Pharmaceutical Electrochemistry: The Electrochemical Detection of Aspirin Utilising Screen Printed Graphene Electrodes as Sensors Platforms

Senee Kruanetr[a], Radhakrishna Prabhu[b], Pat Pollard[c] and Carlos Fernandez[c]

[a] *The Center of excellence for Innovation in Chemistry and Department of Chemistry, Faculty of Science, Mahasarakham University, Kantarawichai District, Mahasarakham, 44150, Thailand, e-mail: Senee.k@msu.ac.th*

[b] *School of Engineering, Riverside East, Robert Gordon University, Aberdeen AB10 7GJ, United Kingdom*

[c] *School of Pharmacy and Life Sciences, Riverside East, Robert Gordon University, Aberdeen AB10 7GJ, United Kingdom*

A sensitive electrochemical sensor was designed for acetyl salicylic acid detection using graphene modified Screen Printed Electrodes. The electrochemical response of the sensor with graphene was improved compared to Screen Printed Electrodes without graphene and displayed an excellent analytical performance for the detection of acetyl salicylic acid. The high acetyl salicylic acid loading capacity on the electrode surface and the outstanding electric conductivity of graphene were also discussed in this manuscript. When a range of different concentrations of acetyl salicylic acid from 0.1 µM to 100 µM into a pH4 buffer solution (*N* defined as the sample size $N = 9$) were plotted against the oxidation peak a linear response was observed. The detection limit was found to be 0.09 µM based on (3-σ/slope). Screen Printed Graphene electrodes sensors methodology is shown to be useful for quantifying low levels of acetyl salicylic acid in a buffer solution as well as in biological matrixes such as humam oral fluid. A linear response was obtained over a range of concentrations from 10 µm to 150 µM into a human oral fluid solution ($N = 10$) giving a detection limit of 8.7 µM.

Keywords: acetyl salicylic acid, electrochemical, sensor, modified Screen Printed Electrodes.

УДК 543.55

INTRODUCTION

Acetylsalicylic acid (ASA) or aspirin which is depicted in Fig. 1, was introduced in the late 1890s [1] and has been used to treat a variety of inflammatory conditions for more than 200 years. In 1763 the active ingredient of Aspirin was discovered by Edward Stone from the bark of the willow.

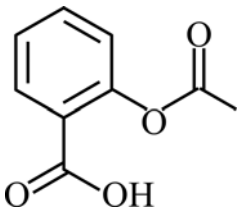


Fig. 1. Chemical structure of Aspirin.

A number of analytical approaches have been employed to analyse ASA such as: high-performance liquid chromatography–mass spectrometry [2–6] and gas chromatography–mass spectrometry [7], ultra performance liquid chromatography tandem mass spectrometry [8] and capillary electrophoresis [9] have also been reported for the determinations of ASA. However, many of these methods require sample pre-treatment, several time-consuming manipulation steps, sophisticated instruments and special training.

In contrast, suggesting of electrochemical sensors is an attractive alternative method for electroactive species detection, because of its inherent advantages of simplicity, high sensitivity and relatively low cost [10].

The utilisation of screen-printed electrodes as sensors platforms have attracted great interest since they provide a low cost, single-shot disposable yet highly reproducible and reliable electrochemical measurement of the target analyte [10].

The electrochemical detection of aspirin has attracted great attention and different strategies have been employed. For instance Srivastava *et al.* [11] used surfactant-modified multiwalled carbon nanotube paste electrode for the determination of ASA in pharmaceutical formulations, urine and blood samples by voltammetry. Tsai *et al.* [12] investigated the electrocatalytic oxidation of acetylsalicylic acid at multiwalled carbon nanotube-alumina-coated silica nanocomposite modified glassy carbon electrodes. Lu *et al.* [13] reported an electrochemical sensor based on AuNPs modified molecularly imprinted polymer film for the detection of ASA. Rynkowski *et. al* [14] reported Voltammetric studies of acetylsalicylic acid electro oxidation at platinum electrode. These reports showed good detection limits and sensitivity however the main drawback is the need of extra time to modify the surface of the electrode which involves various steps.

