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RESEARCH ARTICLE

Electrochemical investigation of allopurinol polymerised carbon paste electrode interface for epinephrine and folic acid sensing in pharmaceutical samples

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ABSTRACT

The performance of simultaneous electro oxidation of epinephrine (EP) and folic acid (FA) was achieved at allopurinol polymerised carbon paste electrode (AlpM-CPE) by cyclic voltammetry (CV) method at physiological pH. The modified electrode showed remarkable sensing activity towards the electrooxidation of EP, involving irreversible 2-electronstransfer with adsorption-controlled kinetics. The results of varying few experimental parameters, for instance – scan rate, solution pH, concentration of the target analyte was examined. It was observed that, the anodic peak current (Ipa) is proportional to the concentration of EP in the range 51.02–318.18 µM with a calculated limit of detection (LOD) 0.46 µM by CV technique. The analytical applicability of the fabricated AlpM-CPE was examined for the resolve of EP in pharmaceutical sample and a good recovery results were observed.

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KEYWORDS
Allopurinol; epinephrine; modified electrode; electrochemical sensor; voltammetry; injection sample

1. Introduction

The direct electrochemical oxidation of pharmaceutical drugs plays a significant role in determining its concentration in biological fluids. Among all the conventional methods, the electro analytical methods based on polymeric films modified electrodes are more promising methodology [1–8]. It has the merit of simple, highly sensitive, good selective, low cost, time saving and accurate method for the detection of biomolecules [9–15]. Therefore, the development of electrochemical sensing platform for the determination of biomolecules needs further in-depth studies.

Epinephrine (EP, adrenaline) (see Table 1) is an important neurotransmitter secreted in the central nervous system (CNS) of mammalian brain. It is widely used as a common health care medicine [16]. This EP drug is an important hormone and is synthesised from as 'L-tyrosine' and exuded by the medulla of the adrenal gland in human body along with norepinephrine [17]. It is an important drug to treat hypertension, heart disease and other allergic conditions. The low level of EP may lead to adverse effects like Parkinson's disease. Therefore, the determination of EP in biological and/or pharmaceutical samples plays a significant role early diagnosis of diseases caused by the deficiency [18,19]. There are various methods available for the determination of EP, such as chromatography [20], fluorescence [21], capillary electrophoresis [22], flow injection electrogenerated chemiluminescence [23], various electrochemical sensors [24–26], fluorimetry [27,28] and chromatography [29,30]. However, these techniques are considered as tedious and time consuming. Folic acid (FA, folate) (see Table 1) is a form of the water-soluble vitamin. It has been recognised as part of the vitamin B complex [31]. Folic acid has a major role in the proper biological functions of cell metabolism and it helps in the synthesis of amino acids and replication/repair in DNA [32]. FA is mainly found in algae, plants, mushrooms, cabbage, fruits, nuts, broccoli& some vegetables and liver of animal [33]. In human body the deficiency of FA leads to anaemia, leucopenia, depression, reduced cognition, cardiovascular disease, devolution of mentality, psychosis and serious illness. Therefore, the quantification of FA plays a significant role in early clinical diagnosis. The individual or simultaneous electrochemical determination of EP and FA is important as these two biomolecules have a major role to play for keeping sound health conditions. Several researchers have developed different electrode materials for the simultaneous determination with significantly distinguishable voltammetric response, high sensitivity and low detection limit [34,35].

Allopurinol (AP) (see Table 1) is a radical sifting clinical drug used in the action of chronic gout and hyperuricaemia [36–38]. AP can also be used in the therapeutic treatment of human heart failure [39]. AP showed significant role in the treatment of Lesh-Nyan disease, kidney problem, high blood pressure, heart disease, diabetes and renal failure [40]. The allopurinol converts into alloxanthin, in presence of xanthine oxidase, which leads to inhibition of uric acid from xanthine and hypoxanthine [41]. The electropolymerisation is a simplest method of immobilising the organic molecules on working electrode surface by adopting the CV method [42]. The thickness of the polymeric layer can be controlled by varying the input parameters during the electropolymerisation process [43]. Therefore, it attracted many electrochemical researchers to develop the sensing interface based on electropolymerised layers.

