Egypt. J. Chem. Vol. 67, SI: M. R. Mahran, pp. **2207 - 2214** (2024)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Carbonaceous nanostructures platform for sensitive voltametric determination of Eletriptan hydrobromide

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Abstract

The present study introduces a novel eletriptan hydrobromide (ELE) sensor based on carbonaceous nanostructures for sensitive voltametric determination of ELE in various pharmaceutical and biological samples. Comprehensive and deep optimization studies were carried out concerning the electrode matrix composition, modification mode, the effect of pH, and other electroanalytical parameters. Surface functionalization of the electrode surface with multiwall carbon nanotubes (MWCNTs) exhibited the highest electrochemical performance with a sharp oxidation peak at about 0.75 V in BR buffer pH 3. Based on the theoretical molecular orbital calculation studies on the ELE molecule and electroanalytical findings, the electrooxidation of ELE undergoes through oxidation of the amine nitrogen atom (N 2) with the transfer of one electron/proton in the electrode reaction. High sensitivity with linear calibration curve were reported within the ELE concentration range from 0.027 to 1.1 µg mL^{-1} with limit of detection 0.008 µg mL^{-1}. The recorded sensitivity of the proposed sensors encouraged their applications for monitoring of ELE residues in pharmaceutical formulation and biological samples.

Keywords: *Eletriptan hydrobromide; Carbonaceous nanostructures; Voltammetric sensor; Pharmaceutical and biological samples*.

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1. Introduction

Eletriptan hydrobromide (ELE, (R)-3-[(1-methyl-2-pyrrolidinyl)methyl]- 5-[2-(phenylsulfonyl)ethyl]-1H-indole mono hydrobromide) is a new member of triptans that are commonly administrated for the treatment of migraine with or without aura [1]. ELE reduces the swelling of the blood vessels surrounding the brain, which may cause pain in the head and be a major reason for headaches. ELE is considered as a selective 5-hydroxytryptamine (5-HT1) receptor agonist [2]. The serotonin receptor agonist that binds to vascular receptors selectively. The effectiveness of 5-HT receptor agonists in treating migraines has been explained by two different theories. One theory proposes that vasoconstriction, which is associated with the alleviation of migraine headaches, is caused by activation of 5-HT1 receptors found on intracranial blood arteries, particularly those on the arteriovenous anastomoses. According to the alternative theory, proinflammatory neuropeptide production is inhibited when 5-HT1 receptors on sensory nerve terminals in the trigeminal system are activated. CYP3A4 and CYP2D6 are the primary enzymes that metabolize eletriptan. Thus, the only known active metabolite of this compound is produced: N-desmethyl-eletriptan [3, 4].

Few analytical approaches were reported for monitoring ELE residues in pharmaceutical and biological samples [5, 6]. Commonly, chromatographic were applied including HPLC [7, 8], RP HPLC [9], LC–MS [10], beside some fluorometric and spectrophotometric measurements [11-14]. Generally, spectrophotometric or fluorometric methods are suitable for higher ELE concentrations such authentic or pharmaceutical samples, while they prone to low selectivity and sensitivity in biological samples. Chromatographic techniques effectively separate and quantify the pharmaceutical compounds, but they are operationally expensive, includes several tedious sample pretreatment steps, with the requirements of high skilled operators. Moreover, several derivatization steps were carried out, with the application of hazard organic solvents. These limitations obstacles to post-marketing pharmaceutical surveillance, and large-scale analysis especially of biological samples. Hence, rapid, low cost, and precise analytical tools are welcomed.

Electrochemical methods offer a unique blend of sensitivity and simplicity of measurement by leveraging various electrode modifications and miniaturization to achieve accurate results. Electroanalytical techniques have been introduced for the analysis of various biologically and pharmaceutically active compounds [15, 16]. Electrochemical sensors became more applicable for pharmaceutical analysis referring to their simplicity and improved sensitivity compared to the traditional spectroscopic and separation techniques. Voltammetric sensors offer several advantages due to the rapid measurement, low-cost instrumentation requirements, and sensitivity reaches sub-nanomolar levels [17, 18]. In this regard, glassy carbon electrodes integrated with graphene oxide/ platinum-iridium nanohybrid, or were reported for voltammetric determination of ELE in pharmaceuticals within the linear concentration ranged from of 1×10^{-7} to

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Receive Date: 07 August 2024, Revise Date: 03 September 2024, Accept Date: 10 September 2024

DOI: 10.21608/ejchem.2024.310435.10153

4×10^{-6} mol L^{-1} with a detection limit of 6.1×10^{-9} mol L^{-1} [19].