Graphene has attracted a great attention since it discovery due to its large surface area, high thermal and electrical conductivities, impressive mechanical properties, and low cost [15, 16]. The application of

graphene in sensors technologies, catalysis, nanocomposites and capacitors amongst others have increased dramatically in the last decade.

Graphene sheets have extraordinary electronic transport properties and high electrocatalytic activities [17–19], and they have been investigated as electrode materials in optoelectronic devices [20], electrochemical super-capacitors [21], fabricated field-effect transistors [22], and constructed ultrasensitive chemical sensors [23], such as pH sensors [24], gas sensors [25], and biosensors [26].

To the best of our knowledge, there is no report based on using graphene modified Screen Printed Electrodes (SPGrE) for the determination of ASA. In this manuscript we proposed a simple, fast and without pre-treatment of the electrode surface methodology in which graphene is already printed in-situ on the screen printed electrode. The electrochemical behaviors of ASA using SPE with and without graphene were also investigated and discussed in this manuscript. Cyclic Voltammetry (CV) techniques were employed in the proposed method for the determination of ASA in drug preparations and human oral fluid as well as a technique to investigate ASA electro-oxidation mechanism.

1. EXPERIMENTAL SECTIONS

1.1. Reagents

All chemical reagents used to prepare solutions were purchased in their purest commercially available forms from Aldrich. All aqueous solutions were made up with water (of resistivity of not less than 18 MΩ·cm) taken from an Elgastat filter system (Vivendi, Bucks., UK). All experiments were undertaken at 23 ± 2ºC. Aspirin containing tablets of different pharmaceutical companies such as Galpharm International Ltd. were purchased from the local market. A stock solution of aspirin was prepared by dissolving the required mass in buffer to give a concentration of 1 mM. Working standards, for initial voltammetric studies, were prepared by dilution of this solution with phosphate buffer to give a final concentration of 0.1 μM. In the same manner a stock solution of aspirin was prepared by dissolving the required mass in human oral fluid to give a concentration of 1 mM. Working standards, for initial voltammetric studies, were prepared by dilution of this solution with human oral fluid to give a final concentration of 0.1 μM.

1.2. Electrodes

Screen Printed Graphene Electrodes (SPGrE) and Screen printed graphite electrodes (SPGE) which both have a 3 mm diameter for the working electrode were obtained from Gwent Electronic Materials Ltd. (Pontypool, Cardiff, UK). Two sets of SPE were employed to obtain the results. One SPE system was composed of three electrodes with graphite as a working and counter electrode and silver/silver chloride for the reference electrode. The other system was composed of three electrodes with graphene as a working electrode and graphite as a counter electrode and silver/silver chloride for the reference electrode.

1.3. Electrochemical measurements

Voltammetric measurements were carried out using a μ-Autolab III (Eco Chemie, Amsterdam, The Netherlands) potentiostat/galvanostat and controlled by Autolab GPES software version 4.9 for Windows XP. The electrodes have been characterised electrochemically and have found to exhibit a heterogeneous electron transfer rate constants of ~ 1.7×10^{-3} cm·s^{-1} using the ferro-cyanide redox couple in 0.1M KCl. The cyclic voltammetric parameters were as follows: initial potential of 0 V, vertex potential 1.5 V, end potential 0 V, step potential 5 mV.

2. RESULTS AND DISCUSSION

2.1. Electrochemical characterization of SPGrE

First of all we turn our attention into the investigation of the SPGrE and the SPE electrodes surfaces. An electrochemical probe containing 1.0×10^{-3} mol·L^{-1} [$K_3Fe(CN)_6$] and 0.1 mol·L^{-1} KCl was employed by using cyclic voltammetry at a scan rate of 100 mV/s which is depicted in Figure 2.

