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Application of Poly(nicotinamide) Modified Carbon Paste Electrode Sensor for the Electrocatalytic Determination of Acetaminophen and Folic Acid

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Abstract- Poly (nicotinamide) modified carbon paste electrode (poly-NA MCPE) was fabricated for the electrocatalytic determination of acetaminophen (AC) and folic acid (FA) by using cyclic voltammetric method. Compared to bare carbon paste electrode (BCPE) the poly-NA MCPE showed better electrocatalytic performance towards the oxidation of AC in phosphate buffer solution (PBS) of pH 7.4. Under the optimized experimental conditions, the influence of scan rate and concentration were studied. The detection limit of AC was calculated to be 0.072 mM by CV technique, in a linear concentration range of 20.66 to 119.04 μ M. The poly-NA MCPE was used for the simultaneous determination of AC and FA in a binary mixture by CV and differential pulse voltammetric (DPV) technique.

Keywords- Acetaminophen, Folic acid, Nicotinamide, Carbon paste electrode, Electrocatalytic activity

1. INTRODUCTION

In recent years, the continuous development of research in analytical electrochemistry, particularly in the field of electrochemical sensors for the electroanalysis of biomolecules and pharmaceutical formulations have a great importance and challenges towards the development of advanced technology. Hence, a novel construction and fabrication of a sensors based on modified electrodes are playing a very significant key role in the study of electroactive species. Therefore, the development of rapidly responsive, highly sensitive and selective, simple and reliable methods for the fast determination of drug formulations is of great importance in modern electroanalytical research [1,2].

Acetaminophen (AC) ([(*N*-(4-hyroxyphenyl) ethanamide, *N*-(4-hydroxyphenyl) acetamide] is commonly known as paracetamol (see table 1), it was generally recommended dosage for the actions against antipyretic, analgesics and anti-inflammatory conditions [3-4]. It is a safe and effective agent used worldwide for the relief of mild to moderate pain associated with headache, backache, arthritis, postoperative pain, joint pain, toothache pain, chronic pain and muscular aches [5]. It is also used for reduction of fever, cough, cold and bacterial or viral infection and in the treatment of mental illness too [6-8]. However, overdose of acetaminophen is toxic in nature and it may cause liver problem, kidney damage and sometimes also causes fatal hepatotoxicity and nephron toxicity [9]. Y. Li et al. [10] reported that at normal therapeutic doses, i.e., 60 to 90% is rapidly metabolized very fast by conjugation to form acetaminophen glucuronide, and sulphate is oxidized at 5 to 10% by mixed-function oxidase enzymes such as cytochrome P-450 to form highly reactive N-acetyl*p*-benzoquinone-imine, which is directly conjugated with glutathione and later excreted as cysteine and mercapturate conjugates. Only 1 to 4% of a therapeutic dose of AC is fully eliminated in urine [11-16].

Many analytical methods have been reported for the qualitative and quantitative determination of AC, such as flow-injection spectrophotometry [17], MEKC method [18], gas chromatography-mass spectrometry [19], HPLC GC-MS [20], automatic sequential injection analysis [21], chemiluminescence [22], spectrofluorometry [23], FT-IR raman spectrometry [24] micellar electro-kinetic chromatography [25], titrimetry [26], TLC [27] and LC-MS-MS [28], spectrophotometry [29] and liquid chromatography [30]. However, all these methods require long duration for analysis and cost expensive. Therefore, electrochemically fabricated sensors based on modified electrodes have more advantages due to their low cost, fast response, simple instrumentation, good selectivity and high sensitivity in the determination of various biological molecules and pharmaceutical formulations. As an electroactive molecule acetaminophen can be detected by numerous voltammetric methods [31-33].

