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Effect of urea on the morphology of Co₃O₄ nanostructures and their application for potentiometric glucose biosensor

Zafar Hussain Ibupoto ¹, Sami Elhag ^{1*}, M. S. AlSalhi ^{2,3}, Omer Nur ¹, and Magnus Willander ¹

¹Department of Science and Technology, Campus Norrköping, Linköping University, SE-60174 Norrköping, Sweden

²Physics and Astronomy Department, College of Science, King Saud University, Riyadh, Saudi Arabia

³Research Chair for Laser Diagnosis of Cancer, King Saud University, Riyadh, Saudi Arabia

* Author to whom correspondence should be addressed; E-Mail: sami.elhag@liu.se; Tel.: +461136 3035; Fax: +46 (0)11 36 32 70.

Abstract: In this study, an effect of different concentrations of urea on the morphology of cobalt oxide (Co₃O₄) nanostructures was investigated. The Co₃O₄ nanostructures are fabricated on gold coated glass substrate by the hydrothermal method. The morphological and structural characterization was performed by scanning electron microscopy, and X-ray diffraction techniques. The Co₃O₄ nanostructures exhibit morphology of flowers-like and have comprised on nanowires due to the increasing amount of urea. The nanostructures were highly dense on the substrate and possess a good crystalline quality. The Co₃O₄ nanostructures were successfully used for the development of a sensitive glucose biosensor. The presented glucose biosensor detected a wide range of glucose concentrations from 1×10^{-6} M to 1×10^{-2} M with sensitivity of a -56.85 mV/decade and indicated a fast response time of less than 10 s. This performance could be attributed to the heterogeneous catalysis effect at glucose oxidase enzyme, nano-flowers, and nanowires interfaces, which have enhanced the electron transfer process on the electrode surface. Moreover, the reproducibility, repeatability, stability and selectivity were also investigated. All the obtained results indicate the potential use of the developed glucose sensor for monitoring of glucose concentrations at drugs, human serum and food industry related samples.

Keywords: Co₃O₄ nanostructures, hydrothermal method, glucose biosensor

1. Introduction

The importance of one dimensional morphologies such as nanowires, nano-belts, and nano-tubes of different nano-materials increasing with a significant number in both scientific study and technology demand due to their unique and attractive properties for the devices fabrication [1-4]. Well controlled preparation of nanowires is a crucial step for achieving the desired objectives [5]. On the other hand, metal oxides nanostructures are capable to fabricate sensitive glucose sensors by immobilizing low isoelectric point (IEP) molecules such as glucose oxidase due to their high IEP which helps in the electrostatic binding among the metal oxides surface and the enzyme molecules. In addition to this, metal oxide nanostructures exhibit high ionic bonding property which also provides polar surfaces for the strong binding of low IEP molecules. Moreover, metal oxide nanostructures have been used for the fabrication of non-enzymatic glucose chemical sensors based on the electro-oxidation of glucose and possess high electro-catalytic properties related to their decreased size, high surface area and fast electron transfer rate [6, 7]. However, the fabrication of none-enzymatic glucose sensor at physiological pH (7.3) value is a difficult and it limits the design of none-enzymatic glucose in addition of their poor selectivity. Therefore, glucose oxidase (GOx) enzyme immobilized metal oxides nanostructures have a solid and wide platform in the development of efficient and sensitive glucose sensors with high selectivity and at physiological pH value.

Cobalt oxide (Co_3O_4) is one of the important transition metal oxides which exhibit worthy sensing properties of potential to the development of effective and efficient amperometric glucose biosensors because of its potential features by exposing a wide response range, detection limit, stability and high selectivity [8-9]. The electrochemical performance of Co_3O_4 may be varied and controlled by several factors including particle size, surface morphology, and proper ability to adhere with conductive substrates. In recent past, Co_3O_4 nanostructures with new morphologies particularly, the self-supported nano-crystalline arrays which grow directly on conductive substrates have demonstrated superb electrochemical performance [10, 11, and 12]. Furthermore, Co_3O_4 nanowires revealed a higher electro-catalytic property because of the fast electron transfer in addition to the high surface area to volume ratio. Therefore, Co_3O_4 nanowires are suitable for sensitive sensing of glucose. The development of a simple and an efficient device for the monitoring of glucose concentrations is of high demanded to control diabetes [13]. The advancement in the field of

nanotechnology has given birth to several attractive nanomaterials which can be replaced by the other nanomaterial during the construction of sensitive glucose sensors, such as a noble metal nanoparticle particularly Au, and Pt. That has been widely used as active transducers and provides suitable microenvironment for the immobilization of GOx [14-17].