The voltammograms obtained at a bare SPE (curve *a*), and SPGrE (curve *b*) are illustrated in Figure 2. The shape of the voltammogram shows a reversible one electron transfer process. At the bare SPE the peak-to-peak separation observed is approximately of 68 mV which corroborates with the reversible redox process of [$K_3Fe(CN)_6$]. The curve *a* shows a voltammogram of $[Fe(CN)_6]^{3-}$ with peak currents at E_{pa} (anodic peak potential) = 0.173 V and E_{pc} (cathodic peak potential) = 0.243 V respectively.

The current increases from 230 to 630 μA when the SPE is modified with Gr (Figure 2b). The dramatic peak current increase is owed to the excellent electric conduction of graphene compared to graphite. The peak potential is also affected by the modification of the electrode surface with graphene. The peak potentials cathodic and anodic of graphene shifted when compared to the bare SPE. The values for graphene were observed to be E_{pa} (anodic peak potential) = 0.113 V and E_{pc} (cathodic peak potential) = 0.283 V respectively, while for the bare SPE were E_{pa} (anodic peak potential) = 0.1373 V and E_{pc} (cathodic peak potential) = 0.246 V.

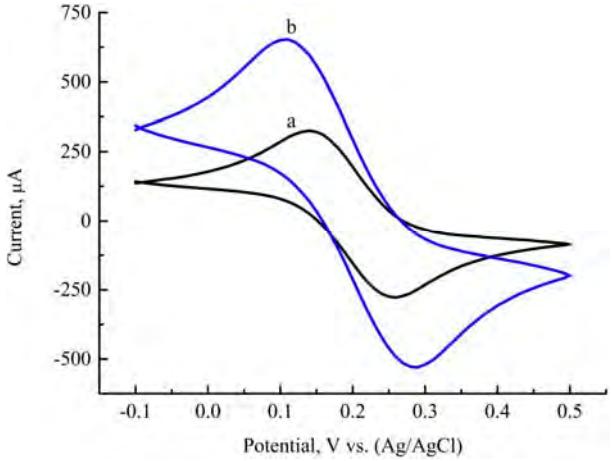


Fig. 2. Cyclic voltammograms response observed for (*a*) a bare SPE and (*b*) SPE modified with Gr in 1.0×10^{-3} mol·L^{-1} $[Fe(CN)_6]^{3-}$ containing 0.1 mol·L^{-1} KCl. Scan rate: 100 mV/s.

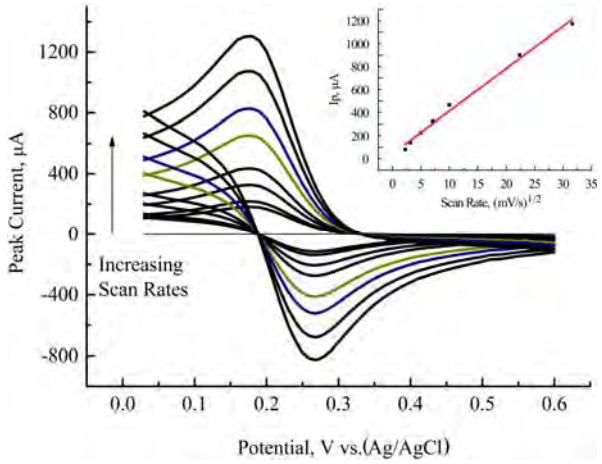


Fig. 3. Cyclic voltammograms response observed for SPE modified with Gr in 1.0×10^{-3} mol·L^{-1} $[Fe(CN)_6]^{3-}$ containing 0.1 mol·L^{-1} KCl at different scan rates (from inner to outer): 5, 10, 25, 50, 75, 100, 500 and 1000 mV/s.

