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RESEARCH ARTICLE

Selective Determination of Acetaminophen in Presence of Ascorbic Acid at Poly (p-Methoxyphenol) Electrode

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ABSTRACT: In the present work, we discuss the modification of a gold electrode with p-methoxyphenol and its application as a sensor for acetaminophen (ACP) in a phosphate buffer solution (pH = 7.4). The modified electrode was subsequently employed to determine acetaminophen in the presence of ascorbic acid (AA) using differential pulse voltammetry (DPV). The peak positions and relative sensitivity of ACP/AA were influenced by the potential window used during polymerization. For polymerization between 0 and 1.0 V, the peak potentials recorded in the phosphate buffer solution (pH = 7.4) were 488 mV for ACP and 280 mV vs. Ag/AgCl for AA. Furthermore, the effects of pH and electrolyte type on the linearity range and detection limit were investigated. The high selectivity and sensitivity for ACP were attributed to charge discrimination and analyte accumulation. The detection limit for the 3σ-test was determined to be 0.2 nM. This study highlights the potential of the modified gold electrode for selective and sensitive detection of acetaminophen, even in the presence of interfering substances such as ascorbic acid. The optimization of polymerization conditions and the comprehensive analysis of pH and electrolyte effects contribute to the electrode's superior performance.

Keywords: Acetaminophen Detection, p-Methoxyphenol Modification, Differential Pulse Voltammetry, Sensor Selectivity

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1. INTRODUCTION

Acetaminophen, better known as paracetamol, is a widely used antipyretic and analgesic drug [1]. It is commonly prescribed to alleviate mild to moderate pain associated with conditions such as arthritis, postoperative recovery, headaches, and back pain [2]. Additionally, acetaminophen is effective in reducing fever caused by bacterial and viral infections [1, 2]. As the most widely used analgesic and antipyretic drug globally, acetaminophen is also employed in treating cold, cough, and asthma, making it a major ingredient in numerous over-the-counter cold and influenza medications [3, 4]. Its non-carcinogenic nature and effectiveness as an aspirin substitute for aspirin-sensitive patients further enhance its appeal, provided it is used within therapeutic doses [5].

Numerous analytical methods have been developed for the determination of acetaminophen (ACP) levels in pharmaceutical and clinical samples. These methods include high-performance liquid chromatography (HPLC) [4], spectrophotometry [5], fluorometry [6], titrimetry [7], UV/Vis spectrophotometry [8], flow injection analysis [9], chemiluminescence [10], and capillary electrophoresis [11]. In addition to these traditional techniques, electrochemical methods have gained significant attention due to their rapidity, simplicity, cost-effectiveness, and high sensitivity [12]. Among these, the use of amperometric biosensors has shown promising results [13, 14].

Electrochemical methods are particularly advantageous for acetaminophen detection because acetaminophen is electro-active and can be oxidized under suitable conditions [15]. This property enables precise and reliable measurements using electrochemical sensors. Various electrode materials, including modified carbon electrodes, metal nanoparticles, and conducting polymers, have been

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explored to enhance the performance of these sensors [15-18].

The present work aims to develop a highly selective and sensitive electrochemical sensor for acetaminophen. By optimizing the conditions for electropolymerization, we have modified a gold electrode with poly(4-methoxyphenol) (p-MP). This Au/poly(4-methoxyphenol) electrode demonstrates the capability to detect micromolar concentrations of acetaminophen even in the presence of millimolar concentrations of ascorbic acid. This selectivity is crucial for practical applications where acetaminophen needs to be detected in complex matrices containing various interfering substances. The high selectivity and sensitivity of the developed sensor are attributed to the unique properties of the modified electrode surface, which facilitates charge discrimination and analyte accumulation. This study not only highlights the potential of the Au/poly(4-methoxyphenol) electrode for acetaminophen detection but also contributes to the broader field of electrochemical sensor development by demonstrating the importance of electrode modification and optimization.

2. EXPERIMENTAL DETAILS

2.1. Chemicals and Materials

p-Methoxyphenol was procured from Merck (Darmstadt, Germany) and used without further purification. All other chemicals used in the study were of analytical grade and were used as received. Solutions were prepared using triply distilled water and were deaerated with prepurified nitrogen gas prior to use to remove dissolved oxygen.

2.2. Apparatus

Electrochemical experiments were performed using a BAS 100 BW electrochemical analyzer (Bioanalytical Systems, Inc.). The electrochemical cell employed a three-electrode configuration comprising a gold working electrode (BAS, MF-2014, 1.98 mm^2), an Ag/AgCl reference electrode (BAS, MF-2063), and a platinum wire coil as the auxiliary electrode.