Recently, there has been significant attention focused on modification of the working electrodes matrices with nanostructures to improve their performance by leveraging the electrocatalytic activity of nanoparticles, facilitating the immobilization of enzymes or molecules, and accelerating of the electron transfer process at the electrode surface [20-22]. Carbonaceous nanomaterial integrated sensors participate as the major category of the tailor-made electrochemical sensors, while the carbon paste electrodes (CPEs) specially offer the advantages of the wide operating potential window, simple modification protocol, and low Ohmic resistance [23-26].

In the present work, homemade carbon paste electrodes enriched with multiwall carbon nanotubes (MWCNTs) were developed for the voltammetric quantification of eletriptan hydrobromide. The sensor performance was evaluated for recovery, linearity, limit of detection, quantification, suitability in biological fluid samples, and selectivity against expected interference. The introduced ELE sensors showed potential applications in pharmaceutical quality control and monitoring of ELE residues in biological samples. As a sensitive disposable sensor, it can facilitate rapid drug screening and on-site detection, enabling early medical intervention for drug abuse cases.

2. Experimental

2.1. Chemicals and eletriptan authentic sample

All chemicals and reagents were of analytical grade and ultrapure water was used throughout the experiments. The bare working carbon paste electrode was fabricated using paraffin oil (PO; Merk, Germany) and graphite powder (GR, 1-2 µm, Aldrich). Different carbonaceous nanostructures were applied as electrode modifier including single-walled carbon nanotubes (SWCNTs, Aldrich), multiwall carbon nanotubes (MWCNTs, Aldrich), or and graphene nanosheets (GNS, Sigma). Britton-Robinson buffer solution (4×10^{-2} mol L^{-1}) was used, and the desired pH value was adjusted using NaOH solution. The eletriptan hydrobromide authentic sample ($C_{22}H_{27}BrN_2O_2S$, M.wt. 463.4 g mol^{-1}, purity 99.25±1.15%) was kindly supplied by the Standard Laboratory, Egyptian Drug Authority (EDA). The stock drug solution was freshly produced by dissolving 30.0 mg of the certified ELE in 25.0 mL hot water and kept at 4°C for two weeks. The standard biological samples were obtained by VACSERA, Giza, Egypt.

2.2. Measuring system and construction of the working electrode

Metrohm electroanalyzers (797VA Computrace version 1.3.1 Metrohm, Switzerland) was used for all the voltammetric measurements. Three electrode electroanalytical cell accompanied with the fabricated carbon paste electrode, Ag/AgCl (3 M KCl) reference electrode, and platinum wire as the auxiliary electrode was used.

The working carbon paste working electrode was fabricated by careful blending of graphite powder (0.5 g) with 0.2 g PO in ceramic mortar for 15 min. The produced carbon paste matrix was packed into the Teflon piston shaped holders as described in details elsewhere [24]. The bulk modified electrodes were constructed in the same manner through replacing 50 mg of the graphite powder by the same amount of the carbonaceous nanomaterial in the paste matrix. The electrode surface was regenerated by polishing with a wet filter paper to obtaining a shiny mirror electrode surface.

Alternately, the electrode surface was integrated by drop casting of three successive 10 µL of the carbonaceous nanomaterial suspension in DMF (2 mg mL^{-1}) on the inverted CPEs and lift to dry for 24 h at 25°C [27]. The working electrodes were rinsed with deionized water and exposed to five cyclic voltammetric runs in the BR buffer before use.

2.3. Recommended analysis protocol

The Britton-Robinson buffer solution at pH 3 was enriched with suitable ascending aliquots of ELE standard solution. Differential pulse voltammograms were recorded at the following electroanalytical conditions: pulse amplitude of 50 mV; pulse width of 100 ms; pulse duration of 40 ms; scan rate of 60 mVs^{-1}; voltage step 6 mV; and voltage step time 0.15 s.

