Hindawi
International Journal of Electrochemistry
Volume 2019, Article ID 6318515, 8 pages
https://doi.org/10.1155/2019/6318515

*Research Article*

# Voltammetric Determination of Uric Acid in Clinical Serum Samples Using DMF Modified Screen Printed Carbon Electrodes

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Received 4 June 2018; Revised 27 October 2018; Accepted 19 December 2018; Published 3 February 2019

Academic Editor: Gerd-Uwe Flechsig



Screen printed carbon electrodes (SPCEs) provide attractive opportunity for sensitive and selective determination target analytes in clinical samples. The aim of the current work was to develop SPCEs based sensor for the determination of uric acid in clinical serum samples. The electrodes were pretreated by soaking in N,N-dimethylformamide for 5 minutes followed by drying in an oven at 100°C for 20 mins. The effect of surface pretreatment was characterized using cyclic voltammetry. The current response of uric acid detection was improved by a factor of 3.5 in differential pulse voltammetric measurement compared to unmodified electrode. Under the optimized conditions, the sensor displayed two dynamic linear ranges 5-100 $\mu$M and 100-500 $\mu$M with correlation coefficient, $R^2$, values of 0.98782 and 0.97876, respectively. The limit of detection and limit of quantification calculated using the dynamic linear range 5-100 $\mu$M were 1.9 x $10^{-7}$ M and 6.33 x $10^{-7}$ M, respectively. The developed sensor displayed well separated and discerned peaks for UA in presence of the potential interferent (ascorbic acid and citric acid). The electrode was successfully applied for the detection of very low level of UA in clinical serum samples in a phosphate buffer solution (pH = 7). The proposed sensor showed a very high reproducibility and repeatability with the relative standard deviation of 0.9%. In conclusion, a simple and low cost sensor based on SPCEs is developed for sensitive and selective detection of uric acid in clinical samples.

## 1. Introduction

Monitoring the level of uric acid (UA) in human physiological fluids is indispensable for the diagnosis of patients suffering from a range of disorders associated with altered purine metabolism [1]. Various electrochemical UA biosensors have emerged from laboratories, because of the advantages of simplicity, short response time, high sensitivity, and selectivity [2]. However, interference from common biological materials such as acetaminophen, dopamine, and ascorbic acid has been the most serious problem encountered when applying reagent based methods for uric acid measurement [3].

Screen printed carbon electrodes (SPCEs) fabricated via thick-film (screen-printing) technology offers the most promising route for sensitive and selective detection of different analytes in clinical samples including microorganisms [1, 4], proteins [5–9], glucose [10–12], or nucleic acids [13, 14]. The reasons for the great interest in the SPCEs include the attractive features of the carbon: chemically inert, low background currents, and wide potential window [15, 16]. Due to the nonelectroactive additives in the inks and hence the relatively low graphitic carbon content imposed by the constraints of screen-printing, however, the redox activity and the overall analytical performance of the electrodes are compromised [17, 18]. The nonelectroactive components (or simply contaminants) including the polymeric binders in the ink block the electrochemically active graphitic particles leading to slower rates of heterogeneous charge transfer kinetics and seriously affect reversibility of electrochemical reactions on the electrode surface. In addition, commercial SPCEs exhibit a wide range of electrochemical reactivity due to variations in (i) the composition of the ink and the graphitic loading, (ii) degree of electrochemical accessibility of the graphitic edges, and (iii) the nature of the graphite particles and its functionalization [17]. Washe et al. 2013 showed a dramatic improvement in the electrochemical performance of SPCEs via the mechanism of increasing graphitic loading and exposure of more pristine graphitic edges by selective etching of surface contaminants with a judiciously selected organic solvent, DMF [19]. In addition, the action of

the solvent could create a nanostructured porous surface on the SPCEs. In this paper, the nonporous surface structures are envisaged to increase surface accumulation of organic analytes and increase sensitivity of electrochemical detection. The proof of concept is demonstrated through differential pulse voltammetric determination clinically important target (UA) in serum samples.

