

High Sensitive Electrochemical Quantification of Isoniazid in Biofluids Using Copper Particles Decorated Graphene Oxide Nano Composite

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The excessive consumption and harming side effects of chemical antibiotics and NSAIDs are lead to the necessity of a simple analytical tool for high sensitive, quantitative detection of hepatotoxic drugs in human body fluids. In this work, we report an electrochemical sensor constructed by the facile electrochemical deposition of copper micro particles over graphene oxide nanosheets modified glassy carbon electrode and their potential application towards quantitative detection of isoniazid (*isonicotinylhydrazide* INH) (hepatotoxic drug) in bio fluids. The constructed Cu/GO/GCE electrode was further characterized by SEM, EDX, and Raman spectroscopy. As constructed electrode displayed excellent synergy and enhanced electrocatalytic activity towards INH. The described sensing platform of INH exhibits low limit of detection (LOD) 23.4nM and wide linear range 0.15 μ M -500 μ M with high sensitivity of 1.2394 μ A μ M⁻¹ cm⁻². The practical feasibility of the Cu/GO/GCE electrode is demonstrated in urine, and human serum sample with direct spiking of INH and achieved good recoveries.

Keywords: Hepatotoxic drugs, Isoniazid, Graphene oxide nanocomposite, Electrocatalysis, Bio-fluid analysis.

1. INTRODUCTION

The consumption of chemically derived non-steroidal anti-inflammatory drugs and antibiotics are raising rapidly from twentieth century. On the other hand, which leads into the rise of chemically induced liver damage (hepatotoxicity) [1]. Some of the most common hepatotoxic drugs in use are acetaminophen, aspirin, phenylbutazone, phenelzine, isoniazid, and etc., These drugs are related to

damaging liver cells and blocking the metabolism of the patients, the number of patients affected by hepatotoxic and idiosyncratic drugs are very high that became a serious issue to be addressed in chemotherapy [2]. Conversely, few of the drugs are vital in therapeutic treatment of illness. Isoniazid (INH) is one of the key antibiotic prescribed for the treatment of tuberculosis as their proposed mechanism with bacteria illustrate the INH participating the metabolic action of bacterial proteins, lipids, nucleic acids, and carbohydrate and thus possess the bacteriostatic or bactericidal action [3]. Hence there are no arguments to accept isoniazid as a vital therapeutic agent in modern medicine for the treatment of tuberculosis. While their superiority comes with the cost of nervous toxicity, therapeutic failure, and resistance over other drugs on long time consumption of INH [4, 5]. The excess dosage of INH in patients will cause severe liver damage and inflammation. The abnormal release of hydrazine during the metabolic hydrolysis of INH can be a critical thread to life and in some cases causes death [6]. Hence, controlling the dosage of INH is very niche to sufferers in medicinal chemistry, which has suggested to develop the simple and sensitive analytical methods for INH. Recently, many reports can be found for the sensitive detection of INH using various techniques such as spectrophotometry [7, 8], HPLC [9], electro-chemiluminescence [10], fluorimetry [11], capillary electrophoresis [12], and electrochemical approach [13-17]. In many instance those are surrounded common drawbacks including expensive instrumentation, complicated sensing matrix and tricky pre-sampling procedure. Meanwhile, over the other existing technique electrochemical methods offers several advantages. (1) Digital read out of signal (2) Highly sensitive, selective, rapid, and low-cost. (3) point- of-care assays and potential for miniaturization and portability. (4) These parameters make electrochemical sensor as a robust analytical tool for clinical analysis. Currently, nanomaterials based electrochemical methods influence the high surface accumulation, improved electron transfer, and reduce the lack of sensitivity. Graphene oxide (GO) has been used for numerous applications in the field of nano technology, energy storage, and electro catalysis owing to their large surface area, greater oxygen functionalities and extensive amount of edge plane like defects [18-20]. The oxidized carbons of GO enhance the binding capacity and increase electrocatalytic activity by easily combining with other electroactive materials such as transition metals and conductive polymers to explore excellent synergy [21].