There are very few reports available where allopurinol is used to prepare modified electrodes to detect neurotransmitters. In our present work, a polymerised allopurinol modified carbon paste electrode (AlpM-CPE) interface was fabricated to

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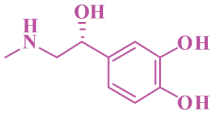
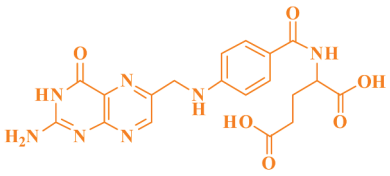
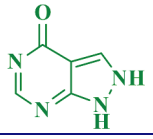
[1]Both the authors contributed equally to this work.

Table 1. The chemical structure and molecular formula of epinephrine, folic acid and allopurinol.

Molecule	Molecular formula	Chemical structure
Epinephrine (EP)	$C_9H_{13}NO_3$	
Folic acid (FA)	$C_{19}H_{19}N_7O_6$	
Allopurinol (AP)	$C_5H_4N_4O$	

determine EP and FA in physiological pH condition. The electrode kinetics at the fabricated electrode was found to be adsorption controlled. Further, the analytical applicability of the proposed sensor was evaluated for the determination of Ep in injection sample and acceptable recovery results were obtained. The electrochemical technique proposed in the present work can be implemented to the determination of other electroactive molecules also.

2. Materials

2.1. Reagents and apparatus

Epinephrine (M_{wt} = 183.204 g/mol, purity >99%) and Allopurinol (M_{wt} = 136.112 g/mol, purity >99%) were procured from Sigma Aldrich Ltd. Folic acid (M_{wt} = 441.40 g/mol, purity ≥99.9%) was purchased from Himedia. The standard stock solutions of EP and FA were prepared by dissolving the appropriate amount in double distilled water and 0.1 M NaOH solution. The 0.2 M phosphate buffer solution (PBS) was prepared and required pH was obtained by mixing calculated amount of 0.2 M Na_2HPO_4 and 0.2 M $NaH_2PO_4 \cdot H_2O$ solutions. The graphite powder and silicon oil were purchased from Merck and Himedia respectively. The chemicals used in the present work were of analytical grade and used as received. An electrochemical workstation model CHI660c (USA) coupled with three-electrodes, namelysaturated calomel electrode (SCE, reference) platinum (counter) and bare CPE or AlpM-CPE as working were used for the electrochemical measurements. At an ambient temperature, the redox potentials of the analytes were reported against SCE.

2.2. Fabrication of working electrode

The bare carbon paste electrode (bare CPE) was prepared by hand mixing of graphite powder and silicone oil (70:30%) in an agate mortar and grinded for about 45 min until a homogeneous paste was formed. The paste was packed into a homemade cavity of PVC tube of 3 mm internal diameter and the electrical contact was provided by a copper wire connected to the end of the tube [3,4]. An electro polymerisation of allopurinol on CPE was achieved by CV technique. The polymerisation of allopurinol on surface of CPE was done by repeated scanning of CPE for 10 multiple cycles between – 0.5 V to +1.6 V with 0.1 V s^{-1} scan rate. The allopurinol solution used for polymerisation was 1.0 mM in PBS (0.2 M, pH 7.4). The AlpM-CPE was then thoroughly washed and rinsed before using it for the determination of EP and FA. After measurements, the fresh surface was regenerated by removing a small quantity of the paste off and again smoothened a piece of paper.

3. Results

3.1. Electropolymerisation of allopurinol and its electrochemical characterisation

The cyclic voltammetry (CV) is one of the most convenient method to immobilise an organic molecule on the surface of a working electrode [3]. The electro polymerisation of allopurinol was done as described in section 2.2. Figure 1 illustrates that the voltammogram was increased at first and becomes almost constant after few cycles. This is an indication of the growth and attainment of the saturation level in the electro polymerisation process. Our experimental observations are in accordance with the previous reports [4,43,44]. The probable electropolymerisation mechanism of allopurinol on CPE is described in Scheme 1.

