



Original scientific paper

A simple, sensitive and cost-effective electrochemical sensor for the determination of N-acetylcysteine

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Abstract

In the present work, we prepared a simple and novel electrochemical sensor based on zeolitic imidazolate framework-67 (ZIF-67) and ionic liquid 1-Butyl-3-methylimidazolium hexafluorophosphate (BMIM.PF6) modified carbon paste electrode (CPE), which was effectively used for the determination of N-acetylcysteine. The cyclic voltammetry studies demonstrated the lowest peak potential and the enhanced peak current response for N-acetylcysteine at the surface of ZIF-67/BMIM.PF6-modified CPE compared to the other CPEs due to the significant catalytic effect of ZIF-67 and BMIM.PF6, as well as the combination of them. Under the optimized conditions, the electrochemical response of ZIF-67/BMIM.PF6/CPE sensor provided a good linear relationship with N-acetylcysteine concentration from 0.04 to 435.0 μM . The limit of detection is estimated to be 0.01 μM for N-acetylcysteine. In further studies and measurements, the estimation of N-acetylcysteine in tablet samples confirms the usefulness of the ZIF-67/BMIM.PF6/CPE sensor.

Keywords

Zeolitic imidazolate framework-67; ionic liquid; carbon paste electrode; metal-organic framework; nanomaterials

Introduction

N-acetylcysteine (as one of the thiol-containing drugs) is an acetylated derivative of the non-essential amino acid L-cysteine. N-acetylcysteine has been primarily used as a mucolytic agent for treating chronic bronchitis and other chronic respiratory disorders characterized by the excessive production of thick mucus [1]. N-acetylcysteine has the ability to break disulfide bonds, transforming them into two sulfhydryl groups. This process reduces the length of the main chain, resulting in the thinning of mucus and makes it easier to eliminate [2]. Also, N-acetylcysteine is widely used as the antidote for hepatotoxicity caused by acetaminophen (paracetamol) overdose [3]. Furthermore, due to

its antioxidant properties, N-acetylcysteine is also known as an antitumor, antiviral, and antiinflammatory agent [4]. It also has a potential therapeutic in the treatment of acquired immune deficiency syndrome (AIDS) [5], types of cancer [6], elimination of heavy metals [7], etc. The antioxidant action of N-acetylcysteine can be primarily attributed to two mechanisms [8,9]. Firstly, N-acetylcysteine acts as a precursor of reduced glutathione (GSH), which indirectly exerts antioxidant effects. GSH is a potent intracellular antioxidant crucial in neutralizing reactive oxygen species (ROS) and minimizing oxidative damage. Secondly, N-acetylcysteine exhibits direct antioxidant activity by directly scavenging reactive radicals. It can directly react with highly reactive species such as hydroxyl radicals (HO) and hydrogen peroxide (H₂O₂), reducing their reactivity and forming less reactive species. This scavenging action helps mitigate ROS's harmful effects on cells and tissues. Therefore, due to N-acetylcysteine's medical and biological importance, a highly sensitive and selective method is required for its determination. To this day, various analytical techniques have been used for the determination of N-acetylcysteine, such as chromatography [10], chromatography-tandem mass spectrometry [11,12], fluorescence [13], spectrophotometry [14], chemiluminescence [15], capillary electrophoresis [16], and electrochemistry [17-19].

In recent years, electrochemical methods have gained more attention than other methods due to simple and low-cost instrumentation, short analysis time, and portability [20-28]. The application of chemically modified electrodes in the design and fabrication of electrochemical sensors has a special place in the field of electroanalysis and has brought significant growth. Progress in this field can significantly help improve the efficiency, sensitivity, and selectivity of electrochemical sensors, making them more practical [29-36]. Therefore, researchers are continuously discovering and investigating new materials as modifiers to improve the performance of chemically modified electrodes.

Nanotechnology has many applications in various fields, and research is being conducted in this field to improve the efficiency and performance of multiple fields [37-47]. Nanostructures are materials with at least one nanometer-range dimension (1-100 nm). Nanostructures have unique physical and chemical properties that make them suitable for enhancing the performance of electrochemical sensors. Many studies have been conducted on developing nanostructures in electrochemical sensors for applications in fields such as environmental monitoring, healthcare diagnostics, and industrial process control [48-55].