Herein, we have designed copper micro particles decorated graphene oxide nano composite for the quantitative determination of INH in human body fluids. In this work we are adapting the known excellency of copper and graphene nanocomposite [22-27]. The Cu/GO/GCE were prepared by simple electrochemical deposition (ECD) of copper over GO/GCE and which the sensor is ready to be utilized. The Cu/GO/GCE revealed superior electrocatalytic activity, stability, repeatability, and reproducibility for high sensitive, quantitative determination of INH in aqueous PB buffer pH 7.0 via amperometry. The developed Cu/GO/GCE electrochemical sensing platform have been efficiently employed to assay the concentration of INH in human biofluids. This described sensor shown excellent selectivity and sensitivity.

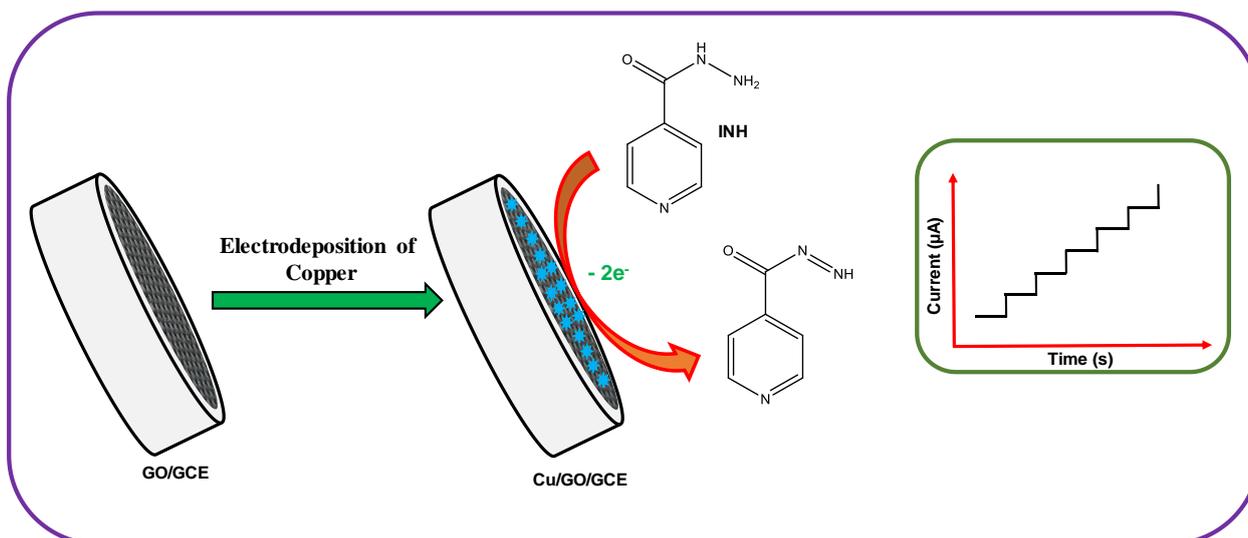


Figure 1. Schematic representation for sensitive detection of isoniazid using Cu/GO/GCE nano composite.

2. EXPERIMENTAL

2.1 Chemicals and Apparatus

Graphite (powder, < 20 µm), Copper(II) chloride, H₂SO₄, Na₂HPO₄, NaH₂PO₄, and all other reagents and solvents were purchased from Sigma-Aldrich and used as received. All the electrochemical measurements were carried out using CHI 612d electrochemical workstation (CH Instruments, Inc., U.S.A) at ambient temperature. The electrochemical studies were performed in a conventional three electrode cell using nanocomposite modified glassy carbon electrode (GCE) (Bioanalytical Systems, Inc., USA) as a working electrode (area=0.071 cm²), saturated Ag/AgCl (saturated KCl) as a reference electrode and Pt wire as a counter electrode. The supporting electrolyte used for the electrochemical studies was 0.1 M phosphate buffer (PB), pH 7.0. The Raman spectrum was studied by employing DongWoo 500i spectrometer. Scanning electron microscopy (SEM), Energy-dispersive X-ray (EDX) spectra and mapping were performed using Hitachi S-3000 H scanning electron microscope and HORIBA EMAX X-ACT (Sensor + 24V=16 W, resolution at 5.9 keV) respectively.