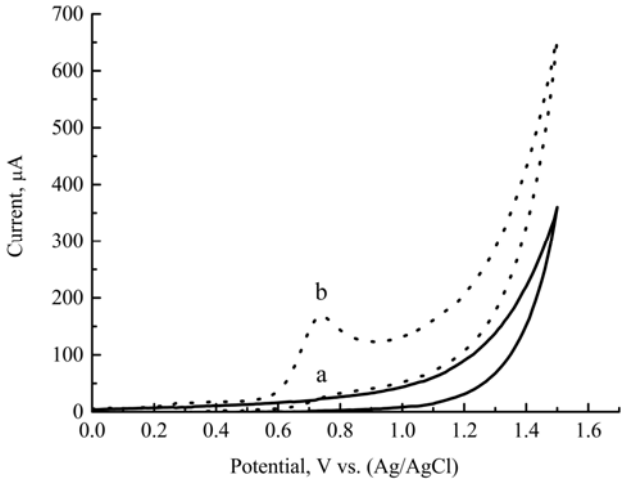


Fig. 4. Cyclic voltammetric response recorded at SPE modified with Gr (*a*) without 10 μM ASA and (*b*) dot line with 10 μM ASA in pH4 phosphate buffer solution. Scan rate: 100 mV/s.

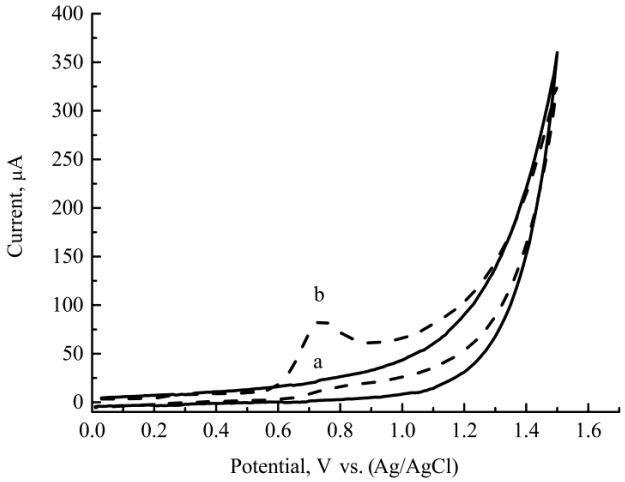


Fig. 5. Cyclic voltammetric response recorded at SPE (*a*) without Gr and (*b*) dash line: modified with Gr in 10 μM ASA in pH4 phosphate buffer solution. Scan rate: 100 mV/s.

Cyclic voltammetry was also employed to extract information related to the electroactive area of the SPGrE compared to SPE electrode. The Randles–Sevcik equation is given by $I_p = 2.69\times10^5\ n^{3/2}AD_0S\ C_0v^{1/2}$. From this equation the electroactive area could be obtained from the slope of a plot of the voltammetric peak current (I_p) versus the square root of scan rate ($v^{1/2}$) which is shown in Figure 3.

As predicted by the Randles–Sevcik equation the redox peak currents at the graphene-modified SPE increased linearly with the scan rate in the range from 5 to 1000 mV/s (inset, Fig. 3; linear regression equation: $I_p = 36.999 + 42.337v$, $R = 0.992$). These values indicate that the modified-electrode reaction is a surface confined process.

