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ORIGINAL ARTICLE

Synergetic signal amplification of multi-walled carbon nanotubes-Cetyltrimethylammonium Bromide and Poly-L-Arginine as a highly sensitive detection platform for Rutin

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Abstract

In this research, a glassy carbon electrode was coated with a thin layer of multi-walled carbon nanotubes in the presence of the surfactant and subsequently was electro-polymerized with Poly-L-Arginine (P-L-Arg). The prepared electrode was used as an effective sensor for the quantitative detection of Rutin (Ru). The fabricated electrode exhibited good electrochemical performance with low electron transfer resistance. The electrochemical behavior of Ru at the prepared electrode was also investigated by cyclic voltammetry and differential pulse voltammetry techniques. For modified glassy carbon electrode, the transfer coefficient (α), the number of electrons involved in the rate-determining step (n_α) and electron transfer rate constant (k_s) calculated. Under the favorable conditions, a linear relationship between the oxidation peak current and concentration of Ru was obtained in the range from 0.1 μM to 10 μM with a detection limit of 0.048 μM and with the extraordinary high sensitivity value of 6.3767, μA/μM was obtained. Interference and stability studies showed that satisfactory detection results are achieved using this electrode. The proposed electrode was successfully applied for the determination of Ru in human blood serum samples.

Keywords: *Modified Electrode; Multi-Walled Carbon Nanotube; Poly-L-Arginine; Rutin; Voltammetry*

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INTRODUCTION

Rutin, (3', 4', 5, 7-Tetrahydroxy-Flavone-3-Rutinoside, Ru), is a flavonoid derived from foods and plants, which is one of the most promising compounds that are effective in some diseases, such as inflammation [1] and oxidative stress [2]. For example, in rats, Ru has been shown to reduce neural damage after intracerebral hemorrhage in rats [3]. It is also thought to be an activating factor for vitamin C [4]. Ru is an oral capillary preservatory drug commonly used for the therapy of chronic venous insufficiency and is also an ingredient in a large number of multivitamin preparations and herbal remedies [5, 6]. Until now, a large number of analytical methods for Ru have been proposed, such as high performance liquid chromatography (HPLC) [7], liquid chromatography-mass spectrometry (LC-MS) [8], solid phase extraction-high performance liquid chromatography-diode array detection (SPE-HPLC-DAD) [9] and ultra performance liquid chromatography-electrospray ionization-tandem mass spectrometry (UPLC-ESI-MS/MS) [10], electrochemical determination methods have also been proposed for the determination of Ru [11-22] for their advantages of high sensitivity, simplicity, low cost and convenient for in-situ detection.

One of the best materials for the construction of electrochemical sensors is carbon nanotubes (CNTs) with single or multiple walls. Owing to their high electrical catalytic properties, high chemical stability and extremely high mechanical strength, multi-walled carbon nanotubes have been focused on the field of electrode modification [23, 24]. Furthermore, CNTs are members of nanostructure materials that can be used as

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support for immobilization of different electron transfer mediators and making ideal miniaturized sensors. Covalent and non-covalent approaches have been used for binding to CNTs. Among these approaches, non-covalent mode is an effective way to preserve the sp^2 structure of CNTs. In addition, strong interaction of aromatic groups with π-staking structure of CNTs is a manner to achieve the desired stability of the nanocomposite, similar to covalent binding [25, 26]. On the other hand, Polymer modified electrodes have been considered by researchers in recent years due to good stability, recyclability, more active sites, homogeneity in electrochemical deposition and strong adherence to electrode surfaces [27, 28]. Electropolymerization is one of the good methods for preparing polymer modified electrodes. This method can control electrochemical parameters such as film thickness, penetration and load transfer characteristics. Also, in recent years, the fabrication of conducting polymers/CNTs modified electrode has gained great interest [29, 30] and it has been demonstrated that the obtained CP/CNTs modified electrode possess properties of the individual components with a synergistic effect [31-36].

In this research, based on our previously reported works [37], a facile approach was developed utilizing glassy carbon electrode modified with Poly-L-Arginine/multi-walled carbon nanotubes-Cetyltrimethylammonium bromide (P-L-Arg/MWCNTs-CTAB) for electrocatalytic oxidation and determination of Ru. The modified electrode showed a synergic effect. High active surface area of both the polymer and carbon nanotubes, giving rise to a remarkable improvement of electrochemical performance of Ru with respect to polymer-modified electrodes and also MWCNTs-modified electrodes. The proposed electrode was successfully used for the determination of Ru in human blood serum samples.