The CV responses at bare CPE (dashed line) and the AlpM-CPE (solid line) were recorded using the standard potassium ferrocyanide in 1.0 M KCl solution with an applying scan rate of 0.05 V s^{-1}. As expected, the voltammogram obtained at bare CPE (dashed line) showed less sensitivity. On the other hand, the AlpM-CPE (solid line) showed an improvement in the current signal with more sensitivity with fast electron transfer kinetics as shown in Figure 2. From this improved result, it can be confirmed that the polymerised layer of allopurinol significantly changed the surface texture of the bare CPE and might have facilitated the electron transfer kinetics. The total active surface area of the proposed modified electrode can be calculated by using Randles-Sevcik equation (1) [3]. The AlpM-CPE (0.03787 cm^2) has more active surface are as compared to bare CPE (0.02748 m^2).

$$Ip = \left(2.69 \times 10^5\right) n^{3/2} A\, D^{1/2} C_0 u^{1\upsilon 2} \quad (1)$$

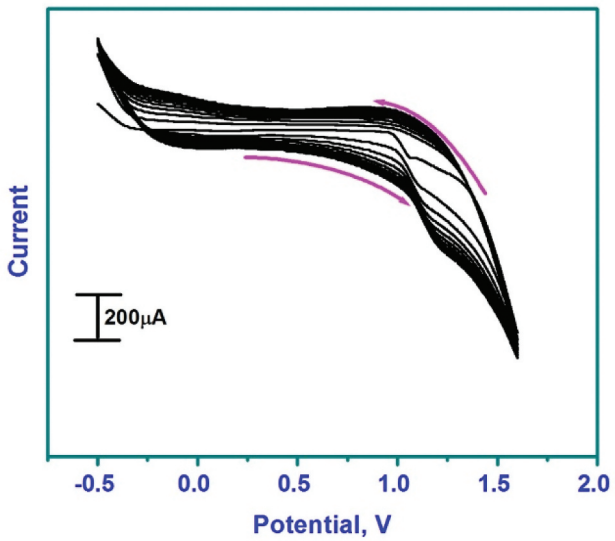
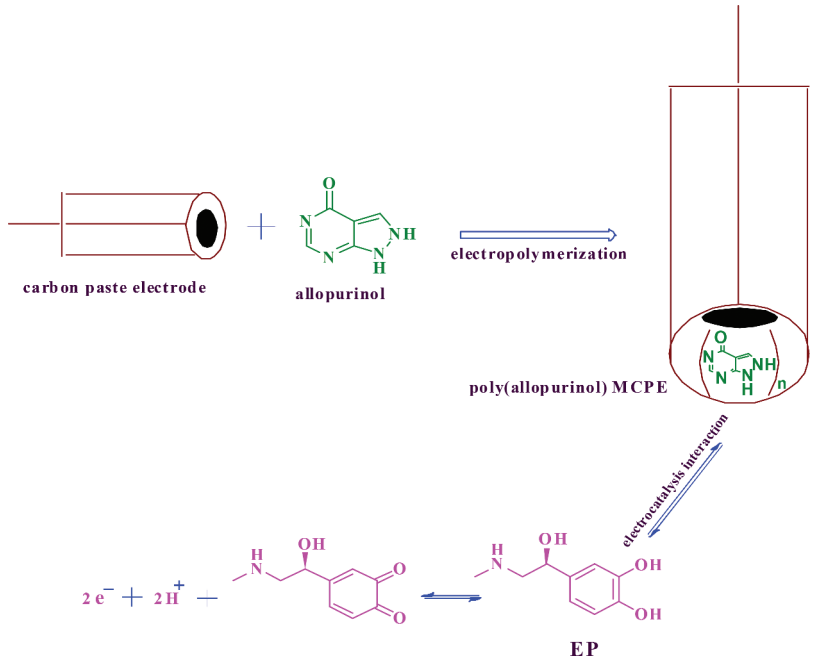


Figure 1. CVs of preparation of AlpM-CPE in 1.0 mM solution of allopurinol in PBS (0.2 M, pH 7.4) at ten cycle sweeps with scan rate of 0.1 V s^{-1}.



