



Determination of Riboflavin by Nanocomposite Modified Carbon Paste Electrode in Biological Fluids Using Fast Fourier Transform Square Wave Voltammetry

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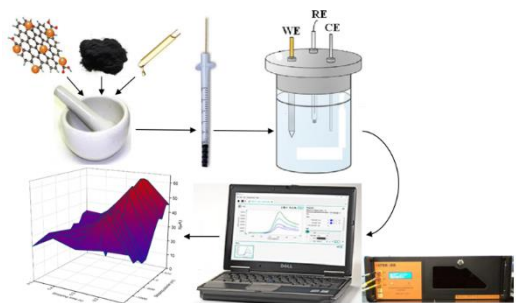
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ABSTRACT

Herein, fast Fourier transformation square-wave voltammetry (FFT-SWV) as a novel electrochemical determination technique was used to investigate the electrochemical behavior and determination of Riboflavin at the surface of a nanocomposite modified carbon paste electrode. The carbon paste electrode was modified by nanocomposite containing Samarium oxide (Sm_2O_3)/reduced graphene oxide (RGO) (2:1) to improve detection sensitivity of Riboflavin under optimal experimental conditions. Furthermore, the signal-to-noise ratio was significantly increased by application of discrete fast Fourier transformation analysis, background subtraction and two-dimensional integration of the electrode response over the selected potential range and the time window. Obtained cyclic voltammograms demonstrated a diffusion-controlled reversible electron transfer reaction for Riboflavin in phosphate buffer solution (pH=7.2). The peak potential values were pH-dependent, involving the same numbers of protons and electrons. To obtain the maximum sensitivity, some effective parameters such as scan rate (10 mV/s), accumulation time (0.2 s) and potential (+400 mV), frequency (1420 Hz) and amplitude (20 mV) were optimized. As a result, determination of Riboflavin using FFT-SWV showed a linear range of response from 10 to 400 nM ($R^2=0.9993$), with limit of detection of 0.86 nM. An acceptable recovery percent was also obtained for Riboflavin in human plasma samples as criteria of measurement applicability of the proposed modified electrode.

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1. INTRODUCTION

Vitamin B2 or Riboflavin is a renowned water-soluble vitamin from Vitamin B group with a chemical structure shown as Scheme 1. Riboflavin could be found in natural foods, like milk and dairy products; meat, eggs, cereals, and fresh vegetables [1]. As this vitamin would not be stored in human body, regular daily consumption would be so critical. In order to ensure the daily

recommendations of riboflavin intake, accurate and fast method for determination of Riboflavin in pharmaceutical and serum samples is crucially important.

Riboflavin comprises two coenzymes, flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). In general, FAD and FMN [2] can easily loss or gain one or two electrons or hydrogen atoms through bonding to specific enzymes, thus Riboflavin participates in redox reactions [3]. Several techniques have been used for determination of Riboflavin such as chemiluminescence [4], high-performance

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chromatography (HPLC) [5] coupled with fluorometric [6] or ultraviolet, voltammetry, surface plasmon resonance (SPR), fluorescence, and spectrophotometry [1]. Although, these methods having their own advantages, they mostly are time-consuming, exclusive instruments, and include intricate sample preparation and procedures. Today, modern electrochemical determination techniques are more striking due to their unique properties like being low-cost, having high sensitivity, long-term reliability and reproducibility [7]. In addition, it is proved that combining classic electrochemical techniques such as SWV with fast Fourier transform (FFT) could successfully lead to gain higher sensitivity compared with using the conventional technique. Based on literature [8], the electro-reduction of Riboflavin is a reversible process including two electrons and two protons (Figure 1).

In electrochemical systems, the working electrode has known to have special place since it has a highly determinative role in the result outcome both from sensitivity and accuracy aspect. One of the most important criteria is being able to be chemically modified by vast range of nanomaterial types. Among all carbon based nanomaterials, graphene, graphene oxide and reduced graphene oxide (RGO) due to their mechanical, chemical and electronic approaches are the center of focus nowadays [9-11]. However, aggregating and stacking of the layers of RGO is known as one of disadvantages [12]. Due to this reason, the presence of oxide state of nanomaterials like samarium oxide could prevent this phenomenon [13] by moving the layer sheets apart for specific period of time [14].

