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# Electroanalytical analysis of guaifenesin from pharmaceuticals on boron doped diamond electrode

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## Abstract

Electrochemical analysis of the expectorant drug guaifenesin was performed on boron doped diamond electrode by cyclic voltammetry, differential pulse voltammetry, and square wave voltammetry techniques. The results of cyclic voltammetry studies indicated that the reaction mechanism of guaifenesin in the anodic direction was irreversible, and diffusion controlled. The linearity ranges of the peak currents versus guaifenesin concentration were between 0.4 and 100 μM with a detection limit of 1.47 nM for differential pulse voltammetry and between 0.8 and 100 μM with a detection limit of 2.92 nM for square wave voltammetry. Quantitative analysis of guaifenesin from the pharmaceuticals was performed using the proposed methods without any pre-separation. Sensitive voltammetric methods with good recovery, high sensitivity and accuracy were developed for the electroanalytical analysis of guaifenesin.

**Keywords:** Boron doped diamond electrode, guaifenesin, pharmaceuticals, validation, voltammetry

## 1. Introduction

Guaifenesin (GFN) is an orally used expectorant drug for the treatment of symptoms of the cold, allergy, and upper respiratory tract infections [1]. It is thought to exert its pharmacological action by increasing the hydration of mucus in the gastric mucosa and decreasing the viscosity of mucus secretion [2,3]. GFN (Fig. 1), 3-(*o*-methoxyphenoxy)-1,2-propanediol, is a highly water-soluble white powder with an empirical formula of $C_{10}H_{14}O_4$ and a molecular weight of 198.22 g/mol.

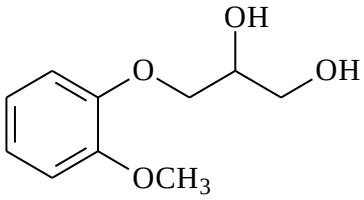


**Figure 1.** Structure of guaifenesin

Drug analysis is carried out at various stages as formulation, stability studies, toxicology, quality control, and pharmacological testing in humans and animals. In hospitals, drug analyzes are performed on patients to support clinical, pharmacokinetic, and bioavailability studies and to monitor abuse of therapeutic drugs. These studies require reliable and validated analytical methods to quantify drugs in complex media such as formulation and biological samples [4]. Sensitive determination of GFN is important both to monitor the effectiveness of the treatment applied and to minimize its side effects such as nausea, vomiting, kidney stone formation, diarrhea, and constipation [5].

Determination studies of GFN with different methods such as spectrophotometric [6,7], chromatographic [8–10], and voltammetric [11–14] methods are available in the literature. Spectrophotometric and chromatographic methods are more time-consuming and expensive than electrochemical methods due to the need for complex sample preparation. Voltammetry, which is one of the electrochemical methods, is a very advantageous method compared to other analytical methods because it requires a minimum amount of organic solvent, uses low-cost equipment, and does not require a pre-separation process for the samples to be analyzed [15]. While cyclic voltammetry (CV), which is one of the most commonly used voltammetric methods, is suitable for qualitative analysis, differential pulse voltammetry (DPV) and square wave voltammetry (SWV) techniques

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allow high-sensitivity quantitative analysis. The use of boron-doped diamond electrode (BDDE) in voltammetry has become widespread and attractive in recent years [16,17]. As a member of carbon-based materials, BDDE has several unique properties such as good mechanical and electrochemical stability in both acidic and alkaline media, high thermal conductivity, wide potential range, low background current, and low sensitivity to dissolved oxygen in aqueous solutions [18].

The aim of this study is to develop validated voltammetric methods for the electroanalytical analysis of GFN from its pharmaceutical dosage forms using BDDE as the working electrode. Quantitative determination of GFN was accomplished using the validated voltammetric techniques proposed in this study, with high sensitivity, low detection limits, and good recovery.

## 2. Experimental

### 2.1. Chemicals and reagents

GFN was purchased from Sigma-Aldrich (USA) and used as a standard without further purification. Vicks Vapo expectorant® syrup (200 mg/15 mL), the pharmaceutical form of GFN, was purchased from the local pharmacy. Stock solutions of GFN ($1.0 \times 10^{-3}$ M) were prepared daily with ultrapure water and stored at +4°C in the dark. Working solutions of GFN were prepared daily by direct dilution of the GFN stock solution with the selected supporting electrolyte.