Metal-organic frameworks (MOFs) are crystalline materials of metal ions or clusters coordinated to organic ligands. The metal ions and organic ligands in MOFs provide flexibility in designing the structure and properties of these materials. MOFs exhibit a highly porous structure with a large surface area, making them useful in various applications, including energy storage [56], catalysis [57], sensing [58], drug delivery [59], environmental remediation [60], and so on. One of the promising applications of MOFs is in electrochemical sensing, which can be used as sensing elements to enhance the performance of electrochemical sensors [61-63]. Ionic liquids (ILs) are compounds that have revolutionized many research fields in recent years due to negligible volatility, high polarity, high thermal stability, high chemical stability, low melting point, non-flammability, high ionic conductivity, large electrochemical window, and structural designability. Focusing on the electrochemical aspects of ionic liquids shows that one of their interesting applications is their use as modifying materials of electrodes for the fabrication of sensors [64,65]. Also, the combination of nanomaterials with ILs can play a key role in the efficiency of electrochemical sensors. Several outstanding attributes are observed when incorporating ILs and nanomaterials into electrodes, including long-term stability, higher conductivity, higher sensitivity, improved linearity, superior catalytic ability, and better selectivity [66-68].

The main objective of this work is to develop a simple and fast platform for the electrochemical determination of N-acetylcysteine by using a CPE modified with zeolitic imidazolate framework-67 (ZIF-67) and 1-Butyl-3-methylimidazolium hexafluorophosphate (BMIM.PF₆) ionic liquid. The electrochemical studies and measurements were performed by cyclic voltammetry (CV), differential pulse voltammetry (DPV), and chronoamperometry (CHA). The developed ZIF-67/BMIM.PF₆/CPE sensor exhibited better electrochemical performance for sensitive determination of N-acetylcysteine than the other CPEs with low limit of detection (LOD) and wide linear range. Importantly, this sensor's great potential in quantifying N-acetylcysteine in N-acetylcysteine tablet samples is also confirmed.

Experimental

Instruments and materials

All electrochemical studies and measurements were done using a potentiostat/galvanostat device (Metrohm Autolab – PGSTAT302N (Utrecht, The Netherlands)), controlled by the GPES 4.9004 software. The electrochemical tests were performed in a typical three-electrode setup by using a reference electrode (RE) (Ag/AgCl/KCl (3.0 M)), counter electrode (CE) (platinum), and working electrode (modified CPE). All solvents and chemicals were commercially available with analytical grade and used directly without further purification.

Synthesis of ZIF-67

For the preparation of ZIF-67, 2 mmol of cobalt(II) nitrate hexahydrate (0.582 g) was dissolved in 10 mL of methanol by stirring for 15 min. Then, 15 mL methanolic solution of 8 mmol 2-methylimidazole (0.656 g) was added slowly into the cobalt solution for 15 min. This prepared solution was stirred at ambient temperature for 24 h. Finally, the prepared precipitate was collected by centrifugation, washed with deionized water and ethanol several times, and dried at 65 °C in a vacuum oven for 14 h.

The morphology of the as-prepared ZIF-67 was observed by the FE-SEM image (Figure 1). It shows the growth of ZIF-67 crystals with regular rhombic dodecahedral morphology and almost uniform size.