2.1. Synthesis and fabrication of Cu/GO/GCE.

Graphite oxide was prepared from graphite by Hummers method and exfoliated to graphene oxide (GO) in water via ultrasonic agitation for 2 h. Then, the GO dispersion was subjected to centrifugation for 30 min at 4000 rpm to remove unexfoliated graphite oxide [28]. GCE surface was polished with 0.05 µm alumina slurry and Buehler polishing kit, then washed with water and dried. 6 µl dispersion of GO was dropped at the pre-cleaned GCE and air dried. Copper have been electro deposited over graphene oxide modified GCE by immersing the Cu/GO into the 0.01M CuSO₄ and

0.1M H₂SO₄ electrolyte by swapping between the potentials -0.8 to +0.5 V for the five cycles of voltammograms as shown in figure 2 [29]. The Cu/GO/GCE electrode is dipped into water to remove excess of electrolyte and dried in air, stored in cold. An electrode modified with GO and bare GCE were taken as control.

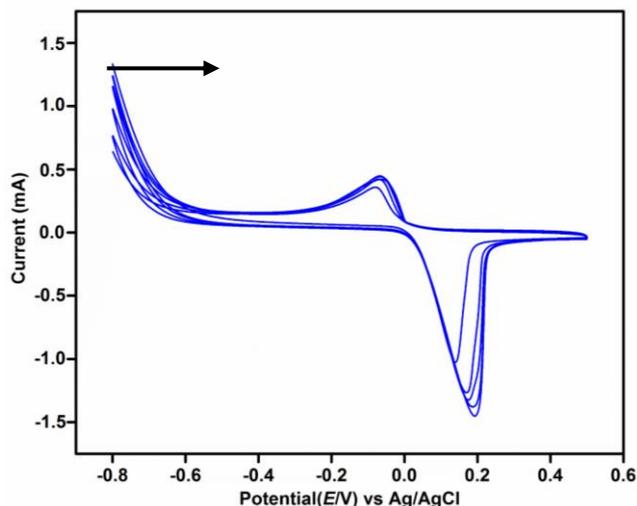


Figure 2. Electrodeposition of Cu/GO into the 0.01M CuSO₄ and 0.1M H₂SO₄ electrolyte in the potential range of -0.8 to +0.5 V.