Britton-Robinson buffer (BRB) solutions (0.04 M), pH 2.0 – 12.0, were prepared from 0.04 M $CH_3COOH$ (Merck, Germany), 0.04 M $H_3BO_3$ (Aldrich, USA), and 0.04 M $H_3PO_4$ (Merck, Germany). Phosphate buffer (PB) solutions (0.1 M) were prepared using $H_3PO_4$ (Merck, Germany) for pH 2.0 – 4.0 and $Na_2HPO_4$ (Aldrich, USA) and $NaH_2PO_4$ (Merck, Germany) for pH 5.5 – 8.0. Acetate buffer (AB, 0.5 M) solutions at pH 3.5, 4.5, and 5.5 were prepared from $CH_3COOH$ (Aldrich, Germany). 5 M NaOH (Aldrich, USA) solution was used for all pH adjustments. Analytical reagents and Sartorius Arium proUV nanopure water (resistivity ≥ 18 MΩ cm) were used to prepare the solutions.

### 2.2. Apparatus and measurements

All voltammetric measurements were performed using Autolab PGSTAT128N potentiostat/galvanostat (Metrohm-Autolab, The Netherlands) with Nova 11.0 software. All electrochemical studies were carried out with an electrochemical cell consisting of three electrodes, a BDDE (Windsor Scientific ϕ: 3mm) as the working electrode, a platinum wire as the counter electrode, and an Ag/AgCl electrode (Bioanalytical Systems, 3.0 M KCl) as the reference.

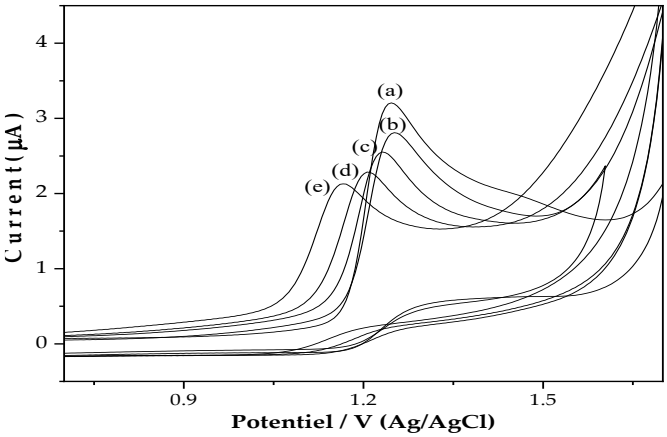


**Figure 2.** Cyclic voltammograms of 60.0 μM GFN in (a) pH 2.0 PB, (b) pH 3.5 AB, (c) pH 5.5 PB, (d) pH 7.0 BRB, and (e) pH 9.0 BRB solutions, Scan rate: 100 mV/s

Hanna HI2211 (Romania) pH meter was used to adjust the pH values of the buffer solutions. All electrochemical measurements were carried out at room temperature (25 ± 1°C).

### 2.3. Preparation of pharmaceutical dosage forms

Determination studies from pharmaceuticals were performed with a stock solution ($1.0 \times 10^{-3}$ M) prepared daily using the syrup formulation of GFN (VICKS® expectorant syrup, 200 mg/15 mL). For this purpose, an adequate volume of syrup was transferred to a 10 mL calibrated flask and the volume was made up with bi-distilled water. Working solutions were prepared fresh daily by diluting the stock solution prepared from the syrup with the selected supporting electrolyte and used for the voltammetric determination of GFN.

## 3. Results and discussion

The electrochemical behavior of GFN on BDDE was investigated by CV, DPV, and SWV techniques. Voltammograms of 100 μM GFN solution on BDDE were obtained by CV at a scan rate of 100 mV/s in the pH 2.0–12.0 range (Fig. 2). As can be seen from the cyclic voltammograms in Fig. 2, GFN gave a sharp oxidation peak on BDDE. The absence of any peaks in the direction of reduction in cyclic voltammograms at all buffers and pH indicated that the redox reaction of GFN on BDDE was irreversible.