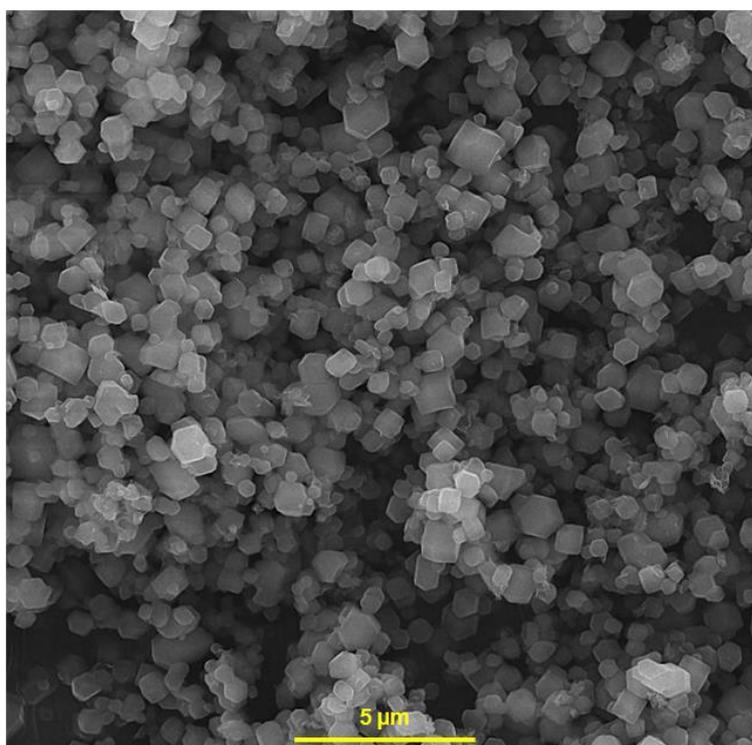


Figure 1. FE-SEM image of ZIF-67

Preparation of ZIF-67/BMIM.PF₆/CPE

The ZIF-67-BMIM.PF₆-modified CPE with a mass of 0.5 g was achieved by hand-mixing 0.47 g of graphite powder and 0.03 g of ZIF-67 for 5 min until a homogeneous blend was formed. Then, paraffin oil and BMIM.PF₆ in the ratio 3:1 was added to the blend of graphite and ZIF-67, which was mixed again for at least 30 min to obtain the ZIF-67/BMIM.PF₆ modified carbon paste. Finally, the modified paste was packed into the glass tube cavity. The electrical contact was established through a conductive copper wire. Also, the surface of the prepared electrode (ZIF-67/BMIM.PF₆/CPE) was polished on a smooth paper to obtain a shiny and smooth appearance.

To calculate the electrochemically active surface area (EASA) of the unmodified CPE and ZIF-67/BMIM.PF₆/CPE, the CVs were recorded at different scan rates in 0.1 M KCl solution containing 1.0 mM K₃[Fe(CN)₆] as a redox probe. By using the Randles–Ševčík equation, the value of the ESCA for ZIF-67/BMIM.PF₆/CPE (0.396 cm²) was 4.4 times greater than unmodified CPE.

Results and discussion

Electrocatalytic response of ZIF-67/BMIM.PF₆/CPE towards N-acetylcysteine

The effect of pH values (from 2.0 to 9.0) of the supporting electrolyte (0.1 M phosphate buffer solution (PBS)) on the electrochemical oxidation of N-acetylcysteine was studied by using the ZIF-67/BMIM.PF₆ modified CPE via the DPV technique. By changing the pH value of PBS, the prepared electrode showed different voltammograms for oxidation of N-acetylcysteine. The peak potential and peak current from the oxidation of N-acetylcysteine showed a strong dependence on pH. By increasing the pH from lower to higher values, the anodic peak potential of N-acetylcysteine was shifted towards the negative potentials. Also, the I_{pa} of N-acetylcysteine gradually increased with the increase of pH from 2.0 to 7.0 and then decreased. The maximum I_{pa} was obtained at pH 7.0 (Figure 2). Therefore, pH 7.0 was used for further electrochemical studies.