3. RESULTS AND DISCUSSION

3.1. Surface morphological analysis.

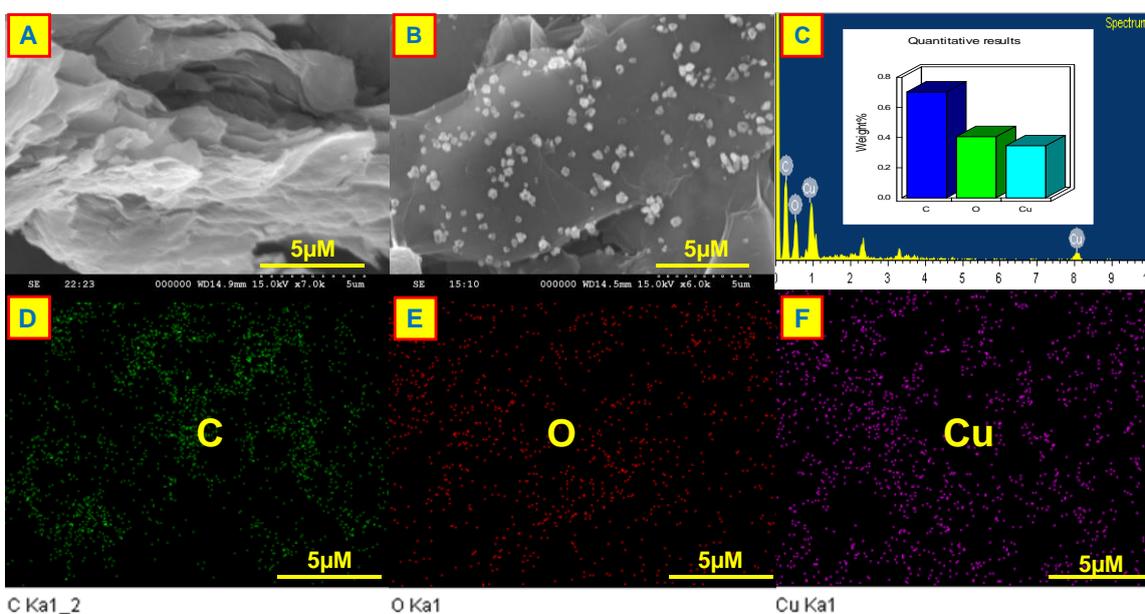


Figure 3. SEM image of GO (A), Cu/GO (B) (scale bar- 5 μM); EDX Spectra of Cu/GO (C); Elemental mapping of Carbon (D), oxygen (E), and copper (F).

The surface morphologies of different film modified electrode have been analyzed by scanning electron microscopy (SEM). Fig. 3A shows the random stacking structure of thin layer carbon characteristic of graphene oxide. Fig.3B displays the surface morphology of Cu/GO/GCE. This SEM image explains copper doped graphene oxide were the copper particles sprinkled all over the surface of graphene oxide. Additionally, the irregular surface delivers abundant surface area for the target analyte adsorption at the modified electrode system. The EDX spectra and elemental mapping confirms the elemental constitutions of Cu/GO/GCE nano composite given in Fig3C-3F.

3.2. Raman spectroscopy.

Raman spectroscopy is widely used for identifying the structural defects of carbonaceous materials during the oxidation and reduction process. The Raman spectra for GO can be seen that the two predominant peaks for GO at 1349 cm^{-1} and 1594 cm^{-1} for G and D band, respectively [30]. The D-band is associated to the vibrations of sp^3 carbon atoms of disordered graphene nanosheets, while the G-band arises from vibrations of sp^2 carbon atom domains of graphite [31]. The intensity ratio of I_D/I_G values for Cu/GO and GO were 0.84 and 0.75, respectively. The decoration of copper particles on the surface of graphene oxide the bands has been shifted towards the positive and I_D/I_G ratio also increased by 0.09. This spectral changes in the band shift and of the composite were attributed by the partial departure of oxygen functional groups over the surface of GO during the electrodeposition of copper particles and the strong interaction between the copper and graphene oxide surface [32]. The clear changes in the D and G bands of Raman spectra attribute the superior electrocatalytic ability of copper particles decorated graphene oxide over pristine graphene oxide. The above literatures also support the enhancement of electrocatalytic activity of Cu doped GO over pristine GO.