## 2. Experimental Part

*2.1. Materials and Chemicals.* Screen printed carbon electrodes (7102 conductor paste based on carbon; DuPont Ltd. (UK)) were kindly donated by the INTERFIBIO group at Universitat Rovira I Virgili, Spain, led by Professor Ioanis Katakis. The group has optimized printing procedure to produce a well adhered and uniform film of electrodes measuring thickness (7.5 $\mu$m). All the chemicals including $K_4[Fe(CN)_6]\cdot 3H_2O$, $K_3[Fe(CN)_6]$, $KNO_3$, and N,N-dimethylformamide (DMF) were of analytical grade and obtained from Sigma Aldrich. Double distilled water was used throughout the study. Standard uric acid material was purchased from VWR International GmbH (Deutschland). The entire experimentation was carried out at room temperature using double distilled water for the preparation of all required solutions.

*2.2. Apparatus.* The electrochemical experiments were carried out in a three-electrode system containing Ag/AgCl as a reference electrode, platinum wire as a counterelectrode and DMF modified screen printed carbon electrode as working electrode. The experiment and processing of data were made using BAS 50W voltammetric analyzer interfaced with a computer. The pH of the buffer solution was measured with a HANNA pH-211 Microprocessor digital pH meter and the mass was measured with ADAM PW124 model digital beam balance.

*2.3. Electrode Pretreatment and Characterization.* The pretreatment was carried out by socking the electrode in DMF according to the procedure previously reported by Washe et al. 2013 [19]. The solvent based approach strictly depends on the nature of the electrode composition. Herein we used SPCE based on 7102 conductor carbon paste provided by DuPont Ltd. (UK). Briefly the polyester plastic strips containing several screen printed electrodes were immersed vertically in a rectangular chromatographic chamber containing N,N-dimethylformamide for 5 min to expose all the electrodes entirely to the solvent. The solvent treated electrodes were then cured at 100°C for 20 min in the oven. The surface area enhancement resulting from the solvent treatment was characterized using cyclic voltammetry (CV). The layer of epoxy insulator was stuck at the middle part of the electrode (5 mm x 20 mm), leaving a defined working area of 5 x 5 $mm^2$ at the bottom, and the remaining upper part was used for electrical contact. Then the epoxy covered electrode was allowed to dry in an oven at 100°C for 10 min. The surface area enhancement resulting from the solvent treatment was characterized using cyclic voltammetry. Electrochemical studies involved a prior preparation of the solvent treated and untreated electrodes to delimit a constant area of the electrode surface. The electrochemical performance of the solvent activated electrode surface of fixed area was investigated by recording cyclic voltammetry of $Fe(CN)_6^{3-/4-}$ redox probe.

*2.4. Real Sample Preparation for Analysis.* The applicability of the current electrode for the detection of uric acid was demonstrated through detection of UA in clinical serum samples. The serum sample was collected from patients in Bethel Higher Clinic around Alamura in Hawassa, Ethiopia. The serial solutions of 1, 10, 100, and 1000 $\mu$M were prepared from 10 mM standard solutions of uric acid to produce calibration curve, determine the concentration of the uric acid in serum sample, and study the figures of merits such as limit of detection (LOD), linear dynamic range (LDR), sensitivity, and limit of quantization (LOQ).

*2.5. Stability, Reproducibility, and Selectivity of the Current Electrode.* In order to investigate the precision of the proposed electrode, the signal was recorded by DPV using 100 $\mu$M UA in 0.1 M PBS (pH 7) for each of the four DMF modified SPCEs at scan rate 10 mV/s, pulse period 100 ms, and pulse amplitude 240 mV (the resulting peak height against the number of electrode was plotted to evaluate the reproducibility of the DMF modified SPCE. The stability of the DMF modified SPCE was evaluated by recording DPV response of the electrodes for 100 $\mu$M UA in 0.1 M PBS (pH 7) during storage for four successive days under same experimental conditions (scan rate 10 mV/s, pulse period 100 ms, and pulse amplitude 240 mV). The resulting peak height was plotted against the days of the measurements. The repeatability, reproducibility, and stability of responses were reported in terms of relative standard deviations (% RSD). The effect of interfering species (citric acid) was studied by preparing different concentrations of citric acid and uric acid in 0.1 M PBS (pH 7). Equal concentration of both UA and CA were prepared in 0.1 M PBS separately in 100 ml volumetric flask by measuring the required amount from the stock. 3 ml of each was mixed and transferred in the cell and their peak current was recorded simultaneously with DPV by the DMF modified SPCE at scan rate of 10 mV/s pulse amplitude of 240 mV and pulse period of 100 ms.