2.4. Analysis of ELE in pharmaceutical and biological samples

The commercial eletriptan hydrobromide samples (Replax, 40 mg/tablet, Pfizer, Egypt) were purchased from local stores. The stock ELE pharmaceutical solution was prepared by dissolving the crushed tablet in water followed by ultrasonication in an ultrasonic bath for 15 min at 50°C. Further dilution to a suitable ELE concentration was carried out and the ELE content was assayed at the optimized voltammetric conditions compared with the spectrophotometric method [12].

The standard plasma samples were spiked with known increments of the ELE authentic solution, vortexed well and mixed with acetonitrile (1:3 ratio). The enriched biological samples were centrifuged to remove the sample protein and the ELE content in the fortified biological samples was assayed using the MWCNTs/CPE following the recommended procedures.

3. Results and discussion

3.1. Voltammetric behavior of eletriptan hydrobromide at carbonaceous nanomaterial-based sensors

At the blank carbon paste electrode, ELE showed a single anodic oxidation peak at 0.946 V with a limited peak current value of 0.65 µA (**Fig. 1**).

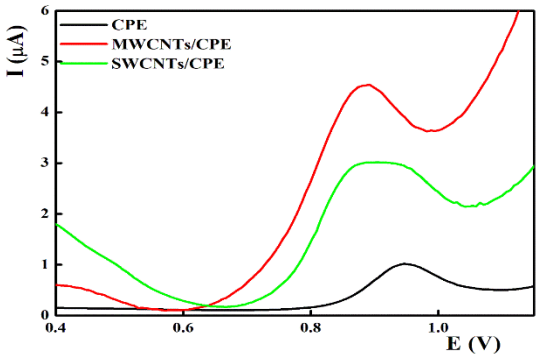
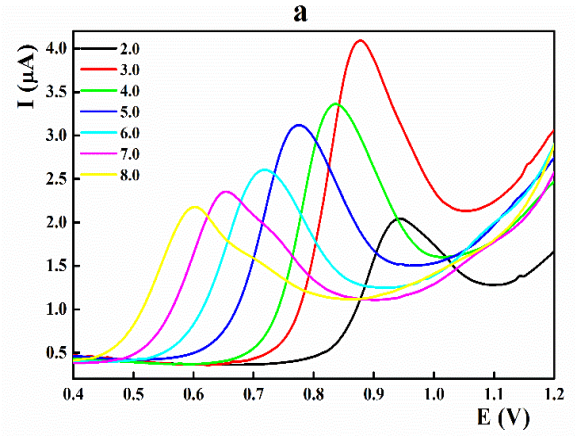


Fig. 1: Differential pulse voltammograms recorded for carbon paste sensors integrated with carbon nanotubes. Measuring conditions; ELE content 0.5 µg mL^{-1}, applied pH 3.0, and scan rate 0.04 Vs^{-1}.

Upon integration of the working carbon paste electrode with carbon nanotube, the oxidation peak current was amplified (about 4 folds for the MWCNTs) with noticeable shifting of the peak potential by about 70 mV to the negative direction compared with the unmodified electrode indicating the electrocatalytic activity of the electrode modifier. Regarding SWCNTs, a broad oxidation peak potential appeared at 0.869 V with peak current value 3 folds compared with the bare electrode. The improved peak performance can be attributed to the acceleration of the electron transfer kinetics at the electrode surface and the electroactive surface area upon modification with the carbon nanostructures. In unreported data, modification with graphene nanosheets (GNS) resulted in high background peak with very limited sensitivity towards the ELE which may be attributed to the residual function groups on the GNS surface. It is noteworthy to mention that the surface modification protocol was more effective compared with the bulk modified electrode. Moreover, other metal oxide nanostructures including CuO, ZnO, and FeO were also tested as electrode modifier and showed limited performance compared to those integrated with MWCNTs.

