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Voltammetric determination terbinafine at carbon paste electrode modified with graphene nanosheets

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Abstract.

Terbinafine (TER) is a well-known potent antifungal administrated for the oral and topical treatment of mycosessince. The present study introduced a novel graphene (Gr) nanosheet integrated carbon paste electrodes (CPEs) for sensitive voltammetric determination of TER in pharmaceutical formulations and surface water samples. On the surface of the Gr/CPEs, terbinafine recorded an irreversible anodic oxidation peak at 1.11 V following a pure adsorption-controlled reaction mechanism accompanied by the transfer of one-electron/proton as predicted by the molecular orbital calculations, scan rate, and pH studies. Integration of the carbon paste matrix with 7.0% graphene nanostructure improved the sensor performance by about 10 folds through the enhancement of the electroactive surface area and the electrocatalytic effect of graphene towards the electrooxidation of the TER molecule at the electrode surface. Details studies were carried out including the impact of the nature and content of the electrode modifier, pH, and the applied scan rate. The cited sensor showed improved sensitivity within the TER concentration range from 0.17 to 10.8 µg mL−1 with a limit of detection of 0.05µgmL-1. A prolonged operational lifetime with high measurement and fabrication reproducibility was reported. The specificity of the fabricated Gr/CPEs was evaluated in the presence of the TER degradation products and other excipients commonly present in pharmaceutical formulations. The reported improved sensor performance encourages the application of the presented voltammetric sensor for the quantification of TER in pharmaceutical formulations, biological fluids, and residues in surface water samples.

Keywords: Graphene nanosheets; Terbinafine; Voltammetric assay; Degradation product; Pharmaceutical analysis; Environmental residues.

Introduction

Terbinafine (TER, E–N–(6,6–dimethyl–2–hepten–4–ynyl)–N–methyl–1–naphthalene-methanaminem) is an allylamine antifungal compound that belongs to the naphthalenes family. Similar to other allylamines, TER inhibits the formation of ergosterol via squalene epoxidase, an enzyme that participates in building fungal cell walls [1]. In layman's terms, TER prevents the development of fungal cell walls, leaving the cell's contents exposed and eventually destined to die. Therefore, it is administrated for the treatment of superficial fungal infections such as seborrheic dermatitis, tinea capitis, and onychomycosis as well as the occurrence of dermatophytoses, pityriasis Versicolor, and cutaneous candidiasis [2]. Based on its lipophilic nature, TER showed the tendency for accumulation in the skin, nails, and fatty tissues causing a number of adverse effects, including an allergic response (which can result in difficulty

breathing, a tightening of the throat, tongue, or cheeks), in addition to a rash, changes in eyesight, and blood issues [3].

Based on the therapeutical importance of terbinafine, its quantification in pharmaceuticals, biological fluids, and environmental samples is of considerable significance. The reported analytical approaches for determination of terbinafine in biological fluids and pharmaceuticals formulations were recently reviewed [4]. These mainly include chromatographic ones [5-7], spectrophotometric approaches [8–11], and capillary zone electrophoresis [12]. Although these techniques demonstrated good selectivity and sensitivity for terbinafine quantification; they necessitate a number of time-consuming manipulation stages, sophisticated equipment, and certain experience. For pharmaceutical analysis, electrochemical analysis detection is considered as a pretty interesting technique that ranked third behind

photometry and spectrophotometry. There is a growing concern for the development of advanced electrochemical sensors for clinical assays, environmental monitoring, and quality control. Electroanalytical approaches with tailor-made sensors fulfill many of these requirements with the advantages of high specificity and sensitivity, rapid response, and simplicity of measuring equipment [13-16].

Adsorption of terbinafine on the hanging drop mercury electrode (HMDE) at pH 6 accompanied with the reduction of the olefinic double bond at -1.47V represents the sole polarographic approach for sensitive assay of TER [17]. However, due to the extreme toxicity of mercury metal and risks of handling in many countries, other electrode materials were developed. Glassy carbon electrodes (GCE) drop casted by cysteic acid/carbon nanotubes composite film were reported for quantification of terbinafine in human serum and pharmokinetic studies [18]. More recently, the voltammetric behavior of TER on boron-doped diamond was investigated for sensitive differential and square wave voltammetric determination of terbinafine [19]. Carbonaceous-based sensor with different carbon allotropes represents a major category of the working electrochemical sensors [17]. Among, carbon paste electrodes (CPEs) showed the advantages of the simple modification, and regeneration protocol with low Ohmic resistance and wide operating potential window [20, 21]. Carbonaceous nanostructures with their promising futures and noticeable electrocatalytic activities towards the oxidation of many biologically and pharmaceutically active compounds were reported as effective modifiers for the construction of sensitive electrochemical sensors [22 - 29].