This work presents the quantitative determination of Riboflavin by a nanocomposite modified carbon paste electrode using fast Fourier transform square wave voltammetry (FFTSWV) under effective experimental optimal conditions. The obtained calibration curve was achieved and then Riboflavin was determined in some biological fluids as the real sample.

2. EXPERIMENTAL

2.1. Chemicals and Apparatus Graphite powder with a 1–2 μm particle size (Merck) and paraffin oil

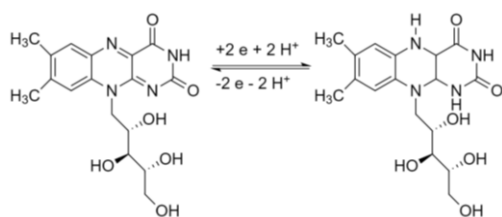


Figure 1. Chemical structure and redox reaction of Riboflavin

(Aldrich) with high purity was used for the preparation of the carbon paste electrodes. Phosphate buffer solutions 0.1 M were prepared using potassium phosphate and D-potassium phosphate salts purchased from Merck. Moreover, for adjusting the pH value of the electrolyte solution NaOH and HCl were used that were also purchased from Merck. The Sm_2O_3 and RGO nanomaterials, which were employed as modifiers were prepared and used through the previous work [15]. A concentrated solution of Riboflavin (10^{-3} M) was obtained by dissolving the appropriate stoichiometric value into double distilled water, other solutions with less concentration values were prepared by diluting the stock solution. Due to the sensitivity of the drug and its lifetime, all solutions of the drug were stored in dark and cold place and prepared freshly every day.

For the real sample analysis, human blood plasma samples were collected from a local blood products organization and stored at -20°C . After slow melting, nitric acid was added to the plasma to precipitate the proteins. Then, the mixture was stirred for 30 min and centrifuged for 10 min at 5600 rpm. The riboflavin also was purchased from a local company.

All electrochemical experiments were carried out using a homemade ultra-voltammetry system designed in center of excellence electrochemistry at University of Tehran. The setup comprised of a PC PIV Pentium 900 MHz microcomputer, equipped with a data acquisition board (PCL-818HG, Advantech. Co.), and a custom-made potentiostat connected to a PC, was assembled with an analog to digital (A/D) board. All data acquisition and data processing programs were developed in Delphi 6[®] program software environment [16]. Also, the employed electrochemical system contained an Ag/AgCl as the reference electrode, a pencil graphite as the counter electrode and modified carbon paste electrodes as the working electrode.

2.2. Carbon Paste Electrode Preparation The bare carbon paste electrode was prepared by mixing a certain amount of graphite powder and the paraffin oil (7:3 w/w) and the modified one was reached through mixing the graphite powder, 300 μL of modifier with the same amount of the oil. In the case of making the modified electrode, the paste materials were sonicated for 15 minutes to spread the materials more appropriately. Besides, in order to have a uniform paste it was then mixed thoroughly with the certain amount of oil for 10 minutes. The paste was then packed into a plastic syringe. The electrical contact was made by copper wire inserted into the opposite end. The surface of all CPEs was polished on a soft clean paper and rinsed with double distilled water prior to each measurement.

3. RESULT AND DISCUSSION

3. 1. Electrochemical Behavior Study of Riboflavin

To perform electrochemical measurements of Riboflavin, selecting the best composition of the electrode material is very important. Figure 2 shows the current changes in terms of different percentages of modifiers in Riboflavin 1.0×10^{-4} M in PBS 0.1M at pH=7.2 using cyclic voltammetry. Therefore, the $\text{Sm}_2\text{O}_3/\text{RGO}$ (2:1) modified CPE had higher sensitivity for the electrochemical determination of Riboflavin and this composition was selected for further steps.