## 3. Results and Discussion

*3.1. Electrode Pretreatment and Characterization.* In this work we used a simple pretreatment procedure where the electrodes are soaked in the DMF for different duration of exposure. As can be seen from Figure 1(a), the electrodes exposed to DMF for 5 min showed dramatically improved performance as evaluated using the values of ΔEp and peak currents. It showed highest peak height and lowest peak potential gap than the others. The 5-minute treated electrode provides increased peak current and improved reversibility as compared to untreated electrodes (Figure 1(b)). Moreover, during the prolonged exposure 30 min did not lead to further

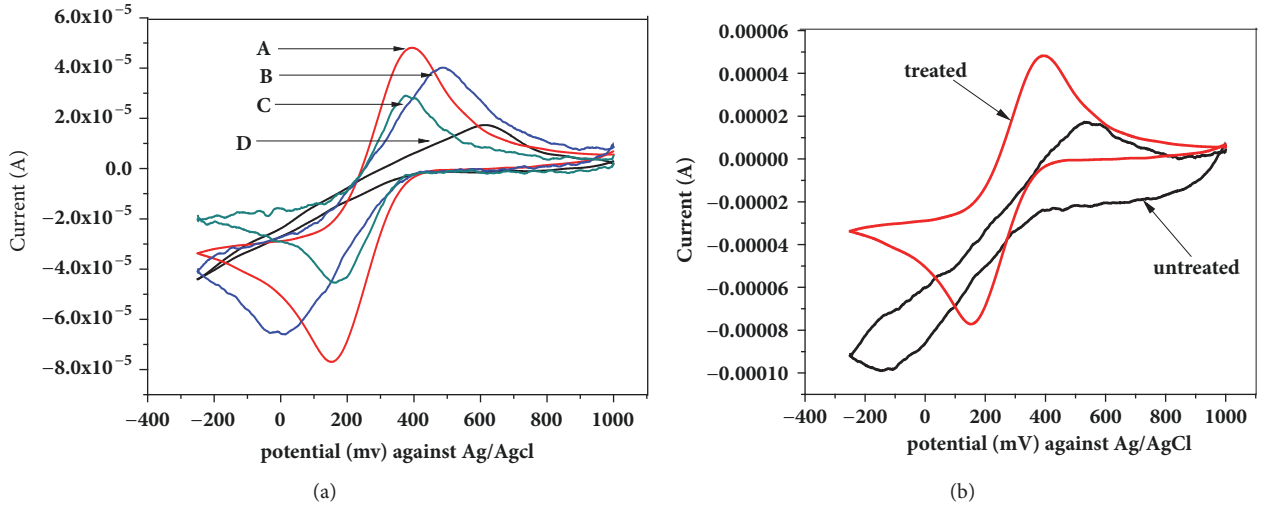



Figure 1: Cyclic voltammograms of 10 mM $K_3Fe(CN)_6$ for (a) different exposure time in DMF (A) 5 min, (B) 30 min, (C) 2 min, and (D) 1 hr and comparison (b) of untreated and 5 min treated SPCE in DMF at a scan rate of 50mV/s.

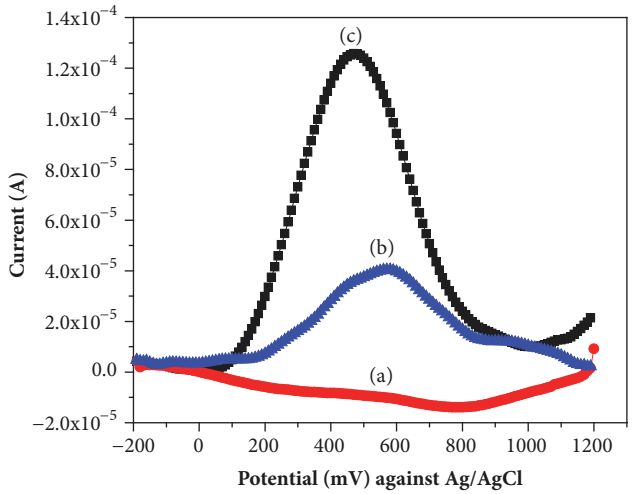



Figure 2: Differential pulse voltammetry recorded in 0.1 M PBS (pH 7) in presence (b and c) and absence (a) of 1 mM uric acid using untreated SPCE (b) and DMF treated SPCE (c) at a scan rate of 10 mV/s, pulse amplitude of 240 mV, and pulse period of 100 ms.

improvement. This might mean disentanglement of the film network as the solvent removes the binders [19].