In the present work, carbon pastes integrated with graphene nanosheets were constructed for sensitive voltammetric determination of terbinafine in pharmaceutical formulations and surface water samples. The impact of the electroanalytical and measuring parameters on the sensor performance was discussed in detail and the oxidation mechanism of terbinafine molecule at the electrode surface was assumed through applying of the molecular orbital calculations and scan rate studies.

2.Experimental
2.1. Reagents
Ultrapure water was used for preparation of the stock TER solution and supporting electrolytes. The carbon paste matrix was prepared using graphite powder (Sigma) and paraffin oil (PO; Merk) as pasting liquids. Graphene nanosheets (Gr, Sigma) and multiwall carbon nanotubes (MWCNTs, Aldrich) were tested as electrode modifiers. As usual, the universal Britton–Robinson (BR) buffer was used and the appropriate pH value was adjusted using NaOH solution.

2.2. Standard terbinafine and samples
Terbinafine HCl authentic sample ($C_{21}H_{26}ClN$; 327.9 g mol^{-1}) was suuplied by the Egyptian Drug Authority with certified purity of 99.99% [30]. A suitable amount of the standard TER sample was dissolved in water to prepare the stock drug solution and kept at 4°C. The pharmaceutical preparation Terbin ® (250 mg/tablet, Global Napi Pharmaceuticals, Cairo, Egypt) was purchased from a local pharmacy. Ten tablets were weighed; ground to fine powder and an amount equivalent to one tablet was dissolved in water, filtered off, and diluted to the appropriate TER concentration. Urine samples from healthy volunteers were spiked with standard TER solutions, mixed with methanol to remove the residual protein, centrifuged, and the content of TER was assayed voltammetrically in comparison with pharmacopoeial protocol. Aliquots of the surface water sample (Nile River, Dokki, Giza Governorate) were sterilized and treated with citrate buffer at pH 5.0 and fortified with TER stock solution to the proper concentration range.

2.3. Oxidative degradation of terbinafine
The degradation of TER was performed under acidic/oxidation conditions similar to its analog butenafine [31]. The stock TER solution (1 mL of 100 μg mL^{-1}) was mixed with HCl solution and the volume was completed to 10 mL with water. In order to track the degradation progress, samples were withdrawn while the absorbance was monitored at 222 and 283 nm. For oxidative degradation, 1 ml of 6% H_2O_2 was added after this partial degradation and left for 60 minutes.

2.4. Working electrode and measuring apparatus
Voltammetric studies were performed using Metrohm Electroanalyzer (model 797 VA, Switzerland) accompanied with a three electrodes measuring, including a working carbon paste electrode, double junctions silver/silver chloride reference electrode, and a platinum wire electrode. The working carbon paste sensor was constructed by careful blending of 0.5 g graphite powder with 200 μL of the paraffin oil till formation of a homogeneous paste. The resulting paste was packed in Teflon piston holder [20]. Integration of the paste was carried out by replacing 14 mg of the graphite powder with graphene nanosheets and the paste was fabricated in the same manner.

2.5. Analysis protocol
Selected increments of the stock TER solution were added to the BR buffer at pH 5 and the corresponding voltammograms were monitored at the following selected electroanalytical conditions; deposition time 90 s, deposition potential 150 mV, pulse amplitude 50 mV, interval time 40 ms; pulse width 100 ms; and scan

rate 50 mVs[-1]. Calibration curves were constructed through plotting the peak heights versus the corresponding TER concentration.