EXPERIMENTAL

Apparatus

Electrochemical measurements, differential pulse voltammetry (DPV), cyclic voltammetry (CV) were performed in an analytical system, Autolab with PGSTAT-12 (Eco Chemie B. V., Ultrecht, The Netherlands) and driven by the GPES software (Version 4.9) in conjunction with a conventional three-electrode system and a personal computer for data storage and processing. A modified glassy carbon electrode employed as the working electrode and a platinum wire as the counter electrode. All potentials were referred to an Ag/AgCl/KCl (3 M) electrode. All electrochemical measurements were performed at room temperature. All of the employed electrodes were purchased from Azar electrode (I. R. Iran). Scanning electron microscopy (SEM) images were obtained using a XL-30 microscope (Philips Co., Nether-lands).

Chemicals and reagents

L-Arginine (L-Arg) and Cetyltrimethylammonium bromide (CTAB) were obtained from Merck (Darmstadt, Germany) and Rutin was from Fluka (Buchs, Switzerland) and was used without further purification. The stock solution of Rutin (2mM) was prepared in ethanol and diluted with 0.1 M phosphate medium (pH 3.0) before use. The multi-walled carbon nanotubes (MWCNTs) (> 95% purity, 10–20 nm diameter, 5–15 nm length) were obtained from Neutrino (Iran–Tehran). All other chemicals used were of analytical-reagent grade. Double-distilled water was used throughout the experiments.

Preparation and Modification of the Electrodes

Prior to electrochemical modification, the bare GCE was polished with 0.05μm alumina slurry on a polishing pad. Then the electrode rinsed with water and sonicated with 1:1 ethanol and distilled water for 10 min, respectively. The modification was performed in two steps:

a) 5 mg of the treated MWCNTs was added to 5 ml of 2.5 mM CTAB aqueous solution and the mixture was sonicated for 35 min to obtain a modifier suspension [37, 38]. Then, 5 μL of the prepared MWNTs-CTAB suspension was dropped on the surface of the cleaned GC electrode using a micropipette. After the solvent is allowed to vaporize, a MWNTs-CTAB nanocomposite film is formed on the surface of the electrode.

b) Electropolymerization of L-Arg (P-L-Arg) was done on the MWCNT–CTAB/GCE using consecutive potential cycling (7 cycles at 100 $mV{\cdot}s^{-1}$) between -2 to 2 V in 0.1 M PBS at pH 7 containing 20.0 mM L-Arg.

Preparation of real samples

Human plasma samples were obtained from the Pastor Laboratory (Khoy– Iran) and aliquots were transferred into microtubes and were frozen at -4 °C until analysis. Human plasma samples frozen at -4°C were thawed at room temperature daily and vortexed to ensure homogeneity. After thawing the samples gently, 2 mL of an aliquot volume of this sample was spiked with Ru, then acetonitrile with the volume ratio of 2:1 (acetonitrile: plasma) was added to precipitate plasma proteins. The mixture was centrifuged for 5 min at 6000 rpm to separate residues of plasma proteins. Approximately, 2 mL of supernatant was taken and added into supporting electrolytes to reach a total volume of 10 mL.

RESULTS AND DISCUSSION

Characterization of the P-L-Arg/MWCNTs-CTAB/GCE films

The surface morphology was performed using Scanning Electron Microscopy (SEM) for MWCNTs, P-L-Arg, and P-L-Arg/MWCNTs-CTAB layers. As shown in Fig. 1a, carbon nanotubes similar to spaghetti filaments are distributed uniformly on the electrode surface. During the polymerization of L-Arg, snow-like crystals formed which is clearly detectable on the electrode surface (Fig. 1b). After the synthesis of P-L-Arg film on the MWCNTs-CTAB matrix, the majority of MWCNTs-CTAB have been entrapped in the P-L-Arg film. The typical morphology of P-L-Arg/MWCNTs-CTAB composite (Fig. 1c) is more complicated than single-step morphology corrections. As seen in Fig. 1C, the composite particles have a nanostructure on the surface of the electrode.