Folic acid (FA) $(N-[p-{[(2-amino-4-hydroxy-6-pteridinyl)methyl] amino}benzoyl]-1-glutamic acid)$ is also known as folate (see table 1) it is a water-soluble vitamin [34]. FA has

a major significant role in biological functions of cell metabolism like DNA replication, repairs DNA, methylates, synthesis of amino acids and nucleotides [35]. FA is mainly found in vegemite or marmite, kidneys, livers of animals, plants, mushrooms, algae and in variety foods such as broccoli, cabbage, fruits and nuts [36]. In human body a deficiency of FA leads to gigantocytic anemia, associated with leucopenia, brain disorders such as depression, reduced cognition, cardiovascular disease, devolution of mentality, psychosis, high homotype cysteine acidemia and serious illness etc.

Nicotinamide (NA) ([pyridine-3 caroxamide] is also known as niacinamide, (see table1), is a derivative of niacin (vitamin B_3) [37]. Nicotinamide is one of the water soluble B-vitamins, required for mammalian daily diet. Nicotinamide is main existing form of nicotinic acid in living organisms and can also be converted into the coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) [38]. The clinical dosage of nicotinamide is potentially benefited in the prevention and treatment of diabetes [39,40]. In the present work nicotinamide was used as a modifier for the modification of carbon paste electrode.



Table 1. The structural and molecular formula of acetaminophen, folic acid and nicotinamide

Cyclic voltammetry (CV) is a powerful electroanalytical technique used for the electroanalysis of electroactive molecules [41,42]. CV allows redox behavior of chemical

species within a wide potential range and which can also plays an important role to diagnose mechanisms of electrochemical reactions, for detection of the species present in solution [43]. Over the past few years, modified carbon paste electrode based sensors played an important role in electrochemical investigations compared to other electrodes because of their low background current, low cost, easy preparation, high sensitivity and good selectivity [44,45].

In the present work, poly-nicotinamide modified carbon paste electrode (poly-NA MCAPE) was fabricated by electropolymerisation of nicotinamide by CV technique. Later the fabricated electrode was used for the electrochemical determination of AC and FA in physiological pH of 7.4. The modified electrode showed enhancement in the oxidation peak current of AC as compared with the bare carbon paste electrode (BCPE). The analytical performance of the modified electrode gives satisfactory results in the analysis of pharmaceutical formulations.

2. EXPERIMENTAL SECTION

2.1. Instrumentation

All the electrochemical studies were carried out by using a CHI-660c (CH Instrument-660 electrochemical workstation, USA). A conventional three electrode system was employed, the saturated calomel electrode (SCE) as a reference electrode, a platinum as a counter electrode and BCPE or poly-NA MCPE as working electrode. All the redox potentials of analytes were reported versus SCE at an ambient temperature of 25 ± 0.2 °C.

2.2. Reagents and chemicals

Acetaminophen (AC) (M_{wt} =151.16 gmol⁻¹, purity 99%) and folic acid (FA) (M_{wt} =441.40 gmol⁻¹, purity 99.5%) were obtained from Himedia Pvt. Ltd., India. Nicotinamide (NA) was purchased from sigma Ltd., India (M_{wt} =122.12, purity 99.5%). The AC containing tablets i.e. Calpol and Dolo were purchased from a local pharmacy (India). The stock solutions of concentration 25×10^{-4} M of AC and 25×10^{-4} M of FA were prepared by dissolving in doubly distilled water and 0.1 M NaOH solution respectively. Phosphate buffer solution (PBS) of same ionic strength was prepared (0.2 M) by mixing appropriate ratio of NaH₂PO₄·H₂O and Na₂HPO₄. Graphite powder (particle size<50µm) purchased from Merck and silicon oil was obtained from Himedia Pvt. Ltd., India was used to prepare carbon paste electrode (CPE). All the chemicals were of analytical grade used as received without any additional purification and double distilled water was used for the preparation of stock solutions.

2.3. Preparation of working electrode

The bare carbon paste electrode was prepared according to our previous report [2]. Electrochemical polymerization of nicotinamide on the surface of CPE was carried out by using CV technique. The CPE was placed in an electrochemical cell containing 1.0 mM of nicotinamide solution in 0.2 M PBS of pH 7.4. The electropolymerisation was achieved by cyclic voltammetric sweep between -0.8 V and +1.8 V at the scan rate of 0.1 Vs⁻¹ for 10 successive cycles. The schematic representation was as showed in scheme 1. After that, the fabricated poly-NA MCPE was rinsed thoroughly with double distilled water and used for the determination of AC.