$$E_p\ (mV) = 1324.5 - 18.0\ pH \quad (1)$$

$(r = 0.997)$ $(pH\ 4.5–11.0,\ n = 9\ for\ CV)$

$$E_p\ (mV) = 1259.4 - 18.5\ pH \quad (2)$$

$(r = 0.995)$ $(pH\ 4.5–11.0,\ n = 9\ for\ DPV)$

$$E_p\ (mV) = 1281.9 - 17.7\ pH \quad (3)$$

$(r = 0.993)$ $(pH\ 4.5–11.0,\ n = 9\ for\ SWV)$

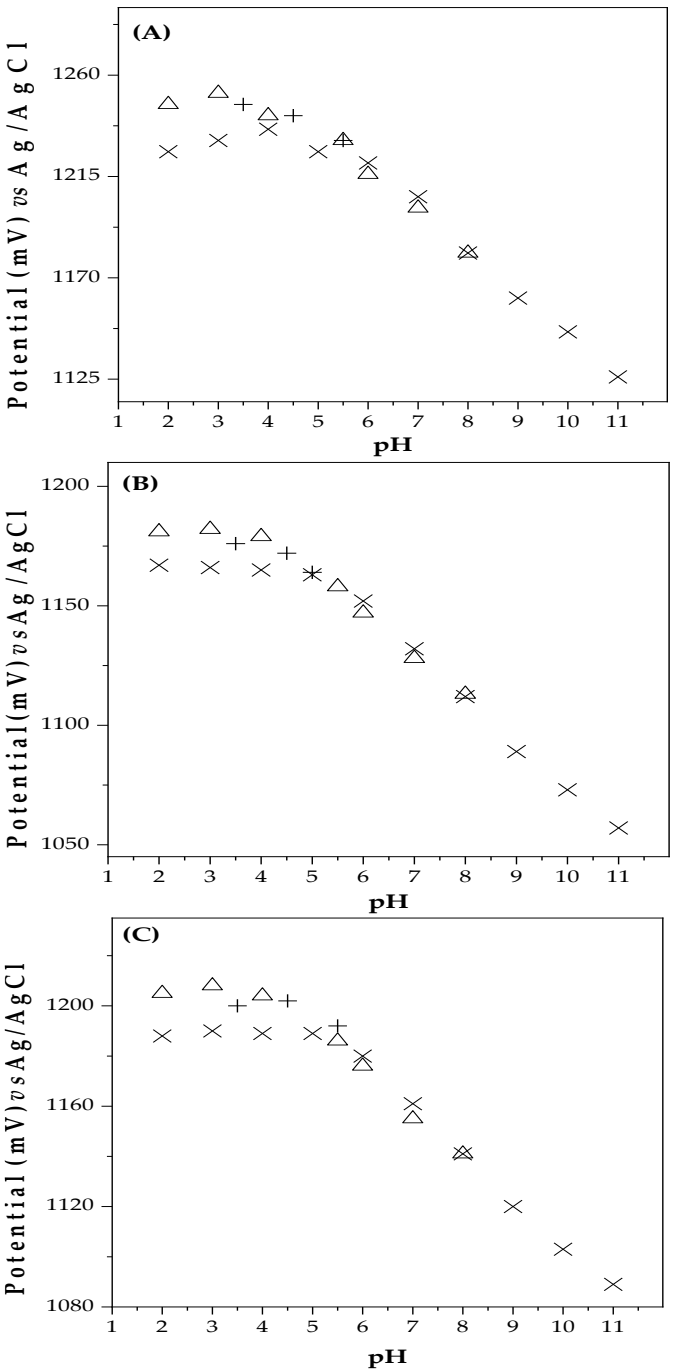


**Figure 3.** $E_P$-pH graphs of 60.0 µM GFN on BDDE by (A) CV, (B) DPV, and (C) SWV techniques. ×: BRB, +: AB, Δ: PB solutions