Electrochemical behavior of the P-L-Arg/MWCNTs-CTAB/GCE for Ru

The typical cyclic voltammograms of Ru (36.46 µM) were obtained on various electrodes in PBS buffer solution (pH = 3.0) (Fig. 2). Curve a, shows the CV of the bare electrode in PBS buffer solution, there was a pair of redox peaks with a low current flow rate of about 1 µA. At the P-L-Arg/MWCNTs-CTAB/GCE (curve d), a significant enlargement in

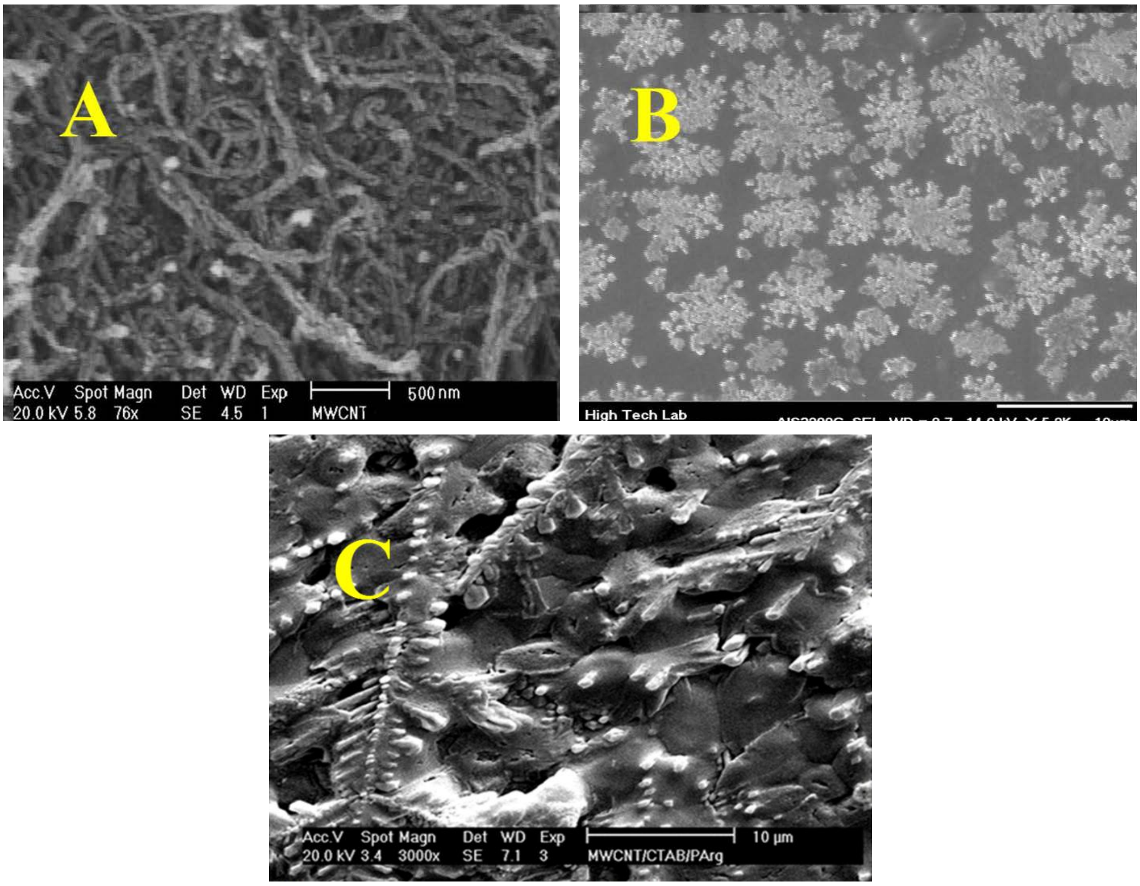

Fig. 1: SEM images of (A) MWCNTs; (B) P-L-Arg; and (C) P-L-Arg/MWCNTs-CTAB films on the glassy carbon electrode.

peak current and a great decrease in the ΔE_p was observed. The same phenomenon was observed for MWCNTs-CTAB (curve c) and P-L-Arg (curve b) layers alone but with less flow intensity. The results showed that the simultaneous presence of carbon nanotubes and Arginine increases the surface area of the electrode, which results in more sensitivity and a further reduction in the difference between anode and cathode peaks.

Optimization of the experimental conditions

Effect of pH values

The effect of pH on the peak current was studied using 38μM of Ru in PBS buffer solution from pH 2.0 to 9.0 (Fig. 3a). The best response (peak current intensity) was observed at pH 3.0. Therefore, PBS buffer with pH 3.0 was selected as supporting electrolyte for obtaining best sensitivity in all voltammetric determinations (Fig. 3b). It was found that the oxidation peak potential of Ru shifted negatively with increasing pH, suggesting that H^+ participates in the oxidation process. A good linear relationship was obtained between $E_{p,a}$ and pH in the range of 2.0–9.0 (Fig. 3c).This relationship can be described by the following equation:

$$E_{p,a}\,(\mathrm{mV}) = -60.3\,\mathrm{pH} + 716.9 \quad (R^2 = 0.9941) \qquad (1)$$

Regarding the slope value of -60.3 mV per pH unit, which is close to the theoretical slope (−59mV per pH unit), it can be concluded that equal numbers of electrons and protons are involved in the electro-oxidation of Ru on the surface of the modified electrode (Fig. 4). This is consistent with that reported in the literature [39].