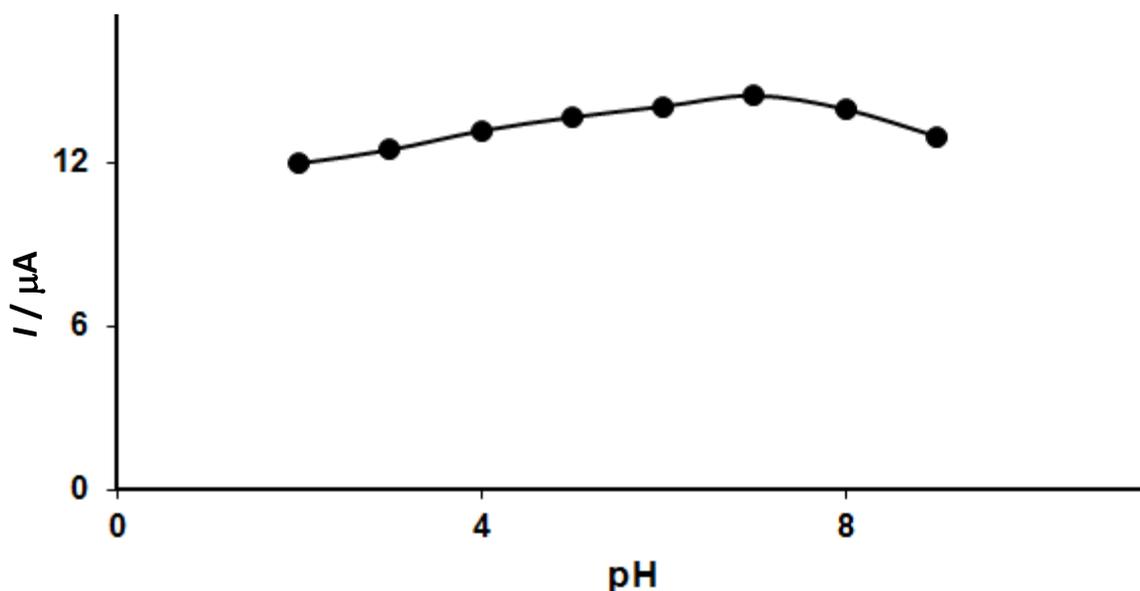


Figure 2. Plot of the oxidation peak current of 200.0 μM N-acetylcysteine as a function of pH solution at ZIF-67/BMIM.PF₆/CPE in 0.1 M PBS at different pH values (2.0 to 9.0)

To assess the electrocatalytic activity of the IL (BMIM.PF₆) and as-prepared ZIF-67, the electrochemical responses of N-acetylcysteine on various electrodes were examined by cyclic voltammetry (CV). Figure 3 shows the cyclic voltammograms from the response of unmodified CPE

(voltammogram a) ZIF-67/CPE (voltammogram b), BMIM.PF₆/CPE (voltammogram c), and ZIF-67/BMIM.PF₆/CPE (voltammogram d) towards the 200.0 μM N-acetylcysteine in 0.1 M PBS (pH 7.0). As can be seen, a broad oxidation peak with a low anodic peak current (I_{pa}) was shown in unmodified CPE. On the other hand, the modification of CPE with ZIF-67 (voltammogram b), BMIM.PF₆ (voltammogram c), and ZIF-67 together with BMIM.PF₆ (voltammogram d) has led to an increase in I_p intensity and a decrease in overpotential. However, the best case of increasing the I_p and reducing the overpotential of the N-acetylcysteine oxidation is related to the voltammogram d, which uses both ZIF-67 and BMIM.PF₆ in the composition of the CPE. This result could be related to the electrocatalytic effect of the BMIM.PF₆ and ZIF-67, as well as their synergistic effects. In addition, the absence of any reduction peak on the reverse scan revealed the irreversible oxidation of N-acetylcysteine over unmodified and modified CPEs.