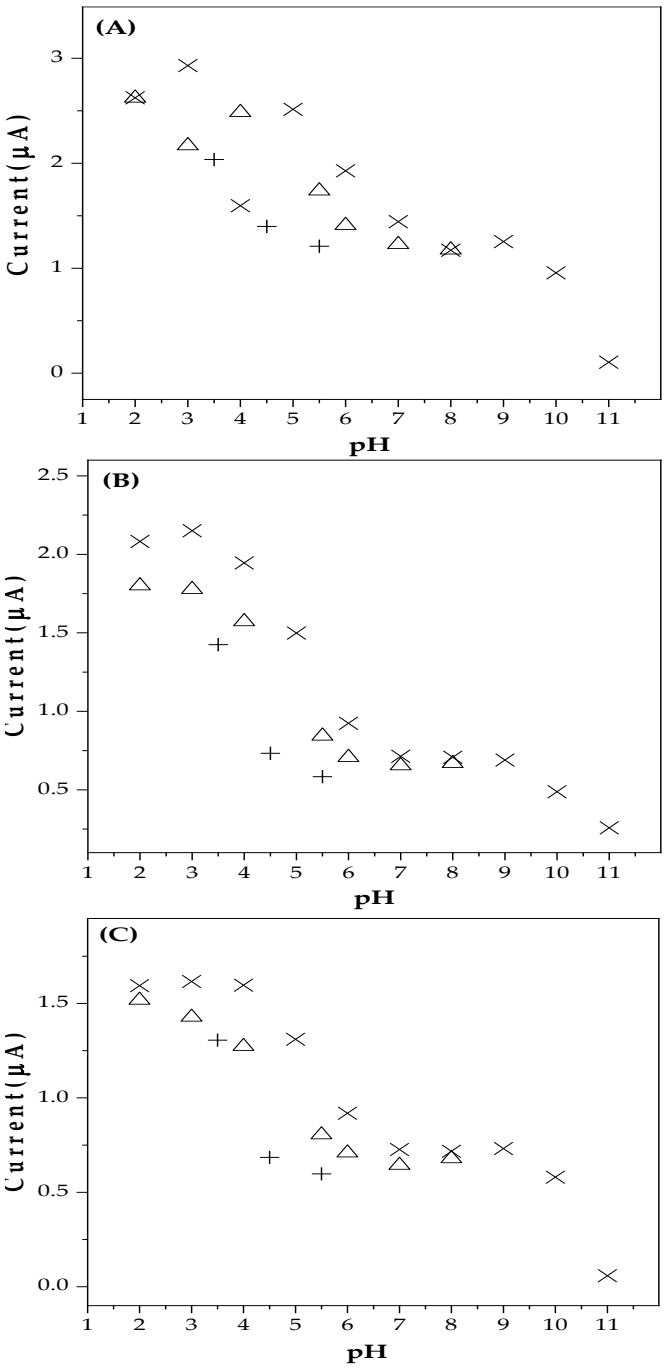


**Figure 4.** $I_P$-pH graphs of 60.0 µM GFN on BDDE by (A) CV, (B) DPV, and (C) SWV techniques. ×: BRB, +: AB, Δ: PB solutions

The effect of pH on the peak potential ($E_P$) and peak current ($I_P$) of GFN was investigated on BDDE by CV, DPV, and SWV techniques in different buffer solutions (Figs. 3 and 4). In Fig. 3, it can be seen that the GFN peak potential decreases linearly as the pH value increases. This indicates that as the pH increases, the oxidation reaction of GFN occurs more easily [19].

$E_P$ values obtained with varying pH showed a good linear relationship with the Equations (1 – 3) for CV, DPV, and SWV between pH 4.5 and 11.0. At pHs lower than 4.5, the peak potential of GFN was pH independent for all techniques (Fig. 3).

The slope values of -18.0, -18.5, and -17.7 were not close to the theoretical -59.0 mV/pH value [20,21], indicating that the number of protons involved in the oxidation reaction of GFN was not equal to the number of transferred electrons. It is postulated that the oxidation of GFN may occur via the primary alcohol group in the molecule, as suggested in some studies in the literature [22,23].

The peak currents obtained by the CV, DPV, and SWV techniques were plotted against pH as shown in Fig. 4. The most symmetrical peak and the highest peak current (Fig. 4) were obtained in pH 3.5 AB solution, therefore, this solution was chosen as the most suitable supporting electrolyte for further studies.

