Electrodeposited Silver-Gold Alloy as A Sensor for Paracetamol Determination

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In the present work, a composite Ag NPs/Au NPs bimetallic alloy was prepared via a one-step electrodeposition strategy. XPS and cyclic voltammogram (CV) measurements were carried out for the characterization of this composite. Paracetamol was successfully electrochemically detected using fabricated Au-Ag bimetallic alloy-modified ITO. Considering the excellent electronic features of these two metallic nanoparticle materials, the electrochemical response of paracetamol was found substantially enhanced by the Au-Ag bimetallic alloy, as shown in the CV experiment results. Optimization of the corresponding parameters was also carried out. It was found that paracetamol showed amperometric oxidation currents linearly related to the concentrations (0.01 - 1 mM), and the limit of detection (LOD) was obtained as 2.4 μM based on a sound to noise ratio of 3. In addition, our developed sensor proved highly reproducible and stable, and it displayed remarkable anti-interference properties; thus, it has the potential for applications in the detection of paracetamol in tablets and spiked human urine specimens.

1. INTRODUCTION

Accurate, sensitive, and facile techniques are urgently needed for the determination of active chemical ingredients, to control the quality of drugs through drug monitoring, and to determine the distinct effect of drug quality on public health. Paracetamol (acetaminophen, N-acetyl-p-aminophenol) has gained extensive use as an analgesic and antipyretic drug. It is considered a safe and effective agent for reducing fevers, relieving colds, reducing coughing, and lessening pain associated with many conditions such as toothaches, backaches, migraine headaches, chronic pain, and muscular aches [1-4]. In general, no detrimental side effects are caused by restricted use of paracetamol. Nevertheless, toxic metabolites can accumulate due to the chronic use of and overdose from paracetamol, resulting in

damage to the liver and kidneys [5, 6]. Therefore, it is essential to develop an accurate, sensitive, rapid and facile analytical technique for the detection of paracetamol in human plasma during pharmaceutical preparations. For the detection of paracetamol in biological fluids and pharmaceutical tablets, many strategies have been reported, including spectrophotometry [7], titrimetry [8], liquid chromatography [9], chemiluminescence [10], and electrochemical techniques [11-16]. Unfortunately, a tedious extraction process is required prior to the determination when using chemiluminescence, titrimetry, and spectrophotometric techniques. In addition, liquid chromatography requires a long analysis time and unsuitable for routine analyses. Electrochemical methods have been reported as more favourable for paracetamol detection compared with the above methods, considering the electroactive property of paracetamol and the selectivity, high sensitivity, low cost, rapid response, non-time-consuming feature, and wide dynamic range of this method compared to most electroanalytical methods [17-22]. The extensive use of electrochemical methods has been reported for the determination of paracetamol in pharmaceutical preparations. For the electrochemical analysis of paracetamol, nanomaterial-modified electrodes have been applied, including carbon nanotube-modified basal-plane pyrolytic graphite electrodes [23, 24], nanogold-modified indium tin oxide electrodes [24], a polyaniline-multi-walled carbon nanotube composite [25], single-wall carbon nanotube-dicetyl phosphate films [26], glassy carbon electrodes (GCEs) modified with carbon-coated nickel magnetic nanoparticles [27], C60-modified GCE [28], and poly(acid yellow 9)-nano-TiO$_2$ modified GCE, and they have shown distinct properties [29]. The above techniques are highly stable, selective, and sensitive and show a low LOD due to the excellent catalytic and electronic features of nanomaterials. It is worth mentioning that this report applied bimetallic alloy electrodes to paracetamol analysis for the first time.

As a film growth process, electrodeposition is typically used in techniques based on electrochemical processes for the deposition of materials onto a surface. This method includes the generation of semi-conductive or metallic coatings on conductive surfaces from metal ion sources in a suitable solvent and occurs via an electron transfer route [30-32]. In addition, it has also been extensively used for the protection of corrosion and the synthesis of coatings. The electrodeposition of metal is a fundamental and important method in many fields, such as aerospace, automotive, sensors, optics, and electronics [33, 34]. Electrodeposited metals include Cd, Zn, Pd, Ag, Au, Cu, Ni, Cr, as well as many Zn-, Ag-, Au-, and Cu-based alloys) [35-39]. In the present work, Au-Ag alloy-modified indium tin oxides (ITO) were used for the fabrication of a new electrochemical sensor, with its electrochemical features studied herein. It has the potential to be applied to the ultrasensitive detection of paracetamol in pharmaceutical products using amperometric detection strategies. The experiment results indicate the remarkable behaviour of the graphene-coated electrode in the determination of paracetamol.