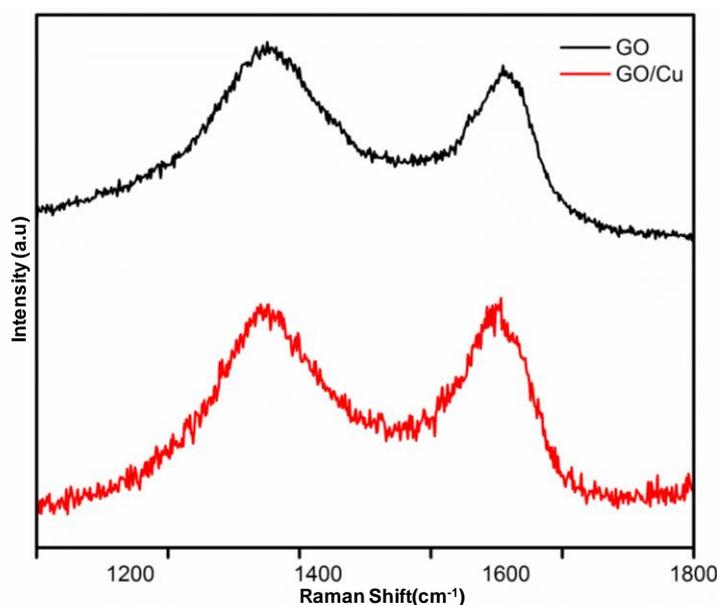


Figure 4. Raman spectra of GO and Cu/GO.

3.3. Electrocatalytic analysis of INH by Cu/GO/GCE.

The electrochemical behavior of Cu/GO/GCE and control electrodes were measured using cyclic voltammogram (CV) studies. Fig. 5A displayed the CVs recorded Bare GCE (a), GO/GCE (b), Cu/GCE (c) and Cu/GO/GCE(d) films modified GCEs in PB (pH 7.0) containing 200 μ M INH measured at a scan rate of 50 mV s^{-1} at potential range of + 0.60 to – 0.10 V. The bare GCE unveiled a faint amount oxidation peak at highly positive potential region (+ 0.34 V) (Fig.5A Curve a). The Cu/GO/GCE electrode showed superior electrocatalytic ability towards the oxidation of INH which enhanced I_{pa} and minimized overpotential 120 mV (peak potential at +0.22V, Ag/AgCl). In fact, the oxidation peak current obtained at Cu/GO/GCE was 15, 12 and 10 fold higher than those of obtained at Bare GCE, GO/GCE and Cu/GCE electrodes, respectively. Fig. 5B displayed the voltammograms of Cu/GO/GCE towards various concentrations of INH. The value of I_{pa} increases linearly as the concentration of INH increases indicating that this electrode can be suitable to fabricate INH sensor. The effect of scan rate towards INH (200 μ M) oxidation was studied by applying different scan rates from 10-100 mV s^{-1} (Fig. 5C and 5D). The value of I_{pa} was linearly related to the square root of scan rate indicated the occurrence of diffusion controlled process.