2.3. Preparation of Poly(4-methoxyphenol) Films

A gold disk electrode was used as the working electrode for the preparation of poly(4-methoxyphenol) films. Prior to each electropolymerization, the working electrode was meticulously cleaned according to the standard procedure. This involved polishing with successively finer grades of diamond polishing compounds followed by an aqueous alumina slurry (Johnson Matthey Catalog, USA) down to 1.5 µm. The electrode was then subjected to ultrasonic cleaning to remove any residual polishing material.

For the electropolymerization process, the cleaned gold electrode was placed in a 0.1 M NaOH solution containing 10 mM 4-methoxyphenol. The electrode potential was cycled between 0.0 V and a positive limit ranging from 0.5 V to 1.3 V at a scan rate of 10 mV/s for a total of eight scans. This process facilitated the formation of a uniform poly(4-methoxyphenol) film on the gold electrode surface, which was subsequently used for the electrochemical detection of acetaminophen.

2.4. Electrochemical Measurements

Differential pulse voltammetry (DPV) was employed to evaluate the performance of the modified electrode in detecting acetaminophen in the presence of ascorbic acid. The electrolyte used for these measurements was a phosphate buffer solution (pH = 7.4). The sensitivity and selectivity of the electrode were investigated under optimized conditions, including the potential window used for the polymerization process.

The electrochemical behavior of the modified electrode was characterized by recording the peak potentials and current responses for acetaminophen and ascorbic acid. The linearity range and detection limit for acetaminophen were determined, and the high selectivity of the electrode was attributed to charge discrimination and analyte accumulation at the modified electrode surface. The detection limit for acetaminophen was found to be 0.2 nM, demonstrating the efficacy of the Au/poly(4-methoxyphenol) electrode for sensitive and selective electrochemical sensing applications.

3. RESULTS AND DISCUSSION

3.1. The Electrochemical Behavior of Acetaminophen at Polymer Electrodes

The preparation of polymerized poly(p-methoxyphenol) was carried out, and the resulting cyclic voltammograms are shown in Fig. 1(a) and (b). Fig. 1 (a) depicts the cyclic voltammogram of the bare gold electrode in the absence of the monomer, while Fig. 1(b) shows the cyclic voltammogram in the presence of the monomer. From the comparison of these voltammograms, it is evident that the monomer begins to oxidize at approximately 0.52 V. The observed decrease in current in subsequent scans indicates the formation of a non-electroactive polymeric film. This behavior is consistent with that observed for other phenolic compounds. Non-electroactive polymeric films have been recognized for their potential use as permselective membranes. In this study, the poly(p-methoxyphenol) film was evaluated for its ability to act as a permselective membrane, specifically for its selectivity towards acetaminophen (ACP) while preventing the permeation of electroactive ascorbic acid through the film.

The selective behavior of the polymeric film is critical in electrochemical sensors, where interference from other electroactive species can significantly affect the accuracy of the measurements. By using poly(p-methoxyphenol) as a permselective membrane, the sensor's response to ACP can be enhanced, improving its sensitivity and selectivity. The formation of the poly(p-methoxyphenol) film on the electrode surface at an oxidation potential of approximately

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0.52 V was confirmed through cyclic voltammetry. This film exhibits permselective properties that are advantageous for the selective detection of acetaminophen in the presence of other electroactive species, such as ascorbic acid. This selective membrane approach has potential applications in the development of more accurate and reliable electrochemical sensors for pharmaceutical and clinical analyses.