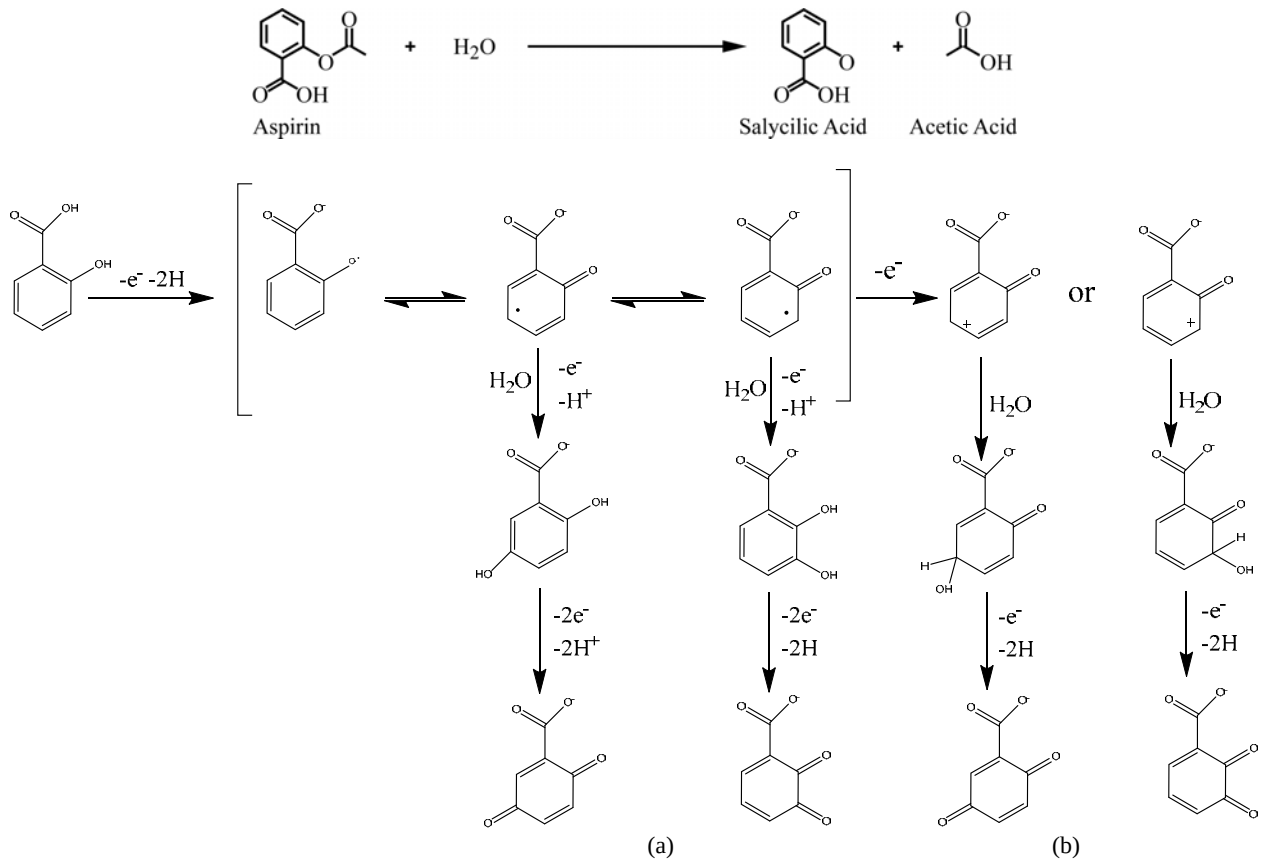
Next, in order to investigate the electrochemical behaviour of ASA on a SPGrE in pH4 phosphate buffer solution a CV was used. Figure 4 shows two voltammograms of the Gr modified electrode in the presence and absence of 10 μM ASA in pH4 phosphate buffer solutions at scan rate: 100 mV/ s.

When aspirin an electroactive specie was not present (curve *a*), no redox peaks were observed in the potential range from 0 to 1.5 V using the SPGrE. This shows that graphene was non-electroactive in the scanned potential window. On the contrary when aspirin was present at 10 μM ASA in pH4 phosphate buffer solution (curve *b*) a very sensitive anodic peak with current of 752 mV was detected when using SPGrE.

2.2. Electrochemical behaviour of Aspirin

2.2.1. The effect of pH

The possible mechanism ASA oxidation is shown in Scheme 1. ASA in aqueous media oxidizes to Salicylic Acid and Acetic Acid as depicted in Scheme 1. The first step of ASA electro-oxidation visible in the voltammograms as a peak which is depicted in Fig. 5 involves an exchange of one electron and is the rate-determining step. The next step, invisible in the voltammograms due to overlapping with oxygen evolution, involves an exchange of the second electron. Assuming that these two steps demand an exchange of two electrons, this indicates



Scheme 1. Suggested mechanism of ASA electro-oxidation in the pH range (a) 2–8 and (b) 8–10.