3.2. Effect of pH

Eletriptan hydrobromide molecule possess a pKa value of 8.37, therefore, the electrooxidation of ELE is expected to be pH-controlled behavior. Figure 2a illustrates the differential pulse voltammograms recorded for ELE at different pH values ranged from 2 to 8. The oxidation potential values were shifted towards the negative direction at higher pH values based on the involvement of protons in the electrode reaction [28-30]. Meanwhile, sharp and distinct differential pulse peaks were recorded at lower pH values (2 to 6), while at higher pH values, the oxidation peak became broad with lower current values. The peak potential values showed a linear relationship against the pH of the supporting electrolyte with Nernstian slope value, [$E_{(V)}$ = 1.0413 – 0.0543±0.0015, [pH], r^2 =-0.9980, **Fig. 2b**] postulating the involvement of an equal number of electrons/protons in the rate-determining steps. The recorded slope value agreed with previously reported GO/Pt-Ir/MWCNT-COOH based electrode [19]. Among different tested pH values, pH 3 was selected as the proper with the highest peak current (**Fig. b**) which disagrees with that reported at GO/Pt-Ir/MWCNT-COOH based electrode [19] which recommended measurement at pH 7.



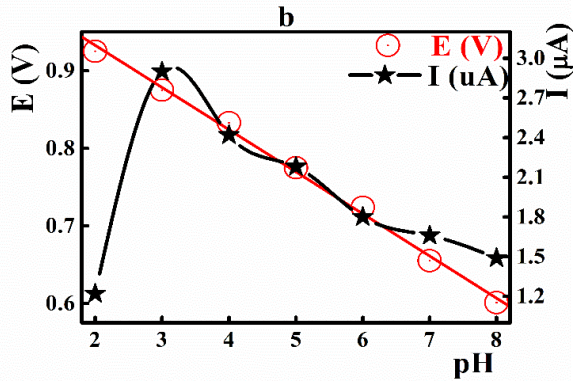


Fig. 2: a) Differential pulse voltammograms recorded for 0.5 µg mL^{-1} ELE at different pH values; and b) the recorded peak potential and current values versus the pH value. Measuring conditions scan rate 0.06 Vs^{-1}.

3.3. Electrochemical behavior of eletriptan at different scan rate value

Performing the cyclic voltammograms at various scan rate values explores the electrochemical behavior of the target analyte at the electrode surface and estimates the number of electrons transferred in the electrooxidation process [28-30]. Within the studied scan rate values ranged from 0.01 to 0.06 V, ELE exhibited a single anodic peak with the absence of reduction peak in the cathodic direction indication the irreversibility of the oxidation process (**Fig. 3a)**. The recorded peak current values were enhanced at higher scan rate values following a linear relationship versus the square root of the scan rate (r=0.9978, **Fig. 3b**) indicating the irreversibility of the electrode reaction.

Moreover, plotting of the logarithmic value of the peak current against the logarithmic value of the scan rate revealed a linear relationship [log $I_{(\mu A)}$=0.7184 + 0.652765±0.0249 *[log (v)], r=0.9978;* **Fig. 3c**] with a slope value (0.5527) suggested a diffusion-controlled mechanism for ELE molecule at the MWCNTs/CPEs [29, 30]. The oxidation potentials of ELE peaks were shifted to the anodic direction at higher scan rate values following a linear dependence [$E_{(V)}$ *=1.2710 + 0.1165±0.0004 log (v), r=0.9975*, **Figure 3d**]. Based on the Laviron equation for irreversible electrode reactions, the number of electrons was estimated to be one electron based on the following equation [31]:

$$Ep = E^{o} + \left(\frac{2.303RT}{\propto nF}\right) log\left(\frac{RTK^{o}}{\propto nF}\right) + \frac{2.303RT}{\propto nF} logv$$

where R: ideal gas constant, T: temperature, α represents the electron transfer coefficient, *n:* total number of electrons transferred, and F: is the Faraday constant.

The study integrated experimental voltammetric data with molecular orbital calculations (MOC) to explain the oxidation mechanism of ELE at the modified electrode surface at pH 3 [32].