Effect of modifier amount on the response of Ru

The amount of MWCNTs-CTAB influences the voltammetric response of Ru. This is related to the thickness of the correction film on the surface of glass carbon electrode. If the film is too thin, the

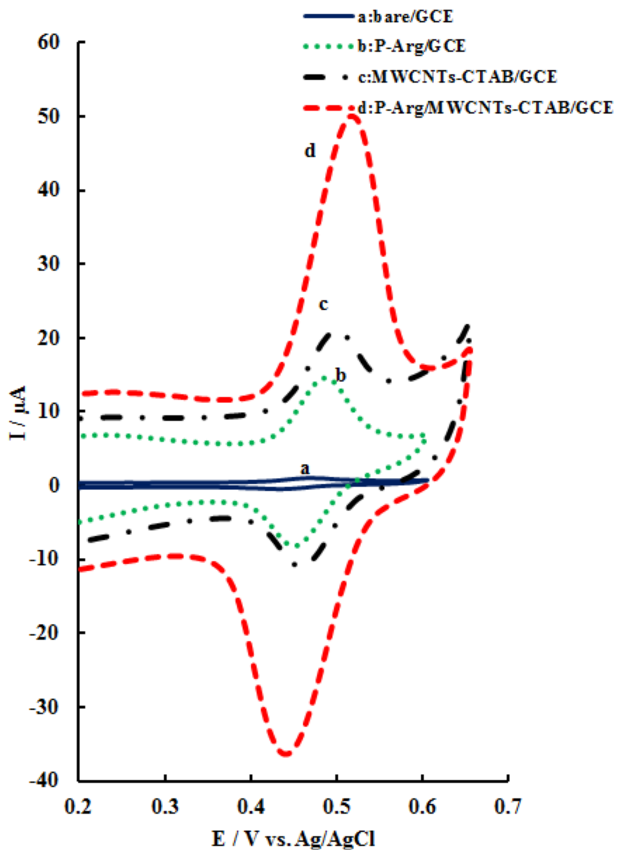

Fig. 2: Cyclic voltammograms of (a) bare GC electrode, (b) P-L-Arg modified GC electrode, (c) MWCNTs-CTAB modified GC electrode, and (d) P-L-Arg/MWCNTs-CTAB/GC electrode in 0.1 M pH 3.0 phosphate buffer solution containing 36.46 μM Ru at a scan rate of 100 mV s^{-1}.