Scheme 1. The probable electropolymerisation mechanism of nicotinamide on the surface of carbon paste electrode

3. RESULTS AND DISCUSSION

3.1. Electrochemical polymerization of nicotinamide on CPE

Cyclic voltammetry is a convenient and effective tool to coat an organic molecule on the surface of solid working electrode. The poly-NA-MCPE was fabricated by potential sweeping the CPE in between the potential limit of -0.8 to +1.8 V with the scan rate of 0.1 Vs⁻¹ for 10 multiple cycles as showed in Fig.1. During the process of multiple scanning the voltammogram was gradually increased at first, after some successive sweeps a steady state voltammogram was observed. It indicates the formation and growth of an electrically conductive layer on the surface of CPE [42]. In the present work a potential window of -0.8 to +1.8 V was chosen, if the potential limit was less than +1.8 V no polymeric film will be obtained. On the other hand, if the initial potential was less than -0.8 V, sufficient free radicals will not be generated for the polymerisation process. Therefore, in order to obtain the uniform thin layer on the surface of CPE we optimized the potential window of -0.8 to +1.8 V. If the thickness of the electroactive layer was more, then it leads to prevent the electron transfer process. Therefore, we controlled the experimental input parameter to 10 cycles. Finally, the fabricated poly-NA-MCPE was rinsed several times with double distilled water and later used for the determination of AC at physiological pH.



Fig. 1. Cyclic voltammograms for the preparation of poly-NA-MCPE. An electrochemical cell containing 1.0 mM of nicotinamide in 0.2 M PBS of pH 7.4 at 10 cycles with scan rate of 0.1 Vs^{-1}

3.2. Characterization of poly-NA-MCPE using standard potassium ferrocyanide probe

The electrochemical characterization of the fabricated poly-NA-MCPE was conducted by CV technique. The cyclic voltammograms were recorded for the oxidation of 1.0 mM potassium ferrocyanide in 1 M KCl as a supporting electrolyte with the scan rate 0.05 Vs⁻¹as showed in Fig. 2. The voltammograms obtained for this redox probe, at BCPE (dashed line) was less sensitive. On the other hand, the poly-NA-MCPE (solid line) showed remarkable enhancement in the current response. This improved result obtained for potassium ferrocyanide obtained at poly-NA-MCPE confirms that, there is a significant change in the surface morphology of the CPE. The total surface area available for reaction of species in solution can be estimated by the Randles-Sevcik equation (1) [46,47].

$$I_{p} = 2.69 \times 10^{5} \, n^{3/2} A \, D^{1/2} \, C_{0} \upsilon^{1/2} \tag{1}$$

Where, I_p is the peak current in A. C_0 is the concentration of the electroactive species (mol cm⁻³), n is the number of electrons exchanged, D is the diffusion-coefficient (cm²s⁻¹), and υ is the scan rate (Vs⁻¹), A is the surface area (cm²). For poly-NA-MCPE the electroactive surface area is maximum (0.0419 cm²) as compared with BCPE (0.0276 cm²).



Fig. 2. Cyclic voltammograms of 1.0 mM potassium ferrocyanide at BCPE (dashed line) and poly-NA-MCPE (solid line) at scan rate of 0.1 Vs^{-1}

3.3. Electrochemical response of AC at poly-NA-MCPE

The Fig. 3 showed CV recorded for the electrocatalytic oxidation of 0.1 mM AC in 0.2 M PBS of pH 7.4 at BCPE and poly-NA-MCPE with the applied scan rate of 0.05 Vs⁻¹. The voltammetric response for the oxidation of AC at BCPE was broad and less sensitive, the anodic oxidation was observed at 0.36 V (versus SCE). However, in the same identical condition the poly-NA-MCPE improved the voltammetric response with the merit of minimization in the redox peak potentials. The electrocatalytic oxidation was located at 0.35 V. Therefore, the fabricated electrode can be used as a sensor for the determination AC in physiological pH.

