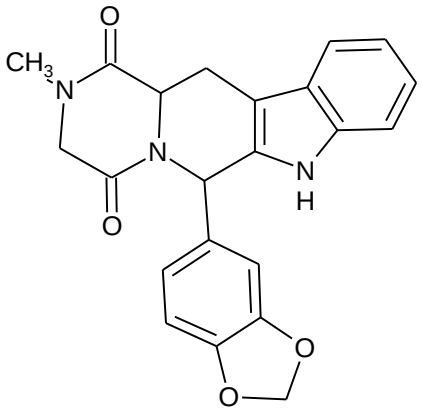

Figure 1. Chemical structure of tadalafil

Ectrochemical methods have many advantages, they are simple, inexpensive, sensitive, and do not need long operation times. The determination of TAD with different electroanalytical methods such as cyclic, stripping, and differential pulse voltammetry has been reported. TAD is oxidized with the production of two protons andtwo electrons, the oxidation reactionis shown in Fig. 2.

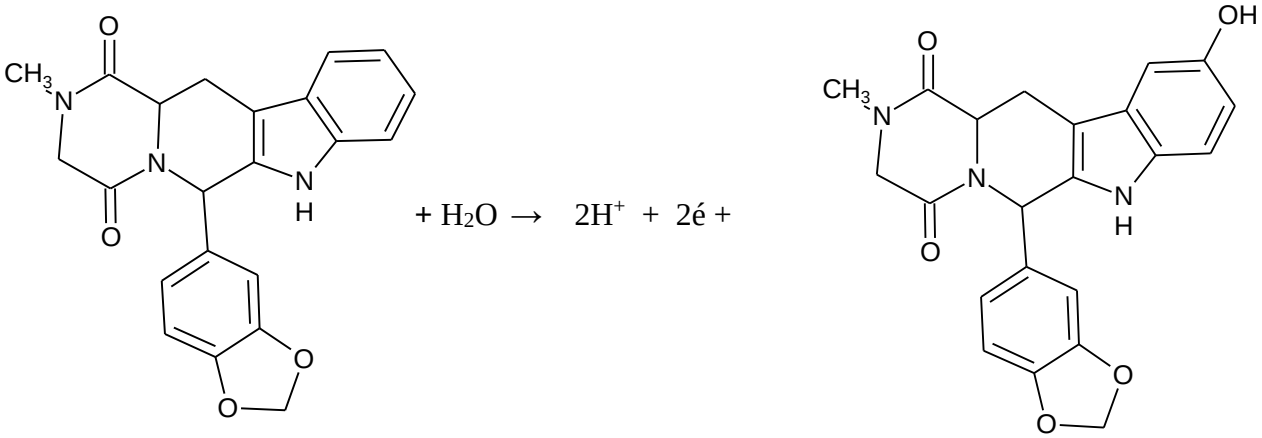

Figure 2. Electro-oxidation of tadalafil

The electrochemical detection of TAD is based on the fabrication of an electrochemical sensor, usually known as the working electrode, that is significantly sensitive and selective toward the target analyte, TAD in this case. The modification is performed with the objective of amplification of the analytical signal in mind. That objective could be fulfilled by elevation of the working electrode conductivity, increasing the electrode surface area, or utilization of a catalyst with an electron-deficient center, which has the ability to oxidize the analyte. As a consequence, a faradaic current will flow, that current could be correlated to the concentration of the electrolyzed species.

Ruthenium forms a wide range of complexes with different ligands such as carbonyls, phosphines, chlorides, and quinolines. Most of the reported complexes exist in an octahedral

arrangement around the metallic center. Ruthenium complexes with nitrogen-phosphorous ligands exhibit three redox peaks, two are ligand based while the third is a metal based activity that is attributed to the Ru(II/III) redox activity. [9-11]

The electrochemical potential of each of the redox processes depends on both steric and electronic nature of the binding ligands. Dichlorobis[8-(diphenylphosphino)quinoline]ruthenium(II), shown in Fig. 3, is an example on ruthenium(II) complexes that could be used for the electroanalysis of different analytes, including TAD.