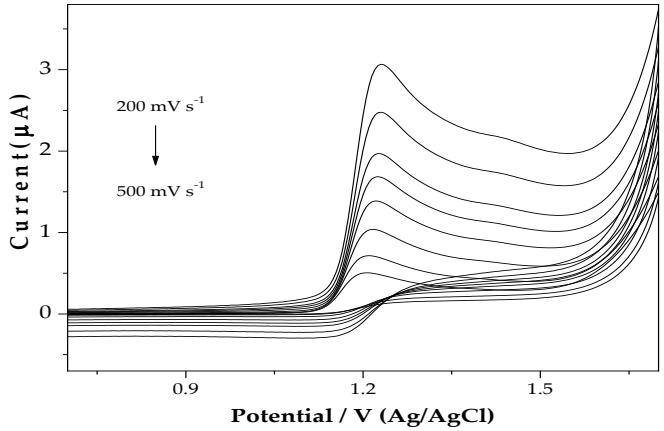


**Figure 5.** Cyclic voltammograms of 60 μM GFN in pH 3.5 AB solution at scan rates of 5, 10, 25, 50, 75, 100, 150, and 200 mV/s on BDDE

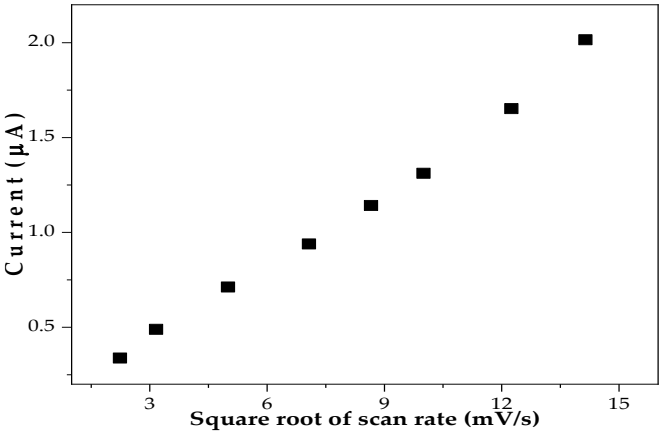


**Figure 6.** $I_p$-$\nu^{1/2}$ graph of 60.0 μM GFN in pH 3.5 AB solution

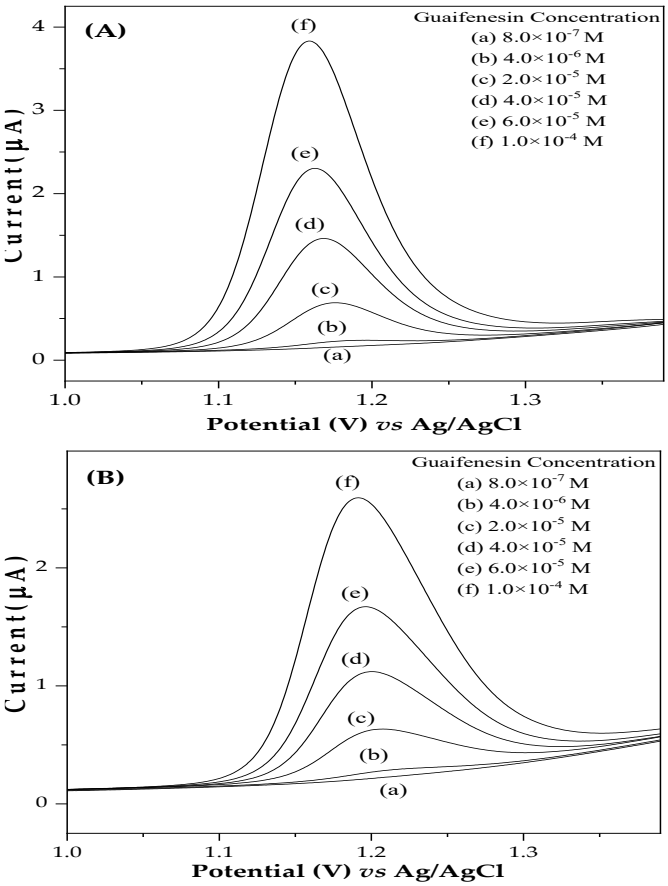


**Figure 7.** (A) DP and (B) SW voltammograms of GFN in pH 3.5 AB solution on BDDE

**Table 1.** Calibration data of GFN obtained by DPV and SWV techniques on BDDE

| | DPV | SWV |
|---|---|---|
| Measured potential (mV) | 1184 | 1184 |
| Linearity range (μM) | 0.4 – 100 | 0.8 – 100 |
| Slope (μA/μM) | $3.63 \times 10^{-2} \pm 5.24 \times 10^{-4}$ | $2.41 \times 10^{-2} \pm 4.39 \times 10^{-4}$ |
| Intercept (μA) | $-7.60 \times 10^{-2} \pm 2.09 \times 10^{-2}$ | $-5.40 \times 10^{-2} \pm 1.89 \times 10^{-2}$ |
| Correlation coefficient (r) | 0.997 | 0.996 |
| LOD (μM) | $1.47 \times 10^{-3}$ | $2.92 \times 10^{-3}$ |
| LOQ (μM) | $4.44 \times 10^{-3}$ | $8.84 \times 10^{-3}$ |
| Intra-day precision of peak current (RSD%)* | 0.53 | 0.58 |
| Inter-day precision of peak current (RSD%)* | 0.80 | 1.27 |