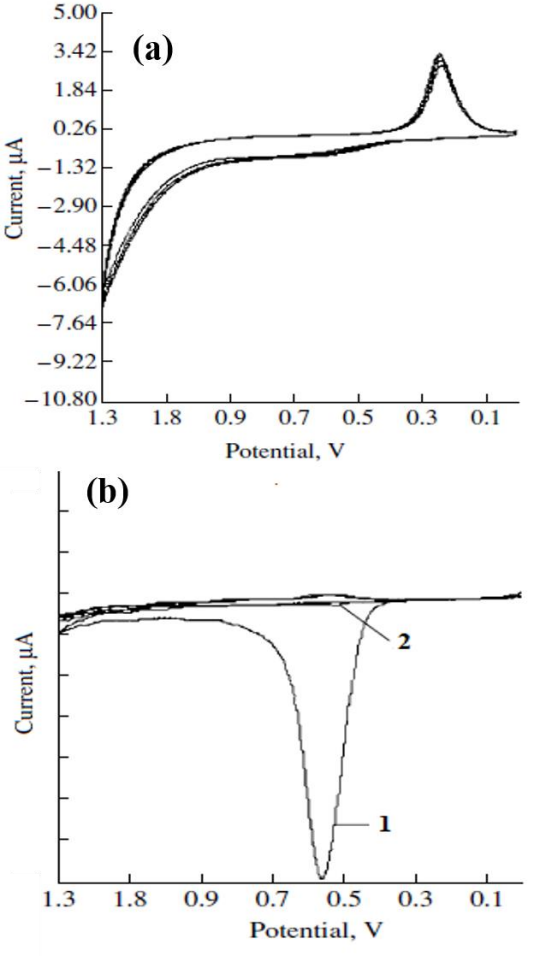

Fig. 1. Cyclic voltammograms obtained with a bare gold electrode in (A) 0.1 M NaOH and (B) 0.1 M NaOH + *p*-methoxyphenol. Scan rate = 10 mV/s.

3.2. Differential Pulse Voltammetry of Acetaminophen (ACP) and Ascorbic Acid (AA) on Poly(p-methoxyphenol)-Modified Electrodes

Fig. 2 displays a series of Differential Pulse Voltammetry (DPV) scans of a binary mixture of ACP and AA, recorded with Au/Poly(p-methoxyphenol) electrodes. These electrodes were modified by scanning the electrode potential in a monomer solution from 0 V to different positive limits (E_{lim}), ranging from 0.6 to 1.3 V. In the case of the smallest potential window, the modified electrode exhibits only a small, broad peak at approximately 0.48 V, attributed to the oxidation of ACP. As the Elim increases, the oxidation peak of AA emerges between 0.28 and 0.48 V. The intensity of this peak dramatically increases with higher Elim values, reaching a maximum at 0.8 V. While the electrode's response to ACP also increases with Elim, these changes are not as pronounced.

However, further increases in E_{lim} result in a decreased sensitivity of the electrode towards both analytes, with the AA peak showing more significant changes. From an analytical perspective, the electrode prepared at Elim = 0.9 V is optimal. It provides the highest response towards ACP and is suitable for the quantitative determination of AA at sufficiently high concentrations (~1 mM). Despite these advantages, this electrode has certain drawbacks.

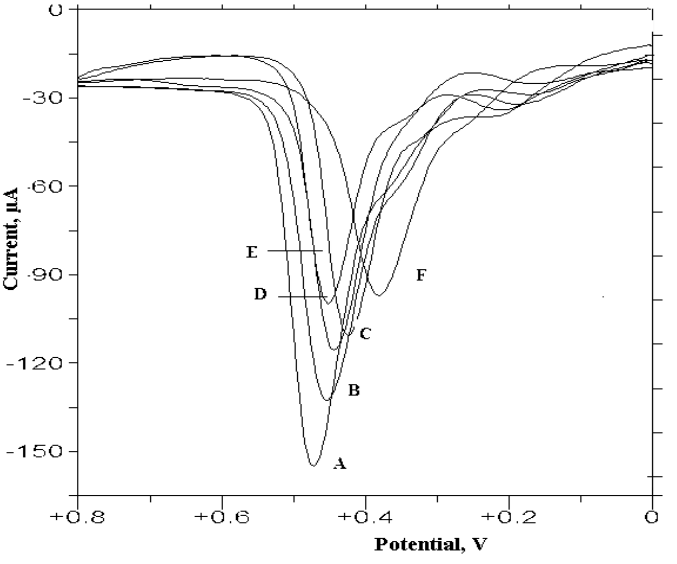

Fig. 2. A series of DPVs of a binary mixture containing 10 mM AA and 0.2 mM Acetaminophen at poly(*p*-methoxyphenol)-coated gold electrodes prepared by monomer polymerization between 0 and (A) 1.1, (B) 1.3, (C) 1.4, (D) 1.7, (E) 1.9 and (F) 2.2 V, respectively. Electrolyte, phosphate buffer (pH = 7.4). Potential sweep 10 mV/s, pulse amplitude 25 mV.

Fig. 3 illustrates the peak currents of ACP for two electrodes prepared at Elim values of 0.9 V and 1.3 V, respectively, during successive measurements. The electrode prepared at E_{lim} = 0.9 V shows a continuous loss of response with repeated measurements. In contrast, the electrode modified at E_{lim} = 1.3 V does not exhibit this issue. It shows remarkable accumulative properties, with the ACP peak after equilibration being more than twice as large as that at Elim = 0.9 V. The response becomes stable after 20 measurements, corresponding to approximately 10 minutes of equilibration time.