3.Results and discussion
3.1. Oxidation of terbinafine at graphene-based sensors

Tailor-made electrochemical sensors offer acceptable improved sensitivity and selectivity against the target analyte utilizing simple measuring equipment with a short analysis time. Nanostructured carbonaceous materials are of choice as electrode modifiers based on their capability to catalyze the electrooxidation of many pharmaceutically and biologically active molecules. Among different carbonaceous nanomaterials, graphene nanosheet was introduced as an efficient electrode modifier for voltammetric assaying of pharmaceutical compounds [32-39]. Therefore, working carbon paste electrodes integrated with graphene nanostructure were characterized and utilized for differential pulse voltammetric determination of TER in various matrices.

Since there is no previous study describing the electrochemical oxidation of terbinafine molecules at the carbon paste electrodes, the present study explored the electrochemical behavior of TER at the bare CPEs and those incorporated with different ratios of graphene or MWCNTs. As described in figure 1, TER exhibited only a single anodic oxidation peak at 1.08 V indicating the irreversibility of the TER oxidation at the electrode surface. Aiming at improving the sensor performance and promotion of the electron transfer process at the electrode surface, the carbon paste matrix was integrated with different ratios of Gr or MWCNTs (7.0%). Replacement of the synthetic graphite with 1.0% of graphene nanosheets resulted in 3 folds amplification of the oxidation peak current. This improvement reached its maximum value (about ten folds) with 7.0% graphene (Fig. 1a).

On the other hand, modification of the electrode matrix with a corresponding 7.0% MWCNTs resulted only in two-fold amplification of the peak current. The enhancement of the electrode performance can be explained on the basis of the electrocatalytic activity of Gr and the improvement of the electroactive surface area which promotes the rate of electron transfer.

The electroactive surface area (EASA) were estimated through recording the cyclic voltammograms at different scan rates in potassium ferricyanide (FCN) solution as a proper redox couple system [40-42]. Upon modification with carbonaceous nanomaterials, the electroactive surface area was enhanced from 0.025 cm^2 for the bare carbon paste to 0.125 and 0.065 cm^2 for Gr/CPE, MWCNTs/CPE, respectively.

Successive recording of the cyclic voltammograms for 5 µg mL^{-1} TER solution on the unmodified carbon paste electrode resulted in a noticeable decrease of the peak current accompanied with shifting of the oxidation potential towards a more positive value

which may be attributed to the adsorption of terbinafine/ or its oxidation product at the electrode surface [31, 43]. Upon integration of the carbon paste matrix with graphene, the electrode performance was enhanced and the poisoning of the electrode surface was diminished based on its antifouling properties.
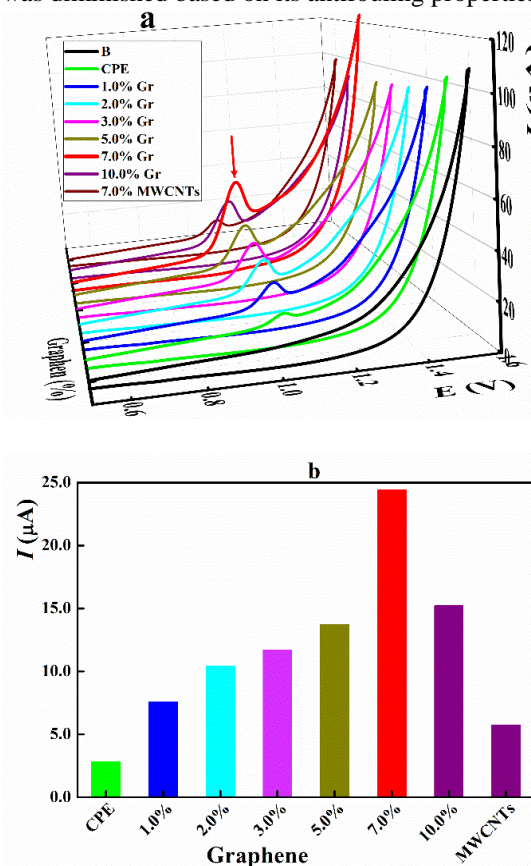

Fig. 1: Cyclic voltammograms recorded for 10.0 µg mL^{-1} TER at carbon paste electrode integrated with graphene and MWCNTs. The scan rate 50 mVs[-1] at pH 5.0.