2. EXPERIMENTS

2.1. Chemicals

KCN, potassium dicyanoargentate KAg(CN)$_2$ and potassium dicyanoaurate (I) KAu(CN)$_2$ were commercially available from the Aldrich Chemical Co. All other reagents were of analytical grade.

The bipolar electrochemical cell employed indium tin oxides (ITO) as bipolar and driver electrodes. All the solution preparation and cleaning was performed using 18.2 MΩ/cm^3 Millipore-Q purified deionized (DI) water. For the preparation of the phosphate buffer solution (PBS), the required amounts of $Na_2H_2PO_4 \cdot 2H_2O$ and $Na_2HPO_4 \cdot 12H_2O$ were dissolved into DI water.

2.2. Electrodeposition of Au-Ag alloy

In a single compartment glass cell, the electrodeposition measurements were carried out, where the potential between two ITO electrodes (separated by 3.5 cm) was controlled by a Hewlett-Packard model 6010 regulated DC power supply. For the immersion of these three electrodes, 200 mM KCN, 5 mM $KAg(CN)_2$, and 5 mM $KAu(CN)_2$ were used to prepare the electrodeposition solution, and KOH was added to obtain an electrolyte pH of 12. For the deposition of the Ag-Au alloy films, 9.9 V was applied across the driver electrodes at ambient temperature for 60 s.

2.3. Characterizations

An Mg K_α X-ray source was used to obtain the X-ray photoelectron spectroscopy (XPS) spectra (ESCALAB 220, VG Microtech, UK) for the specimens. The SERS patterns were recorded with a dispersive Raman microscope equipped with a diode laser (λ_{ex} = 785 nm), a thermoelectrically cooled (−40 °C) charge-coupled detector (CCD), and a holographic grating (Kaiser Optical Inc., USA). A conventional three-electrode geometry in a home-built glass cell was used throughout the conventional electrochemistry experiments, with an Epsilon electrochemistry workstation controlling this electrochemical cell. In addition, the working, reference and counter electrodes were made from ITO, an Ag|AgCl (sat) electrode and a Pt wire. Paracetamol was determined through CV measurements in PBS (0.1 M) from 0 to 0.6 V (scan rate: 50 mV/s).
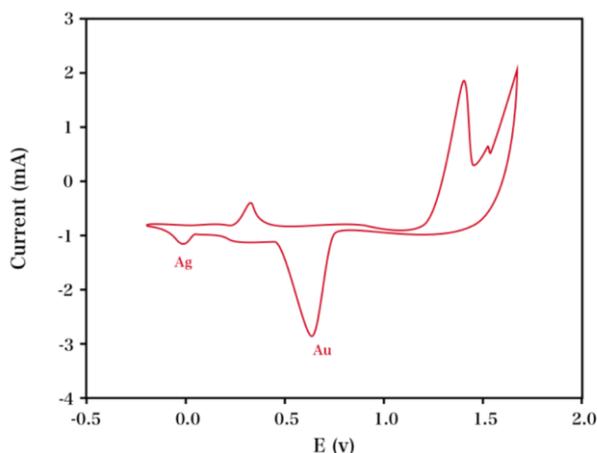
3. RESULTS AND DISCUSSION

Figure 1. Cyclic voltammogram (CV) acquired for the Au-Ag bimetallic alloy in a solution of 0.5 M H_2SO_4.

The Au-Ag bimetallic alloy was characterized via CV in H_2SO_4 (0.5 M) to provide evidence for the deposition of Ag and Au, as shown in Fig. 1. The obvious observable Ag and Au reduction peaks confirmed the bimetallic composition. Compared with Au, Ag showed a significantly lowered peak intensity. This was because the atomic percentage of Ag was low in the alloy. These results apparently showed that Ag and Au exhibited a bimetallic composition. It can be concluded that Au–Ag alloy NPs were formed rather than either a segregated metal or core/shell-type structure [40].