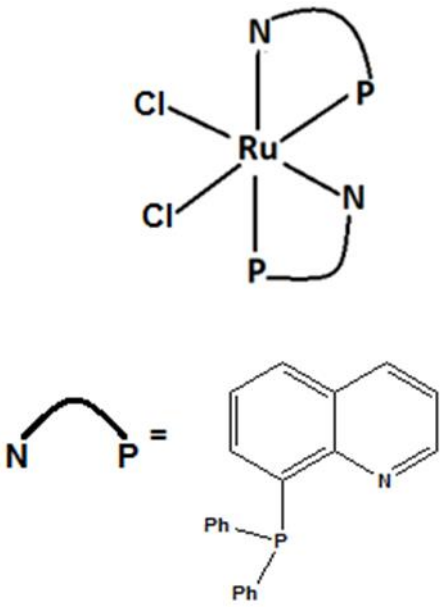

Figure 3. Chemical structure of dichlorobis[8-(diphenylphosphino)quinoline]ruthenium(II)

In this article, the modification of bare glassy carbon electrodes with Ru(II) complex is described. The utilized method is simple; modification of the working electrode was performed using the dip-dry approach. The method is of reasonable sensitivity and could be used for quantification of tadalafil in pharmaceutical products, and to the best of our knowledge, ruthenium complexes have never been used for tadalafil analysis. In this work, The ruthenium modified surface was used for the oxidation of tadalafil and quality of the employed method was evaluated based on the obtained linearity range, limits of detection and quantitation, and recovery percentages.

2. EXPERIMENTAL

2.1 Chemicals and Solutions

Tadalafil was obtained from Al-Taqaddom Pharmaceutical Industries, Jordan. Sodium hydroxide, potassium chloride (to adjust the ionic strength), boric acid, and phosphoric acid were all provided by VWR chemicals, NY, U.S.A. Glacial acetic was purchased from S. D. Fine-Chem Ltd.,

Mumbai, India. The commercial products were purchased from the local market.dichlorobis[8-(diphenylphosphino) quinoline] ruthenium(II) was prepared as described in ref. 11.

The measurements were carried out using Britton-Robinson pH = 1.00 to 7.00 buffer solutions. To prepare the buffer solutions, the appropriate amounts of phosphoric, boric, and glacial acetic acids were dissolved in ultrapure water (Ultra Max 372, Yong Lin Instrument Co., Ltd, Anyang, Korea). The pH of the buffer solutions was adjusted by the addition of the required amount of 0.100 M NaOH. The pH values were determined by SevenGo Duo pH meter supplied by Mettler-Toledo, AG, Analytical, Schwerzenbach, Switzerland.

2.2 Instruments and Measurements

All of the voltammetric experiments were performed in three compartment glass cell using Ag/AgCl and platinum as the reference and the counter electrodes, respectively. The glassy carbon working electrode (3.0 mm i.d.) was provided by Pine Research Instrumentation, NC, U.S.A. PGSTAT101 Autolab potentiostat (Metrohm, Utrecht, The Netherlands) operated by NOVA 2.2 and connected to a personal computer was used to perform the electrochemical experiments.

2.3 Electrode Fabrication

The glassy carbon electrodes were polished, then rinsed with distilled water, and oven dried. A sample of 3 μL drop of previously prepared ruthenium(II) complex dissolved acetonitrile (5mg in 1 ml solvent) was applied on the dried glassy carbon surface and then left to dry for 15 minutes.Herein after, the modified electode will be referred to as Ru(II)/GCE.

2.4 Analytical Procedure

For the preparation of the standard solutions, 5.00 mM stock Britton-Robinson buffer solutions were prepared. Standard solutions of TAD were then prepared from stock by serial dilution. The prepared series was employed for establishing the calibration curve that correlates TAD oxidation peak current to the corresponding analyte concentration.

Most of the voltammetric measurements were performed using the differential pulse voltammetric (DPV) mode with the following parameters;

Potential Step 0.005 V
Modulation amplitude 0.025 V
Modulation time 0.05 s
Interval time 0.5 s
Scan rate 0.01007 V/s

To establish the calibration curve, the potential of the Ru(II)/GCE electrode was scanned between 0.70 and 1.0 V versus Ag/AgCl. The oxidation peak current obtained from each measurement was plotted versus the corresponding solution concentration.Dependence of the oxidation peak current

on the scan rate was performed using the linear scan voltammetric mode, with variation of the scan rate from 5 to 30 mV/s.

