Electrochemical detection of cholesterol in a buffer solution with a glassy carbon electrode doctored by ZnO/SnO2/RuO2 nanomaterials

Md Mahmud Alam (alam-mahmud@hotmail.com)  
Shahjalal University of Science and Technology  
https://orcid.org/0000-0002-2636-5038

M.T. Uddin  
Shahjalal University of Science and Technology

Abdullah M. Asiri  
King Abdulaziz University

Mohammed M. Rahman  
King Abdulaziz University

M.A. Islam  
Shahjalal University of Science and Technology

Research Article

Keywords: ZnO/SnO2/RuO2 nanoparticles, Cholesterol sensor, Pathological diagnosis, Electrochemical method, Glassy carbon electrode

DOI: https://doi.org/10.21203/rs.3.rs-227092/v1

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Abstract

This electrochemical study performed to develop a cholesterol sensor using a glassy carbon electrode (GCE) coating with ternary low-dimensional ZnO/SnO$_2$/RuO$_2$ nanomaterials (NMs). The ZnO/SnO$_2$/RuO$_2$ NMs characterized using FESEM, XPS, EDS and XRD analysis. The desired cholesterol sensor fabricated by coating a GCE with ZnO/SnO$_2$/RuO$_2$ NMs as a film of the thin-layer using suspension of ethanol with 5% Nafion binder, which performed to the analysis of cholesterol electrochemically in the phosphate buffer phase. The resulted electrochemical responses have exhibited the linearity from 0.1nM ~ 0.01mM of cholesterol in current versus concentration plot, which defined as a calibration curve of this sensor development. The linear concentration (0.1nM ~ 0.01mM) of cholesterol corresponding with the current response is known as the dynamic range (LDR) for detection of target analyte. The sensitivity is calculated from the slope of calibration-curve found as 11.3513 µAµM$^{-1}$cm$^{-2}$. The lower limit of detection (91.42 ± 4.57 pM) is obtained from signal/noise (S/N = 3) at 3. In the real-samples detection process, the fabricated cholesterol sensor is exhibited good reproducibility, fast response time and ability to perform in long-duration of sensor elapse time. In the end, this method is shown the reliable detection of cholesterol in the buffer phase and would be very perspective in the recent future in-term of a simple as well as reliable technique in the field of pathological diagnosis.

Introduction:

The cholesterol is a steroid wax of fat and essential element of the cell membrane in mammalian. It performs a precursor to the formation of varies biochemical such as steroid hormones, vitamin D, and bile acid [1, 2]. The cholesterol concentration in blood is a fundamental indicator of the detection of numerous diseases as coronary heart disease, hypertension, lipid metabolism dysfunction, brain thrombosis, arteriosclerosis, and myocardial infarction [3–5]. Therefore, imbalanced cholesterol in human blood (low and high) is responsible for human health hazardous effects [6–9]. Herein, a sensitive and reliable method to detect cholesterol is necessary. Up to date, the spectrometric [10], colourimetric [11] and electrochemical methods [12] are applying for this purpose. An alternative approach of the electrochemical technique is a popular topic to researchers due to its reliable detection of numerous biochemical using metal oxides (semi-conductive) on GCE [13–16]. Therefore, this study performed to fabricate a sensor by a mixture of semi-conductor metal oxides coating a GCE.

The ZnO p-type semiconductor has 3.37 eV bandgap energy, and 60 meV exciting binding energy. As a result, it exhibits the attractive photosensitivity, electrochemical properties, and stability, essential for the fabrication of reliable biochemical sensor [17–18]. Several types of research have shown ZnO as successive sensing mediator for the detection of benzaldehyde [20], bisphenol A [21], acetone [22], ethanol [23] and melamine sensor [24] and others. The SnO2 is another semi-conductive metal oxide having bandgap energy of 3.6 eV, and due to the useful physio-electro-chemical properties, it has widely applied as a catalyst, biosensor, lithium battery, gas sensor and monitoring electronic device for environmental monitoring [25–29]. The transition metal oxide is RuO2 containing the favourable the electrochemical properties for technological application. For its the high stability (chemical), and
conductivity with excellent diffusion barrier properties, the various application of RuO2 have been executed such as supercapacitors, the electrode of chlorine generator, catalyst for splitting the water, CO2 methanation and CO sensor [30, 31].