An XPS measurement was also used to investigate the atomic composition of the Au-Ag bimetallic alloy, in addition to the confirmation of the bi-metal deposition via CV methods. The Au-Ag bimetallic alloys produced from the electrodeposition solution was characterized via XPS patterns, as shown in Fig. 2. Two peaks at $4f_{5/2}$ and $4f_{7/2}$ were found for Au, when the applied potentials were 88.3 and 84.4 eV, respectively. For Ag, two peaks at $3d_{3/2}$ and $3d_{5/2}$ were observed when the applied potentials were 374.6 and 370.1 eV, respectively [41]; however, they showed lower intensities because of the decreased concentration. The above results showed the presence of only one Ag and one Au form in solution, namely, Au^0 and Ag^0. Based on the XPS analysis, all the silver and gold ions involved in the synthesis of the nanoparticles were reduced and were in their metallic form [42-44].
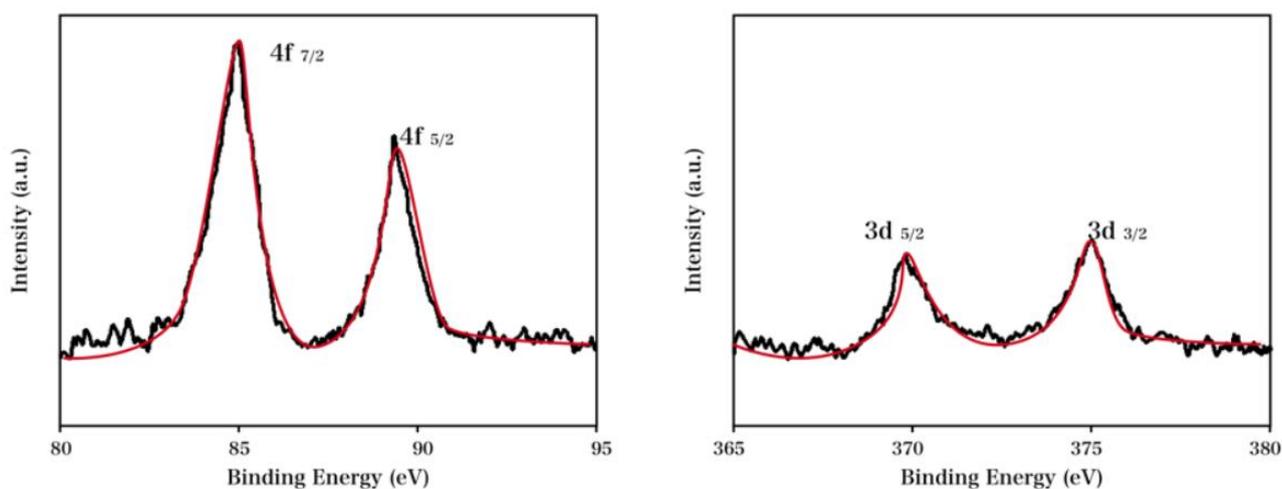

Figure 2. XPS spectra of Au-Ag bimetallic alloy synthesized using electrodeposition.

CV measurements were also used to obtain the electrochemical responses of paracetamol using various electrodes. It was found that the irreversible oxidation peak of paracetamol only appeared when using bare ITO, as displayed in curve a of Fig. 3A. As shown in curve b, a pair of well-defined redox peaks was observed for the Au-Ag bimetallic alloy-coated ITO, which corresponded to the reduction and oxidation of paracetamol at 0.35 V and 0.40 V. The above enhancement may result from the high conductivity and high surface area of the Au-Ag bimetallic alloy NPs. Moreover, the remarkable electric conduction of the Au–Ag alloy NPs could promote electron transfer. These results confirmed that the Au-Ag bimetallic alloy could electrochemically determine paracetamol with significant sensitivity as a distinct interface.