In the present work, Co₃O₄ nano-flowers are fabricated on gold (Au) coated glass substrate by varying the concentration of urea which is one of the reacting species for preparation of the Co₃O₄ nanostructures. There is no report till date about the effect of urea concentration on the morphology of Co₃O₄ nanostructures. Furthermore, Co₃O₄ nano-flowers comprised on the Co₃O₄ nanowires are used for the development of a sensitive enzyme based glucose potentiometric biosensor.

2. Experimental Section

2.1. Chemicals

Cobalt chloride hexahydrate, urea, glucose oxidase, glucose, uric acid, ascorbic acid, copper nitrate, potassium dihydrogen phosphate, disodium hydrogen phosphate, potassium chloride, and sodium chloride were purchased from Sigma Aldrich Sweden. All the chemicals used were of an analytical grade.

2.2. Synthesis of Co₃O₄ nanostructures on Au coated glass substrate

The coating of the thin Au layer on the glass slides was done according to the reported work [17]. The synthesis of cobalt oxide nanostructures was fabricated on an Au coated glass substrate by the following growth steps: Firstly, Au coated glass substrates were sonicated in ultrasonic bath for 10 minutes in isopropanol and followed by acetone and washed with distilled water and dried by nitrogen gas. Then a seed solution was prepared by using a 0.1 M of cobalt acetate anhydrous in 125 mL methanol and 65 mL of 0.035 M KOH were mixed. This seed solution was deposited on the cleaned Au coated glass substrates by the dip coating method. The substrates containing the seed particles were then annealed at 120 °C for 20 minutes. The concentration of the urea was varied in order to monitor the effect on the morphology of the synthesized Co₃O₄ nanostructures. The amount of urea added in the growth solution was in the order of 0.23, 0.27, 0.3, and 0.4 M respectively, while the concentration of the cobalt chloride was kept constant at 0.1 M. The growth solution was prepared in a 100 mL of deionized water. The substrates containing Co₃O₄ nano-particles were fixed vertically in

the Teflon sample holder and dipped in the growth solution for 5 hrs. in a preheated electric oven at 96 °C. After the completion of growth time, the samples were cooled naturally at room temperature then washed gently with deionized water in order to remove solid residual particles from the surface of nanostructures. The cobalt hydroxide nanostructures were annealed at 450 °C for 3 hrs. for the conversion of the hydroxide phase of cobalt into oxide phase.

The morphological and structural investigations of the different nanostructures of Co₃O₄ were performed by the LEO 1550 Gemini field emission scanning electron microscope (SEM) working at 5 kV. The crystal quality of cobalt oxide nanostructures was examined by the X-ray powder diffraction (XRD) using a Phillips PW 1729 powder diffractometer equipped with CuK α radiation ($\lambda=1.5418$ Å) using a generator voltage of 40 kV and a current of 40 mA.

2.3. Immobilization of glucose oxidase on Co₃O₄ nanostructures and the electrochemical measurement

The glucose oxidase solution was prepared by dissolving 10 mg of enzyme in 1 mL of 10 mM phosphate buffer solution with a pH value of 7.3. The Co₃O₄ nanostructures were gently dipped in the glucose oxidase solution for 5 minutes and then left to dry at room temperature. The glucose oxidase immobilized cobalt oxide electrodes were kept at 4 °C when not in use. The electrochemical response of the enzyme immobilized cobalt oxide electrodes was measured against a silver-silver chloride as a reference electrode at room temperature using electrical instrument Keithley 2400 model. A 100 mM of glucose analyte was prepared in 10 mM phosphate buffer solution having a pH of 7.3 and low concentrations of glucose were prepared in phosphate buffer solution by dilution.