Therefore, the objective of this study is to the development of a biochemical sensor applying ZnO/SnO2/RuO2 NMs as a thin film on GCE using 5% Nafion suspension as a binder to the selective detection cholesterol in the buffer phase. From the linear relation of current versus concentration of cholesterol, the analytical parameters of cholesterol sensor calculated. Furthermore, the fabricated cholesterol admired in the analysis of real bio-samples. Thus, this is a unique technique for the development of future sensor technology in pathological diagnosis.

**Experimental:**

**Materials and methodology:**

The nanoparticles of ZnO/SnO2/RuO2 prepared to apply wet-chemical synthesis method using the analytical grade of Zn(CH3COO)2·2H2O, SnCl4, ruthenium(III)2,4-pentanedionate and urea as precursors obtained from Sigma-Aldrich. Moreover, D-glucose, uric acid, folic acid, L-leucine, bilirubin, testosterone, L-lactic acid, choline, tannic acid and cholesterol in the form of analytical grade were procured from the Sigma-Aldrich and supporting chemicals such as mono- & disodium phosphate and 5% Nafion in ethanol was used to execute this study. The Thermo-scientific XPS with K-α1 radiation source, 300.0 µm beam and 200.0 eV pass energy performing at 10-8Torr implemented to investigate the ionization states of the existing atoms (Ru, O, Sn and Zn). The morphology of the prepared NMs figured out by FSEM (JEOL, JSM-7600F, Japan) attached to EDS analysis. The unit cell crystallinity and grain size of NMs evaluated by the powder X-ray diffraction analysis. The electrochemical characterization of ZnO/SnO2/RuO2 NMs on GCE examined through a Keithley electrometer as the source of a constant supply of potential (volts).

The synthesized of ZnO/SnO2/RuO2 NMs:

ZnO/SnO2/RuO2 nanoparticles prepared by homogenous precipitation technique, where, zinc acetate dihydrate (Zn(CH3COO)2·2H2O) and tin tetrachloride used as precursors, and urea as a precipitating agent. In a typical procedure, the 5 mL of SnCl4 and 20 g of urea added in 100 mL water (deionized) into a 200 mL beaker. The solution stirred with a magnetic bar at 90° C for four hours with reflux. At these high alkaline conditions, the white precipitates obtained. Then, it centrifuged to separate from the aqueous reaction medium and successively washed with deionized water to till neutral. At 110° C, the resultant white precipitate dried overnight in an oven, and after that, it crashed into a mortar to make nano-sized particles. Subsequently, the nano-powder calcined into a muffle furnace at 500° C in the presence of atmospheric air for 5 hours to obtain SnO2 nanoparticle. A similar procedure applied to prepare ZnO nanoparticle. At this procedure, 3.12 g Zn(CH3COO)2·2H2O dissolved in 200 mL of water (deionized) with 12 g of urea into 300 mL beaker and stirred until homogeneous mixture obtained. Then, it followed keeping at 90°C around 4 hours on the heating plat to precipitate out quantitatively. After the
separation and washing with deionized water successively of resultant precipitate mass, it dried at 110°C overnight. Then, the calcination carried out into muffle furnace at the same procedure as in above. To form 10% of ruthenium in a mixture (10% RuO₂, 45% SnO₂ and 45% ZnO), the calculated amount of ruthenium (III) 2, 4-pentanedionate dispersed into 50 mL deionized water with SnO₂ and ZnO in 100 mL beaker following by stirring at room conditions. Then, water removed by drying in an oven at 110 ºC overnight. The obtained powder was then ground and calcined at 500 ºC for two hours in the air to achieve the desired ZnO/SnO₂/RuO₂ NMs.

The fabrication of GCE by ZnO/SnO₂/RuO₂ NMs:

The working electrode is the heart of an electrochemical sensor, and it assembled by the modification of GCE with prepared ZnO/SnO₂/RuO₂ NMs. In this typical fabrication method, a thick ethanolic slurry of synthesized ZnO/SnO₂/RuO₂ NMs prepared, and applied to layer on a GCE as a thin film very carefully. Subsequently, it dried at the room conditions. For the necessary stability of NMs layer on GCE, few drops of Naon added on the dry modified surface of GCE and followed keeping at 35˚C into an oven for a satisfying duration to dry it again. The sensor assembling using Keithley electrometer did, where ZnO/SnO₂/RuO₂ NMs/GCE and Pt-wire connected at electrometer in a series manner performing as working and counter electrode respectively. The mother solution of cholesterol (0.1 mM) used to prepare several solutions ranging from 0.1 mM to 0.1 nM acting as a targeted analyte in I-V analysis. The sensors parameters sensitivity, LDR, and DL calculated from the slope, obtained from a linear plot of current versus concentration of cholesterol named calibration curve. The buffer solutions formed by the equimolar mixing of mono- & disodium phosphate in deionized water. In the I-V investigation, the buffer solution took 10 mL in the measurement as constant through the experiment. The sensor applying electrochemical (I-V) approach is a simple two-electrode system (working and counter).