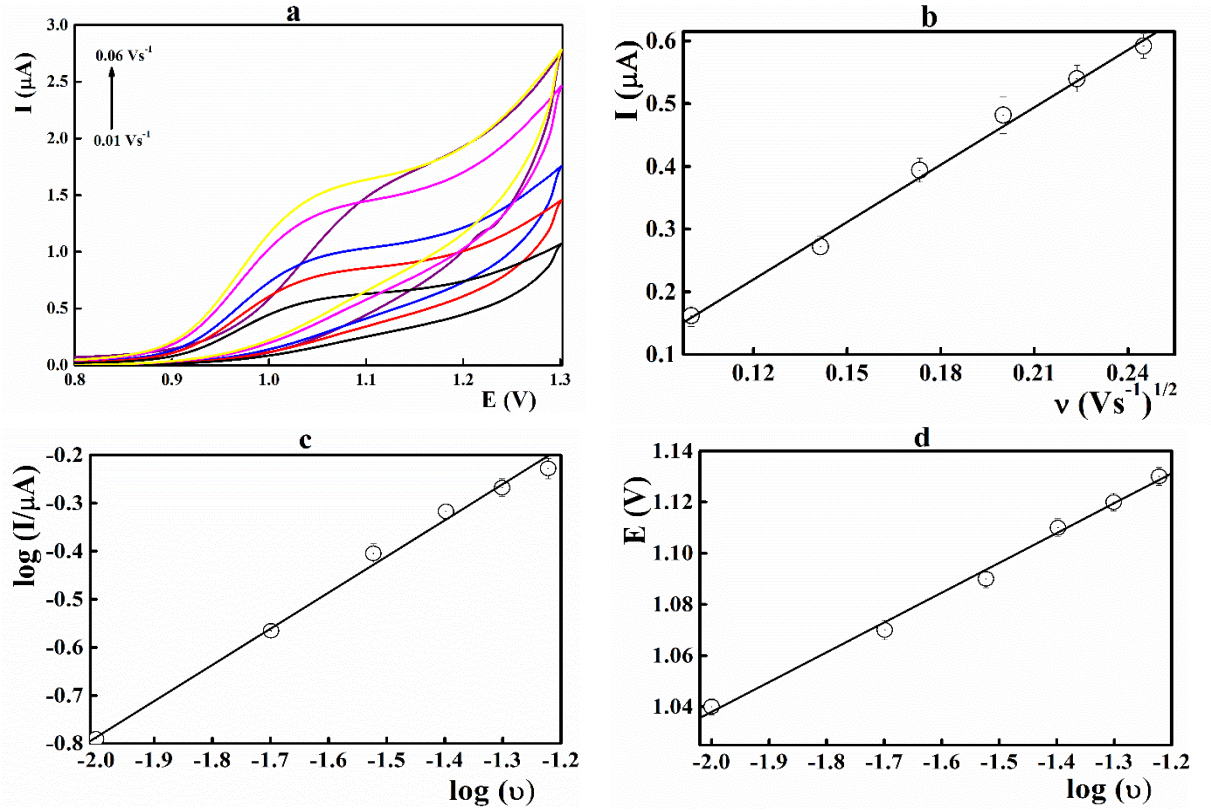
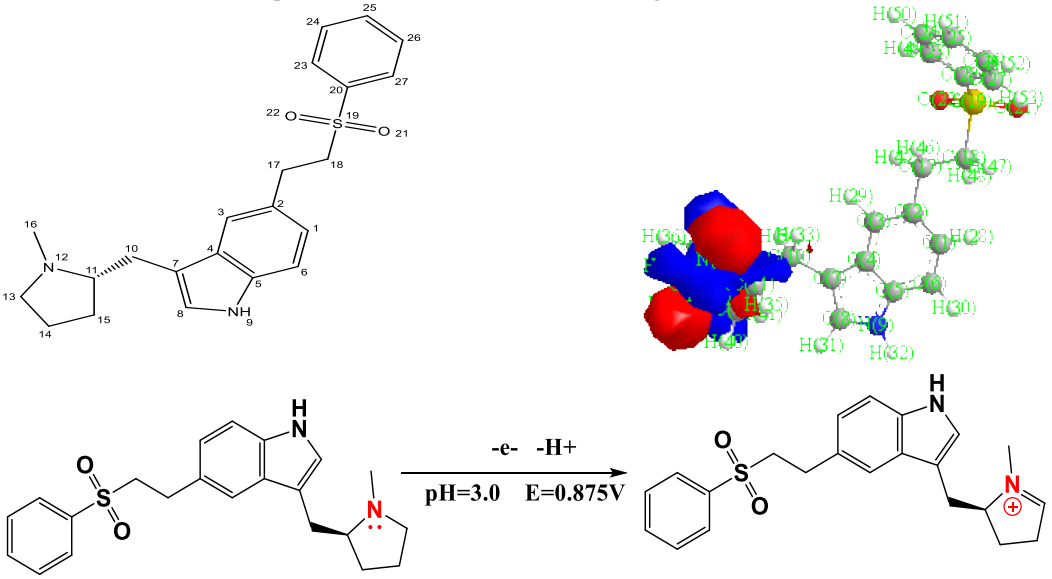