*Obtained from five measurements

**Table 2.** Results of recovery studies from pharmaceutical dosage form

| | DPV | SWV |
|---|---|---|
| Labeled amount (mg) | 200.00 | 200.00 |
| Amount found (mg) | 199.45 | 200.35 |
| Relative standard deviation% | 0.64 | 0.48 |
| Bias% | -0.28 | 0.18 |
| Added amount (mg) | 0.039643 | 0.039643 |
| Found amount (mg) | 0.039342 | 0.039813 |
| Average recovered% | 99.24 | 100.43 |
| Number of experiments | 5 | 5 |
| RSD% of recovery | 0.68 | 0.39 |
| Bias% | -0.76 | 0.43 |

**Table 3.** Comparison of parameters obtained with different electrodes for GFN determination

| Electrode | Method | Medium | Linear Range (μM) | LOD (μM) | Ref. |
|---|---|---|---|---|---|
| PtE | DPV | pH 2.0 BRB | 100 – 303 | — | [11] |
| PCFE | DPV | pH 7.0 PB | 0.1 – 25 | 0.023 | [12] |
| MWCNT/ILGCE | DPV | pH 7.0 PB | 1.5 – 480 | 0.85 | [13] |
| Au-Pt/NH/CNE | DPV | pH 2.2 BRB | 0.05 – 300 | 0.0175 | [14] |
| PBP/GCE | DPV | pH 3.0 PB | 0.1 – 20 | 0.00366 | [27] |
| PAO/GCE | DPSV | pH 7.0 BRB | 0.2 – 100 | 0.0578 | [28] |
| BDDE | DPV | pH 3.5 AB | 0.4 – 100 | 0.00147 | This study |
| | SWV | pH 3.5 AB | 0.8 – 100 | 0.00292 | |

PtE: Platinum electrode

PCFE: Anodized nanocrystalline graphite-like pyrolytic carbon film electrode

MWCNT/ILGCE: Multiwalled carbon nanotube-ionic liquid modified glassy carbon electrode

Au-Pt/NH/CNE: Carbon nanotube bimetallic Au-Pt inorganic-organic nanofiber hybrid nanocomposite electrode

PBP/GCE: Poly(bromocresol purple) modified glassy carbon electrode

PAO/GCE: Poly(acridine orange) modified glassy carbon electrode

Scan rate study was performed by CV technique to understand whether the electro-oxidation reaction mechanism of GFN is diffusion-controlled or adsorption-controlled. For this purpose, the electrochemical behavior of 60.0 μM GFN in AB solution at pH 3.5 was investigated in the range of 5 – 200 mV/s (Fig. 5).

The plot of the peak current of GFN versus the square root of the scan rate showed linearity with a slope of 0.1348 (Equation 4), as shown in Fig. 6. Also, the regression equation from the log $I_p$ - log ν plot gave a slope of 0.464, which is very close to the theoretical value of 0.5 (Equation 5), which indicates diffusion-controlled process [24,25]. This result indicated that the electro-oxidation process of GFN was controlled by the diffusion on the BDDE surface [24].

$$I_p\,(\mu A) = 0.1348\ v^{1/2}\,(mV/s) + 0.0212 \quad (r = 0.993,\ n = 8) \tag{4}$$

$$log\ I_p\,(\mu A) = 0.464\ log\ v\,(mV/s) - 0.795 \quad (r = 0.995,\ n = 8) \tag{5}$$

Quantitative analysis of GFN was performed using DPV and SWV techniques. Because of their high sensitivity, selectivity, low detection limits, and rapid response, these techniques were used for the determination of GFN. DP and SW voltammograms for different concentrations of GFN were given in Fig. 7. Linear ranges were obtained between 0.40 and 100.0 μM for DPV and between 0.80 and 100.0 μM for SWV. Characteristics of calibration equations and the validation parameters for both DPV and SWV are reported in Table 1. Limit of detection (LOD) and limit of quantification (LOQ) values were calculated from 3s/m and 10s/m, respectively; where s is the standard deviation of the response and m is the slope of the calibration curve [26].