Results And Discussions:

The surface composition analysis by XPS:

The binding energy (eV) and ionizations of NMs analyzed by the XPS investigation. The resultant data presented at Fig. 1 showing the orbitals of Zn2p level located at 1022 and 1045 eV with the respect of Zn2p3/2 and Zn2p1/2 spin orbitals separately. The Zn2p level's spin orbitals separate with 23 eV, a characteristic value of Zn²⁺ oxidation, which has been reported previously [32-34]. The O1s orbital shows an XPS peak located at 531 eV and can recognize as chemisorbed oxygen on NMs surface involved the oxidation of O²⁻[35-37]. The orbitals of Sn3d level recognized as the spin orbitals of Sn3d₅/₂ and Sn3d₃/₂ are shown in Fig. 1(c) and positioned at 487 and 495 eV correspondingly with the binding energy separation of 8 eV, which is conformed Sn⁴⁺ oxidation in the synthesized ZnO/SnO₂/RuO₂ NMs [38-40]. XPS peak of Ru3d shows two recognized orbitals (spin) located at 281.08 and 285.12 eV, which are corresponded to Ru3d₅/₂ and Ru3d₃/₂ spin orbitals shown in Fig. 1(d), but the spin-orbital of Ru3d₃/₂
overlapped with C1s orbital. The spin energy difference between Ru3d_{5/2} and Ru3d_{3/2} is equal to 4.04 eV, a characteristic value of Ru^{4+} ionized state [41, 42].

**The morphology of synthesized ZnO/SnO\textsubscript{2}/RuO\textsubscript{2} NMs:**

The FESEM analysis performed to evaluate the structural morphology as-prepared ZnO/SnO\textsubscript{2}/RuO\textsubscript{2} NMs exemplified in Fig. 2(a-b) showing the low and high magnifying images of prepared nanomaterials. As seemed at Fig. 1(a-b), the prepared nanomaterials consist of grains of distinct shapes and sizes. The similar information's explores in EDS report as in Fig. 2(c), and it confirms that the synthesized NMs have contained various shape and sizes containing Zn, O, Sn and Ru only shown in Fig. 2(d). The weight compositions of nanomaterials are Zn 43.29%, Sn 48.99%, O 1.26% and Ru 8.97%.

**Powdered X-ray diffraction pattern of ZnO/SnO\textsubscript{2}/RuO\textsubscript{2} NMs:**

To assess, the grains crystallinity and size of ZnO/SnO\textsubscript{2}/RuO\textsubscript{2} NMs evaluate by XRD analysis performed at 2\theta degree (20~80° range) shown in Fig.3, and the resultant XRD data confirms the existence of the crystalline phases of ZnO, SnO\textsubscript{2} and RuO\textsubscript{2} only. The crystalline peaks of SnO\textsubscript{2} are (110), (201), (220), (310), (301) and (321) perceive in Fig. 3, and identified by JCPDS no. 0045-0937 and previously reported articles on SnO\textsubscript{2} [43,44]. Besides this, the diffracted peaks associated with ZnO such as (002), (101), (200) and (202) verified by JCDS no. 0036-1451 and prior authors illustrated in Fig. 3 [45,46]. Moreover, the trace RuO\textsubscript{2} shows two pecks associated with plans of (211) and (220) as explored in Fig. 3 and identified by reported articles [47,48]. The average crystal size ZnO/SnO\textsubscript{2}/RuO\textsubscript{2} NMs estimates following the Scherrer Equation.

\[
D = \frac{(0.94 \lambda)}{\beta \cos \theta} \quad \text{(v)}
\]

Herein \( \lambda \) (wavelength of X-ray radiation) and \( \beta \) (the width at half of peak). The calculated crystal size of synthesized NRs is 7.75 nm at SnO\textsubscript{2} (110).