*3.2. Differential Pulse Voltammetry of UA Using DMF Treated SPCE.* Differential pulse voltammogram (DPV) was recorded for untreated and DMF treated electrodes. Figure 2 shows the DPV recorded in 0.1 M PBS (pH 7) in presence (b and c) and absence (a) of 1 mM uric acid using untreated SPCE (b) and DMF treated SPCE (c) at scan rate of 10 mV/s, pulse period 100 ms, and pulse amplitude of 240 mV. The modified screen printed carbon electrode gave symmetrical differential voltammetric peak compared to unmodified. From the result it can be concluded that DMF modification of the given SPCE could lead to better charge transfer kinetics and narrow peak shaped voltammogram than the unmodified one. The modification greatly improves the sensitivity of uric acid determination. In addition, the modified electrode showed a 3.5-fold increase in current response as compared to unmodified.

*3.3. Effect of pH and Type of Supporting Electrolyte.* The medium at which the supporting electrolyte is prepared and the type of the buffer solution can affect the electrochemical performance of the screen printed carbon electrode. The effect of pH of the supporting electrolyte on the anodic peak current and peak potential of UA at DMF modified screen printed carbon electrode was studied over a pH range of 5 to 9 in a 0.1 M supporting electrolyte solution of each containing 1 mM of UA at scan rate of 10 mV/s. As shown in Figure 3, the peak current varied with changes in the pH of the solution. Anodic peak current increases with increasing pH up to pH 7. The current starts to decrease when pH was increased to 9. The increase in current as pH of solution increases is expected as this could activate UA towards charge transfer. But the latter trend might be due to deprotonation of surface groups leading to negative charges on electrodes surface that could screen the analyte. Thus changing pH can remarkably change the electrochemical behavior of UA on electrode surface. Because pH can alter the form (dissociated or undissociated) of analyte participating in the charge transfer process at the interface, the peak current and peak potential are affected by the pH of the working solution [18]. The pH effect was studied by preparing acetate (pH 5, 6), phosphate (pH 7), and borate (pH 9.0) buffers and recording the current responses of 1 mM UA. The result is indicated in Figure 3. The better sensitivity and shape of the voltammogram were obtained at pH 7. Therefore, pH 7 of working buffer solution was chosen. Based on the experimental data, uric acid oxidation by losing two electrons and two proton and most probable reaction

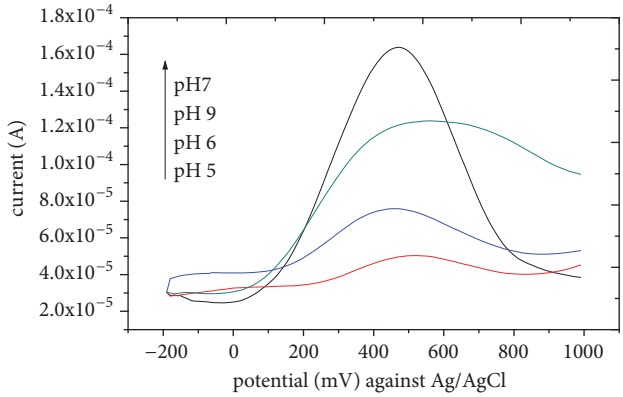
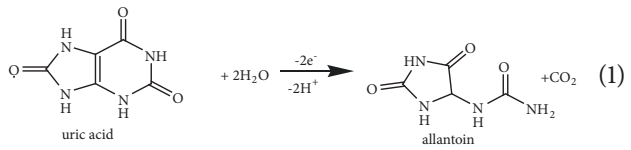



Figure 3: Differential pulse voltammogram of 1 mM uric acid by DMF modified SPCE at a scan rate of 10 mV/s, pulse amplitude of 240 mV, and Pulse period of 100 ms at different pH values (0.1 M).

Table 1: Comparison of the electrochemical performance of current sensor with reported ones.

| Electrode | Modifier used | Method | LDR | LOD (M) | Reference |
|---|---|---|---|---|---|
| CPE | NiHCF | DPV | 2 - 12 $\mu$M | 1.8 x $10^{-7}$ | [1] |
| SPCE | NiHCF | CV | 50 $\mu$ - 1.5 mM | 5.5 x $10^{-6}$ | [15] |
| GCE | SWCNTs | DPV | 100 nM to 3400 $\mu$M | 30 nM | [21] |
| SPCE | DMF | DPV | 5-100 $\mu$M and 100 - 500 $\mu$M | 1.9 x$10^{-7}$ | This work |

mechanism for the oxidation of UA at DMF/SPCPE surface is shown below [20].