Quantitative determination of GFN from the pharmaceutical dosage form was carried out by DPV and SWV techniques on BDDE using the corresponding calibration equation. For this purpose, syrup form of GFN containing 200 mg of GFN and inactive ingredients per 15 mL was used and recovery studies were performed. The results obtained are given in Table 2.

The data obtained in this study for GFN were compared with the data from other voltammetric studies in the literature (Table 3). The linearity range obtained with platinum electrode [11] was much narrower than the linearity ranges obtained for both techniques in this study. Linearity ranges obtained in the studies with multiwalled carbon nanotube-ionic liquid modified glassy carbon electrode [13], carbon nanotube bimetallic Au-Pt inorganic-organic nanofiber hybrid nanocomposite electrode [14], and poly(acridine orange) modified glassy carbon electrode [28] were wider than the linearity ranges obtained in this study. The linearity range of the DPV technique in this study is the same as that of the anodized nanocrystalline graphite-like pyrolytic carbon film electrode [12] and almost the same as that obtained with poly(bromocresol purple) modified glassy carbon electrode[27]. Although the linearity ranges vary according to the electrodes used and the developed techniques, the LOD values obtained by DPV and SWV techniques in this study were found to be much lower than the LOD values of other studies in the literature in Table 3. In addition, GFN analysis was performed in a very practical process with bare BDDE without any modification.

## 4. Conclusion

The electro-oxidation behavior of GFN was investigated on BDDE by voltammetric techniques. As a result of voltammetric studies, it was observed that GFN had an irreversible and diffusion-controlled oxidation reaction on the surface of BDDE. Developed DPV and SWV techniques enabled rapid, sensitive, selective, inexpensive, and simple determination of GFN from its pharmaceutical formulation. As a result, accurate and precise voltammetric techniques were developed for GFN analysis using unmodified BDDE.

## Conflicts of interest

The authors declare no conflict of interest.

## References

[1] W.W. Storms, J.E. Miller, Daily use of guaifenesin (Mucinex) in a patient with chronic bronchitis and pathologic mucus hypersecretion: A case report, Respiratory Med Case Rep, 23, 2018, 156–157.

[2] H.H. Albrecht, P.V. Dicpinigaitis, E.P. Guenin, Role of guaifenesin in the management of chronic bronchitis and upper respiratory tract infections, Multidiscip Respir Med, 12, 2017, 31.

[3] J.A. Ohar, J.F. Donohue, S. Spangenthal, The role of guaifenesin in the management of chronic mucus hypersecretion associated with stable chronic bronchitis: A comprehensive review, Chronic Obstr Pulm Dis, 6, 2019, 341–349.

[4] N.A. El-Maali, Voltammetric analysis of drugs, Bioelectrochemistry, 64, 2004, 99–107.

[5] Martindale. Guaifenesin. In Martindale: The Complete Drug Reference. Edited by S. Sweetman, 2016, London, The Pharmaceutical Press.

[6] A.A. Bankar, S.R. Lokhande, R. Sawant, and A.R. Bhagat, Spectrophotometric estimation of guaifenesin and salbutamol in pure and tablet dosage form by using different methods, Der Pharma Chemica, 5, 2013, 92–97.

[7] N.C. Patel, D.B. Patel, P.K. Chaudhari, Spectrophotometric estimation of ambroxol hydrochloride, guaifenesin and levosalbutamol sulphatein syrup, AJRC, 6, 2013, 407–414.

[8] H. Patil, S. Sonawane, P. Gide, Determination of guaifenesin from spiked human plasma using RP-HPLC with UV detection, J Anal Chem, 69, 2014, 390–394.

[9] H.M. Maher, S.M. Al-Taweel, M.M. Alshehri, N.Z. Alzoman, Novel stereoselective high-performance liquid chromatographic method for simultaneous determination of guaifenesin and ketorolac enantiomers in human plasma, Chirality, 26, 2014, 629–639.