2.5 Samples Preparation

To obtain percentage recovery of the active ingredientin the commercial drugs (herein after will be refered to as drug A and drug B) using the modified GCEs, one tablet of each of the provided drugs was weighed and powdered with mortar and pestle. The powder was then accurately transferred to 100 ml volumetric flask and diluted to the mark with the prepared buffer solutions. The solutions were then sonicated for 10 minutes, filtered, and a fraction of the filtrate was pipetted and used for the recovery evaluation.

% recovery was then estimated based on the following equation;

$$\% \text{ recovery} = ([(S_{x+s}) - S_x]/S_s) \times 100\%$$

Where S_x and S_s are the oxidation peak current values for the sample and the standard pharmaceutical solutions, respectively, and S_{x+s} is the oxidation peak current for mixtures of equal volumes of the standard and the sample solutions.

3. RESULTS AND DISCUSSION

The oxidation of tadalafil at bare as well as at the ruthenium modified glassy carbon electrodes occurs around 900 mV vs. Ag/AgCl. At the modified electrode, the oxidation reaction takes place with the flowing of higher faradaic current, as shown in Fig. 4.

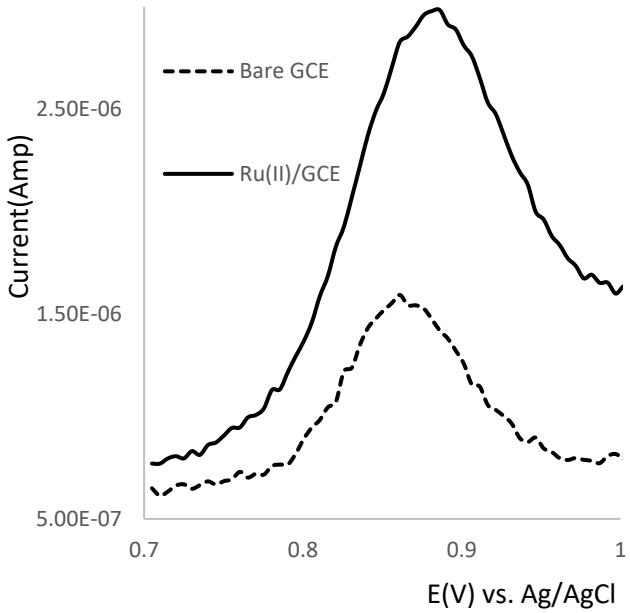

Figure 4. Differential pulse voltammograms of bare GCE and of Ru(II)/GCEin pH 4.00 BR buffer solution containing 10.0 mM TAD

The observed enhancement in the current could be attributed to the role of the ruthenium center. At potentials more positive than 0.800 V vs. Ag/AgCl, ruthenium is oxidized from the divalent to the 3+ oxidation state, therefore, an electron-deficient metallic center is generated. That process facilitates the direct oxidation of TAD as shown in Fig. 3.

Potentiometric and chromatographic studies have been conducted to estimate acidity of tadalafil, and the reported pKa values are about 3.50 [12]. At pH values lower than the mentioned pKa, the indole moiety of tadalafil is exposed to protonation, as a consequence, tendency of TAD toward oxidation is reduced and the fraction of the drug exists in the unprotonated form decreases, as predicted by the Henderson–Hasselbalch equation. As shown in Fig. 5, the maximum oxidation current was reported at pH equals 4.00, the current decreases as the employed pH varies toward whether lower or higher pH values. Therefore, the present work was performed with the utilization of a pH 4.00 BR-buffer solution.