Scheme 1 A probable electropolymerisation mechanism of allopurinol on carbon paste electrode and its electrocatalytic interaction with epinephrine.

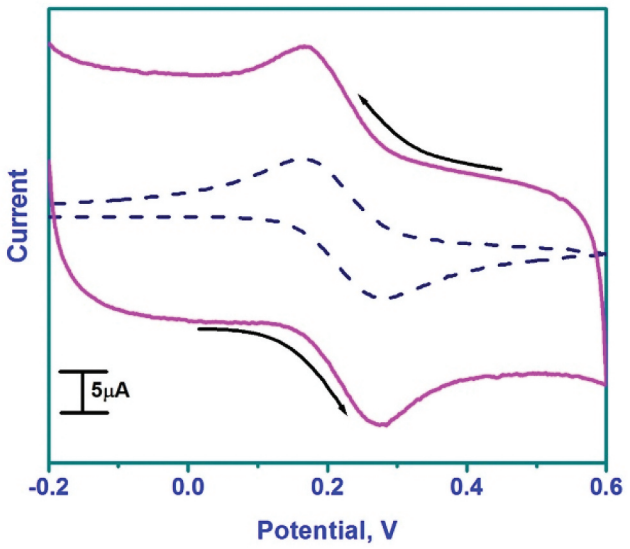


Figure 2. CVs of 1.0 mM potassium ferrocyanide in 1 M KCl at bare CPE (dashed line) and AlpM-CPE (solid line) at scan rate of 0.05 V s^{-1}.

where, *Ip*, *A*, *n* and C_0 are peak current (A), surface area of the working electrode (cm^2), number of electrons involved and concentration of the electro active species (mol cm^{-3}), respectively. The *D* and *v* are the diffusion-coefficient (cm^2s^{-1}) and scan rate (V s^{-1}).

3.2. Electrochemical oxidation of EP at AlpM-CPE

The electrochemical behaviour of 0.1 mM EP was recorded at bare CPE and AlpM-CPE in 0.2 M PBS (pH 7.4) as supporting electrolyte with scan rate 0.05 V s^{-1} as shown in Figure 3A. A slow electron transfer process at bare CPE for EP yielded a broad voltammogram and an oxidation signal was appeared at 0.19 V. On the other hand, in the same identical situation, an electrooxidation of EP at AlpM-CPE (solid line) showed a significant enhancement in current signal the peak potential was located at 0.16 V. This minimisation of over potential confirms the electrocatalytic oxidation of EP at AlpM-CPE interface. Therefore, the AlpM-CPE is a promising sensing platform for an electrochemical sensing of EP.

A detailed study on the electrochemical behaviour of EP at AlpM-CPE was carried out using CV technique with varying the scan rate (0.05–0.2 V s^{-1}) as shown in Figure 3B [17,45]. The concentration of EP was used was 0.1 mM in PBS (0.2 M, pH 7.4) as supporting electrolyte. From Figure 3B, it can be observed that the anodic peak current was gradually increased with increasing scan rate, and also there is a slight shift in the peak potential. This observation obeyed the Randles-Sevcik relationship. To evaluate the electrode process, a graph of anodic peak current (*Ipa*) *versus* scan rate (*v*) was plotted and it produced a linear graph with correlation coefficient (r^2) of 0.9937 as shown in Figure 3C. Further, a plot of Ipa versus square root scan rate ($\upsilon^{1/2}$) also produced good linearity with r^2 of 0.9873 as shown in Figure 3D. From these results, it can be confirmed that the electrode process is dominated by adsorption-controlled kinetics [18]. For an adsorption-controlled and irreversible electrode process, E_p is defined by the following equation proposed by Laviron [46],

$$\mathrm{Ep} = \mathrm{E}^0 + (2.303\mathrm{RT}/\alpha\mathrm{nF}).\log\left(\mathrm{RTk}^0/\alpha\mathrm{nF}\right) + (2.303\mathrm{RT}/\alpha\mathrm{nF}).\log \mathrm{v} \quad (2)$$