As shown in Fig. 3B, the effect of the scan rate on the redox current of paracetamol was studied with the proposed Au-Ag bimetallic alloy-coated ITO. As the scan rate and the peak separation were increased and enlarged, an increase in the cathodic and anodic peak current was observed. In addition, as shown in the inset of Fig. 5B, these two peaks were linearly related with the scan rate (20 - 200 mV/s). This indicates the adsorption-controlled property of the reaction of paracetamol in the presence of this proposed electrode [45, 46]. Based on Laviron's model,[47, 48], the charge transfer coefficient constant was obtained as 0.439, the number of the reaction-involved electrons was 1.944. These results confirm the involvement of the above two electrons in the electrochemical redox process of paracetamol [49].
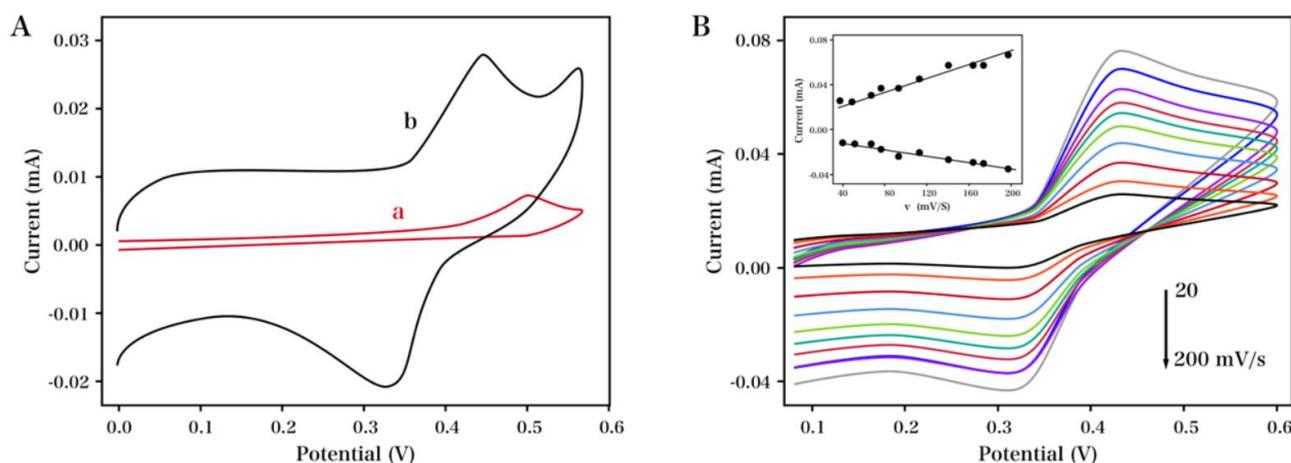

Figure 3. (A) CVs of (a) the bare and (b) Au-Ag bimetallic alloy-coated ITO in 0.2 M PBS (pH 7.0) in the presence of paracetamol (0.1 mM) at a scan rate of 50 mV/s. (B) CVs of Au-Ag bimetallic alloy-coated ITO in paracetamol (0.1 mM). Scan rate: 20 - 200 mV/s. Inset: corresponding plots of the current responses with different scan rates.

Fig. 4A shows the amperometric response of the proposed Au-Ag bimetallic alloy-coated ITO after adding paracetamol into PBS at pH 7.0. The response of this electrode to the variation in the paracetamol concentration was found to be rapid. The current became steady within 5 s after adding paracetamol. The calibration curve of the current response with different paracetamol concentrations (0.01 - 0.1 mM) is shown in the inset of Fig. 4A. In addition, the LOD was obtained as 2.4 μM (S/N=3). To allow for comparison to previous reports, the characteristics of different electrochemical sensors for paracetamol are summarized in Table 1.

I also investigated the effect of possible interference agents on the electrochemical performance of paracetamol. The amperometric response of the proposed electrode after adding paracetamol and interference agents such as glucose, ascorbic acid, dopamine, and uric acid is shown in Fig. 4B. In addition, the current response became rapid after adding paracetamol (0.01 mM), whereas it was not affected after adding glucose, ascorbic acid, dopamine, and uric acid (0.1 mM). Therefore, our proposed electrode is significantly selective in the presence of even a 10-fold concentration of interfering agents.

Table 1. Comparison of the major characteristics of electrochemical sensors used for the detection of paracetamol.