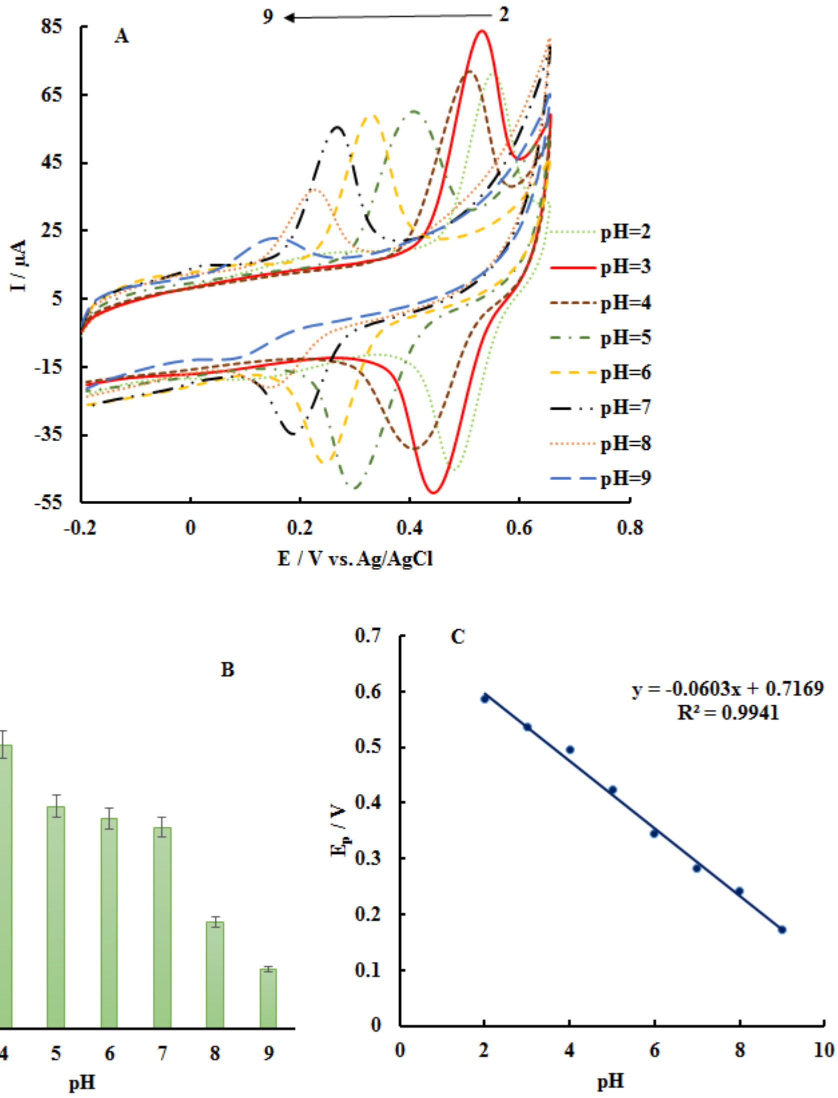

Fig. 3. A) Cyclic voltammograms of P-L-Arg/MWCNTs-CTAB/GCE to 38μM Ru in 0.1 M of different pH: 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 and 9.0. (B) Effects of pH on the peak current. (D) Effects of pH on the peak potential. Scan rate: 100 mV s^{-1}. The arrow indicates scanning direction.

amount of absorbed Ru is low and as a result, the peak flow is small; on the other hand, the surface of the electrode with the modifier is not completely covered. When the film is too thick, the background current and the electrode resistance of the modified electrode for electron and Ru transitions have increased, leading to widespread and undesirable peak, as well as in more film thicknesses, MWCNTs-CTAB becomes unstable and it is released from the surface of the electrode. Therefore, the amount of 5 μL of suspension (1mg/mL MWCNTs-CTAB) was used as the optimal volume for preparing the modified electrode.

Effect of accumulation time

Fig. 5 depicts the influence of accumulation time on the oxidation peak currents of Ru at the P-L-Arg/MWCNTs-CTAB film-modified GCE. When extending the accumulation time from 0 min to 14 min, the oxidation peak currents remarkably increase. However, the oxidation peak currents increase slightly when further improving the accumulation time from 14 min to 16 min, suggesting that the amount of Ru tends to a limiting value at the P-L-Arg/MWCNTs-CTAB film. Considering sensitivity and working efficiency, 14-min accumulation was employed.

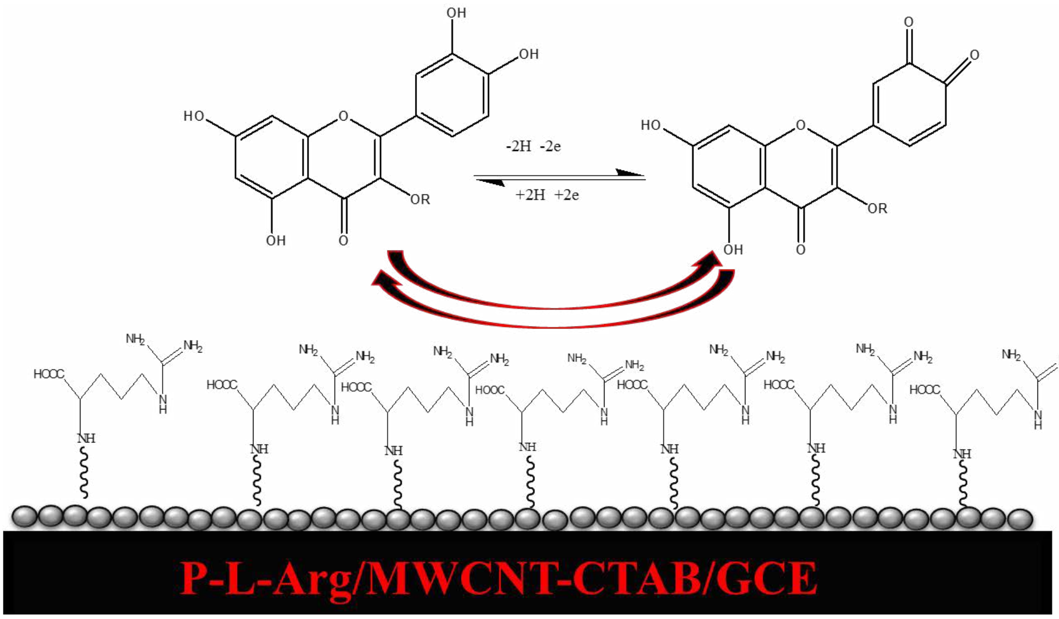

Fig. 4: Mechanism of rutin redox processes.