Where α, k°, *n*, *v*, E° are well explained in previous literature [46], *R*, *F* and *T* are having their usual scientific significance. Thus, the value of αn can be easily calculated from the slope of E_p vs. log *v* (data not shown). In this system, the slope was 0.065, taking *T* = 298 K, and substituting the values of *R* and *F*, αn was calculated to be 0.91. Generally, α is assumed to be 0.5 in total irreversible electrode process [47]. Further, the number of electron (*n*) transferred in the electro oxidation of EP was calculated to be 1.82 □ 2. The value of k^0 can be determined from the intercept of the above plot if the value of E° is known. The value of E° in Eq. (2) can be obtained from the intercept of E_p vs. *v* curve by extrapolating to the

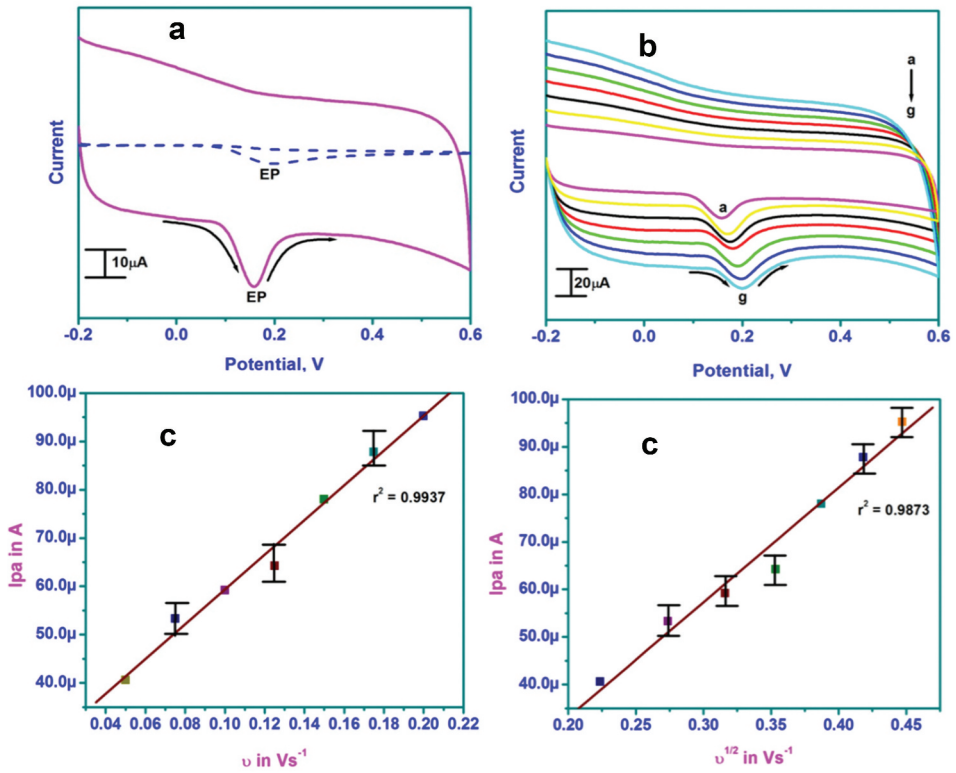


Figure 3. **(A)** CVs for 0.1 mM EP at bare CPE (dashed line) and AlpM-CPE (solid line) in PBS (0.2 M, pH 7.4) at scan rate 0.05Vs^{-1}. **(B)** CVs for 0.1 mM EP at AlpM-CPE in PBS (0.2 M, pH 7.4) with different scan rate (a–g; 0.050, 0.075, 0.100,0.125,0.150, 0.175 and 0.2 V s^{-1}). **(C)** Plot of Ipa versus ν. **(D)** Plot of *Ipa* versus $\upsilon^{1/2}$.