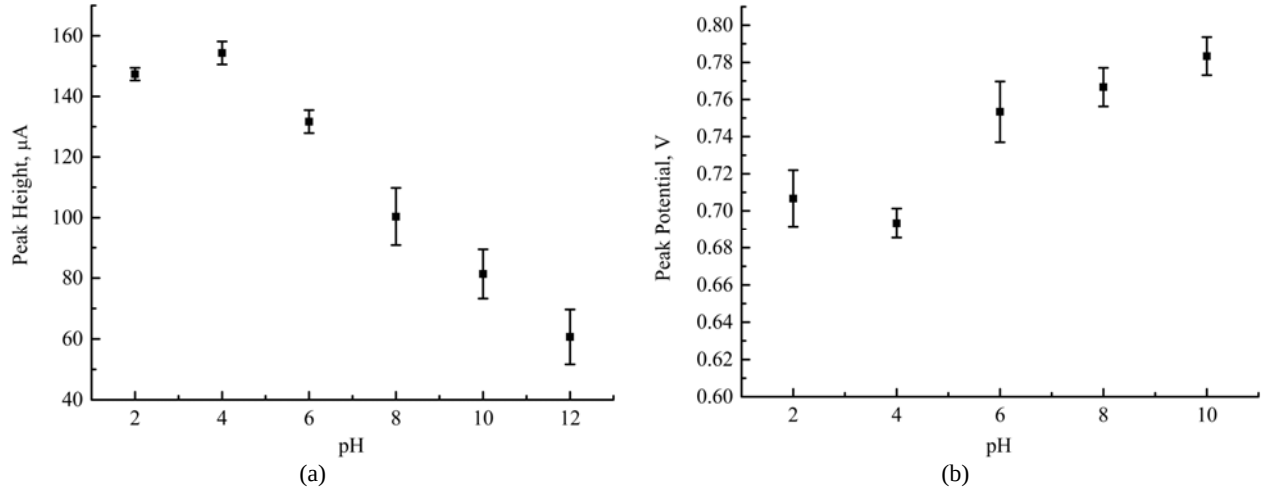


Fig. 6. (a) A plot of peak height as a function of pH for the electrochemical oxidation of 10 μM ASA using SPE modified with Gr. Scan rate: 100 mV/s. (b) A plot of peak potential (E_p) as a function of pH for the electrochemical oxidation of 10 μM ASA using SPE modified with Gr at Scan Rate: 100 mV/s.

that 3 protons are possibly exchanged. If pH values are higher than 8 (Scheme 1b), E_p and $E_{1/2}$ values are independent on pH. This means that protons are no longer involved in the ASA electro-oxidation. Probably, this result from the fact, that at higher pH values, hydrolysed form of ASA is already chemically deprotonated.

The dissociation constant or pKa is an important factor to consider, the pKa of ASA is reported to be 3.49 within the literature [27]. ASA therefore was prepared in a phosphate buffer solution at pH4 where the electro-oxidation of ASA will be more favourable.

At pH4, ASA is easily oxidised compared to more basic pHs as illustrated in Fig. 6a and b, these values are in agreement with ASA mechanism which is depicted in Scheme 1a.

Figure 5a shows an irreversible voltammogram of ASA with a relative weak redox current peak at E_{pa} (anodic peak potential) = 712 mV when bare SPE were utilised. Figure 5b illustrates an irreversible voltammogram of ASA on the graphene-modified SPE in which a well-defined oxidation peak at E_{pa} = 752 mV is observed. This peak can be assigned to the oxidation of ASA to Salycilic Acid, as reported in literature [14]. The increase of the

peak current in Fig. 5b compared to Fig. 5a can be attributed to the graphene effect.

Next, the effect of peak height current vs. pH and Peak Potential vs. pH were investigated.

In order to investigate the effect of peak height current versus pH the peak height current of 10 μM ASA solution in phosphate buffer with SPGrE was measured over a solution range of pHs from 2 to 10 as illustrated in Figure 6a. Figure 6a illustrates that the maximum peak height current value for ASA in SPGrE was observed at pH4 which is according to the pKa value. This high value of peak height current indicates that the electro-oxidation process of ASA is favourable at pH4 compared to others pHs. The lowest peak height value can be observed at basic pH10 indicating that the electro-oxidation process of ASA is less favourable which is in agreement to the Scheme 1b.