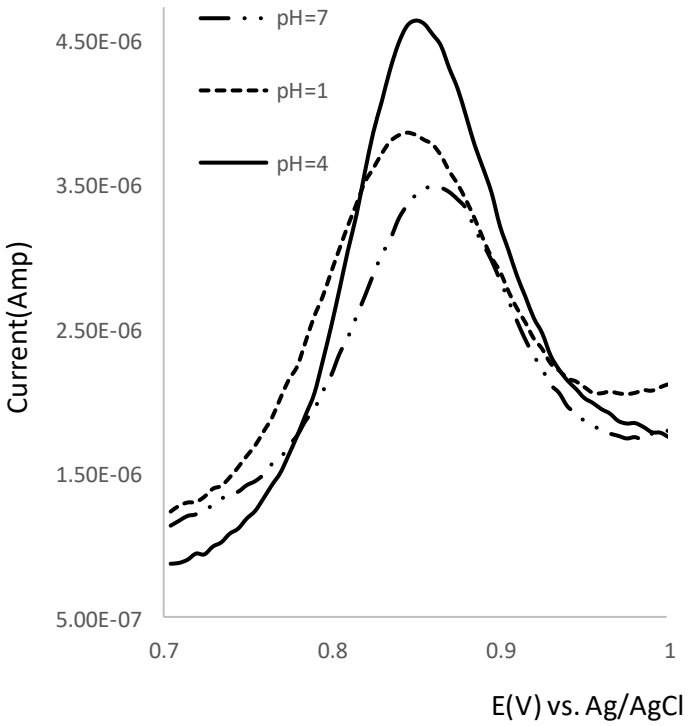

Figure 5. Differential pulse voltammograms of Ru(II)/GCEin pH 1.00, 4.00, and 7.00 BR buffer solutions containing 10.0mM TAD

Although the conducted work has been done with the static mode, without rotating the working electrode, the effect of scan rate on the oxidation current was investigated, as shown in Fig. 6. The oxidation current exhibited a significant linear relationship with square root of the scan rate, which points to diffusion, and then electrolysis, of the analyte at the modified surface. When the oxidation current values were plotted versus the utilized corresponding scan rates, a lower correlation coefficient was reported (results not shown).

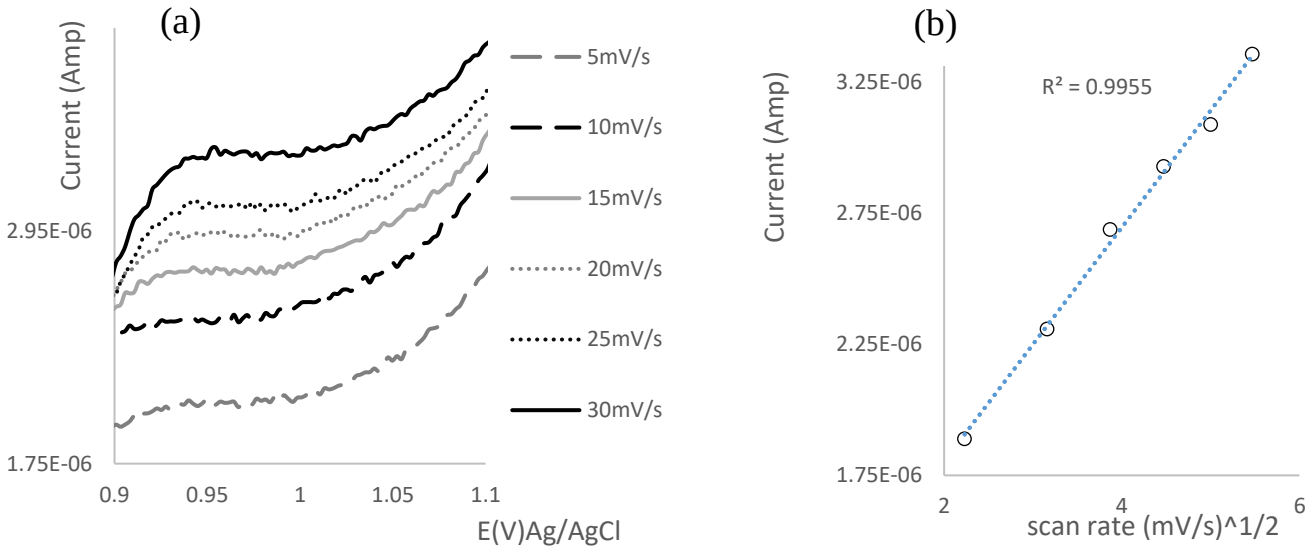

Figure 6. Linear scan voltammograms of Ru(II)/GCE in 10.0 mM TAD in BR pH 4.00 solution at different scan rates (a), and the corresponding dependence of the current on square root of the scan rate (b)