3. 2. Electrode Surface Characterization

Field emission scanning electron microscopy (FESEM) was used for investigation of the surface of bare and nanocomposite modified carbon paste electrodes. FESEM images of bare (a) RGO (b) and $\text{Sm}_2\text{O}_3/\text{RGO}$ (2:1) (c) modified electrodes are shown in Figure 3. As shown in this figure, nanoparticles could fill the holes in the bare electrode surface and distributed uniformly through the whole of electrode surface. Samarium oxide nanoparticles also could fill the empty space between graphene single layers and prevent the restacking of the RGO sheets. Hence, using these nanocomposite has effectively increased the electrode surface. The scattering pattern of carbon, oxygen, and samarium were shown in Figure 4. These images clearly indicate presence of samarium oxide in the electrode. Also, Table 1 shows the EDX analysis resulted in from the related SEM image for the nanocomposite modified CPE.

3. 3. Effective Parameters

3. 3. 1. Effect of pH

Due to the dependence of the redox reaction mechanism of Riboflavin to pH value of the reaction solution, the pH effect was studied in the value range of 3.2 to 8.2. As shown in Figure 5, by increasing the pH of the solution from 3.2 to 7.2, the

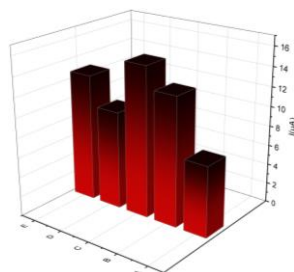


Figure 2. Current changes of different type of CPEs A: Bare CPEs, B: RGO, C: $\text{Sm}_2\text{O}_3/\text{RGO}$ (2:1), D: $\text{Sm}_2\text{O}_3/\text{RGO}$ (1:1) and E: $\text{Sm}_2\text{O}_3/\text{RGO}$ modified CPEs (1:2) in Riboflavin solution 1×10^{-4} M in PBS at pH=7.2 at scan rate of 10 mV/s

TABLE 1. EDX Analysis obtained from the nanocomposite modified CPE SEM image

Element	W%	A%
C	84.07	91.47
O	9.79	8.00
Sm	6.14	0.53
	100.00	100.00

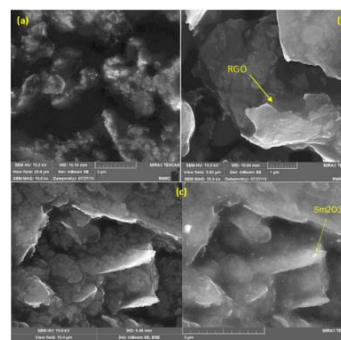


Figure 3. SEM images of bare CPE (a), the RGO modified CPE (b) and $\text{Sm}_2\text{O}_3/\text{RGO}$ (2:1) modified CPE (c)

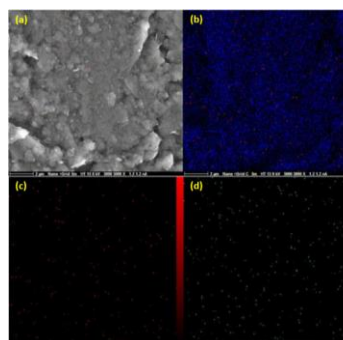


Figure 4. (a) SEM image of the nanocomposite modified CPE used for map analysis, disperse pattern of carbon (b), samarium (c), oxygen (d)

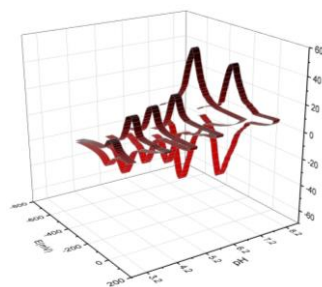


Figure 5. Effect of pH on the redox reaction of Riboflavin solution 1×10^{-4} M

potential of the cathodic and anodic peaks were shifted to more negative ones, and the current response of the cathodic and anodic peaks increased as well. In the case

of alkaline solutions, Riboflavin structure could have been destroyed and absorption would be increased due to the protonation process enhancement [17]. Also, the anodic and cathodic peaks shifted toward positive potentials, and the current intensity decreased and it totally disappeared in more alkaline solutions. Regarding the current intensity in these voltammograms at various pH values, PBS with pH=7.2 was selected as optimum pH value.