After reaching equilibrium, the electrode response remains very stable, with a Relative Standard Deviation (RSD) of only 0.91% for measurements between the 10th and 20th repetitions. Notably, when the electrode is allowed to equilibrate under open-circuit conditions, the stabilization time is shorter (~5 minutes). Additionally, the peak current is

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a linear function of the bulk concentration of acetaminophen.

The poly(p-methoxyphenol)-modified electrode prepared at E_{lim} = 1.3 V demonstrates superior stability and accumulative properties, making it highly effective for the electrochemical detection of ACP. Its linear response to ACP concentration further supports its potential use in analytical applications for the precise and reliable measurement of acetaminophen.

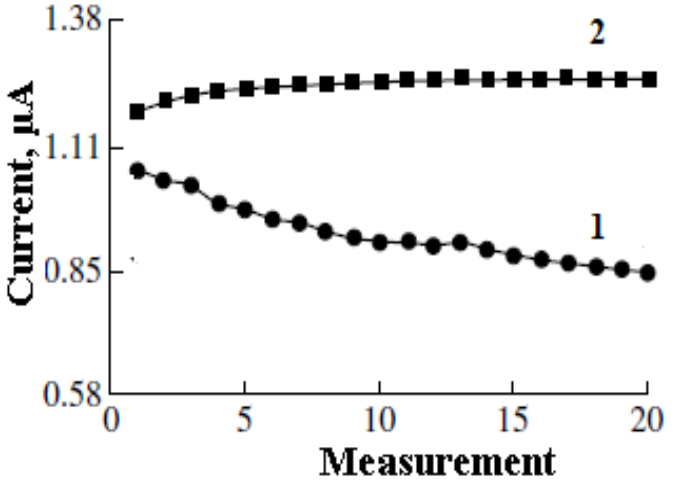

Fig. 3. Change of Acetaminophen peak current during repeated measurement for two different poly(p-methoxyphenol) electrodes. Polimer films polymerized between 0 and E_{lim} (**1**) 0.9, and (**2**) 1.3 V.

3.3. Effect of electrolyte type and its pH

The scientific investigation explored the impact of different electrolyte types and their pH values on the voltammetric response of Acetaminophen (ACP) using Differential Pulse Voltammetry (DPV). Four types of electrolytes — Britton-Robinson, Sörensen, phosphate buffer, and acetate buffer — were evaluated, with phosphate buffer yielding the highest peak current for ACP. The study focused on pH ranges from 1 to 9 to ascertain the optimal conditions for detecting ACP.

Fig. 4 illustrates that the phosphate buffer at pH 7.4 provided the maximum voltammetric response, indicating its efficacy as the ideal electrolyte for these measurements. The optimized DPV parameters were a potential sweep rate of 10 mV/s and a pulse amplitude of 25 mV.

Fig. 5 presents the DPVs obtained for varying micromolar concentrations of ACP in the presence of 1 mM ascorbic acid (AA), accompanied by the calibration curve for the ACP peak. Linear regression analysis yielded the parameters: slope of 61.459 nA/mM, intercept of 0.22 nA, and a high correlation coefficient (r^2 = 0.996), indicating a strong linear relationship between the peak current and ACP concentration. Furthermore, the detection limit, assessed using the 3s-test, was found to be 0.2 nM, underscoring the sensitivity of the method in detecting low concentrations of ACP.

The study systematically optimized the DPV parameters and identified phosphate buffer at pH 7.4 as the most effective electrolyte for achieving maximum sensitivity in detecting ACP, supported by robust analytical performance characteristics including a low detection limit and high correlation coefficient in the calibration curve.

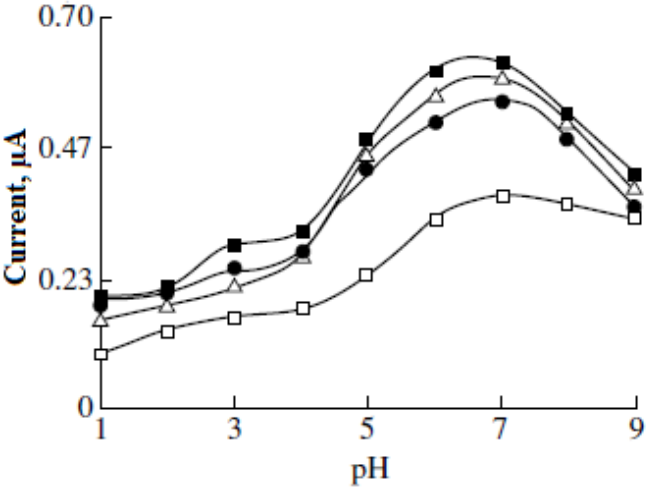

Fig. 4. The effect of electrolyte type and its pH. (●) Britton-Robbinson, (■) Phosphate, (Δ) Sörensen and (□) Acetate Buffer Solutions.