Influence of scan rate on the electrooxidation of Ru using P-L-Arg/MWCNTs-CTAB/GCE

The effect of potential sweep rate was examined on the cyclic voltammetric response of P-L-Arg/MWCNTs-CTAB/GCE in a potential range of 0.2 – 0.65 V in PBS (0.1 M, pH 3.0). The sweep rate was varied in the range of 10 – 500 mV/s (Fig. 6). Both anodic and cathodic peak currents of Rutin at P-L-Arg/MWCNTs-CTAB/GCE were increased with scan rate (Fig. 6a). A linear dependence of peak currents on scan rate was obtained in the whole range of sweep rates (Fig. 6b), as predicted theoretically for a surface-confined redox couple. For scan rates higher than 200 mV s^{-1}, because of semi-infinite linear diffusion behavior, the peak currents of redox are proportional to $v^{1/2}$, usually associated with a diffusional process for solution species (Fig. 6c).

Fig. 6d shows the relationship between peak-to-peak separations (ΔE_p) and the logarithmic value of scan rate (log v) for Ru. At $\Delta E_p > 0.2/n$ (n is the number of electrons involved in redox process), the anodic peak potential (E_{pa}) showed a linear relationship with log v.

According to Laviron's theory for quasi-reversible systems, [40] the charge transfer coefficient (α), the number of electrons involved in redox process (n) and the apparent heterogeneous electron transfer rate constant (k_s) can be deduced using the next formula:

$$\Delta E_{pa} = 2.3\frac{RT}{(1-\alpha)nF}\log\frac{RTk_s}{(1-\alpha)nF} - 2.3\frac{RT}{(1-\alpha)nF}\log \nu$$

The calculated values for n_α, α and ks were found to be 2.02, 0.45 and 1.6 $cm.s^{-1}$.

Calibration curve

In this work, differential pulse voltammetry (DPV) was employed due to its higher sensitivity compared to other voltammetric techniques to generate the calibration curve plot for Ru. The voltammograms (DPV) were obtained with an increase in Ru concentration at P-L-Arg/MWCNTs-CTAB modified GCE in pH 7.0 PBS solution. The peak currents for Ru increase linearly with increase in the concentration of respective analyte with a linear rage of 0.1 to 10 µM clearly shown in Fig. 7. From the slope value, the sensitivity value of P-L-Arg/MWCNTs-CTAB modified GCE towards the Ru was found to be 6.3767 µA/µM. The correlation coefficient was found to be 0.9961 (shown in Fig. 7b inset), furthermore, the calculated limit of detection (LOD) was 0.048 µM for Ru at P-L-Arg/MWCNTs-CTAB modified GCE. The detection limits, linear dynamic, and pH worked reported at different Electrodes are tabulated in Table 1. Although, a wider linear dynamic in most cases was observed ratio to the proposed method but, lower LOD for Ru were obtained at P-L-Arg/MWCNTs-CTAB/GCE than those at GR/CILE [11], PAO-GR/CILPE [12] and PVP/CPE [15]. Also, the electrode preparation is very easy,

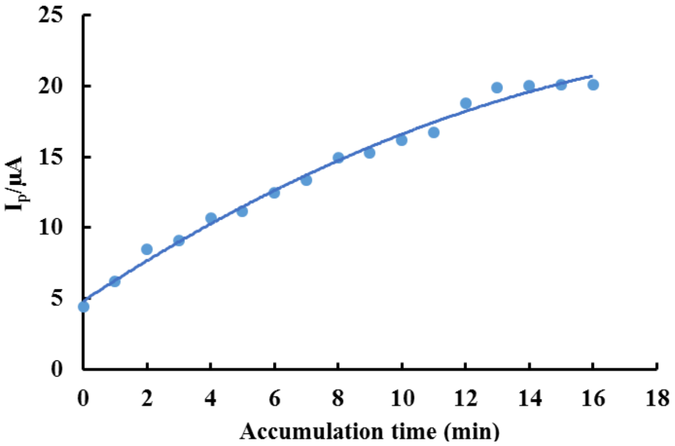

Fig. 5: Effect of (A) accumulation time on the oxidation peak current of 2.4 μM Ru in 0.1 M PBS (pH 3.0).