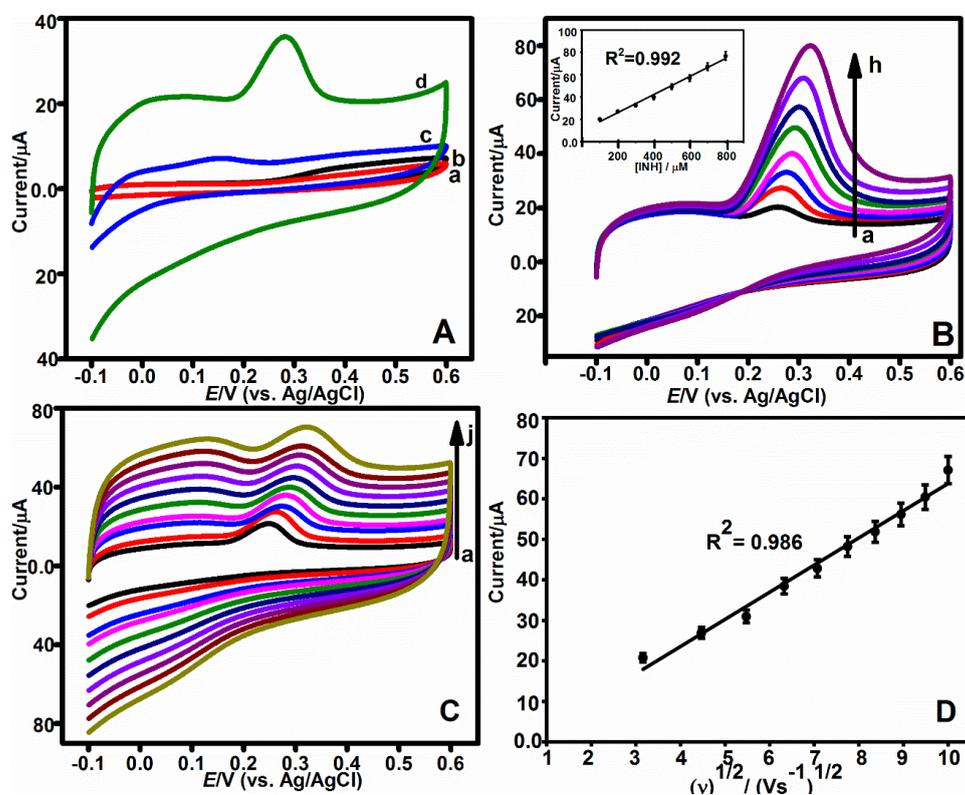


Figure 5. A) CVs recorded in PB buffer, pH 7.0 solution containing 200 μ M of Isoniazid at the bare GCE in (a), GO/GCE (b), Cu/GCE (c), and Cu/Go/GCE (d) film modified electrode. B) CVs obtained at the Cu/GO/GCE in PB buffer, pH 7.0 with increasing concentration of isoniazid (100–800 μ M), Inset: I_{pa} (μ A) vs. [INH]. C) CVs acquired at the Cu/GO/GCE in PB buffer, pH 7.0 containing 200 μ M of Isoniazid at different scan rate from 10 mV s^{-1} to 100 mV s^{-1} . D) I_{pa} vs. square root of scan rate.

3.4. Sensitive determination of INH by Cu/GO/GCE via amperometry.

The electrochemical detection of INH is carried out amperometrically and the Fig. 6 represents amperometric response of the Cu/GO/GCE modified electrode (rotation speed=1200 RPM) upon successive injections of INH into PB (pH 7.0) at a regular intervals of 50 s ($E_{app}= +0.22$ V). Well-defined and quick responses were obtained and steady-state current was reached in less than 5s. The linear range was $0.15\mu\text{M}$ to $500\mu\text{M}$ and limit of detection (LOD) was 23.4 nM. The sensitivity was calculated to be $1.2394 \mu\text{A } \mu\text{M}^{-1} \text{ cm}^{-2}$. Such a low detection limit at nanomolar level illustrated the outstanding sensing performance of the electrode. The sensor parameters were comparable over existing electrochemical approaches for the sensitive detection of INH. In the beginning of the decade Jena *et al.*, (2010) and Atta *et al.*, (2011) had reported the electrochemical detection of INH employing Au NPs and PEDOT/Pt electrodes respectively, despite the fact that the electrodes displayed good electrocatalytic parameters, the noble metal in the electrode materials are quite expensive which limiting the practicality of the electrodes in bulk production [13, 39]. Reports can be found for the detection of INH using noble metals free electrodes which are comparatively cut off the production cost and cheaper than their noble metal counterparts, these electrodes suffered with the limitations such as poor working range and limit of detection [14, 34-38]. Our constructed electrochemical sensor has displayed high electrocatalytic performance than the previous reported amperometric sensors of INH. The electrocatalytic and electrochemical parameters of the previous reports of INH have been compared with our Cu/GO/GCE electrode and tabulated as Table 1. The sensor proved the feasibility of electrochemical determination and notable analytical performance than that of previously reported INH sensors. The fabricated Cu/GO/GCE electrode overcome the limitations of production cost and broad working range, with the meaningful limit of detection which makes the constructed sensor stands out as good analytical tool for the electrochemical detection of INH in clinical analysis of biofluids.