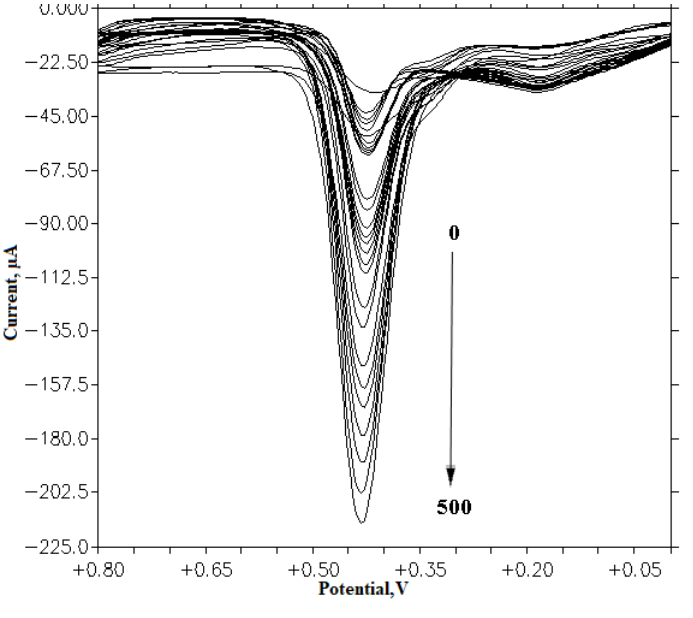

Fig. 5. A series of DPVs for a mixture containing 1 mM AA and an increasing concentration of Acetaminophen at a Poly(*p*-methoxyphenol) electrode. Acetaminophen concentrations are 0-500 µM, respectively.

3.4. Electrode stability and reversibility

The stability and reversibility of the electrode used in the study were evaluated to ensure reliable and repeatable

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measurements of Acetaminophen (ACP) using Differential Pulse Voltammetry (DPV).

Electrode Stability: The electrode preparation process was noted to be straightforward and quick, suggesting that long-term stability may not be critical. Nevertheless, the electrode's stability over time was assessed by measuring its response after periods of 1, 5, and 10 days of dry storage. The results indicated that the electrode retained 95%, 91%, and 85% of its initial response, respectively. This level of stability was deemed acceptable for practical applications, implying that the electrode could maintain consistent performance over several days.

Electrode Reversibility: The electrode's reversibility, crucial for its reusability across samples with varying analyte concentrations, was also investigated. Due to the pre-concentration process during measurements, the electrode could retain a significant portion of its response when transferred from an ACP-containing medium to an analyte-free electrolyte. This retention was advantageous for ensuring consistent measurements across different samples.

To renew the electrode's performance, a simple method involving soaking the modified electrode in a phosphate buffer solution (pH 7.4) and cycling its potential between 0 and 1 V was employed. This procedure effectively refreshed the electrode's surface for subsequent measurements. Depending on the ACP concentration, 30 to 150 cycles were found to be sufficient for effective renewal.

It was noted that the peak potentials for ACP remained stable between the initial and renewed electrodes, indicating minimal changes in electrochemical behavior after renewal. However, slight shifts towards more positive potentials were observed for Ascorbic Acid (AA), which did not significantly affect the overall performance of the electrode for ACP measurements. The study demonstrated that while the electrode preparation was straightforward and stable over several days, its renewability through a simple cyclic potential method ensured its reliability and longevity for repeated use in detecting ACP, thus meeting the practical demands of analytical applications.

4. CONCLUSION

In conclusion, this study has highlighted the promising electrocatalytic properties of poly(p-methoxyphenol) films, which can be tailored through varying polymerization conditions. The modification of electrodes with poly(p-methoxyphenol) has been shown to enhance selectivity in voltammetric measurements, particularly in the detection of Acetaminophen (ACP) amidst the presence of excess Ascorbic Acid (AA). The modifier effectively excludes interference from ascorbate while favoring the uptake of ACP, thereby improving the accuracy and sensitivity of electrochemical measurements. While the application of these enhancements in neurochemical studies would necessitate electrode miniaturization and further investigation, initial experiments have yielded promising results. Moreover, the poly(p-methoxyphenol) film offers advantages such as low cost and ease of preparation, making it highly suitable for continued development in sensor technology. Future research endeavors could focus on refining electrode design and exploring additional applications, thereby leveraging the unique properties of poly(p-methoxyphenol) for broader analytical and sensing purposes.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

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