(1)

*3.4. Effect of Concentration and Detection Limits.* Based on the optimum conditions, the effect of varying uric acid concentration on the DPV peak current response was studied at DMF modified SPCE. Results showed two linear segments with different slopes for UA concentrations: for the first segment (5-100 $\mu$mol $L^{-1}$ UA), the regression equation was Ip($\mu$A) = 0.0415[UA] + 0.6042 ($R^2$ = 0.98782) and for the second segment (100- 500 $\mu$mol L-1 UA), the regression equation was Ip ($\mu$A) = 0.00482[UA] + 4.26814 ($R^2$ = 0.97876), where [UA] is $\mu$M concentration of UA (Figures 4(a), 4(b), and 4(c)).

The linear regression equation corresponding to the first dynamic range, Ip($\mu$A) = 0.0415[UA] + 0.6042 ($R^2$ = 0.98782), was used to calculate the limit of detection (LOD) and limit of quantification (LOQ). LOD and LOQ were calculated from the peak current using the following equations: LOD = 3 s/m, LOQ = 10s/m, where s, the noise estimate, is the standard deviation of the peak currents (five runs) of the sample and m is the slope of the calibration curve. Accordingly, the LOD and LOQ of current sensor were found to be 1.9 x $10^{-7}$ and 6.33 x $10^{-7}$ M. [21]. Other key findings from the current study are that as the duration of exposure to DFM is increased beyond 5 min and concentration of UA increases the peak width also increases. This suggests a better sensitivity and selectively of the sensor at no longer than 30 min exposure to DMF and lower concentration ranges than higher as demonstrated by the higher slopes (higher sensitivity) for lower concentrations (Figure 4(b)) than higher concentrations ((Figure 4(c))). This could be due to surface deactivation by competitive adsorption of reaction products of the organic analyte on a carbonaceous material (SPCE) and consequent deactivation of the surface. The magnitude of detection limit and the working concentration ranges of the current study are compared with some recent studies reported in literature along with modifier material and the technique employed (Table 1).

*3.5. Accuracy of UA Determination.* The accuracy (validity) of the current UA determination using the proposed electrode was studied by spiking known amount of UA standard in a serum sample whose concentration is previously recorded. The percent recovery results calculated using the formula [(spiked sample result – unspiked sample result)∗100% / known spike added concentration] are presented in Table 2. The percent recoveries were studied in the two linear segments. The percentage of recovered quantity of uric acid varies from 93 % to 107 %. Interestingly, the first linear segment displayed not only better sensitivity but also better percent recovery values. As can be seen from Table 2, the detected concentration of uric acid in serum sample is in line with the literature value [20] with standard deviations less than unity. Thus the proposed sensor is suitable for determination of uric acid in human serum.

*3.6. Interference Study and Selectivity.* The influence of potential interfering substances that can be found along with UA