3.2. Electrochemical behavior of terbinafine at different pH values

Terbinafine hydrochloride possessed a pKa value of 7.1 [44], therefore, the electrochemical behavior of TER is expected to be pH-dependent. Herein, cyclic voltammograms were monitored at different pH values ranging from 2.0 to 8.0. As described in Fig. 2a, TER recorded sharp and sensitive oxidation peaks within the pH range of 3.0 -7.0 with a maximum peak current at pH 5.0 which was selected for the proceeding measurements. The selected pH value is near that reported for terbinafine at the mercury and boron-doped diamond electrodes [17, 19]. Following, the peak potential (Ep) was shifted towards a more negative value at the evaluated pH illustrating the rule of the proton exchange mechanism in the oxidation of TER (Fig. 2b). Plotting of the E_p against the pH values revealed a near Nernstian slope value ($E_{P (V)} = 1.2729 - 0.0463$[pH], r^2=0.9976) sustaining the involvement of an equal number of protons/ electrons in the

oxidation of TER molecule [45-48]. The small intercept value indicates that there is no side reaction at the electrode surface.
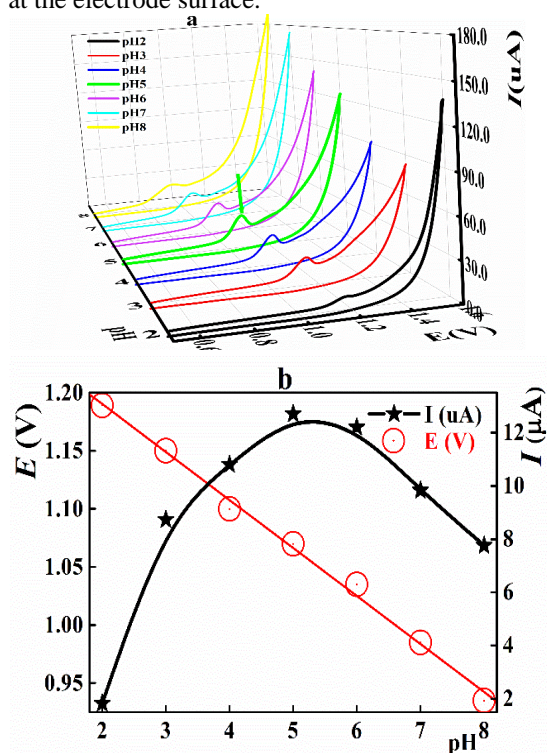

Fig. 2: a) Impact of the pH on the cyclic voltammograms recorded for 5.0 µg mL⁻¹ terbinafine; b) peak potentials and peak current for TER against pH values. Scan rate 50 mV s⁻¹.

3.3. The effect of scan rate

For an explanation of the electrochemical oxidation process at the electrode surface, electrode reaction mechanism, and to estimate the number of electrons that involved in the electrode reaction, cyclic voltammograms (CVs) were recorded at different scan rates [45]. Herein, CVs were monitored for 5.0 µg mL⁻¹ TER at pH 5.0 using carbon paste electrodes integrated with 7.0% graphene applying a broad range of sweep rates ranging between 0.02 to 0.180 V (Fig. 3 a). The recorded peak current was enhanced by shifting the peak positions toward the positive direction sustaining the irreversibility of the oxidation reaction. The peak current showed a linear relationship against the scan rate value (r=0.9991) as the oxidation process is irreversible (Fig. 3b).