The oxidation steps of AC were located on acetamide benzene ring containing one hydroxy group on 4th-para position, which represents a typical redox system with two electron oxidation process as showed in scheme 2. This type of mechanism was proposed in earlier reports [48].



Scheme 2. Oxidation mechanism of acetaminophen (AC)



Fig. 3. Cyclic voltammograms for 0.1 mM AC at BCPE (dashed line) and poly-NA-MCPE (solid line) in 0.2 M PBS of pH 7.4 at scan rate 0.05 Vs^{-1}



Fig. 4. (A) Cyclic voltammograms for 0.1 mM AC at poly-NA-MCPE in 0.2 M PBS of pH 7.4 at different scan rate (a-i; 0.05 to 0.25 Vs⁻¹); (B) Graph of peak current (I_p) versus scan rate (u); (C) Graph of peak current (I_p) versus square root of scan rate ($\upsilon^{1/2}$)

3.4. Effect of scan rate on the peak current of AC

The effect of scan rate for 0.2 mM of AC in 0.2 M PBS of pH 7.4 was investigated by CV technique at poly-NA-MCPE. Fig. 4A showed an increase in redox peak currents with increase in the scan rate according to Randles-Sevcik equation in the range 0.05 to 0.25 Vs⁻¹. It can be observed that the oxidation peak potential was shifted to slight positive side and reduction peak potential towards negative side. In order to study the electrode process, a graph of peak current (I_p) versus scan rate (υ) and The I_p versus square root scan rate ($\upsilon^{1/2}$) were plotted as shown Fig. 4B and Fig. 4C respectively. A good linearity with the correlation coefficient (r^2) of 0.9991 and 0.9988 was observed for the graph of I_{pa} vs υ . Therefore, the result confirms the adsorption controlled electrode process at poly-NA-MCPE [49-53].

3.5. Effect of pH value on the determination of AC at poly-NA-MCPE

The pH of PBS has a significant role in the electrochemical determination of electroactive molecules. The influence of pH for the determination of 0.2 mM AC in different pH solutions was investigated by CV technique at poly-NA-MCPE in the range of 5.5-7.5. The Figure 5A showed the oxidation peak potential shifts towards the negative side with increase in the solution pH. The linear establishment between the E_{pa} versus pH graph clearly indicated that the catalytic oxidation peak depends linearly on pH in the range of 5.5-7.5 with slope of 0.0636 V/pH (r²=0.9972) as illustrated in Fig. 5B. This signifies the involvement of equal number of protons and electrons in the redox mechanism according to Nernst equation. This was consists with the reported literature [54,55].



Fig. 5. (**A**) Cyclic voltammograms obtained for the oxidation of AC at poly-NA-MCPE in 0.2 M PBS solution at different pH values (a–e: 5.5 to 7.5) at scan rate of 0.05 Vs^{-1} ; (**B**) The effect of pH on the peak potential response of AC

3.6. Effect of AC concentration

The electrocatalytic oxidation of AC was carried out by varying its concentration at poly-NA-MCPE in the linear range of 20.6 to 119.0 μ M in 0.2 M PBS of pH 7.4 with the scan rate 0.05 Vs⁻¹ as showed in Fig. 6A. By increasing the concentration of AC, the I_{pa} goes on increasing with shifting E_{pa} towards slight positive side. The graph of I_{pa} versus concentration of AC was illustrated in Fig. 6B, it showed almost straight line with good linearity. The linear regression equation can be expressed as, I_{pa} (10⁻⁵A)=0.0375(C_o μ M/L)+4.1450, (r²=0.9983). The limit of detection (LOD) was calculated using the following equation (2).