Electrode	Linear detection range	Detection limit	Reference
$Ni_{0.1}Co_{0.9}Fe_2O_4$	8-208 μM	1.102 μM	[50]
GO/MIPs	0.1-80 μM	20 nM	[12]
Poly(diallyldimethylammonium chloride) functionalized graphene	0.5-100 μM	0.221 μM	[51]
Au-Ag bimetallic alloy coated ITO	0.01 – 0.1 mM	2.4 μM	This work

To investigate the reproducibility of our proposed electrode, 7 successive scans were run in PBS containing 0.1 mM paracetamol. In addition, the relative standard deviation was obtained as 3.2%, which suggested that the proposed electrode was easily reproduced.
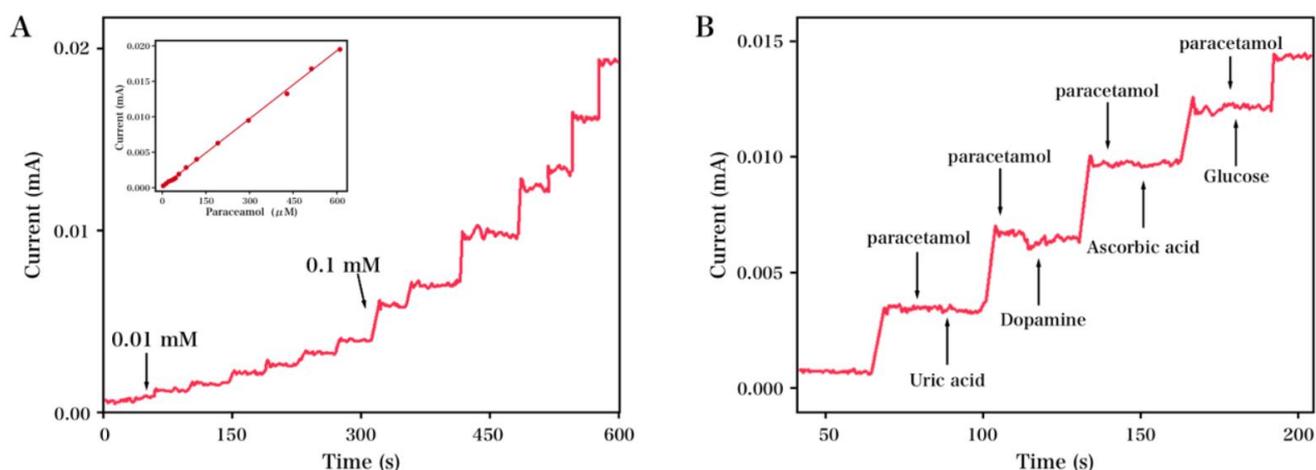

Figure 4. Typical current-time response of Au-Ag bimetallic alloy-coated ITO after successively adding 0.01 and 0.1 mM paracetamol. (B) Amperometric response of Au-Ag bimetallic alloy-coated ITO after adding paracetamol, uric acid, dopamine, ascorbic acid and glucose (0.1 mM) into PBS at +0.4 V.

The concentrations of paracetamol in tablets and urine were measured to investigate the analytical utility of our proposed electrode in practical use. Tables 2 and 3 display the analysis results (triplicate analysis). The paracetamol results determined using this sensor were consistent with those of the conventional HPLC technique. Furthermore, the electrode stability in analysing real pharmaceuticals and urine specimens was also studied. After ten experiments using tablets and urine, the RSD was obtained as 4.05 % and 3.57 % (small), suggesting the high stability of our proposed electrode in the detection of paracetamol in real specimens. These results indicate the excellent performance of the proposed electrode in the detection of paracetamol in tablets and in human urine specimens.

Table 2. Determination of paracetamol in tablets.

Sample number	Label amount (g/tablet)	Detection			
		Au-Ag bimetallic alloy modified ITO	RSD (%)	HPLC	RSD (%)
1	0.5	0.4984	1.05	0.5012	4.59
2	0.5	0.4992	1.57	0.5007	2.58
3	0.5	0.5044	2.56	0.5038	3.33

Table 3. Determination of paracetamol in urine samples

Sample number	Added (mM)	Detection			
		Au-Ag bimetallic alloy modified ITO	RSD (%)	HPLC	RSD (%)
1	0.05	0.0492	3.57	0.0489	5.69
2	0.2	0.2041	2.78	0.1987	3.21

4. CONCLUSIONS

The present work reported the fabrication of a new electrochemical sensor towards the detection of paracetamol using Au-Ag bimetallic alloy-modified ITO. A facile electrodeposition technique was used for the synthesis of the Au-Ag bimetallic alloy. The synergistic effect of Ag NPs and Au NPs contributes to significant enhancements in the electrochemical properties of paracetamol. It is worth mentioning that our proposed configuration exhibited a linear detection range of 0.01 to 1 mM, and the LOD was obtained as 2.4 μM, which suggested the remarkable anti-interference properties of our proposed sensor. In addition, this sensor provided excellent performance in the detection of paracetamol in human urine and tablet specimens and could be successfully applied to the practical detection of drugs in clinical applications.