Figure 6a also illustrates a linear response over pH4 to pH10 and the linear equation for that is showed to be: I_p/μA(pH4–10) = -11.5x + 196 798 versus Ag/AgCl for ASA with correlation coefficients of 0.99.

Next the effect of peak potential and pH were investigated as it is illustrated in Figure 6b. Figure 6b shows that at pH4 there is a drop of the potential which indicates that pH4 is the optimum pH for the electro-oxidation of ASA. At higher pHs the electro-oxidation process of ASA is less favourable.

The peak potential (E_p) versus pH plot is linear (from pH4 to pH10) and dependent on the anodic peak potential of the analyte on the pH. The linear equation can be presented by the relation: E_p/V(pH4–10) = 0.0075 V/pH + 0.6958 versus Ag/AgCl for ASA with correlation coefficients of 0.99.

The above results indicated that the peak current (I_{pa}) and peak potential (E_{pa}) were affected by the pH of the solution. For the subsequent analytical experiments pH4 was chosen to be the most favourable condition to occur the electro-oxidation of ASA.

2.2.2. Effect of concentration

Next, the effect of ASA concentration on SPGrE was explored. A range of ASA concentrations from 0.1 to 100 μM in phosphate buffer pH4 on SPGrE was investigated using cyclic voltammetry as indicated in Figure 7a. Figure 7a shows the electro-oxidation of ASA at height positive potential +750 mV. The peak height current (I_{pa}) values increases in magnitude upon the addition of ASA. The ASA concentrations range from 0.1 to 100 μM was plotted against the measured peak height current (I_{pa}) values as illustrated in Figure 7b. Figure 7b displays a good linear relationship between I_{pa} and ASA concentrations. A linear regression equation was given by (I_p/μA = 1.4079x + 15.803 with N = 9, RI = 0.9903) with a detection limit of 0.09 μM (based on 3-σ/slope).

2.3. Electroanalytical Applications of the proposed method to detect Aspirin in human oral fluid

The viability of the analytical protocol was tested in relation to detection within analytically relevant media, following confirmation that successful determination of ASA was possible in ideal conditions utilising a standard pH4 phosphate buffer.

It is considered worthwhile to determine the concentration of ASA in human oral fluid as ASA is clinically employed for analgesic and antipyretic effects and it is taken orally. The human oral fluid samples were taken from three healthy individuals; consequently, additions of ASA were made into human oral fluid solution over the concentration range from 10 to 150 μM which are depicted in Figure 8. Each concentration was repeated three times and the appropriate error bars were added to the points and plotted. Figure 8 illustrates the calibration plot of peak height current values (I_{pa}) versus ASA concentrations in human oral fluid. The response was linear over the ASA concentrations range from 10 to 150 μM and the regression line was given by the following equation: I_p/μA = 0.7092x + 103.92, R^2 = 0.9879 and N = 10 (where N is the number of points analysed) with a detection limit of 8.7 μM (based on 3-sigma). The human oral fluid solution employed was not modified in any way prior to use.

The main advantage of this protocol was the lack of either sample or electrode surface pre-treatment and its great potential to be utilised in real-world applications.

3. CONCLUSIONS

It has been demonstrated for the first time the successful application of SPE modified with Gr towards the electrochemical determination of ASA in an ideal buffer solution as well as in a biological matrix such as human oral fluid samples with excellent sensitivity and selectivity.

The sensor offers a long term stability and excellent reproducibility with essentially no pre-treatment or maintenance towards the routine analysis of ASA. A linear response is observed for a buffered solution given by the equation: (I_p/μA = 1.4079x + 15.803, RI = 0.9903 and N = 9) over the range from 0.1 μM to 100 μM into a pH4 buffer solution with a detection limit of 0.09 μM (based on 3-sigma). The determination of ASA was also linear over the concentration range from 10 to 150 μM in a biological matrix such as human oral fluid. The linear regression equation is given by: (I_p/μA = 0.7092x + 103.92, R^2 = 0.9879 and N = 10) with a detection limit of 8.7 μM (based on 3-sigma).