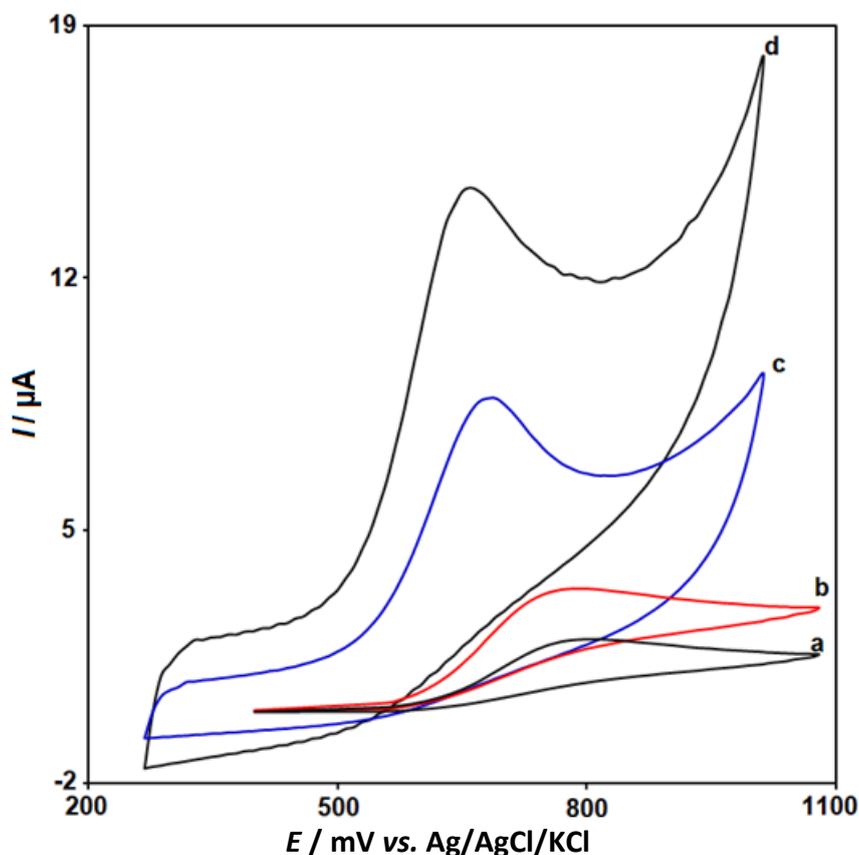


Figure 3. CVs of unmodified CPE (a), ZIF-67/CPE (b), BMIM.PF₆/CPE (c), and ZIF-67/BMIM.PF₆/CPE (d) in 0.1 M PBS (pH 7.0) containing 200.0 μM N-acetylcysteine at a scan rate of 50 mV s⁻¹

Effect of scan rate on the oxidation reaction of N-acetylcysteine

To investigate the effect of scan rate, CVs of the ZIF-67/BMIM.PF₆/CPE were recorded at different scan rates (10 to 500 mV s⁻¹) in 0.1 M PBS containing 100.0 μM N-acetylcysteine (Figure 4). An increase in the anodic peak current (I_{pa}) with an increase in scan rate can be observed. Also, from the obtained voltammograms, it was possible to observe a linear dependence between I_{pa} of N-acetylcysteine and the square root of scan rate ($v^{1/2}$) (Figure 4 inset). This observation suggests that the oxidation reaction is controlled by the diffusion of N-acetylcysteine species from the bulk solution to the surface of ZIF-67/BMIM.PF₆/CPE.

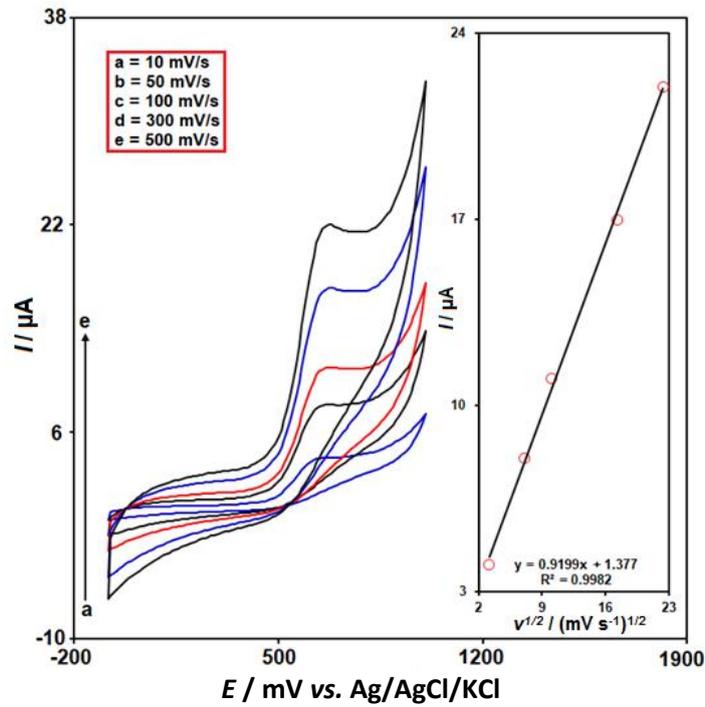


Figure 4. CVs of ZIF-67/BMIM.PF₆/CPE performed at different scan rates in 0.1 M PBS (pH 7.0) containing 100.0 μM N-acetylcysteine. Inset: the linear dependence between I_{pa} vs. $v^{-1/2}$

Chronoamperometric measurements of N-acetylcysteine at ZIF-67/BMIM.PF6/CPE

To measure the diffusion coefficient (D) of N-acetylcysteine, the chronoamperometric responses of ZIF-67/BMIM.PF₆/CPE was plotted for different concentrations of N-acetylcysteine from 0.1 to 1.6 mM at a fixed potential of 0.71 V (Figure 5).