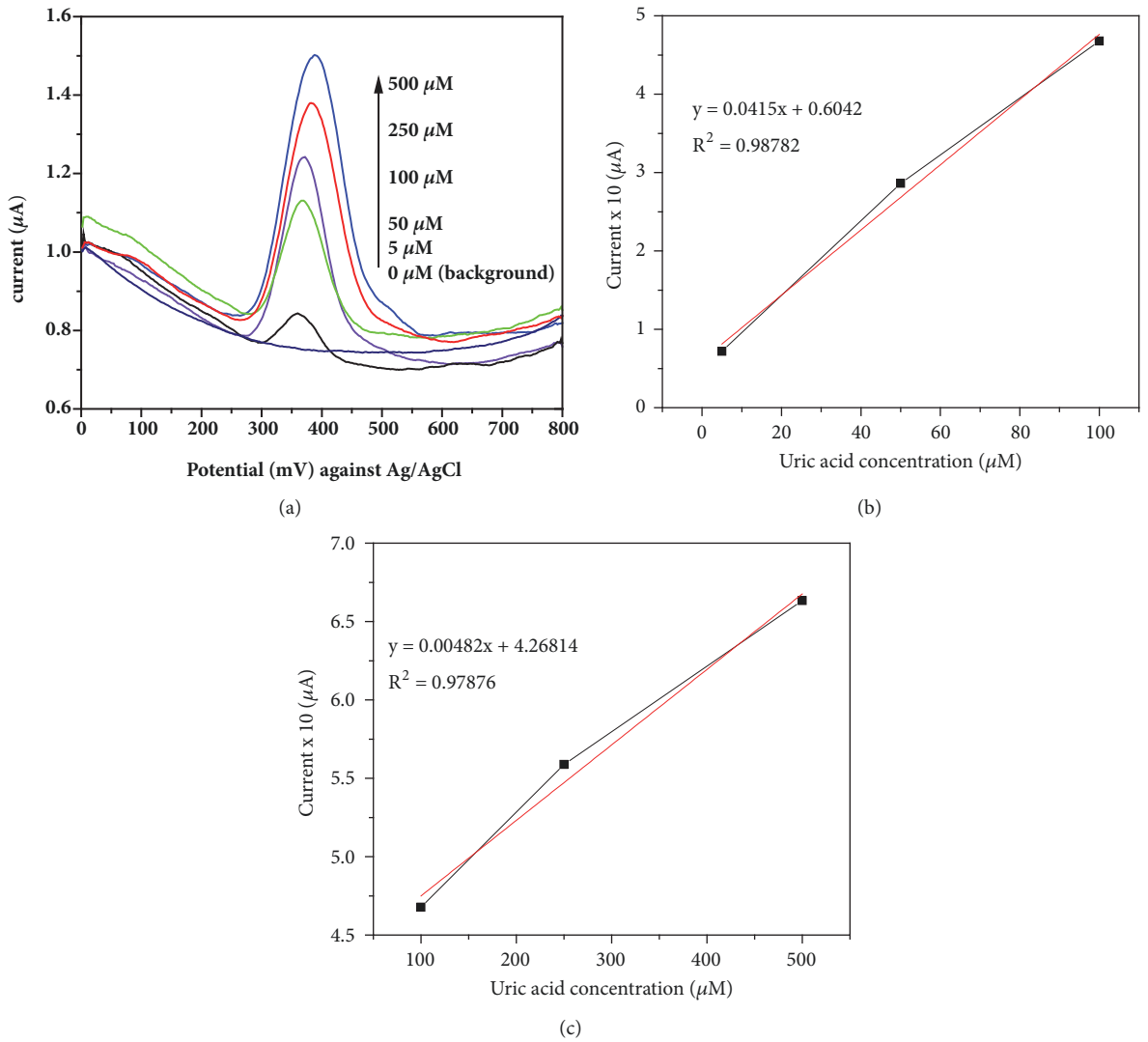



Figure 4: (a) Differential pulse voltammetry (a) of different concentrations of uric acid (0 $\mu$M, 5 $\mu$M, 50 $\mu$M, 100 $\mu$M, and 500 $\mu$M) in 0.1 M PBS (pH 7) at scan rate of 10 mV/s, pulse amplitude of 240 mV, and pulse period of 100 ms, and plot of peak current versus the linear dynamic range concentration of UA (1-100 $\mu$M (b) and 100-500 $\mu$M (c)).

Table 2: Accuracy of UA detection with the developed sensor evaluated through determination of percent recovery.

| Sample | Signal (peak current ($\mu$A)x10) | | | | Concentration of uric acid added ($\mu$M) | | | % Recovery |
|---|---|---|---|---|---|---|---|---|
| | $E_1$ | $E_2$ | $E_3$ | Mean | Spiked | Expected UA ($\mu$M) | Found UA ($\mu$M) | |
| **Serum sample** | 1.02 | 1.15 | 1.05 | 1.17 | 0.00 | ----- | 13.7 ± 0.125 | ----- |
| | 2.67 | 2.69 | 2.57 | 2.64 | 36.3 | 49.05 | 52.67 ± 0.013∗ | 107.33 ± 1.12 |
| | 5.28 | 5.30 | 5.29 | 5.30 | 0.00 | ------- | 213.7 ± 0.017 | ------- |
| | 5.48 | 5.46 | 5.44 | 5.46 | 36.3 | 250 | 247.7 ± 0.0125∗∗ | 93.7 ± 2.35 |

∗(52.67-13.7)x100%/36.3; ∗∗(230.7-213.7)x100%/36.3.