The logarithmic values of the recorded peak current (log $I_{µA}$) showed a linear relationship versus the log value of the corresponding san rate (log ν) with a slope value of 1.001 (Fig. 3c) assuming a pure adsorption-controlled reaction mechanism for TER at the electrode surface [47, 49].
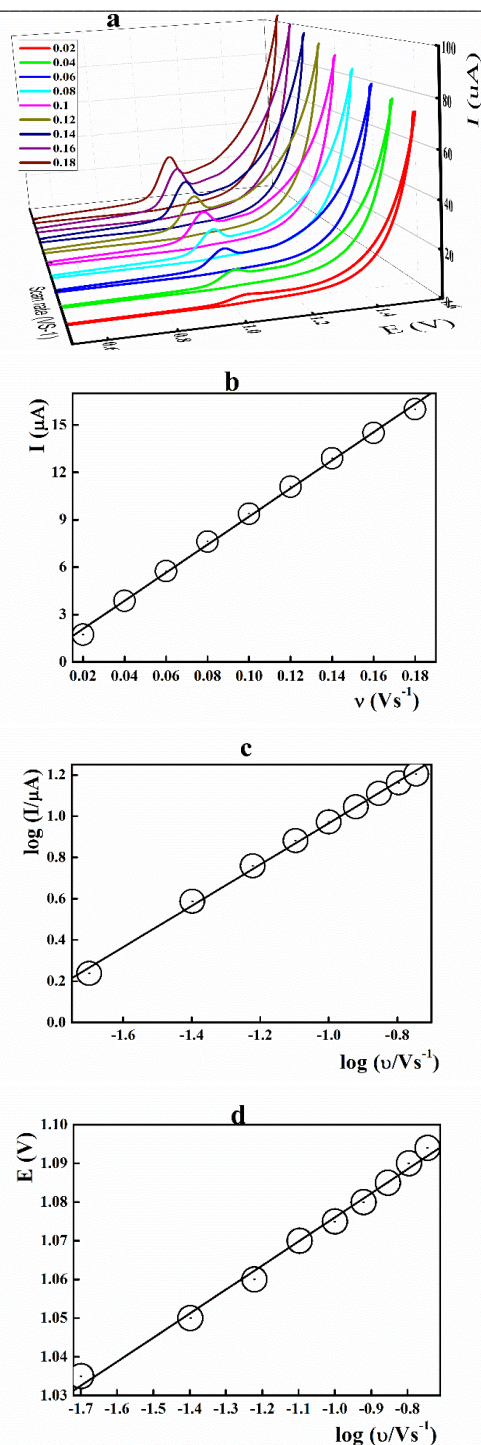

Fig. 3: Voltammetric behavior of 5.0 µg mL⁻¹ terbinafine at the Gr/CPE at pH 5.0 performed at different scan rate values.

The adsorption behavior of TER may be attributed to the π–π interaction of the residual carboxylic groups on the graphene surface with the aromatic rings in TER moiety. Finally, the oxidation potential was shifted to a more positive value with the sweep rate following the linear equation: ($E_{Ox(V)}$ = 1.1383 +

0.0622 [log (υ/Vs^{-1})], r = 0.9966; Fig. 3d) postulating the transfer of 0.994 electrons in the TER oxidation process [48-50]. The obtained results disagree with that reported for electrochemical oxidation of terbinafine on mercury electrode [17] and agreed with that reported on cysteic acid/carbon nanotubes composite film [18].

As the postulated electrode reaction for the oxidation of TER was estimated to follow an adsorption-controlled reaction mechanism, therefore, the impact of both the accumulation potential and deposition time on the peak height was tested (Fig. 4). At more negative deposition potential, the recorded cyclic voltammograms showed lower peak currents. As the applied deposition potential moved to the positive value the peak current increased to reach its maximum value at 0.150 V. Oxidation peaks recorded after different accumulation intervals revealed a noticeable enhancement of the peak current from 0 to 120s and 90 s will be selected for further measurements.
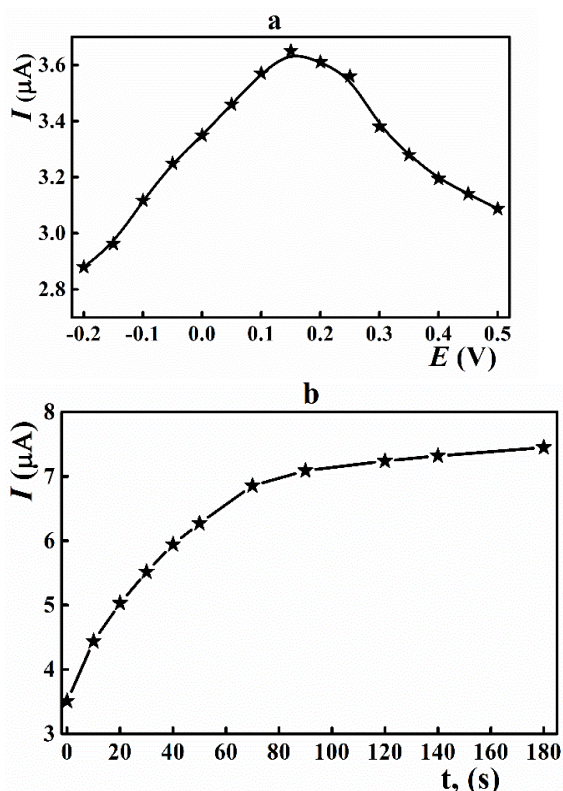
Fig. 4: Peak current for cyclic voltammograms of 5.0 µg ml^{-1}TER at Gr/CPE surface recorded: a) after different deposition potential and, b) after different deposition time. pH value was 5.0 with scan rate 50 mVs^{-1}.