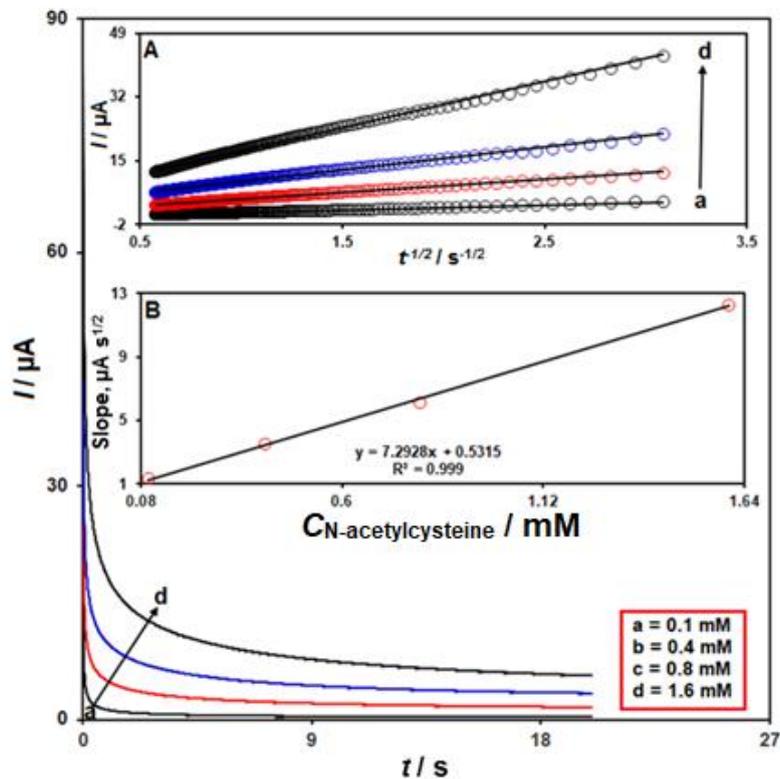


Figure 5. Chronoamperometric response of ZIF-67/BMIM.PF₆/CPE in 0.1 M PBS (pH 7.0) containing different concentrations of N-acetylcysteine. Inset A: the linear dependence between I_{pa} vs. $t^{-1/2}$ and Inset B: linear dependence between slope values of $I-t^{-1/2}$ plots vs. N-acetylcysteine concentrations

The current-time curves reflect the change in concentration gradient of the electroactive species (N-acetylcysteine) in the vicinity of the electrode surface as time progresses. In order to determine the D , the Cottrell curves (I versus $t^{1/2}$) were plotted over a certain range of time for different concentrations of N-acetylcysteine (Figure 5A). Then, the slope of the obtained Cottrell curves was plotted vs. the different concentrations of N-acetylcysteine (Figure 5B) and a straight line with a slope of $7.2928 \mu\text{A s}^{1/2} / \text{mM}$ was obtained. From the slope of the resulting plot and using Cottrell's equation, the D of N-acetylcysteine on the surface of ZIF-67/BMIM.PF₆/CPE was found to be $2.2 \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$.