in physiological fluid was studied by exposing the DMF modified SPCE in a solution containing 1 mmol $L^{-1}$ UA, 100 $\mu$mol $L^{-1}$ each of ascorbic acid (AA) and citric acid (CA) at a pH 7.0 (Figure 5(I)). While AA and UA showed peak responses, practically no response was observed with CA. Whether the peaks corresponded to AA or UA was verified by recording by using varied concentration of UA while keeping the concentration of AA constant. Figure 5(II) shows the DPV response of different concentrations of UA (100 $\mu$M (a), 500 $\mu$M (b), and 1 mM (c) in the presence of AA. The increment in the peak current as the concentration of UA was increased and a practically no change in the AA peak as for a constant concentration (100 $\mu$mol $L^{-1}$) demonstrated a selective response of the sensor to the UA.

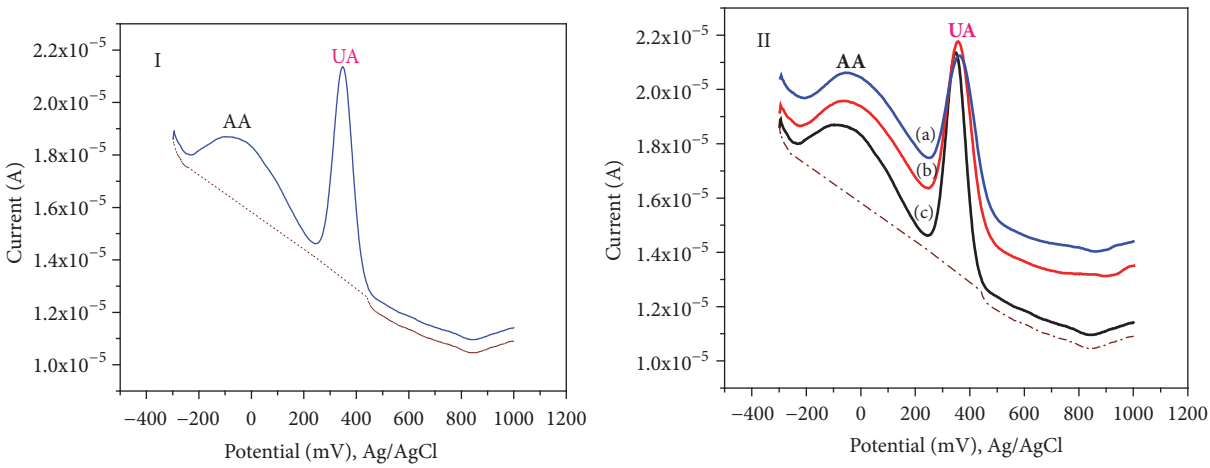



FIGURE 5: Differential pulse voltammetry of UA (1 mM), AA (100 $\mu$M), and 100 $\mu$M CA in a 0.1 M PBS (pH 7.0) and (II): different concentrations of UA (100 $\mu$M (a), 500 $\mu$M (b), and 1 mM (c)) in the presence of 100 $\mu$M each of AA and CA in a 0.1 M PBS (pH 7.0) at the DMF modified SPCE at scan rate of 10 mV/s, pulse amplitude of 240 mV, and pulse period of 100 ms.

But, it is important to note that if the concentration of AA is varied simultaneously a reduction in the sensor's response was observed because of adsorptive accumulation of the excess species on the carbonaceous material blocking the electroactive surface. Therefore, if the DMF treated SPCE is intended for a simultaneous determination of UA and AA, the surface needs to be modified with other electrocatalytic materials such as polymers or nanomaterials [22, 23].

*3.7. Reproducibility and Stability of the Current Sensor.* In order to evaluate the reproducibility of the current sensor, four sensors were separately chosen from the prepared electrodes by the same modification in DMF results at similar experimental conditions and the currents for each electrode were recorded that were obtained after subsequent usage of different electrodes. These peak heights were plotted against the number of electrodes. It was observed that some percent of the initial voltammetric performance of the given electrode decreased after 4$^{th}$ electrode measurements at a constant uric acid concentration of 1 mM (Figure 6). The repeated measurement of 1 mM UA solution showed good reproducibility of the analytical signal over each of four different electrodes with no significant changes in the electrode properties. The relative standard deviation (RSD %) was calculated and it was found to be 0.9%. The sensitivities remained the same at all four modified electrode, confirming that the results are reproducible.