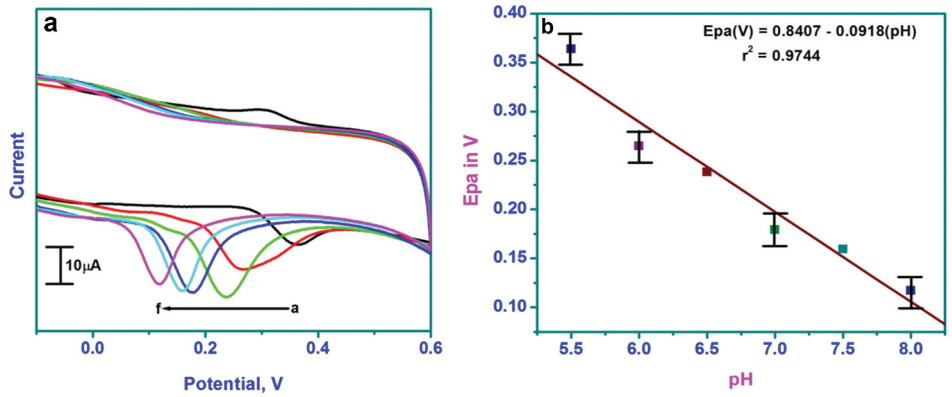


Figure 4. **(A)** CVs of 0.2 mM EP at AlpM-CPE in PBS (0.2 M) with different pH values (a–f: 5.5–8.0) at scan rate of 0.05 V s^{-1}. (**B**) The graph of Epa versus pH.

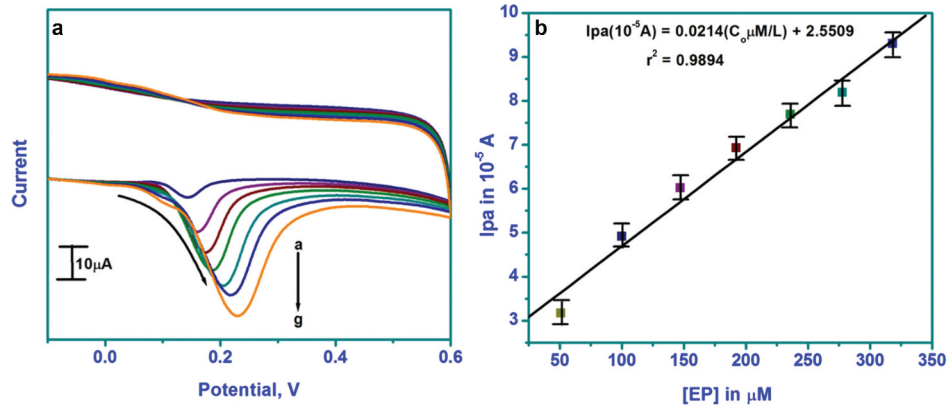


Figure 5. **(A)** CVs of epinephrine at AlpM-CPE in PBS (0.2 M, pH 7.4) with varying concentrations (a–g: 51.02 μM, 100.0 μM, 147.05 μM, 192.30 μM, 235.84 μM, 277.77 μM, 318.18 μM). (**B**) Graph of Ipa versus concentration of EP.

Table 2. Comparison of obtained LOD at AlpM-CPE for EP with previous reports.