3. Results and Discussion

3.1. Morphological and structural characterization of Co₃O₄ nanostructures

During the preparation of a specific nanostructure of particular material specific basic substances of the reacting species will be chosen. Varying the concentration of the reactants would result in the formation of a new nanostructure, i.e. the effect is mostly on the morphology. Because of the concentration of alkaline reactant has a direct effect on the pH of growth solution and finally the morphology is tuned [18]. In this study, we have investigated the significance of various narrow range concentrations of urea on the morphology of Co₃O₄ nanostructures with keeping the 0.1 M concentration of cobalt chloride constant. The

distinctive SEM images of Co₃O₄ nanostructures synthesized using different concentrations of urea (with low and high magnifications) are shown in Figure 1 (a-h). The average diameter of the nanowires forming is about 200 nm. It can be seen that, as the urea concentration is increased, the morphology transform to be with denser flowers-like nanostructures grow on top of the uniform layer of nanowires i.e. new morphology has been grown on top of the nanowires-like structures when increasing the concentration of the urea. That might be due to the change in the pH of the growth solution with the change of the concentration of the urea [18]. The possible reactions involved in the synthesis of Co₃O₄ nanostructures can be summarized as:

the cobalt hydroxide (Co (OH)₂) is thermodynamically unstable and it can be changed into Co₃O₄ phase by annealing at 450 °C [19]. Eq. (3) play important role in the growth process. With more amount of urea more basic growth solution and will affect the growth morphology [20]. That also is inconsistent with [21] where they produced a needle-like ZnO nanostructure from basic solutions.

The XRD technique was used for the study of crystalline structure of Co₃O₄ nano-flowers. The most intense peak can be correlated to the Au substrate. The XRD spectrum is shown in Figure 2 which demonstrates the pure-phase of Co₃O₄ and all the diffraction peaks can be assigned to (JCPDS No. 43-1003) of the cubic symmetry. The measured diffraction peaks for Co₃O₄ nanostructures include (111), (220), (311), (400), (422), (511), and (440). The well signified diffraction peak at $2\theta = 36^\circ$ (3 1 1) describes good crystalline arrays of the Co₃O₄ substance.

3.2. Glucose sensing based on Co₃O₄ nano-flowers comprised on nanowires

A GOx immobilized nano-flowers of Co₃O₄ were used for sensing of glucose molecules using the potentiometric method as has been shown in Figure 3 (a). The detection of glucose

was performed in phosphate buffer solution of pH 7.3 and before the insertion of GOx immobilized sensor electrode in glucose concentration, it was soaked in phosphate buffer solution in order to achieve a stable response as well as to remove the extra molecules of GOx on the surface of electrode. The GOx immobilized Co₃O₄ nano-flowers based electrode detected a wide range of the glucose concentrations from 1 μM to 10 mM with a high sensitivity of -56.85 mV/decade as shown in Figure 4. From the calculations a limit of detection was found to be 0.058×10^{-6} M, and the limit of quantification was found to be 0.175×10^{-6} M. During the experiments the glucose biosensor based on the Co₃O₄ nano-flowers has shown a Nernst response given by:

$$E = E^0 - 0.05916 \text{ V} / n \log [H^+]$$

Where E: is the output potential of working electrode such as (the glucose oxidase immobilized Co₃O₄ nanoflowers), E⁰: is the constant output potential of reference electrode such as (Ag/AgCl), and n is the number of electrons involved in the oxidation of glucose. The high sensitivity of the presented glucose sensor based on the nano-flowers of Co₃O₄ could be attributed to their large surface area to volume ratio which carried high degree of the GOx molecules and exposed large surface for the oxidation of the glucose molecules on the surface of the enzyme immobilized Co₃O₄ nano-flowers [22]. Moreover, the presented glucose sensor has also showed a fast response time of less than 10 s. The fast response time is shown in Figure 5 could be assigned to efficient electro-catalytic surface activity of the nano-flowers of the Co₃O₄ for a rapid oxidation of the glucose molecules during the measurement. The sensing mechanism of the enzyme based glucose sensor can be explained according to previously reported work [17]. During the interaction of the immobilized GOx with a glucose molecule, then two products are released in the reaction vessel including gluconolactone and hydrogen peroxide. The glucose concentration may be monitored by these two molecules or by the consumption of oxygen molecules during the oxidation of glucose molecules. The gluconolactone is unstable molecule which rapidly produces gluconic acid and finally gluconic acid is reacting with water molecules and this is resulting in gluconate ion and hydronium ions in the reaction vessel and by doing so a charge environment is created in the reaction vessel. The possible reactions that are taking place in the electrolytic solution in the vessel at the time of experiment could be summarized as [23]:

These two products could be used for the glucose determination using indirect methods [23]. Because of the generation of charge environment in the reaction vessel and flow of these charges on the surface of a compound semiconductor nanomaterial which provide a solid platform for the production of strong electrical signals and this results in an output potential (Figure 3 (b)). Figure 6 show that the present sensor possesses a reproducible response. The reproducibility measures the sensor to sensor response of the presented glucose biosensor in 5×10^{-4} M concentration of glucose. For this experiment six independent sensor electrodes were fabricated under a similar set of conditions and it can be inferred that, the response of each sensor differ from another sensor electrode by a relative standard deviation of less than 5%. In addition to the five times replication of each calibration points, the sensor electrode was tested for three consecutive days in the detected range of glucose concentrations in order to examine the repeatable response of the fabricated glucose biosensor . The measured results including detection range, sensitivity and response time are shown in table 1 and it can be seen that the sensor electrode is capable of showing similar performance for a given period of examination. The selectivity of the fabricated glucose biosensor was monitored in the presence of common interferences in the human serum along with glucose. The selectivity of a presented glucose biosensor was measured with a 50 μ M of the glucose and a 0.5 mM of the copper ion, ascorbic acid, uric acid, and urea respectively, and the observed response is shown in Figure 7. The presented GOx immobilized in Co₃O₄ nano-flowers based sensor is a very selective in the detection of glucose due to the favorable oxidation offered by GOx for only the glucose molecules using a potentiometric method. The presented glucose biosensor has shelf life time of three weeks as has been extracted from Figure 8. The stability of the proposed biosensor based on the Co₃O₄ nano-flowers was investigated in 5×10^{-4} M concentration of glucose up to 25 days. The proposed sensor maintained its configuration for up to 21 days. Therefore we can infer that the electrodes cannot be stable after this period and that can be attributed to; in one hand, could be assigned to a well suited network and good compatibility of nano-flowers of Co₃O₄ for GOx at the time of immobilization [24] and on the other hand, the short-term stability of enzymatic glucose biosensor is probably due to the thermal and chemical instability of GOx [25]. Table 2 shows comparative data for the glucose determinations using different electrodes immobilized and non-immobilized GOx. The majority of available data reveal that Co₃O₄ nanostructures have been used as the main catalytic part. Here, we have used a heterogeneous-catalysis of Co₃O₄ and glucose oxidase

enzyme, we believe that, the properties of each component can be retained due to the compatibility of Co_3O_4 (isoelectric point around 8) [24], and the potentiometric measurements which is to some extent benign to glucose oxidase, and can even be used to acquire improved properties due to a synergistic effect. In addition, it is go to emphasize that the potentiometric sensors are valuable technology since they don't require power source and do not passes electron current which can destroy biological tissues.

Conclusion

In this work, Au coated glass substrate and a hydrothermal method were used for the synthesis of Co_3O_4 nanostructures. The Co_3O_4 nanostructures exhibit morphology of flowers-like nanostructures and have comprised on nanowires upon the increase of the concentration of urea. The Co_3O_4 nanostructures were used for the development of an enzyme based sensitive glucose biosensor. The presented glucose biosensor detection is in a wide range of glucose concentrations (1 μM to 10 mM) with a sensitivity of -56.85 mV/decade and a good response time of 10 s. Heterogeneous catalysis effect at the GOx/nanoflowers/nanowire interfaces were enhanced, and the resulted electron communications processes on the electrode surface were efficient. Therefore, a high sensitivity towards the detection of glucose molecules has been demonstrated. The Co_3O_4 nanostructures based glucose biosensor showed a reproducible, repeatable, stable and selective response towards the detection of glucose molecules. All the obtained results are showing that, the presented glucose biosensor could be used as an effective analytical tool for the regulation and monitoring of glucose concentration in drugs, human serum, and the food industry.

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Figure captions

Figure 1(a-d): Typical SEM images of Co_3O_4 nano-flowers comprised on nanowires fabricated on the gold coated glass substrate using different concentrations of urea (a & b) 0.23, (c & d) 0.27, (e & f) 0.3, and (g & h) 0.4 M with a low and high magnification, respectively.

Figure 2: XRD spectrum of C_3O_4 nano-flowers comprised on nanowires.

Figure 3: Schematic of the potentiometric measurements; (a) working electrode is made of heterogeneous catalysis ($\text{GOx}/\text{C}_3\text{O}_4$ nanostructures) and homogeneous catalysis (nano-flowers/nanowire) interfaces on gold coated glass based biosensor for the detection of glucose, electron transfer process of the composites on the electrode surface have been enhanced, and (b) charge environment of a proposed biosensor.