Fig. 3: a) The recorded cyclic voltammograms recorded for 2.0 µg mL^{-1} at pH 3 at different scan rate values; b) the peak current values against the square root of the scan rate; c) the logarithmic value of the peak current against the logarithmic value of the scan rate, and d) the peak potential versus the logarithmic value of the scan rate.

This comprehensive approach, combining experimental data with theoretical calculations, provides a deeper understanding of the electrochemical behavior of ELE and underscores the value of such integrated methods in elucidating reaction mechanisms in electroanalytical chemistry. It was observed that the oxidation process involves a single electron and proton transfer, contrasting with previous studies. MOC results, presented in Scheme 1 and Table 1, revealed that the highest electron density was located at the amine nitrogen (N12) in the five-membered ring, which is more basic than the pyrrole nitrogen at position 9. This amine group also possesses delocalized lone-pair electrons. These findings led to a proposed oxidation mechanism that differs from earlier reports using a GO/Pt-Ir/MWCNT-COOH electrode [19], which suggested a two-electron, two-proton transfer involving the indole ring.



Scheme 1: Tentative oxidation mechanism of eletriptan hydrobromide at MWCNTs/CPE

Table 1: Molecular orbital calculation studies of ELE molecule

Atom	Atom Type (MM2)	Charge (MM2)	Mulliken Charges (Mopac Interface)	Atom Type (MMFF94)	Charge (MMFF94)	Charge (Huckel
C(1)	C Alkene	0	-0.1834	AROMATIC CARBON, E. G. IN BENZENE, PYRIDIN	-0.15	-0.12472
C(2)	C Alkene	0	-0.03437	AROMATIC CARBON, E. G. IN BENZENE, PYRIDIN	-0.1435	-0.01102
C(3)	C Alkene	0	-0.19403	AROMATIC CARBON, E. G. IN BENZENE, PYRIDIN	-0.15	-0.12087
C(4)	C Alkene	0	-0.08231	AROMATIC 5-RING C, b TO N, O, OR S	0	-0.0572
C(5)	C Alkene	0	0.136775	AROMATIC 5-RING C, a TO N, O, OR S	0.084	0.064711
C(6)	C Alkene	0	-0.27261	AROMATIC CARBON, E. G. IN BENZENE, PYRIDIN	-0.15	-0.09929
C(7)	C Alkene	0	-0.08755	AROMATIC 5-RING C, b TO N, O, OR S	-0.181	-0.2109
C(8)	C Alkene	0	-0.06273	AROMATIC 5-RING C, a TO N, O, OR S	-0.066	-0.02252
N(9)	N Pyrrole	0	-0.56782	ENAMINE OR ANILINE NITROGEN, DELOC. LP	-0.168	0.442927
C(10)	C Alkane	0	-0.3689	ALKYL CARBON, SP3	0.181	-0.10142
C(11)	C Alkane	0	0.050123	ALKYL CARBON, SP3	0.27	0.102602
N(12)	N Amine	0	-0.5139	AMINE NITROGEN	-0.81	-0.14437
C(13)	C Alkane	0	-0.16712	ALKYL CARBON, SP3	0.27	0.039779
C(14)	C Alkane	0	-0.38993	ALKYL CARBON, SP3	0	-0.08817
C(15)	C Alkane	0	-0.40492	ALKYL CARBON, SP3	0	-0.09322
C(16)	C Alkane	0	-0.37681	ALKYL CARBON, SP3	0.27	-0.03688
C(17)	C Alkane	0	-0.34126	ALKYL CARBON, SP3	0.1435	-0.07066
C(18)	C Alkane	0	-0.70704	ALKYL CARBON, SP3	0.1052	-0.22029
S(19)	S Sulfone	0	2.30645	SULFONE SULFUR	1.2038	2.46195
C(20)	C Alkene	0	-0.43948	AROMATIC CARBON, E. G. IN BENZENE, PYRIDIN	-0.009	-0.04668
O(21)	O Oxo	0	-0.93452	ONE OF 2 TERMINAL O'S ON SULFUR	-0.65	-1.11572
O(22)	O Oxo	0	-0.93471	ONE OF 2 TERMINAL O'S ON SULFUR	-0.65	-1.11642
C(23)	C Alkene	0	-0.12042	AROMATIC CARBON, E. G. IN BENZENE, PYRIDIN	-0.15	-0.0273
C(24)	C Alkene	0	-0.23358	AROMATIC CARBON, E. G. IN BENZENE, PYRIDIN	-0.15	-0.02386
C(25)	C Alkene	0	-0.15917	AROMATIC CARBON, E. G. IN BENZENE, PYRIDIN	-0.15	-0.03019
C(26)	C Alkene	0	-0.2305	AROMATIC CARBON, E. G. IN BENZENE, PYRIDIN	-0.15	-0.0237
C(27)	C Alkene	0	-0.12198	AROMATIC CARBON, E. G. IN BENZENE, PYRIDIN	-0.15	-0.02666