Based on the above-discussed scan rate and pH results, and with the aid of the molecular orbital calculations [51], the postulated oxidation mechanism of TER molecule takes place through the oxidation of the amino group via transferring of one electron/proton (Scheme 1, Table S1). This postulated oxidation mechanism is similar to that reported for terbinafine at

cysteic acid/carbon nanotubes composite film [18] butenafine at MWCNTs/CPE [31].
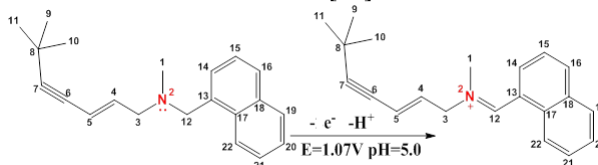
Scheme 1: Computed electrooxidation mechanism of terbinafine at the graphene based carbon paste electrode surface

3.4. Method validation

Applying the optimized experimental and electroanalytical parameters, the performance of the proposed TER voltammetric sensors was evaluated through successive fortification of the measuring cell with certain aliquots of the terbinafine stock solution. For each addition, the adsorptive differential pulse voltammograms were monitored and the subtractive peak current value was plotted against the corresponding TER concentration (Figure 5, Table 1). Within the tested TER concentration range, calibration graphs showed a high correlation coefficient value (r=0.9996) and low standard deviation which confirm the applicability of the proposed sensor for TER quantification. Moreover, the improved limit of detection (LOD) and limit of quantification (LOQ) values of 0.05 and 0.15 µg mL^{-1}, respectively were reported.
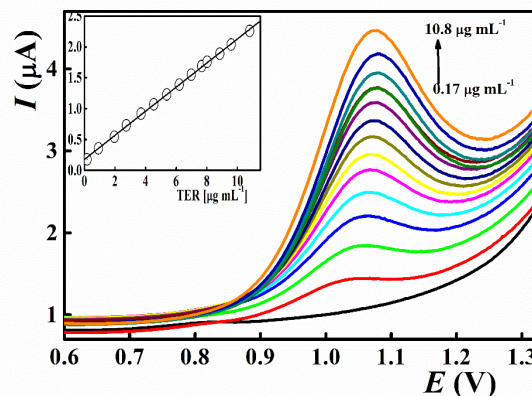
Fig. 5: Differential pulse voltammetric determination of terbinafine with graphene integrated sensors at pH 5.0 with scan rate 50 mVs^{-1}

It is noteworthy to mention that bulk modification of the carbon paste matrix with the graphene nanostructure resulted in the prolongation of the operational lifetime by up to 3 months, and a new working surface can be achieved through the pushing of the paste surface with a wet filter paper that minimizes the adsorption of the TER molecule at the electrode surface. Further storage of the sensor resulted in the deterioration of the sensor sensitivity by about 10 %.

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Table 1: Differential pulse voltammetric determination of terbinafine at graphene integrated carbon paste electrode

Parameters	
Optimal pH	5.0
Peak potential	1.07
Linear range ($\mu g\ mL^{-1}$)	0.17-10.8
Slope ($\mu A cm^{-2}$)	0.194
S_{slope} ($\mu A cm^{-2}$)	0.002
Intercept ($\mu A\ mL\ \mu g^{-1}$)	0.180
$S_{intercept}$ ($\mu A\ mL\ \mu g^{-1}$)	0.003
RSD %	1.94
r	0.9996
LOD ($\mu g\ mL^{-1}$)	0.05
LOQ ($\mu g\ mL^{-1}$)	0.15
Repeatability of the peak height (RSD %)	1.24
Reproducibility of the peak height (RSD %)	0.95
Repeatability of the peak potential a (RSD %)	1.02
Reproducibility of the peak potential a (RSD %)	0.722

Average of five replicates

Comparing the performance of the presented Gr/CPES with TER voltammetric sensors, the proposed sensors possess improved LOD and LOQ values with simple fabrication and regeneration protocol which in turn prolonged the operational lifetime and reproducibility of measurements (Table S 2). In addition, a more detailed discussion about the electrooxidation mechanism of the TER molecules was reported.