To assess the long-term stability of the DMF modified screen printed carbon electrode, the response of the modified electrode prepared under optimum condition was measured for a period of 4 consecutive days at constant uric acid concentration (100 $\mu$M). The result of four measurements during this period was plotted against peak current as shown in Figure 7. It was observed that slight change on the electrocatalytic reaction was observed; that is, the activity of initial voltammetric response decreased to some extent at the end of the last day. This indicates that, upon storing for more days, only slight changes in voltammetric response of the modified electrode can be observed.

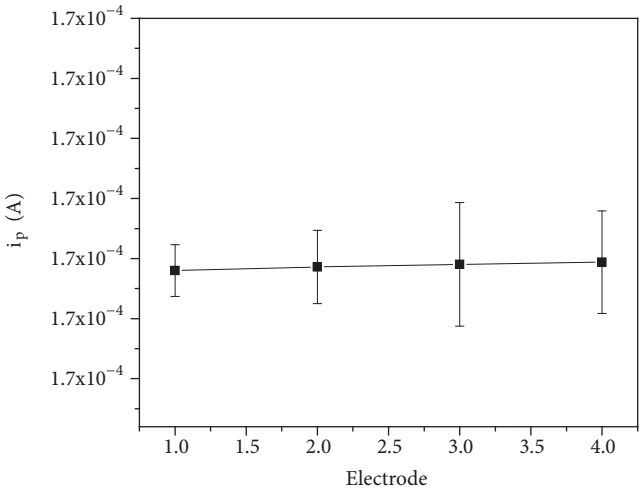



FIGURE 6: Electrode to electrode reproducibility of SPCE in 1 mM UA solution in 0.1 M PBS (pH 7) solution at scan rate of 10 mV/s, pulse amplitude of 240 mV, and pulse period of 100 ms.

## 4. Conclusions

N,N-Dimethylformamide (DMF) modified screen printed carbon electrode showed effective electrocatalytic effect on the differential pulse voltammetric determination of uric acid. The DMF modified electrode exhibited improved sensitivity and selectivity for the detection of UA in clinical serum samples in a PBS (pH = 7). The DMF treated electrodes showed a peak current that is 3.5 times improved compared to unmodified electrode. The limit of detection and limit of quantification improved significantly for UA detection with the modified electrode. The developed electrode displayed

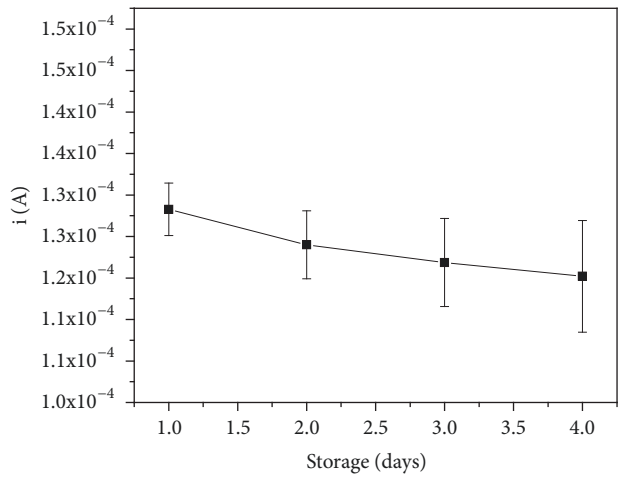



Figure 7: The differential pulse voltammetric response of DMF modified SPCE for 1 mM uric acid in a 0.1 M PBS (pH 7) during storage for four consecutive days.

well separated and discerned peaks for the potential interferent (ascorbic acid). The electrode was successfully applied for the detection of very low level of UA in clinical serum samples in a phosphate buffer solution (pH = 7) with a very high reproducibility and repeatability with the relative standard deviation of 0.9%. In conclusion, a simple and low cost voltammetric detection based on SPCEs is developed for sensitive and selective detection of uric acid in clinical samples.

## Data Availability

The experimental data used to support the findings of this study are included within the article.

## Conflicts of Interest

We declare that we do not have any conflicts of interest with anybody regarding publication of this work.

## Acknowledgments

We are grateful to Hawassa University for providing laboratory facility for the conduct of the experiments. Melaku Metto is thankful to the FDRE Ministry of Education for giving financial support.

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