LOD=3S/M

(2)

where, S is the standard deviation of the six blank measurements and M is slope of the calibration curve. The detection limit of AC at poly-NA-MCPE was calculated to be 0.072 μ M in the linear range of 20.6 to 119.0 μ M. The detection limits reported for different classical methods and electrodes are tabulated in Table 2. This proposed method showed better detection limit compared to other reported classical/electrochemical methods [56-70].



Fig. 6. (A) Cyclic voltammograms of AC in 0.2 M PBS solution of pH 7.4 at poly-NA-MCPE at scan rate of 0.05 Vs⁻¹with different concentrations (a–f: 20.66 to 119.04 μ M); (B) Graph of anodic peak current versus concentration of AC

Classical methods	Electrode/modifier biosensors	Linear working range (µM)	Detection limits (M)	Ref.
ATSDPV	ETPGE	0.05-2.5	2.5×10 ⁻³	[56]
AdsSWV	D50wx2/GNP/GCPE	0.0334-42	4.7×10 ⁻³	[57]
DPV	N-(3,4-dihydroxyphenethyl)-3,5- dinitrobenzamide -MWCNT/CPE	15-270	1.0×10 ⁻⁵	[58]
CV	C ₆₀ /GCE	50-1500	0.5×10 ⁻⁵	[59]
Multi- commutated flow system	Nafion-modified glassy carbon tubular electrode	50-500	1.7×10 ⁻⁵	[60]
CV	GCE/Cu complex	20-5000	0.5×10 ⁻⁵	[61]
CV-SWV	SWCNT/EPPGE	500-1000000	0.029×10 ⁻⁶	[62]
AdsSV	MWCNT-BPPGE	0.01-2	0.01×10 ⁻⁶	[63]
CV-SWV	PANI-MWCNT	1-100	0.25×10 ⁻⁸	[64]
EIS	Lt/fMWCNT/MGCE	0.9-80	0.78×10 ⁻⁶	[65]
EIS-CV-DPV	AuNPs/MWCNT/GCE	0.09-35	0.03×10 ⁻⁶	[66]
DPV	C-Ni/GCE	7.8-110	2.3×10 ⁻⁶	[67]
CV-SWV	Graphene/GCE	0.1-20	0.032×10 ⁻⁶	[68]
CV-DPV	PEDOT/SPE	4-400	1.39×10 ⁻⁶	[69]
CV	PEDOT/GO/GCE	10-60	0.57×10 ⁻⁶	[70]
CV	Poly-nicotinamide MCPE	20.6 -119.0	0.072 mM	Present

Table 2. Comparison of linear range and detection limits for AC with different classical methods and electrodes.

3.7. Electrocatalytic response of FA at poly-NA-MCPE

The CVs were recorded for the oxidation of 0.2 mM FA at BCPE (dashed line) and poly-NA-MCPE (solid line) in 0.2 M PBS of pH 7.4 with the scan rate 0.05 Vs⁻¹ as showed in Figure 7. The voltammogram obtained for the irreversible oxidation of FA at BCPE was broad and less sensitive, the anodic peak potential was observed at 0.721 V. On the other hand, in the same identical condition the poly-NA-MCPE exhibited an enhancement in peak current with minimization in the oxidation over potential. A sharp oxidation for FA at poly-NA-MCPE was located at 0.67V. Therefore, the fabricated poly-NA-MCPE can be used for the determination of FA at physiological pH.



Fig. 7. Cyclic voltammograms of 0.2 mM FA in0.2 M PBS solution of pH7.4 at BCPE (dashed line) and poly-NA-MCPE (solid line) at scan rate of 0.05 V s⁻¹

3.8. Simultaneous determination of AC and FA

The CVs were recorded for the binary mixture containing 0.4×10^{-4} M AC and 2.0×10^{-4} M FA in 0.2 M PBS of pH 7.4 at scan rate of 0.05 Vs⁻¹. The Figure 8 Showed, the voltammetric response of the binary mixture of analytes at BCPE (dashed line) was poor in sensitivity and gives a partially overlapped signal. This makes their individual identification difficult. However, the poly-NA-MCPE showed an enhanced current response for the selective oxidation of AC and FA. The oxidation potentials were located at 0.36 V and 0.67 V respectively for AC and FA, which was as same as in their individual determination. Differential pulse voltammetry (DPV) was used for its better sensitivity and absence of background current. A clear separation of 0.4×10^{-4} M AC and 2.0×10^{-4} M FA in 0.2 M PBS of pH 7.4 was observed at poly-NA-MCPE. There solved DPV peaks of AC and FA were located at 0.33 V and 0.66 V, respectively as showed in Fig. 9. This result was good enough to make out and resolve oxidation peaks of AC in the presence of FA at poly-NA-MCPE.