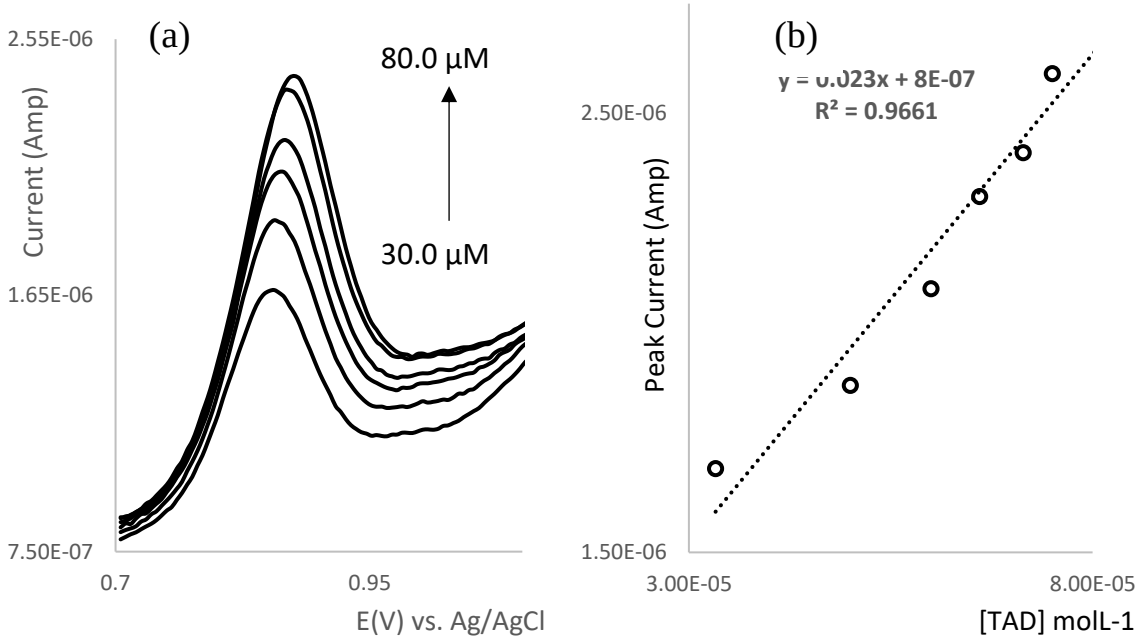

Figure 7. Differential pulse voltammograms of Ru(II)/GCE in BR pH 4.00 solutions containing TAD of concentrations increasing from 30.0 to 80.0µM (a) and the corresponding dependence of the oxidation peak current on TAD concentration (b)

Fig. 7 presents the calibration curve obtained with utilization of the ruthenium modified electrode, based on sets of three trials per concentration. The reported correlation coefficient could be attributed to the degradation of the modifier layer among the trials. That deterioration may cause a significant variation in the measured current values and as a result, reduces the R^2 value. The reported corresponding L.O.D. and L.O.Q. reported values were 3.85 μM and 11.7 μM, respectively.

Recovery of tadalafil in the two commercial dosage forms is shown in Fig. 8. Recovery percentages of 92 (Fig. 8-a) and 111% (Fig.8-b) were obtained for the two drugs shown in Fig. 8. The reported values are within the acceptable recovery range between 80 and 120%. The results reported in this work were compared to those obtained by other research groups, as shown in Table 1. The detection parameters reported in this work could be improved mainly by variation of certain parameters, such as the addition of dispersing agents or the utilization of a working electrode with low background current, such as boron-doped diamond.