References

1. Y. Zhang, X. Liu, L. Li, Z. Guo, Z. Xue and X. Lu, *Analytical Methods*, 8 (2016) 2218.
2. J. Li, J. Liu, G. Tan, J. Jiang, S. Peng, M. Deng, D. Qian, Y. Feng and Y. Liu, *Biosensors and Bioelectronics*, 54 (2014) 468.
3. H. Karimi-Maleh, M. Hatami, R. Moradi, M.A. Khalilzadeh, S. Amiri and H. Sadeghifar, *Microchimica Acta*, 183 (2016) 2957.
4. A. Kutluay and M. Aslanoglu, *Analytica chimica acta*, 839 (2014) 59.
5. L. Fu, G. Lai and A. Yu, *RSC Advances*, 5 (2015) 76973.
6. A.T.E. Vilian, M. Rajkumar and S.-M. Chen, *Colloids and Surfaces B: Biointerfaces*, 115 (2014) 295.
7. A.R. Khaskheli, A. Shah, M.I. Bhanger, A. Niaz and S. Mahesar, *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 68 (2007) 747.
8. M. Knochen, J. Giglio and B.F. Reis, *Journal of pharmaceutical and biomedical analysis*, 33 (2003) 191.
9. P.S. Selvan, R. Gopinath, V.S. Saravanan, N. Gopal, A.S. Kumar and K. Periyasamy, *Asian Journal of chemistry*, 19 (2007) 1004.