**The cholesterol detection with ZnO/SnO\textsubscript{2}/RuO\textsubscript{2} NMs sensor:**

The sensor selective to cholesterol amassed with wet-chemically prepared ZnO/SnO\textsubscript{2}/RuO\textsubscript{2} NMs layered on GCE as a film. The GCE modified by the slurry of ZnO/SnO\textsubscript{2}/RuO\textsubscript{2} NMs in ethanol, and the coating did as an efficient way to form a layer of NMs film. The stability of NMs film on GCE enhanced by adding a few drops of Nafion, which improved it's the working duration in buffer solution. The Nafion is known as conductive co-polymer. Therefore, the use of Nafion in the working electrode is enhanced the electron transfer rate of the sensor. As a result, the sensor shows high I-V performances, in the buffer phase, in the cholesterol analyze. The observations like this have reported detecting chemicals and biochemical [49-53]. It appears ZnO/SnO\textsubscript{2}/RuO\textsubscript{2} NMs first time onto GCE to analyze cholesterol and any report regarding this not available. The sensor in the I-V technique is a two-electrode system (working and counter electrode). In the electrochemical investigation of cholesterol in the buffer phase, the holding time in Keithley electrometer set as 1 s.
Initially, the fabricated sensor based on ZnO/SnO$_2$/RuO$_2$ NMs/GCE was applied to investigate several biochemical including D-glucose, uric acid, folic acid, L-leucine, bilirubin, testosterone, L-lactic acid, choline, tannic acid and cholesterol and achieved data presented in Fig. 4(a). The experimented results show in Fig. 4(a), which did at 0.1 µM of each biochemical and applied volts ranging from 0 to +1.5V in the buffer phase of pH 7.0. It explores in Fig. 4(a) that cholesterol exhibits the uppermost current against the applied potential ($v$) and on a comparison of the highest I-V outcome, the cholesterol identifies as selective for the sensor with ZnO/SnO$_2$/RuO$_2$ NMs/GCE. Then, the selected cholesterol subjected to analyze in a rage of concentration of 0.1nM~0.1mM in buffer system of pH 7.0 as exemplified in Fig. 4(b). From the explored I-V curve in Fig. 4(b), it is found that the I-V responses of cholesterol increased with increasing of cholesterol concentration from lower to higher and the resulted I-V outcomes are completely a parted from each other in the sequence of lower-higher concentration of cholesterol. Thus, as shown, the I-V plots are varied with the corresponding concentration of cholesterol as a similar observation has described by earlier authors [54-59].

As illustrated in Fig. 4(c) current versus concentration of cholesterol plot is known as calibration of cholesterol biosensor, and it shows the linearity of current density on a line with corresponding potential (volt) from 0.1nM to 0.01mM of cholesterol, which identified a dynamic range (LDR) to measure. The obtained LDR is consist of a wide range of concentration. To identify the linearity of LDR, current versus log (conc.) was plotted, which matched with the regression coefficient (R2=0.9901) and provided evidence of the linearity of LDR. The sensor sensitivity is an important parameter and calculated from the slope of calibration-curve divided by the cross-section of GCE (0.0316 cm$^2$), and exceptional sensitivity of 11.3513 µAµM$^{-1}$cm$^{-2}$ is apparent. The lower limit of the sensor is calculated by applying 3 (S/N) as the signal-noise ratio and found as 91.42±4.57 pM, which might be appreciable.

The response time measures the sensor efficiency, which defines as the minimum time required to complete the I-V analysis of an analyte. The cholesterol sensor’s response time executed by the plotting of current versus time shown in Fig. 5(a). As perceived in Fig. 5(a), the currents versus time relation become steady at around 20 s. Therefore, it can conclude that the proposed sensor can complete I-V analysis within 20 s and provides the evidence of high efficiency of cholesterol sensor with ZnO/SnO$_2$/RuO$_2$ NMs/GCE. As known, the prepared nanomaterials are a doped mixture of ZnO, SnO$_2$ and RuO$_2$. Thus, the I-V activities of single, binary and ternary metal oxides compared in the detection of cholesterol in the buffer phase and illustrated in Fig. 5(b). As it is exemplified in Fig. 5(b), the doped ZnO/SnO$_2$/RuO$_2$ NMs exhibited the highest electrochemical response, and it is due to the combinational effect of ternary compositions. The reproducibility measures the reliability of a sensor and is an ability to generate identical I-V responses in the analysis of an analyte. For the reliability, the sensor subjected to I-V analysis of cholesterol in the similar conditions such as 0.1 µM concentration, potential range 0~+1.5V in the buffer of pH 7.0 in the continuous seven hours and the outcomes demonstrated in Fig. 5(c). The I-V responses do not change after washing of the electrode in each analysis. The precision of currents data measure at applied potential +1.5V in term of relative standard deviation (RSD), and the outcome is 0.55% (RSD), which is to confirm the high precision. A similar method, the longtime performing ability of
sensor tested as shown in Fig. 5(d) at a similar condition as in reproducibility test. The outcomes are analogous with the reproducibility. Thus, the projected cholesterol sensor with ZnO/SnO$_2$/RuO$_2$ NMs/GCE is well enough to analyze the cholesterol in real bio-samples in electrochemical approach.