3.4. Method validation

At the optimum electroanalytical conditions, the electroanalytical futures of the MWCNTs/CPEs were validated under against ELE [33]. The supporting electrolyte with the selected pH value 3 was spiked with known increments of the authentic ELE solution covering the concentration ranged from 0.027 to 1.1 µg mL^{-1}, and the corresponding DPVs were recorded after each addition (**Fig. 4 and Table 2**).

Based on the linearity parameters such as the standard deviation of intercept (SD) and the slope of the linear line (S), the limit of detection (LOD) and limit of quantification (LOQ) values were estimated according to the following equations: LOD value (3.3 SD/S) and LOQ value (10 SD/S) to equal 0.008 and 0.027 µg mL^{-1}, respectively.

To explore the operational life time of the fabricated sensors, the sensor performance was monitored within the storage period of 8 weeks at 4°C. Reproducible and stable voltammetric peaks (98.24±2.6% of the original peak current for the freshly fabricated sensors) were obtained within the first three weeks. The sensors performance decreased to 95.29±3.2% after the sixth week and to about 88.02±4.5% after 8 weeks of storage. The performance of the proposed MWCNTs/CPEs was compared with the previously reported ELE sensor based on GO/Pt-Ir/MWCNT-COOH [17]. Based on the recorded LOQ and LOD values, the proposed voltammetric sensors showed improved sensitivity within the tested ELE concentration range. The simplicity of the electrode fabrication protocol and the prolonged lifetime offers the advantage of the presented sensors (Table 3).

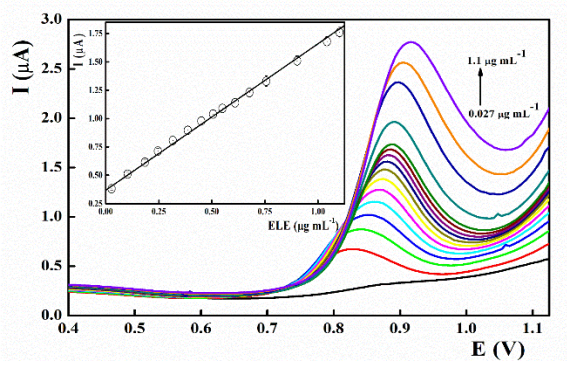


Figure 4: Differential pulse voltammograms of eletriptan hydrobromide at MWCNTs/CPE recorded at pH 3 and scan rate 0.06 Vs^{-1}.

Table 2: Validation and electroanalytical futures of eletriptan hydrobromide at MWCNTs/CPEs

Parameter	Value *
Oxidation potential	0.875 V
Measuring pH value	3
Concentration range (µg mL^{-1})	0.027-1.1
Intercept (µA cm^{-2})	0.3845
$SD_{intercept}$ (µA cm^{-2})	0.0115
Slope (µA mL^{-1} $µg^{-1}$)	1.2731
SD_{slope} (µA mL^{-1} $µg^{-1}$)	0.0188
R square	0.9972
RSD %	2.1972
LOQ (µg mL^{-1})	0.027
LOD (µg mL^{-1})	0.008
Reproducibility of the peak current a (RSD %)	0.738
Reproducibility of the peak potential a (RSD %)	0.77