Quantitative analysis of N-acetylcysteine by DPV

To study the detection efficiency of ZIF-67/BMIM.PF₆/CPE, the DPV measurements were performed with the successive addition of N-acetylcysteine (0.04 to 435.0 μM) in 0.1 M PBS (pH 7.0) (Figure 6). From the recorded voltammograms, the increase of the I_{pa} is proportional to the increase of N-acetylcysteine concentration in a wide range from 0.04 to 435.0 μM . Furthermore, the linear dependence between the enhanced I_{pa} of N-acetylcysteine and its concentration is presented in the Inset of Figure 6. This dependence can be expressed by $I = 0.0683C_{\text{N-acetylcysteine}} + 0.9501$ with a correlation coefficient 0.9996. The LOD was calculated according to the ensuing formula $3S_b/m$, where S_b denotes the standard deviation of the blank (PBS) signal (obtained based on 15 measurements on the blank solution), and m denotes the slope of the corresponding calibration curve, and it was found to be 0.01 μM . The performance comparison of the developed electrode (ZIF-67/BMIM.PF₆/CPE) in this study with some previous studies is shown in Table 1.

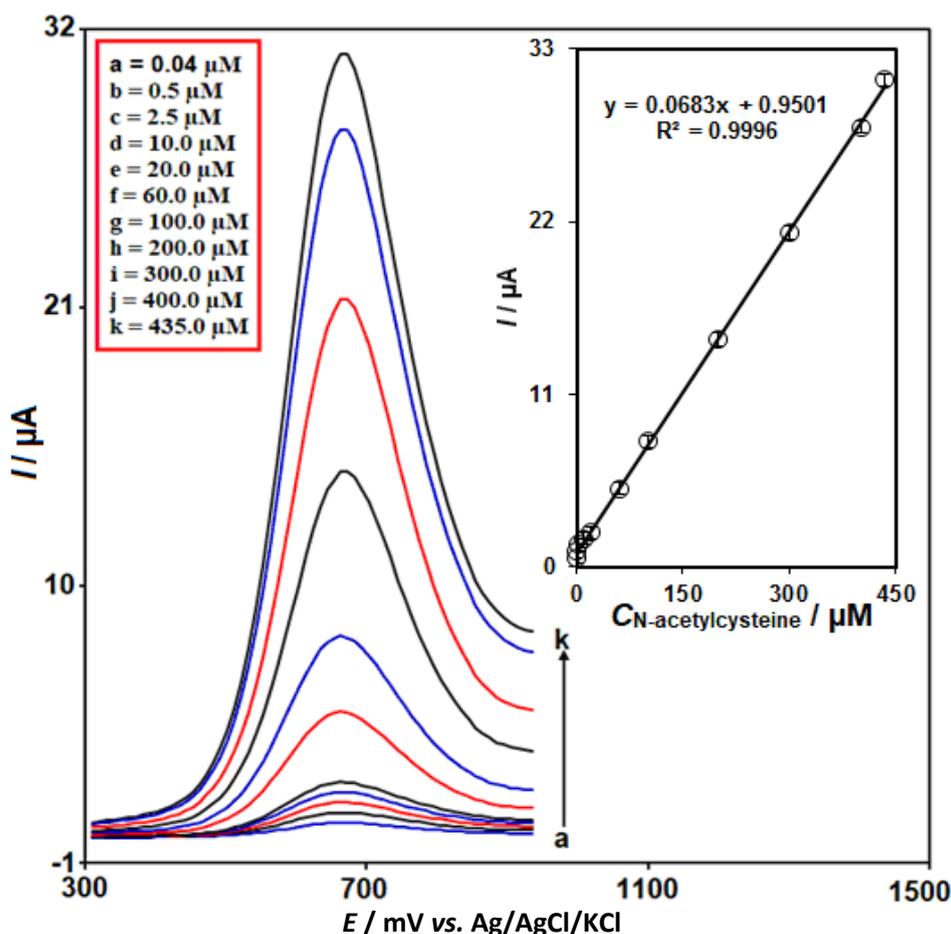


Figure 6. DPVs of ZIF-67/BMIM.PF₆/CPE performed in 0.1 M PBS (pH 7.0) containing different concentrations of N-acetylcysteine. Inset: the linear dependence between I_{pa} vs. N-acetylcysteine concentration

Table 1. Comparison of the ZIF-67/BMIM.PF₆/CPE sensor with previously reported N-acetylcysteine sensors