10. D. Easwaramoorthy, Y.-C. Yu and H.-J. Huang, *Anal. Chim. Acta.*, 439 (2001) 95.
11. S.S. Hassan, S. Panhwar, A. Nafady, A.M. Al-Enizi, S.T.H. Sherazi, M.S. Kalhoro, M. Arain, M.R. Shah and M.Y. Talpur, *Journal of The Electrochemical Society*, 164 (2017) B427.
12. J. Luo, J. Cong, R. Fang, X. Fei and X. Liu, *Microchim. Acta.*, 181 (2014) 1257.
13. S. Cheemalapati, S. Palanisamy, V. Mani and S.-M. Chen, *Talanta*, 117 (2013) 297.
14. K.S. Ngai, W.T. Tan, Z. Zainal, R.M. Zawawi and J.C. Juan, *Science of Advanced Materials*, 8 (2016) 788.
15. Y. Teng, L. Fan, Y. Dai, M. Zhong, X. Lu and X. Kan, *Biosensors and Bioelectronics*, 71 (2015) 137.
16. J.V.H. Ramos, F. de Matos Morawski, T.M.H. Costa, S.L.P. Dias, E.V. Benvenutti, E.W. de Menezes and L.T. Arenas, *Microporous and Mesoporous Materials*, 217 (2015) 109.
17. L. Zhang, X. Yin and S.F.Y. Li, *Chemical Engineering Journal*, 276 (2015) 185.
18. L. Liu, H. Lv, C. Wang, Z. Ao and G. Wang, *Electrochimica Acta*, 206 (2016) 259.
19. X. Liu, X.-Y. Zhang, L.-L. Wang and Y.-Y. Wang, *Microchimica Acta*, 181 (2014) 1439.
20. M. Zidan, R.M. Zawawi, M. Erhayem and A. Salhin, *Int. J. Electrochem. Sci*, 9 (2014) 7605.
21. Y. Peng, Z. Wu and Z. Liu, *Analytical Methods*, 6 (2014) 5673.
22. M. Baccarin, F.A. Santos, F.C. Vicentini, V. Zucolotto, B.C. Janegitz and O. Fatibello-Filho, *Journal of Electroanalytical Chemistry*, 799 (2017) 436.
23. R.T. Kachoosangi, G.G. Wildgoose and R.G. Compton, *Analytica chimica acta*, 618 (2008) 54.
24. R.N. Goyal, V.K. Gupta, M. Oyama and N. Bachheti, *Electrochemistry communications*, 7 (2005) 803.
25. M. Li and L. Jing, *Electrochimica Acta*, 52 (2007) 3250.
26. D. Sun and H. Zhang, *Microchimica Acta*, 158 (2007) 131.
27. S.-F. Wang, F. Xie and R.-F. Hu, *Sensors and Actuators B: Chemical*, 123 (2007) 495.
28. R.N. Goyal and S.P. Singh, *Electrochimica Acta*, 51 (2006) 3008.
29. X. Kang, J. Wang, H. Wu, J. Liu, I.A. Aksay and Y. Lin, *Talanta*, 81 (2010) 754.
30. H. Tao, T. Hu, J. Yan and J. Di, *Sensors and Actuators B: Chemical*, 208 (2015) 43.
31. A. Abbaspour and F. Norouz-Sarvestani, *International Journal of Hydrogen Energy*, 38 (2013) 1883.
32. H.A. Hansen, C. Shi, A.C. Lausche, A.A. Peterson and J.K. Nørskov, *Physical Chemistry Chemical Physics*, 18 (2016) 9194.
33. I. Taurino, G. Sanzò, R. Antiochia, C. Tortolini, F. Mazzei, G. Favero, G. De Micheli and S. Carrara, *TrAC Trends in Analytical Chemistry*, 79 (2016) 151.
34. K. Hou, C. Chen, B. Wu, D. Zhu, W. Zhong, X. Wang, X. Xie, Q. Chem,.Biomedical Research., 28 (2017) 129-133.
35. J. Ji, P. Li, S. Sang, W. Zhang, Z. Zhou, X. Yang, H. Dong, G. Li and J. Hu, *AIP Advances*, 4 (2014) 031329.
36. H. Jia, P. Gao, H. Ma, D. Wu, B. Du and Q. Wei, *Bioelectrochemistry*, 101 (2015) 22.
37. X. Ke, Z. Li, L. Gan, J. Zhao, G. Cui, W. Kellogg, D. Matera, D. Higgins and G. Wu, *Electrochimica Acta*, 170 (2015) 337.
38. P. Dong, Y. Wu, W. Guo and J. Di, *Plasmonics*, 8 (2013) 1577.
39. A.P. Abbott, A.I. Alhaji, K.S. Ryder, M. Horne and T. Rodopoulos, *Transactions of the IMF*, 94 (2016) 104.
40. S. Mandal, P. Selvakannan, R. Pasricha and M. Sastry, *Journal of the American Chemical Society*, 125 (2003) 8440.
41. D. Li, L. Meng, S. Dang, D. Jiang and W. Shi, *Journal of Alloys And Compounds*, 690 (2017) 1.
42. J. Dong, Y. Ye, W. Zhang, Z. Ren, Y. Huo and H. Zheng, *Luminescence the Journal of Biological & Chemical Luminescence*, 30 (2015) 1090.
43. J. Sun, F. Yang, D. Zhao, C. Chen and X. Yang, *ACS applied materials & interfaces*, 7 (2015)
44. J. Sun, F. Yang, D. Zhao, C. Chen and X. Yang, *ACS applied materials & interfaces*, 7 (2015)

6860.
45. J. Li, J. Liu, G. Tan, J. Jiang, S. Peng, M. Deng, D. Qian, Y. Feng and Y. Liu, *Biosensors & bioelectronics*, 54 (2014) 468.
46. M. Devaraj, R.K. Deivasigamani and S. Jayadevan, *Analytical Methods*, 5 (2013) 3503.
47. E. Laviron, *J. Electroanal. Chem.*, 52 (1974) 355.
48. E. Laviron, *J. Electroanal. Chem.*, 101 (1979) 19.
49. L. Fu, G. Chen, N. Jiang, J. Yu, C.-T. Lin and A. Yu, *Journal of Materials Chemistry A*, 4 (2016) 19107.
50. A.K. Vidyadharan, D. Jayan and T.E.M. Nancy, *Journal of Solid State Electrochemistry*, 18 (2014) 2513.
51. O.K. Okoth, K. Yan, L. Liu and J. Zhang, *Electroanalysis*, 28 (2016) 76.