The potential of electrochemical reaction of Riboflavin observes the following equation

$$E'_{ox} = E_{ox} - (2.303mRT/2F)pH \quad (1)$$

In which, m , R , T , F and E_{ox} are number of electrons involved in the reaction, universal gas constant, temperature, Faraday constant and potential of oxidation at pH=0, respectively. Hence we expected E'_{ox} to be changed linearly as a function of pH. The linear relationship for the reduction process was also observed.

Oxidation-reduction of Riboflavin in different pH values shows that by increasing the pH, the redox peaks shifted to more negative potential values. The obtained experimental results are in agreement with the theoretical principles of redox reactions, which suggested that both of the half-electrochemical reactions followed the same mechanism of proton transfer [18, 19].

3. 3. 2. Scan Rate Effect

In order to investigate the scan rate effect on the experimental system, the response of the nanocomposite modified CPE in 1.0×10^{-4} M Riboflavin in PBS (pH=7.2) was exposed to the various scan rates in the range of 1–12 mV/s. As shown in Figure 6(a) the current intensity of the cathodic and anodic peak was increased by enhancing the scan rate from 6.2 to 14.3 and 6.0 to 16.4, respectively. The nanocomposite modified CPE showed the maximum current value at scan rate of 10 mV/s. In addition, as Figure 6(b) presents, linear relationship between I_{pa} , I_{pc} vs. square root of scan rate. This linear relationship could be the indication of diffusion-controlled behavior of Riboflavin electrochemical, which is essential for the quantitative measurements.

3. 4. FFTSWV Measurements

In this step, the measurement applicability of the nanocomposite modified CPE was studied. Prior to the step, in order to reach the maximum efficiency, the electrochemical technique parameters such as frequency and amplitude were investigated and optimized.

3. 4. 1. Frequency And Number of Cycles Effect

Since every redox reaction at the electrode surface has kinetic limitation, the rate of applied potential can be considered as a key factor for the method sensitivity. The applied potential rate is highly dependent on the frequency range of the amplitude [20]. On this

approach, frequency was changed in the range of 88–1420 Hz and the result is shown in Figure 7(a). Although the sensitivity could be increased at higher frequencies, but it was also limited by some parameters such as solution resistance and electrode diameter as well. On the other hand, the capacitance could be increased in the same manor. The frequency in square wave voltammetry has the same role as the sweep rate in cyclic voltammetry so, as expected as it increased, the scanning time and current enhanced, but in frequencies higher than 1420 Hz, due to the electrode capacitance, the peak was broaden. Therefore, frequency of 1420 Hz was selected for quantitative measurement of Riboflavin.

One of the advantages of the FFTSWV method is the ability to apply multiple cycles in each step of the potential. By changing the number of cycles, it would be possible to average the obtained data and record the result. Averaging the obtained data could successfully increase the signal-to-noise ratio. As shown in Figure 7(b), by enhancing the number of cycles from 2, the electrode response decreased due to the occurrence of the very fast redox reaction of Riboflavin at the electrode surface. Besides, the decrease in response could be allotted to the surface saturation and reduced active sites.

3. 4. 2. Effect of Accumulation Time and Potential

From another point of view, the sensitivity of electrochemical systems depends on the

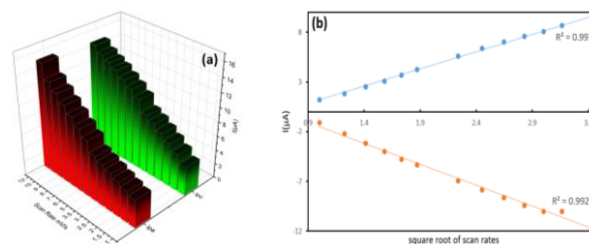


Figure 6. (a) The electrode response for cathodic and anodic peaks based on different scan rates and (b) anodic and cathodic currents vs. square root of scan rate for Riboflavin solution 1×10^{-4} M in PBS pH=7.2