A proposed scheme for cholesterol electrochemical oxidation is presented below. The molecules of cholesterol are adsorbed on ZnO/SnO$_2$/RuO$_2$ NMs/GCE surface and oxidized to cholesta-4,6-dien-3-one. In this oxidation of cholesterol, few electrons are formed, which enhances the conductivity buffer solution. As result, the enhanced I-V responses record in the Keithley electrometer. The cholesterol oxidation like similar has described previously [60,61].

The contrast of similar studies are demonstrated in Table 1 in term of the analytical performances of sensor such as LDR, sensitivity and DL [62-64]. Based on the parameters, the cholesterol sensor with ZnO/SnO$_2$/RuO$_2$ NMs/GCE shows the appreciable performances.

Table 1: The contract of the similar studies in term of analytical parameters of cholesterol sensor with ZnO/SnO$_2$/RuO$_2$ NMs/GCE.

| Modified GCE | LDR     | Sensitivity       | DL     | Ref. |
|--------------|---------|-------------------|--------|------|
| ChEt-ChOx/MWCNT/SiO$_2$-CHIT/ITO/GCE | 10~500μM | $3.8\times10^{-3}$ μAμM$^{-1}$cm$^{-2}$ | ———— | 62   |
| Ti/NPAu/ChOx–HRP–ChE/GCE | ———— | $2.93\times10^{-2}$ μAμM$^{-1}$cm$^{-2}$ | ———— | 63   |
| ZnO NRs/GCE | 0.001~45 mM | $10\times10^{-3}$ μAμM$^{-1}$cm$^{-2}$ | ———— | 64   |
| ZnO/SnO$_2$/RuO$_2$ NMs/GCE | 0.1nM~0.01mM | 11.3513 μAμM$^{-1}$cm$^{-2}$ | 91.42 pM | This work |

*DL (detection limit), LDR (linear dynamic range), pM(picomole), mM(millimole).

The analysis of bio-samples applying recovery method:

To appropriate the validation of cholesterol sensor with ZnO/SnO$_2$/RuO$_2$ NMs/GCE assembly, the bio-samples such as human, mouse and rabbit serums were collected and analyzed by I-V approach. The resulted data are presented in the Table 2 and it seemed to quit satisfactory.

Table 2: The analysis of real environmental samples using ZnO/SnO$_2$/RuO$_2$ NMs/GCE chemical sensor by recovery method.
| Sample            | Added cholesterol conc. (µM) | Measured cholesterol conc.\(^a\) by ZnO/SnO\(_2\)/RuO\(_2\) NMs/GCE(µM) | Average recovery\(^b\) (%) | RSD\(^c\) (%) |
|-------------------|-------------------------------|-------------------------------------------------|-----------------------------|---------------|
|                   |                               | R1      | R2      | R3      |                                          |                |
| Human serum       | 0.01000                       | 0.01026 | 0.01022 | 0.01013 | 102.03                                    | 0.65           |
| Mouse serum       | 0.01000                       | 0.01044 | 0.01047 | 0.01031 | 104.06                                    | 0.82           |
| Rabbit serum      | 0.01000                       | 0.01012 | 0.01004 | 0.01000 | 100.56                                    | 0.61           |

\(^a\)Mean of three repeated determination (signal to noise ratio 3) ZnO/SnO\(_2\)/RuO\(_2\) NMs/GCE.

\(^b\)Concentration of cholesterol determined/Concentration taken. (Unit: µM)

\(^c\)Relative standard deviation value indicates precision among three repeated measurements (R1,R2,R3).

**Conclusion:**

Here, the wet-chemically prepared ZnO/SnO\(_2\)/RuO\(_2\) NMs were totally characterized by using FESEM, XRD, EDS and XPS. The cholesterol sensor with ZnO/SnO\(_2\)/RuO\(_2\) NMs/GCE was subjected to analysis of cholesterol in phosphate buffer phase to evaluate the sensor analytical parameters such as reproducibility, stability, response time, sensitivity, LDR and DL and found as satisfactory. To validate this sensor, it was applied to detect cholesterol in real bio-samples by recovery method and showed the acceptable results. Thus, this technique for the development of electrochemical sensor to analyze the biochemicals would be a prospective approach in the field of pathological diagnosis in a broad scale.

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