Electrode	Classical methods	Linear working range (μM)	Detection limits (M)	Refs.
Pen SAM-MAuE	CV	100–0.1	0.1×10^{-6}	[17]
MWCNT/CFE	DPV	up to 100	0.900×10^{-6}	[45]
P(1-methylpyrrole)GCE	SWV	0.75–200	0.168×10^{-6}	[50]
FePc-ME	CV	1–300	0.5×10^{-6}	[51]
poly(caffeic acid)MGCE	CV	2–300	0.6×10^{-6}	[19]
CNT/SSE	DPV	2.0–100	2.000×10^{-6}	[52]
DH-CN/CPE	DPV	5.0–20 20-600	1.0×10^{-6}	[53]
p (taurine)ME	DPV	2–600	0.3×10^{-6}	[54]
MnO_2/Nafion/GCE	CV	0.5–100 100-700	0.100×10^{-6}	[55]
PolyCafA/GCE	CV	2.0–80	0.200×10^{-6}	[56]
CNT/GCE	CV	1.0–50	0.100×10^{-6}	[57]
TTABMCPE	DPV	0.15–30	0.12×10^{-6}	[58]
GCE-MWCNT-CoTSPc	Amp	3.0–15	0.45×10^{-6}	[59]
`AlpM-CPE	CV	20.66–192.30	0.46×10^{-6}	Present work

vertical axis at $v = 0$ [48]. In our system the intercept for E_p vs. log v plot was 0.2420 and E° was found to be 0.147; k^0 was calculated to be 1.026×10^3 s^{-1}.

3.3. Effect of pH and concentration of EP

The observed CV were analysed to investigate the impact of pH on the electro oxidation of0.2 mM EP at AlpM-CPE at scan rate of 0.05 V s^{-1}. Figure 4A shows the change in peak potential of EP at AlpM-CPE with varying different pH (5.5–8.0) of PBS. It is observed that, with the increasing value of pH the oxidation potential shifts to more positive potential scale. The linear establishment of anodic peak potential (*Epa*) versus pH indicates the electrooxidation of EP depends on pH as shown in Figure 4B. The corresponding linear regression equation was: *Epa* (V) = 0.8407–0.0918 (pH) (r^2 = 0.9744) signifying that there is an involvement of equal number of protons and electrons in the redox mechanism as reported earlier [43,49].

The electrochemical oxidation of EP with its varying concentration in PBS (0.2 M, pH 7.4) was studied at AlpM-CPE at scan rate 0.05 V s^{-1}. From Figure 5A, we observed that the *Ipa* of EP was increased with increased concentration (51.02–318.18 μM) with a slight shift in *Epa*. The linearity graph of *Ipa* versus concentration of EP is established in Figure 5B. The graph showed good linearity and the linear regression equation can be expressed as;

Ipa (10^{-5}A) = 0.0214 (C_o μM/L) + 2.5509 (r^2 = 0.9894).

As explained in the previous literature the limit of detection (LOD) was calculated using the relationship 3 *s*/*m* [43]. Where, *s* and *m* are the standard deviation of six blank measurements and slope of the calibration curve. The calculated LOD of EP at AlpM-CPE was calculated to be 0.46 μM, which is relatively lower compared to reported literatures as shown in Table 2 [17,19,45,50–59].

3.4. Electrochemical oxidation of FA

The CV curves were recorded for the electrooxidation of 0.1 mM FA in PBS (0.2 M, pH 7.4) at bare CPE (dashed line) and AlpM-CPE (solid line) with the scan rate 0.05 V s^{-1} as shown in Figure 6A. From Figure 6A, it can be seen that at bare CPE the oxidation signal of FA showed poor response with the appearance of broad voltammogram, the *Epa* was located at 0.681 V. On the other hand, the AlpM-CPE showed increment in current signals with the appearance of *Epa* at 0.694 V. This enhancement of current response reflects the better electrochemical sensing performance of the fabricated AlpM-CPE towards FA determination.