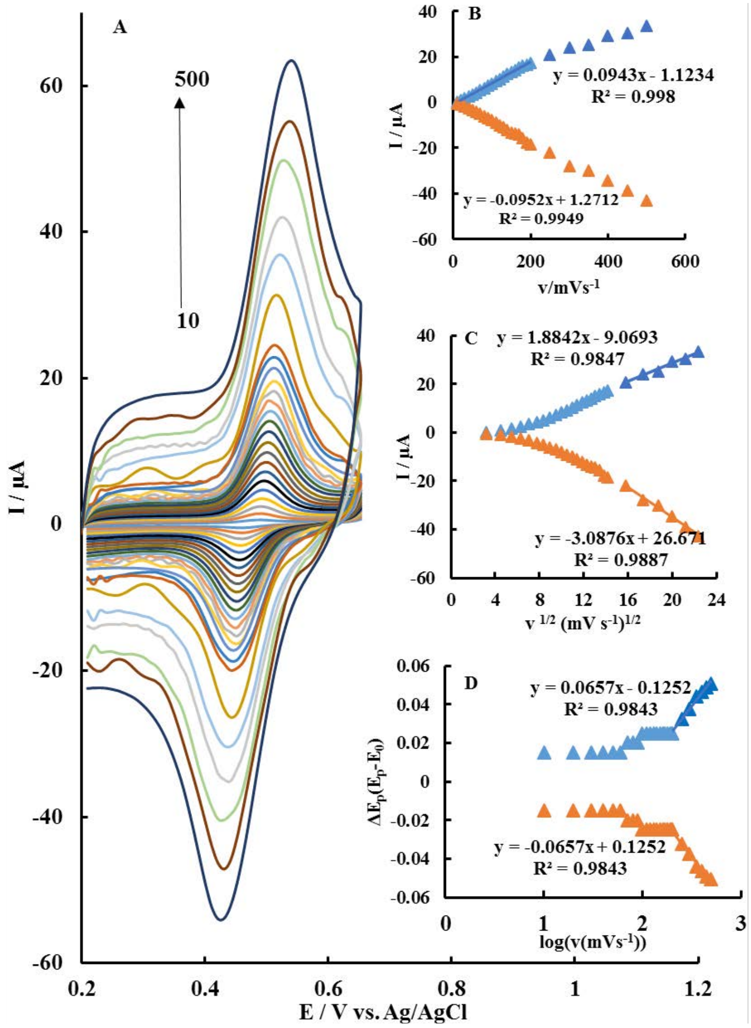

Fig. 6: (A) Cyclic voltammetric response of P-L-Arg/MWCNTs-CTAB/GCE in buffer solution (pH 3.0) at different scan rates. (B) and (C) represent the variation of the cathodic (a) and anodic (b) peak current of the same electrode vs. scan rate and square root of scan rate, respectively .(D) Variation of peak potential separation vs. log v.

fast and low cost, the present electrode seems to be of great utility for making the voltammetric sensor for the detection of Ru.

Repeatability and long-term stability of the electrode

By repetitive CV of the P-L-Arg/MWCNTs-CTAB/GC electrode for approximately 30 times in PBS solution at a scan rate of 100 mVs^{-1}, the peak current value decreases less than %3 indicating good stability. The modified electrode retained its initiate activity for more than 25 days when kept in air at ambient conditions. A decrease of 7% was observed in the current response of the electrode at the end of 25th day. In addition, repetitive recording of cyclic voltammograms in Ru