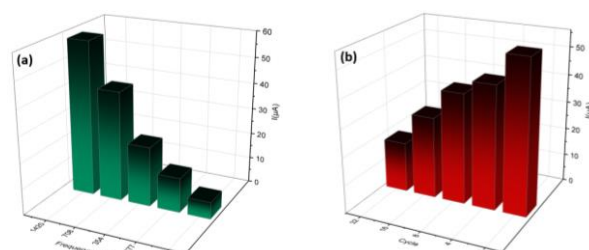


Figure 7. Effect of frequency (a) and number of cycles (b) on redox reaction of Riboflavin solution 1×10^{-4} M at pH=7.2

preconcentration of the analyte through physical, chemical, and electrochemical adsorption. On this basis, if the optimum time is not given to the analyte to be accumulated at the electrode surface, the outcome response would be decreased and if accumulation time is considered much more than the optimum value, the electrode response would also decrease due to the saturation of the species at the electrode surface.

To investigate the effect of these parameters, the accumulation potential and time were changed from -1400 to +800 mV in the range of 0.1 to 0.5 s, respectively for Riboflavin 1.0×10^{-4} M of in PBS at pH=7.2. As shown in Figure 8, the accumulation time of 0.2s and potential of +400mV were selected as the optimum values (Figure 8).

3. 4. 4. Effect of Amplitude In FFT measurements, factor of amplitude, as well as frequency, is one of the effective parameters in the electrode response, background noise and voltammogram peak width [21]. To investigate the effect of amplitude, it was changed in the range of 10-40mV. The results showed that the electrode response was increased by increasing the amplitude value up to 20mV and after that, in more amplitude values, the electrode response decreased, so the 20mV was selected as the optimized amplitude for the next steps.

3. 5. The Calibration Curve In order to evaluate the measurement applicability of the nanocomposite modified CPE in Riboflavin determination, the concentration series of Riboflavin in the range of 0.06 to 100000 nM was prepared in PBS pH = 7.2 and the electrode was exposed to them and the related signal was recorded. As shown in Figure 9, there were two linear regions of response, the first region was related to high concentrations, so had less sensitivity and was not been considered, and the second region was associated with low concentrations of Riboflavin. One of the other important criterias in determination is the relative standard deviation (RSD) percentage that was 1.2% for 5 times determination and was calculated through the following equation:

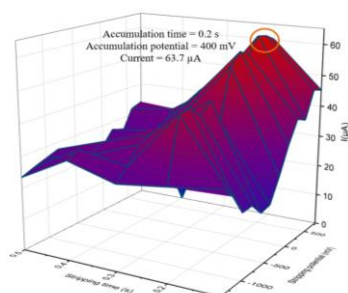


Figure 8. Effect of accumulation time and potential for Riboflavin solution 1×10^{-4} M in PBS 0.1 M at pH=7.2

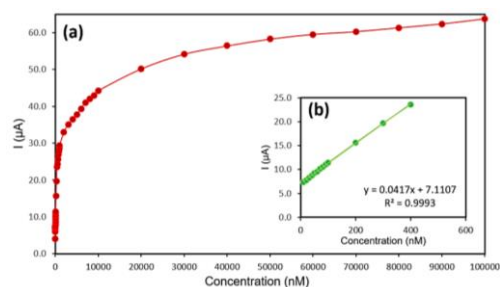


Figure 9. Calibration curve of Riboflavin in PBS 0.1 M at pH=7.2, frequency 1420 Hz, accumulation time 0.2 s, accumulation potential +400 mV, cycles 2 and amplitude 20 mV

$$\%RSD = \frac{s}{\bar{x}} \times 100 \quad (2)$$

Where s is standard deviation and \bar{x} is the mean of the data.

Also, the detection limit of 0.86nM was calculated for 10-400 nM linear range ($R^2 = 0.9993$) using the equation below:

$$LOD = 3 S_b/m \quad (3)$$

where S_b is the standard deviation obtained from the PBS without Riboflavin and m is the slope of the calibration curve.