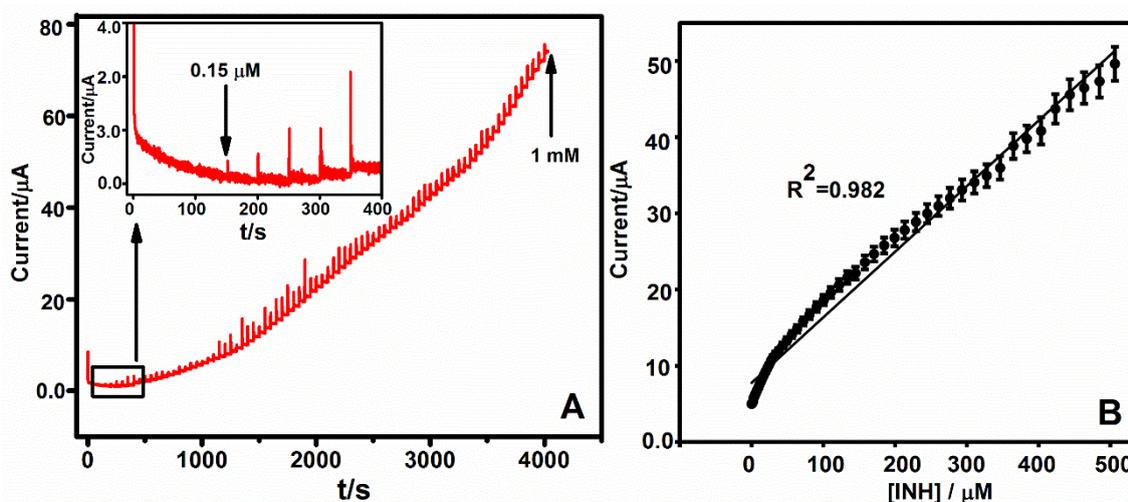


Figure 6. (A) Amperometric response at Cu/GO/GCE modified electrode (rotation speed=1200 RPM) upon successive addition of Isoniazid ($0.15 \mu\text{M}$ - $500\mu\text{M}$) into 0.1 M PB buffer, (pH 7.0) with applied potential ($E_{app}= +0.24$ V) with intervals of 50s (B) [INH](μM) vs. Current (μA).

Table 1. Comparison of analytical parameters of earlier stated INH sensor using different modified electrodes

Type of Electrode	Linear Range (μM)	Limit of Detection (μM)	Reference
^a PEDOT/Pt	10 -100	0.045	13
Nafion- ^b OMC/GCE	0.1 - 370	0.084	14
^c GA- ^d RGO/GCE	0.05 – 783	0.01	33
^e CA/ ^f EGR/GCE	0.1 -200	0.03	34
Tyrosine/GCE	25 – 125	6.93	35
^g BiO- ^h SPEs	5 – 100	1.85	36
ⁱ MWCNT/ ^j CPE	1 -100	0.8	37
Polypyrrole/GCE	3.9 - 1260	3.15	38
^k Au NPs	100 - 1000	0.0001	39
^l ERGO/GCE	2 – 70	0.17	40
Cu/GO/GCE	0.1 - 500	0.0234	This work

^aPEDOT= poly(3,4-ethylenedioxythiophene) ^bOMC= ordered mesoporous carbon, ^cGA= Gallic Acid, ^dRGO= reduced grapheneoxide, ^eCA=Cysteic acid, ^fEGR= electrodeposited graphene, ^gBiO=bismuth oxide, ^hSPEs=screen printed electrodes, ⁱMWCNT=multiwalled carbon nano tubes, ^jCPE= carbon paste electrode, ^kAu NPs=gold nano particles, ^lERGO = electrochemically reduced grapheneoxide.