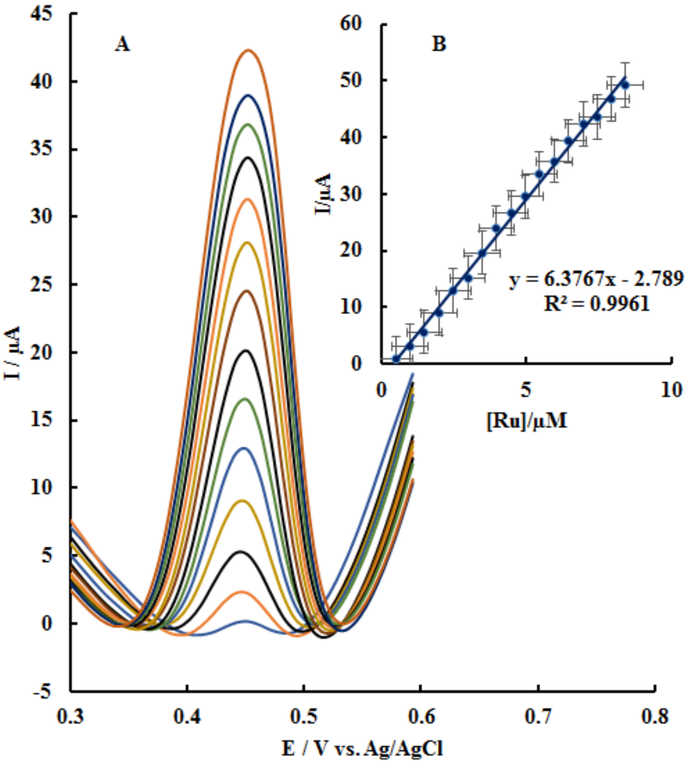

Fig. 7: (A) DPV of different concentrations of rutin (in the range of 0.49 to 8.4 μM) and (B) concentration calibration curve of the DPV current response for rutin in PBS buffer pH 3.0 at scan-rate of 20 mV s^{-1} and 50 mV pulse amplitude.

Table 1: Merits of comparable methods for determination of Ru.

Electrode	pH	Limit of detection (μM)	Linear dynamic range (μM)	Ref.
GR/CILE	2.5	0.24	0.07-100	[11]
PAO-GR/CILPE	2	0.082	0.03– 800	[12]
IL/CPE	3.29	0.01	0.04– 10	[13]
IL-CCE	2.0	0.09	0.3-100	[14]
PVP/CPE	6.0	0.15	0.39–13	[15]
IL-CPE	2.5	0.0358	0.05-100	[16]
LF/GCE	4.6	0.0025	0.005-0.01	[17]
SWNTs/Au electrode	5	0.01	0.02-5	[18]
GR-MnO_2/CILE	2.5	0.00273	0.01-500	[19]
CTAB/ABPE	-	0.004	0.006-10	[20]
GR/Au/CILE	2.5	0.0255	0.08-80	[21]
MWNTs/ β-CD	-	0.02	0.04-1000	[22]
P-L-Arg/MWCNTs/GCE	3.0	0.048	0.1-10	This work

Table 2: Experimental results for the determination of Ru in human blood serum (n =3).

No.	Spiking (μM)	Found (μM)	Recovery(%) (%)	RSD (%)
1	0		Not detected	
2	0.99	1.03	104	1.3
3	1.99	2.01	101	0.99
4	2.49	2.39	96	2.82
5	2.99	2.93	97.9	2.1
6	3.48	3.57	102	1.61

solution tested the reproducibility electrochemical behavior effect of the modified GCE. It was found that the relative standard deviation (R.S.D.) of the peak currents of 9.9 µM Ru for five replicate determinations was 3.3%.

Interference study

One of the most important problems in practical applications of sensors is the effect of interfering species possibly present in real samples. The influence of various potentially interfering substances with the determination of Ru (1.99 µM) was studied under the optimum conditions at pH 3.0, using DPV.

The tolerance limit was defined as the maximum concentration of the interfering substance that caused an error of less than ±5% for the determination of Ru. It was found that 100-fold Cu^{2+}, 200-fold NH_4^+ and K^+, 40-fold Mg^{2+}, Al^{3+}, 20-fold ascorbic acid, and quercetin, for epinephrine 120-fold, for glycine 50-fold and for cysteine approximately 40-fold, had no effect on the detection of Ru. From these results, it may be concluded that the method is free from interference by most foreign substances. In view of its inherent selectivity combined with its great operational stability, the proposed sensor shows promising properties for use in real samples with minimal sample preparation.

Determination of Ru in human blood serum

The modified electrode was applied to the determination of Ru in human blood serum. Although there are ascorbic acid and some other interfering substances, such as proteins and quercetin, they do not interfere with the determination of Ru. Using the proposed methods described above, the results were shown in Table 2. The recovery and R.S.D. were acceptable, showing that the proposed methods could be efficiently used for the determination of Ru in human blood serum.

CONCLUSIONS

The present study has demonstrated the development of electrochemical detection of Ru that is based on the electropolymerization of polymeric film and MWCNTs-CTAB composites. The surface morphology of the modified electrode has been examined by using SEM analysis. The resulting P-L-Arg/MWCNTs-CTAB modified electrode showed a significant voltammetric response to Ru. High stability, good reproducibility, rapid response, easy surface regeneration and fabrication are the important characteristics of the proposed electrode.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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