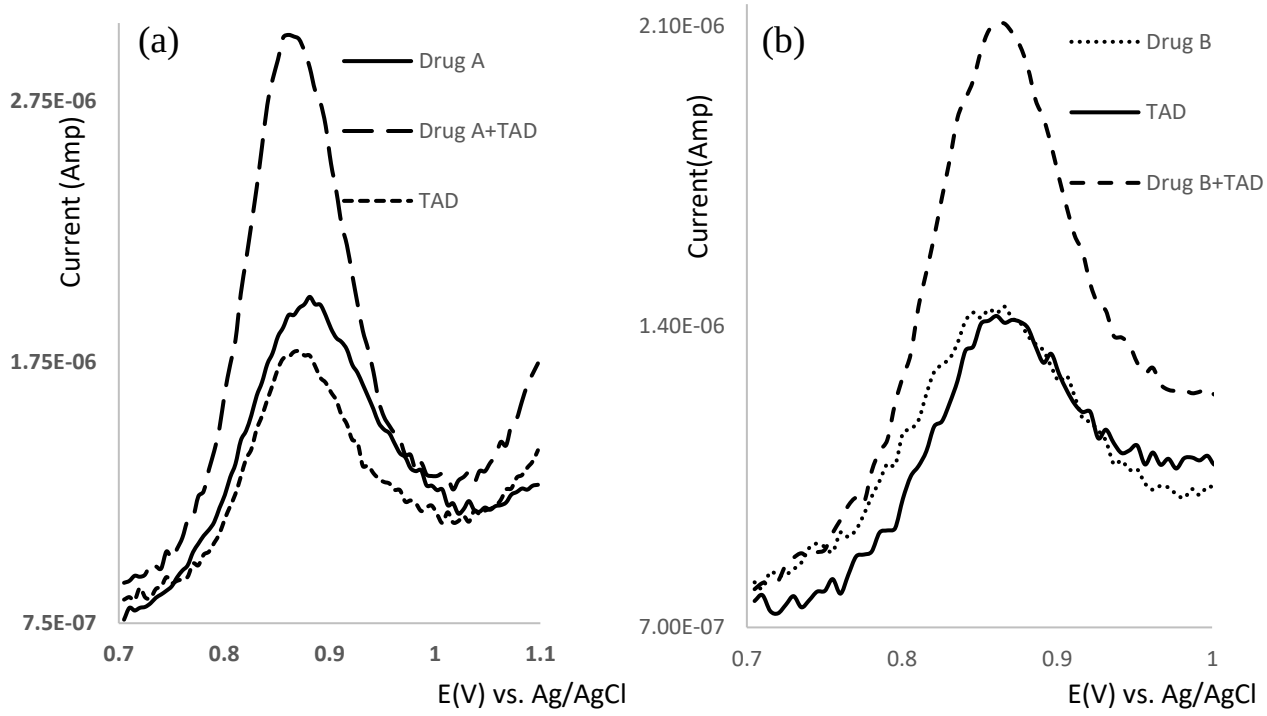

Figure 8. Differential pulse voltammograms of Ru(II)/GCEin pH 4.00 BR buffer solutions containing standard TAD, the commercial formulation, and a mixture of the standard and the commercial formulations ofdrugA (a), and drug B (b), respectively

Table 1. Comparison of different modified electrodes used for TAD analysis

Electrode	Sample	Linearity	L.O.D.	L.O.Q.	Reference
Ru(II)/GCE	Commercial tablets	30.0 -80.0 μM	3.85 μM	11.7 μM	This work
MWCNT composite paste electrode	Serum and commercial tablets	3.6–8.1 and 12.7–61.1 μM	0.11 μM	0.36 μM	5
β-cyclodextrin functionalizedAu@SiC	Serum and herbals	0.01–100 μM	2.5 nM	N.A.	6

Pretreated boron-doped diamond	Pharmaceutical formulations	0.15–1.28μM	19.5 nM	N.A.	7
Pt nanoparticles supported on nitrogen-doped porous graphene	Serum	1.30–489μM	0.268μM	N.A.	8

4. COLCLUSIONS

The detection of tadalafil at ruthenium (II) modified glassy carbon electrode was performed successfully in this work, and the modified surface has demonstrated improved performance over its bare counterpart, due to the presence of the electron-deficient ruthenium center. In the future, complexes other than the dichlorobis[(8-diphenylphosphino)quinoline]ruthenium(II) could be examined as potential catalysts for the oxidation reaction. Improvement of the detection conditions could also include the fabrication of more stable modifiers that do not deteriorate during the course of the analysis. The method described in this work is simple, reasonably sensitive, and genuine due to the utilization of ruthenium complex for tadalafil detection.

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