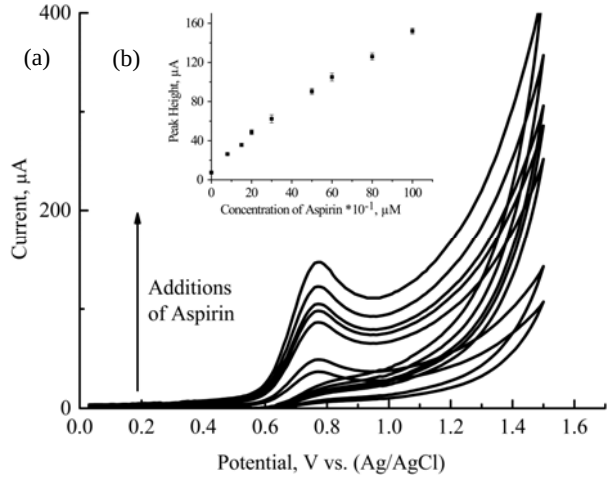


Fig. 7. (a) Cyclic voltammogram response observed for phosphate buffer solution pH4 at SPE modified with Gr over a range of ASA concentrations from 0.1 μM to 100 μM Scan Rate: 100 mV/s. (b) A plot of peak height (I_p), as a function of ASA concentration using SPE modified with Gr at a scan rate: 100 mV/s.

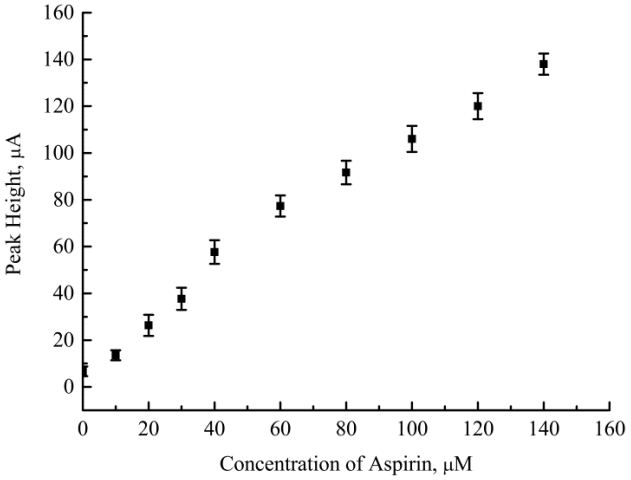


Fig. 8. A calibration plot of peak height (I_p), as a function of ASA concentration corresponding to the addition of ASA into human oral fluid sample solution over the concentration range 10–150 μM using SPE modify with Gr. Scan Rate: 100 mV/s.

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Реферат

Представлен разработанный авторами чувствительный электрохимический датчик с графеновым электродом, изготовленным методом трафаретной печати, для распознавания ацетилсалициловой кислоты. Для поставленной задачи, у датчика с графеном выявлен как улучшенный электрохимический отклик по сравнению с электродом, изготовленным методом трафаретной печати, но без графена, так и превосходные аналитические характеристики устройства. В работе рассмотрены также высокая несущая способность ацетилсалициловой кислоты на поверхности электрода и исключительная электропроводность графена. При концентрации ацетилсалициловой кислоты от 0,1 μM до 100 μM и pH 4 буферного раствора (*N* рассматривается как размер образца *N* = 9), нанесенными на график в зависимости от пика окисления, наблюдался линейный отклик. Предел обнаружения был равен 0,09 μM, на основании наклона 3-σ/на наклон. Было продемонстрировано, что методология применения датчиков с графеновым электродом, изготовленным методом трафаретной печати, подходит для распознавания низкого уровня ацетилсалициловой кислоты в буферном растворе, а также в биологических смесях, например, в ротовой жидкости человека. Линейный отклик был получен при концентрациях от 10 μm до 150 μM в растворе ротовой жидкости человека (*N* = 10), с пределом обнаружения 8,7 μM.

Ключевые слова: ацетилсалициловая кислота, электрохимический датчик (прибор обнаружения), модифицированные электроды, изготовленные методом трафаретной печати.