Electrochemical sensor	Method	Linear range, mM	LOD, μM	Ref.
Fe ₃ O ₄ /reduced graphene oxide/glassy carbon electrode	DPV	0.10 - 10.0	11.1	[17]
Graphene oxide-copper pentacyano-nitrosylferrate(III)/graphite paste	CV	0.30 - 6.00	29.7	[69]
Copper nitroprusside adsorbed on the 3-aminopropylsilica/CPE	CV	0.099 - 0.890	0.41	[70]
Copper(II) hexacyanoferrate(III)/CPE	Linear sweep voltammetry (LSV)	0.12 - 0.83	63.0	[71]
Cobalt salophen complex/carbon nanotube-paste electrode	DPV	0.0001 - 0.100	0.05	[72]
ZIF-67/BMIM.PF ₆ /CPE	DPV	0.00004 - 0.435	0.01	This work

Stability and repeatability studies of ZIF-67/BMIM.PF₆/CPE sensor towards the determination of N-acetylcysteine

Studies related to the stability of ZIF-67/BMIM.PF₆/CPE sensor were performed by recording the current response of the designed sensor towards 60.0 μM N-acetylcysteine every 7 days over 14 days. The obtained results showed that the electrode response retained 97.5 % of its initial value after 7 days and 95.1 % after 14 days. These results indicated that the designed sensor had good stability.

Also, to investigate the repeatability of the ZIF-67/BMIM.PF₆/CPE sensor, the measurements were repeated in 0.1 M PBS (pH 7.0) containing 60.0 μM N-acetylcysteine. The acceptable repeatability was obtained with an RSD of 2.9 % after using the same sensor for seven continuous measurements.

Interference studies

The interference studies were also carried out to investigate the selectivity of ZIF-67/BMIM.PF₆/CPE sensor towards the determination of N-acetylcysteine in the presence of various species. The DPV responses of ZIF-67/BMIM.PF₆/CPE was recorded by adding various species into 0.1 M PBS (pH 7.0) containing 50.0 μM N-acetylcysteine. According to the findings, 700-fold of Na⁺, K⁺, Ca²⁺, Al³⁺, NH₄⁺, F⁻, Cl⁻, and Br⁻; 250-fold of urea, glycine, alanine, and phenylalanine; 8-fold of cysteine did not show significant interference (no signal change more than ± 5 %) for the determination of N-acetylcysteine.

N-acetylcysteine analysis in real samples

To evaluate the practical performance of the developed sensor (ZIF-67/BMIM.PF₆/CPE), the determination of N-acetylcysteine in the N-acetylcysteine tablet sample was conducted. The standard addition method was employed for the analysis of N-acetylcysteine by the DPV technique. Measurements were performed by adding the known concentrations of N-acetylcysteine to the N-acetylcysteine tablet sample. The recovery and RSD values are summarized in Table 2.

Table 2. Real sample analysis for the determination of N-acetylcysteine spiked into the N-acetylcysteine tablet sample at ZIF-67/BMIM.PF₆/CPE

Sample	Spiked amount, μM	Found amount, μM	Recovery, %	RSD, %
N-acetylcysteine tablet		6.0	-	3.4
	1.0	6.9	98.6	1.9
	2.0	8.3	103.7	2.4
	3.0	9.1	101.1	2.9
	4.0	9.6	96.0	2.5

The summarized results in Table 2 show acceptable recovery values (between 96.0 and 103.7 %) and RSD values ($n = 5$) of ≤ 3.4 %, which confirm that the developed sensor could be used for real-time analysis.

Conclusion

In this work, we demonstrated the application of a high-performance electrochemical sensor (ZIF-67/BMIM.PF₆/CPE) for the determination of N-acetylcysteine. The ZIF-67/BMIM.PF₆-modified CPE showed more prominent electrocatalytic activity toward N-acetylcysteine oxidation than the other electrodes, with enhanced response current and lowered over-potential. The ZIF-67/BMIM.PF₆/CPE showed a sensitive peak current response toward N-acetylcysteine in the linear range from 0.04 to 435.0 μ M, with a LOD ($S/N = 3$) of 0.01 μ M. Finally, the developed sensor was successfully used for the estimation of N-acetylcysteine in N-acetylcysteine tablet sample with acceptable recoveries (96.0 and 103.7 %) and RSDs values not more than 3.4 %.

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