Fig. 8. Cyclic voltammograms for simultaneous determination of 0.4×10^{-4} M AC and 2.0×10^{-4} M FA at BCPE (dashed line) and poly-NA-MCPE(solid line) at scan rate of 0.05 Vs⁻¹



Fig. 9. Differential pulse voltammograms for simultaneous determination of 0.4×10^{-4} M AC and 2.0×10^{-4} M FA at poly-NA-MCPE at scan rate of 0.05 Vs⁻¹

3.9. Detection of AC in Tablets

In order to evaluate the practical performance of poly-NA-MCPE, it was subjected for the determination of AC content in commercial tablets (Calpol 500 mg AC/tablet and Dolo 650 mg AC /tablet). The recovery of the sample by CV method was also studied to evaluate the reliability of the method. As in the Table 3, a good recovery with acceptable SD±RSD was obtained at poly-NA-MCPE. Therefore, the fabricated electrode can be used as an

electrochemical sensor for the quantification of AC in pharmaceutical and biotechnological sectors.

Formulation Sample	PC added	Detected ^a	Recovery (%)	$SD \pm RSD$ (%)
	-	Not detected	-	-
	2.0×10^{-6}	$2.050 imes 10^{-6}$	102.5	0.0353 ± 0.0252
Tablet (Calpol, 500 mg)	4.0×10 ⁻⁶	$3.901\times 10^{\text{-6}}$	97.5	0.0700 ± 0.0500
	6.0×10 ⁻⁶	$6.120 imes 10^{-6}$	102.0	0.0848 ± 0.0607
	8.0×10^{-6}	$7.990\times 10^{\text{-6}}$	99.8	0.0070 ± 0.0050
	1.0×10^{-5}	$1.012\times 10^{\text{-5}}$	101.2	0.0084 ± 0.0060
	3.0×10 ⁻⁵	3.103×10^{-5}	103.4	0.0728 ± 0.0520
	-	Not detected	-	-
	2.0×10 ⁻⁶	1.905×10 ⁻⁶	95.25	0.00717 ± 0.4797
Tablet (Dolo, 650 mg)	4.0×10 ⁻⁶	3.895×10 ⁻⁶	97.3	0.0742 ± 0.0530
	6.0×10 ⁻⁶	6.110×10 ⁻⁶	101.8	0.0777 ± 0.0555
	8.0×10^{-6}	8.010×10 ⁻⁶	100.1	0.0007 ± 0.0005
	1.0×10^{-5}	1.03×10 ⁻⁵	103.0	0.0212±0.0151
	3.0×10 ⁻⁵	2.901×10 ⁻⁵	96.7	$0.07{\pm}0.05$

Table 3. Determination of AC in commercial pharmaceutical sample

^aAverage of five determination

4. CONCLUSION

In the present work, we demonstrated a simple method for the modification of carbon paste electrode via the electropolymerisation of nicotinamide by cyclic voltammetric (CV) technique. The fabricated poly-NA-MCPE was used for the electrochemical determination of acetaminophen (AC) in physiological pH by CV technique. Further, the fabricated electrode was used for the voltammetric separation of AC and folic acid (FA) by CV and differential pulse voltammetric techniques. The validation of the modified electrode was tested by subjecting it to the tablet analysis and obtained results were satisfactory. Therefore, the poly-NA-MCPE can be used as an analytical tool in the quantification AC in tablets and pharmaceutical formulations.

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