[10] O.A. Saleh, A.M. Yehia, A.A.-E.S. El-Azzouny, H.Y. Aboul-Enein, A validated chromatographic method for simultaneous determination of guaifenesin enantiomers and ambroxol HCl in pharmaceutical formulation, RSC Adv, 5, 2015, 93749–93756.
[11] I. Tapsobab, J.E. Belgaieda, K. Boujlel, Voltammetric assay of guaifenesin in pharmaceutical formulation, J Pharm Biomed Anal, 38, 2005, 162–165.
[12] M. Hadi, Electrochemical determination of guaifenesin in a pharmaceutical formulation and human urine based on an anodized nanocrystalline graphite-like pyrolytic carbon film electrode, Anal Methods, 7, 2015, 8778–8785.
[13] M.B. Gholivand, M. Khodadadian, Simultaneous voltammetric determination of theophylline and guaifenesin using a multiwalled carbon nanotube-ionic liquid modified glassy carbon electrode, Electroanalysis, 26, 2014, 1975–1983.
[14] M.B. Gholivand, A. Azadbakht, A. Pashabadi, An electrochemical sensor based on carbon nanotube bimetallic Au-Pt inorganic-organic nanofiber hybrid nanocomposite electrode applied for detection of guaifenesin, Electroanalysis, 23, 2011, 2771–2779.
[15] M.J. Arcos, M. Alonso, M.C. Ortiz, Genetic-algorithm-based potential selection in multivariant voltammetric determination of indomethacin and acemethacin by partial least squares, Electrochim Acta, 43, 1988, 479–485.
[16] J.H.T. Luong, K.B. Maleb, J.D. Glennon, Boron-doped diamond electrode: synthesis, characterization, functionalization and analytical applications, Analyst, 134, 2009, 1965–1979.
[17] S.J. Cobb, Z.J. Ayres, J.V. Macpherson, Boron doped diamond: A designer electrode material for the twenty-first century, Annu Rev Anal Chem, 11, 2018, 463–484.
[18] P. Talay Pınar, Electrochemical behaviour of ofloxacin in pharmaceutical and biological samples using a boron-doped diamond electrode in using anionic surfactant, GU J Sci, 31, 2018, 66–80.
[19] Ö. Selçuk, C. Erkmen, B. Bozal-Palabıyık, B. Uslu, Electroanalytical investigation and simultaneous determination of etodolac and thiocolchicoside at a non-modified glassy carbon electrode in anionic surfactant media, Electroanalysis, 33, 2021, 1290–1298.
[20] J. Wang, Electroanalytical Techniques in Clinical Chemistry and Laboratory Medicine,1988, New York: VCH Publishers.
[21] P.T. Kissinger, and W.R. Heineman, Laboratory Techniques in Electroanalytical Chemistry (2nd edition), 1984, New York, Markel Dekker.
[22] S. Shi-Gang, S. Hong-Mei, S. Han-Wen, Mechanism and kinetics of guaifenesin oxidation by bis(hydrogenperiodato)argentate(III) complex anion, Acta Phys -Chim Sin, 23, 2007, 409–413.
[23] Puttaswamy, A. Sukhdev, Oxidation of mephenesin and guaifenesin with chloramine-B in hydrochloric acid medium: Design of kinetic model, Ind J Chem, 48A, 2009, 339–345.
[24] E. Laviron, L. Roullier, C. Degrand. A multilayer model for the study of space distributed redox modified redox modified electrodes: Part II. Theory and application of linear potential sweep voltammetry for a simple reaction, J Electroanal Chem Interfacial Electrochem, 112, 1980, 11–23.
[25] D.K Gosser, Jr., Cyclic Voltammetry, Simulation and Analysis of Reaction Mechanisms, 1993, New York, VCH Publishers, pp. 43, 97–99.
[26] I.R. Berry, and D. Harpaz. Validation of Active Pharmaceutical Ingredients (2nd edition), 2001, Washington, CRC Press.
[27] F. Ağın, Voltammetric determination of guaifenesin in pharmaceuticals and urine samples based on poly(bromocresol purple) modified glassy carbon electrode, Curr Pharm Anal, 16, 2020, 633–639.
[28] H. Işık, G. Öztürk, F. Ağın, D. Kul, Electroanalytical analysis of guaifenesin on poly(acridine orange) modified glassy carbon electrode and its determination in pharmaceuticals and serum samples, Comb Chem High T Scr, 24, 2021, 376–385.