Furthermore, Table 2 shows the limit of detection of some recent methods employed for Riboflavin determination. As it can be seen, the proposed electrode and the used electrochemical method in this study has provided acceptable detection limit compared with the other methods besides, the obtained linear range was wide in low concentration values and the proposed method procedure was much more simple.

3. 6. The Real Sample Analysis The purpose of this step is to demonstrate the feasibility of the proposed method for measuring Riboflavin in some biological environments. Real sample analysis and the experiment was done using standard addition method. Based on the

TABLE 2. Riboflavin determination results in comparison with some recent applied methods

Method	Detection Limit	Linear Range	Ref.
CV ^a -with modified CPE	7.1 μ M	1.7-34 μ M	[22]
DPV ^b -with modified GCE ^c	0.027 μ M	2.0-110 μ M	[23]
SWAdSV ^d -with BiFE ^e	0.1 μ M	1.0-9.0 μ M	[24]
SWV-with SMDE ^f	0.1 μ M	-----	[25]
FFT-SWV	0.86 nM	10-400 nM	This work

^a: Cyclic voltammetry, ^b: differential pulse voltammetry, ^c: glassy carbon electrode, ^d: square wave adsorptive stripping voltammetry, ^e: bismuth film electrode, ^f: static drop mercury electrode

method, the first sample contained no added volume of standard solution of Riboflavin. Then, for other samples, constant values of Riboflavin in the biological sample were considered and the final concentration for each sample was reached by adding various volumes of standard solution of Riboflavin. Finally, each solution response was recorded as mentioned in previous sections. As shown in Table 3, the added and found values besides the relative standard deviation and the recovery percents are available. Appropriate results indicated that the proposed electrode had high selectivity to determine Riboflavin in complex biological matrices.

TABLE 3. Results of drug measurement in plasma

No.	Added (nM)	Founded (nM)	Number of runs	Recovery (%)	RSD (%)
1	0	20.2	3	-	-
2	80	92.5	3	115.6 %	3.1 %
3	200	215.2	3	107.6 %	3.9 %
4	300	319.7	3	106.5 %	2.9 %

4. CONCLUSION

In the present study Riboflavin was determined by $\text{Sm}_2\text{O}_3/\text{RGO}$ nanocomposite modified carbon paste electrode under optimized experimental conditions using FFTSWV. The nanocomposite proved to have uniformed structure and successfully catalyzed Riboflavin redox reaction at the electrode surface. Furthermore, based on the obtained results, a wide linear range of response in low concentrations were obtained and also the detection limit of 0.863 nM was achieved. The proposed electrode in combination with the developed electrochemical determination technique was shown to have simplicity of procedure, non-toxic besides having appropriate sensitivity and accuracy, while having adequate performance ability in Riboflavin determination specifically in some biological complex matrices.

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Persian Abstract

چکیده

برای بررسی رفتار الکتروشیمیایی و اندازه‌گیری ریپوفلاوین در سطح الکتروود خمیر کربن اصلاح شده از روش ولتامتری عاری‌سازی موج مربعی با تبدیل فوری استفاده شد. برای بهبود حد تشخیص، الکتروود خمیر کربنی با نانوکامپوزیت ساماریم اکساید/گرافن اکساید کاهش یافته با نسبت ۲ به ۱ اصلاح گردید. مطالعات ولتامتری چرخه‌ای نشان داد ویتامین B2 در بافر فسفاتتی در یک فرآیند انتقال الکترون برگشت پذیر تحت کنترل نفوذ شرکت می‌کند و پتانسیل اکسایش-کاهش به pH محیط بستگی دارد. برای بهبود حد تشخیص و افزایش حساسیت اندازه‌گیری به بهینه‌سازی پارامترهای موثر در اندازه‌گیری پرداخته شد. شرایط بهینه اندازه‌گیری در فرکانس موج مربعی ۱۴۲۰ هرتز، زمان تجمع ۲ ثانیه، پتانسیل تجمع ۴۰۰ میلی ولت و دامنه موج مربعی ۲۰ میلی ولت بدست آمد. ناحیه خطی برای ریپوفلاوین ۴۰۰-۱۰ نانومولار با حد تشخیص ۸۶ نانومولار می‌باشد.