3.5 Selectivity

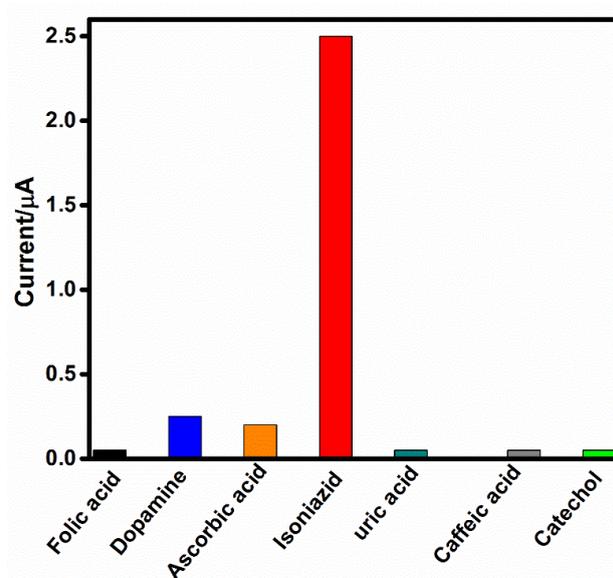


Figure 7. Amperometric response of Cu/GO/GCE film modified electrode towards 5 μM of INH and 500 μM varies interfering species into 0.1 M PB (pH 7.0) electrode rotation speed = 1200 RPM and applied potential = +0.22 V.

The selectivity of the sensor was evaluated by performing the interference experiments in presence of likely interfering agents. Fig. 7 showed the results of 5 μM of INH (a), in presence of various interfering species of 0.5 mM of dopamine, uric acid, ascorbic acid, folic acid, catechol, and caffeic acid. The electrode quickly responded to INH; however, it was lack of sensitive with the other species, thus, the electrode has higher affinity towards the oxidation of INH and able to assay INH in presence of other analytes.

3.6 Stability, repeatability and reproducibility of Cu/GO/GCE.

In order to evaluate durability and storage stability of the electrode the sensor performance of the Cu/GO/GCE modified electrode was monitored every week, while the electrode was stored at 5°C when not in use. The electrode retained 95.38% of its initial current even after 4 weeks of its continuous use, which endorsed applicable durability. The repeatability has been assessed by carry out amperometric experiments in optimized conditions with different concentration of INH. The constructed sensor indicates good repeatability with a relative standard deviation (R.S.D) of 3.6 % for 3 individual measurements. Furthermore, it reveals good reproducibility with an R.S.D of 2.96% for 3 successive measurements with different glassy carbon electrodes.

3.7 Practical application; Quantitative detection of INH in bio fluids.

The practical feasibility of the fabricated sensor was demonstrated in human blood serum and urine. As healthy human bio fluids do not have INH these samples are spiked with INH and make up stock solution of concentration 10mM. These INH spiked test solutions are directly injected into the supporting electrolyte and amperometric experiments were performed by following the optimized experimental conditions of lab sample procedures. The obtained amperometric results are consistent with lab sample results. The obtained results of the human blood serum and urine samples given in Table 2. From the results, the Cu/GO/GCE modified electrode displayed satisfactory practicality for the determination of INH in human blood serum and urine samples.

Table 2. Determination of INH Spiked in Human Blood Serum and Urine samples

Samples	Added/ μM	Found/ μM	Recovery/%	*RSD/%
Urine sample-1	5	4.82	96.4	3.62
Urine sample-2	2.5	2.56	102.4	3.41
Blood serum-1	5	4.83	96.6	3.38
Blood serum-2	2.5	2.44	97.6	2.96

* Relative Standard Deviation of 3 individual measurements

4. CONCLUSIONS

A simple, high sensitive electrochemical sensor (Cu/GO/GCE) have been constructed by electrochemical deposition of copper over graphene oxide modified GCE for the nano molar detection

of isoniazid. As constructed electrode was characterized by SEM, EDX, and Raman spectroscopy. The electrode displayed excellent electrocatalytic activity towards the oxidation of isoniazid (INH) with high sensitivity of $1.2394 \mu\text{A } \mu\text{M}^{-1} \text{ cm}^{-2}$ and linear range of $0.1 \mu\text{M}$ to $500 \mu\text{M}$ with lower limit of detection of 23.4 nM . The practicality of constructed electrode tested with urine sample and blood serum with the good recovery rate.

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