3.5. Simultaneous electroanalysis of EP and FA

The CVs were recorded for the simultaneous determination of 0.5×10^{-4} M of EP and 1.0×10^{-4} M of FA in PBS (0.2 M, pH 7.4) at scan rate of 0.05 Vs^{-1}. Figure 6B shows that at bare

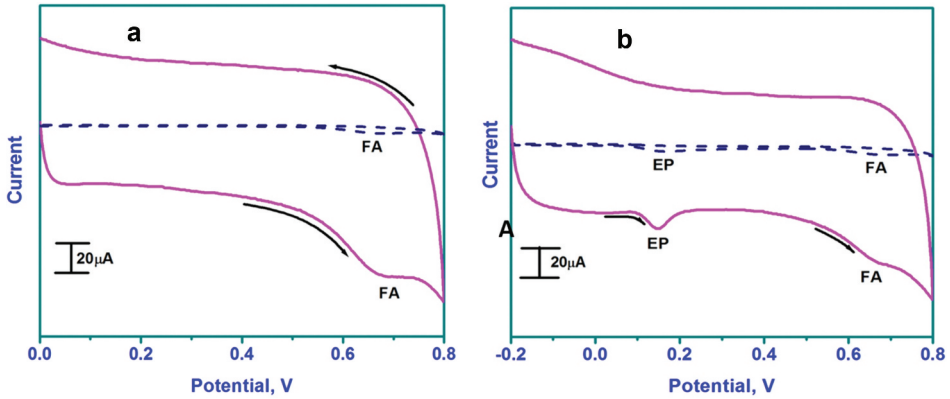


Figure 6. (A) CVs of 0.1 mM FA in PBS (0.2 M, pH 7.4) solution of pH7.4 at bare CPE (dashed line) and AlpM-CPE (solid line) at scan rate of 0.05 V s^{-1}. **(B)** CVs for simultaneous determination of 0.5×10^{-4}M EP and 1.0×10^{-4}M FA in a binary mixture at bare CPE (dashed line) and AlpM-CPE (solid line) at scan rate of 0.05 V s^{-1}.

Table 3. Analytical applicability of AlpM-CPE towards the determination of EP in injection sample.

Sample	Added (μM)	Found (μM)	RSD (%)	Recovery (%)
1	5	4.87	1.81	97.21
2	10	9.93	1.95	99.21
3	15	15.07	2.11	100.41
4	20	20.11	2.14	100.51

CPE (dashed line) the CV response for the simultaneous determination of EP and FA was with poor sensitivity and exhibited a low and weak current signal. However, the CV curve obtained for the EP and FA under same condition at AlpM-CPE was with enhanced current signal and also with improved sensitivity. The oxidation potentials were well separated and Epa of EP and FA was located at 0.148 V and 0.691 V, respectively. The difference in peak potential separation between EP and FA was calculated to be 0.543 V by CV technique. This well separation was more than enough for the determination of EP and FA in a binary mixture.

3.6. Analytical applicability of AlpM-CPE

In order to evaluate the analytical applicability of the AlpM-CPE, the EP was determined in the injection sample. The required quantity of pre-standardised sample solution was transferred to an electrochemical cell and followed the standard addition method to evaluate the efficacy of the fabricated electrode. The obtained results are tabulated in Table 3, the recovery ranged from 97.21% to 100.51% and the obtained relative standard deviation (RSD) was acceptable. The results for real sample analysis are satisfactory and attributed to the practical analytical applicability of AlpM-CPE. Therefore, the proposed modified electrode can be employed for the determination of EP in pharmaceutical samples and biological fluids in early clinical diagnosis.

4. Conclusion

In the present work explained fabrication of allopurinol polymerised carbon paste electrode (AlpM-CPE) for the determination of EP and FA individually as well as simultaneously at physiological pH. The influence of applied scan rate and solution pH was studied to analyse the electrode performance, and found to be adsorption-controlled kinetics. For the determination of EP, the modified electrode showed a lower LOD of 0.46 μM by cyclic voltammetry method. The analytical applicability of the proposed method was evaluated for the determination of EP in injection sample and an acceptable recovery rate was obtained. This proposed protocol can be applied to the determination of other electroactive molecules also.

5. Conflict of Interest

The authors declare no conflict of interest.

6. Credit author statement

A.B.T and P.S.G conceptualised the experimental idea and equally contributed. A.B.T, P.S.G and S.D.L performed the experiments. A.B.T and P.S.G took lead in the writing of the manuscript and equally contributed. S.N.D and B.E.K supervised the whole work. All authors agreed to the final version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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