3.5. Sensor applications
3.5.1. Interference studies

Following the ICH guidelines [52], studying the possible degradation of the pharmaceutically active ingredient may explain the possible degradation products that can interfere with the assaying of the parent compound and cooperate to assess the degradation mechanisms of the drug molecule. Herein, the stress degradation studies were carried out under acidic/oxidative degradation conditions, where the progress of the degradation process was followed spectrophotometrically at 222 nm. Under the acidic/oxidative degradation conditions, complete degradation of the parent TER molecule was performed as indicated by the disappearance of the absorption peak at 222 nm. Similar to its analog, butenafine, the degradation process may undergo through the removal of the electroactive amino group accompanied with the disappearance of the characteristic voltammetric oxidation peak characteristic for TER molecule at 1.07 V. Therefore, TER can be assayed along in the presence of its degradation product while maintaining acceptable sensitivity and accuracy.

Nowadays, the simultaneous monitoring of the main pharmaceutically active compound in the presence of various impurities while maintaining the required sensitivity becomes a quite crucial issue. Different excipients and contaminates are usually present in the commercial pharmaceutical formulations which may resulted in a false recovery; therefore, the selectivity of the method must be tested. Differential pulse voltammograms were recorded at certain TER concentrations in the presence of selected interfering species such as citric acid, starch, glucose, propylene glycol, and some metal ions. DPV peaks for the standard TER solution in the presence and absence of the interferent species were recorded and the average recoveries were calculated as a percentage of the two peaks. The tolerance limit was defined as the interferent level which resulted in a relative error of ±10.0%. The presented method showed a tolerance limit with high sharp and sensitive peaks with high tolerance limit in the presence of the aforementioned interfering species.

3.5.2. Analysis of terbinafine samples

The presented TER sensors fortified with graphene nanostructure showed improved performance towards TER, therefore, they can be introduced for sensitive voltammetric quantification of TER in pharmaceutical formulations, biological fluids, and surface water samples. The collected samples were spiked with known TER concentrations and analyzed voltammetrically in compassion to the UV detection at 222 nm (Table 2). The achieved high recoveries with lower relative standard deviations encourage the applicability of the presented sensor.

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Table 2: Differential pulse voltammetric determination of terbinafine in biological fluids, surface water samples and pharmaceutical formulations

Sample	Added (µg/mL)	Found (µg/mL)	Bias%*	Recovery (%)	RSD (%)
Human urine	0.9	0.91	-1.111	101.11	0.987
	5.0	5.03	-0.6	100.60	1.15
	8.0	7.94	0.75	99.25	1.22
water	0.8	0.78	1.86	98.13	0.75
	5.0	5.06	-1.2	101.20	0.85
	7.0	6.87	1.86	98.14	1.32

Terbin ®	Added (µg/mL)	Found (µg/mL)	Bias%*	Recovery (%)	UV
	0.90	0.91	0.91	101.11	99.95
	2.00	1.97	1.50	98.50	100.05
	7.00	7.10	-1.43	101.43	98.40
	10.00	10.15	-1.50	101.50	100.10
Mean				100.63	99.63
Variance				2.05	0.67
Observations				4	4
df				3	3
F	3.06				
t Stat	1.22				
t Critical two-tail	2.45				
F Critical	9.28				

*n=3 measurements of test

Conclusion

The present study demonstrates the construction and the electrochemical characterization of a novel terbinafine voltammetric carbon paste sensor integrated with graphene nanosheets. Based on the electrocatalytic activity of graphene towards the oxidation of TER, enhanced sensitivity was reported within the TER concentration ranging from 0.17 to 10.8 µg mL^{-1}. Terbinafine molecule was irreversibly oxidized with an adsorption-controlled through the transfer of one electron/proton. The effect of various interfering species and terbinafine degradation products was also studied. The recorded sensitivity of the sensors offers a simple voltammetric protocol for the quantification of TER in pharmaceutical, biological and surface water samples with acceptable average recoveries compared with the traditional spectrophotometric methods.

Conflicts of interest
There are no conflicts to declare. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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