*Average of five experiments

Table 3. Comparison of different eletriptan hydrobromide

Parameters	**Ref. 19**	**Present study**
Electrode	GCE	CPE
Modifier	GO/Pt-Ir/MWCNT-COOH	MWCNTs
Optimal pH value	7.0	3.0
Voltammetric technique	DPV	DPV
Peak potential (V)	0.600	0.875
Linearity	1×10^{-7} to 4×10^{-6} mol L^{-1}	0.027-1.1 (µg mL^{-1})
LOD	6.1×10^{-9} mol L^{-1}	0.008 (µg mL^{-1})
LOQ		0.027 (µg mL^{-1})
Lifetime	------	8 weeks
No of electrons/protons	Two electrons/protons	One electron/proton

3.5. Specificity of the method

Impurities present in the pharmaceutical formulations and degradation profiling described the studying and quantifying of possible manufacturing impurities and degradation products in the final pharmaceutical formulations. Monitoring of contaminants and degradation products represents a crucial consideration for the modern pharmaceutical industry. To ensure the safety of the final pharmaceutical product, the applied analytical approaches must be applied to determine the parent active pharmaceutical compounds, degradants, and impurities [34].

Moreover, the impact of different excipients and additives that are may present in the final pharmaceutical formulation such as microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, titanium dioxide (E171), hypromellose, lactose monohydrate, glycerol triacetate and Sunset Yellow FCF Aluminium Lake (E110) was tested by recording the DPVs for 500 ng mL^{-1} ELE presence of these interferents. High tolerance values were recorded even in the presence of a 100-fold of the interferents.

3.6. Analysis of ELE sample

The introduced carbon paste sensors fortified with MWCNTs exhibited high sensitivity towards eletriptan hydrobromide, therefore they were tested for monitoring of ELE in pharmaceutical and biological fluids. The recorded data **(Table 4)** showed high recovery values with low standard deviation which encouraged the application of the MWCNTs/CPEs for quality control of eletriptan hydrobromide.

Table 4: Assay of eletriptan hydrobromide in pharmaceutical formulations and biological samples

Sample	Taken ($\mu g\ mL^{-1}$)	Found ($\mu g\ mL^{-1}$)	Residuals (%)	Recovery (%)	UV [45]
Migrablok	0.2	0.20	0.50	100.50	98.82
	0.5	0.50	0.80	100.80	100.81
	0.7	0.69	1.14	98.86	100.22
	0.9	0.91	1.11	101.11	99.50
Mean				100.32	99.84
Variance				0.76	0.75
Observations				5	4
df				4	3
t-test	1.01				
F	0.72				
t Critical two-tail	9.12				
F Critical one-tail	2.45				
Sample	Added ($\mu g\ mL^{-1}$)	Found ($\mu g\ mL^{-1}$)	Residuals (%)	Recovery (%)	UV [45]
Plasma	0.15	0.15	-0.67	100.67	100.30
	0.45	0.45	-0.44	100.44	99.61
	0.7	0.71	-1.14	101.14	99.94
	0.85	0.847	0.35	99.65	100.70
Mean				100.48	100.14
Variance				0.39	0.22
Observations					4
df				3	3
t- test	0.56				
F	-0.87				
t Critical two-tail	9.12				
F Critical one-tail	2.45				

4. Conclusion

Fabrication and characterization of a novel carbon paste sensor drop casted with different carbonaceous nanomaterials was characterized in detail for selective and sensitive voltammetric determination of eletriptan hydrobromide in its biological and pharmaceutical samples. Enrichment of the electrode surface with MWCNTs improved the sensor performance based on the electrocatalytic activity towards the oxidation of ELE molecule at the electrode surface with a diffusion-controlled mechanism. Calibration curves were linear within the ELE concentration ranged from 0.027 to 1.1 µg mL^{-1} with LOD value of 0.008 µg mL^{-1}. The constructed sensors showed high measurement reproducibility with a long shelf lifetime of up to 8 weeks. The MWCNTs/CPEs voltammetric sensor can be considered as a reliable analytical approach for the sensitive quantification of eletriptan hydrobromide in the real biological and pharmaceutical formulations.

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