Figure 4: The calibration curve of the fabricated glucose biosensor based on C_3O_4 nanoflowers for the concentrations of glucose from $1\mu\text{M}$ to 10 mM and the linear calibration equation is: $y = -56,9x - 213,7$.

Figure 5: Response time curve of the developed glucose biosensor for all detected concentrations.

Figure 6: Reproducible response of the developed glucose biosensor based on C_3O_4 nano-flowers in 0.5 mM of glucose.

Figure 7: The selective response of the fabricated glucose biosensor in the presence of common interferents at concentrations of 100 μL of 100 mM copper, ascorbic acid, uric acid, or urea, respectively.

Figure 8: The stability curve of the fabricated glucose biosensor for the period of three weeks.

Table 1: Shows the repeatability of the presented glucose biosensor based on C_3O_4 nano-flowers.

Table 2: Comparison for the glucose determinations using different electrodes immobilized with GOx and proposed glucose biosensor.

Fig. 1(a-d):

Fig. 2:

Fig. 3:

Fig.4:

Fig. 5:

Fig. 6:

Fig. 7:

Fig. 8:

Table 1:

Experiment NO.	Linear range M	Sensitivity mV/decade	Response time S
1	$1 \times 10^{-6} - 1 \times 10^{-2}$	-56.85	6
2	$1 \times 10^{-6} - 1 \times 10^{-2}$	-56.15	7
3	$1 \times 10^{-6} - 1 \times 10^{-2}$	-56.05	6

Table 2

No	Detection Method	Electrodes	Sensitivity ($\mu\text{A mM}^{-1} \text{cm}^{-2}$)	Slope (mV/decade)	Response time (s)	Sensibility (slope of calibration/ time of response)	Linear Range (M)	Lower detection of limit (M)	Reference
1	Amperometric (Non-enzymatic)	$\text{Cu}_2\text{O}/\text{MWCNT}$ nanocomposites	6.53		10		$0.05 \times 10^{-6} - 10 \times 10^{-6}$	0.05×10^{-6}	[6]
2	Amperometric (Non-enzymatic)	$\text{Co}_3\text{O}_4/\text{PbO}_2$ core-shell nanorods	460.3		2		$5 \times 10^{-6} - 1.2 \times 10^{-3}$	0.31×10^{-6}	[7]
3	Amperometric	Ni-Cu-oxide nanowire array	1600		4		$0.1 \times 10^{-6} - 1.2 \times 10^{-3}$	0.1×10^{-6}	[8]
4	Amperometric	Co_3O_4 nanoparticles and carbon electrode	520.7		6		$5 \times 10^{-6} - 8 \times 10^{-4}$	0.13×10^{-6}	[9]
5	Amperometric (Non-enzymatic)	graphene/ Co_3O_4 nanowire composite.	3.39		3.7		Up to 10^{-3}	$< 25 \times 10^{-9}$	[10]
6	Amperometric	Platinum Nano-particles and Carbon Nano-tubes	3570	-	3		$25 \times 10^{-9} - 10 \times 10^{-6}$	25×10^{-9}	[14]
7	Amperometric	Chitosan hydrogel and gold nano-particles	-	-	7		$5 \times 10^{-6} - 2.4 \times 10^{-3}$	2.7×10^{-6}	[15]
8	Potentiometric	ZnO nano-rod	-	40	1	40	$0.5 \times 10^{-6} - 1 \times 10^{-3}$	-	[16]
9	Potentiometric	CuO nanoleaves	-	61.9 ± 2.0	5	12,38	$1 \times 10^{-6} - 2 \times 10^{-3}$	-	[17]
10	Amperometric (Non-enzymatic)	Co_3O_4 nanofibers	36.25	-	7		Up to 2.04×10^{-3}	0.97×10^{-6}	[26]
11	Amperometric (Non-enzymatic)	Cobalt oxide acicular nanorods	571,8		20-40		Up to 3.5×10^{-3}	$0,058 \times 10^{-6}$	[27]
12	Potentiometric	Co_3O_4 nano-flowers	-	-57	10	5.7	$1 \times 10^{-6} - 1 \times 10^{-2}$	0.058×10^{-6}	Recent work