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Voltammetric Behaviour of Esomeprazole at Screen Printed Carbon Electrode and its Determination in Capsule Dosage Form

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Abstract

The anodic voltammetric behavior of esomeprazole (ESO) was explored at screen printed carbon electrode (SPCE) in phosphate buffer (PB) solutions over the pH range (2.0–11.0) using cyclic and differential-pulse voltammetry (CV; DPV). The oxidation of ESO was shown to be irreversible and diffusion-adsorption controlled driven process. Under optimized conditions, the DPV peak currents were in a linear relationship to ESO concentrations in the range of 1.0×10^{-6}-1.0×10^{-4} mol L^{-1} with a detection limit of 3.5×10^{-8} mol L^{-1}. The DPV was successfully employed for the determination of ESO in capsules. The results were compared with those obtained by the spectrophotometric method. No difference was found statistically. The voltammetric procedure was successfully also applied for rapid analysis of ESO in stability studies without interference from the degradation products.

Keywords:

Esomeprazole, Voltammetry, Screen-Printed Carbon Electrode, Stability, Pharmaceutical Analysis, UV-Vis Spectrophotometry

1. Introduction

Esomeprazole magnesium trihydrate, chemically known as bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl) magnesium tri-hydrate, (Scheme 1) is the first proton pump inhibitor developed as a single optical isomer for the treatment of acid-related diseases. In common with omeprazole, esomeprazole demonstrates highly effective inhibition of gastric acid secretion [1, 2]. ESO differs from omeprazole, however, in displaying lower first-pass hepatic metabolism and slower plasma clearance, resulting in higher plasma concentrations [3, 4]. The increased systemic bio-availability of esomeprazole offers the prospect of improved clinical efficacy and more effective management of acid-related diseases. The compound accumulates in the acidic compartment of the parietal cells where the molecule is transformed to its active form, the suphenamide. The intrinsic clearance being lower for ESO than for R-omeprazole and the racemate provides better clinical effect in the treatment of acid related diseases [5]. Furthermore, an almost twofold higher AUC with resulting higher intra-gastric pH for ESO than for omeprazole was shown in patients with symptomatic gastroesophageal reflux disease (GERD) [6].

Up to now, few works about esomeprazole analysis have been reported. Spectrophotometric methods have been reported for determination of ESO in its magnesium trihydrate salt or tablet dosage form. [7-9] Chromatographic methods for the determination of ESO in tablets [10], impurities in ESO magnesium gastro resistant tablets [11] and

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determination of enantiomeric purity of ESO magnesium trihydrate have been developed. [12] Some of those are stability indicating methods [11, 13].

So far to the best of our knowledge, no literature data were reported on the electrochemical behaviour of ESO in general or its voltammetric determination in particular till date. Therefore, the aim of the present study is to investigate the oxidative behaviour of ESO at SPCE using CV and DPV techniques, and to optimize the experimental conditions for determination of this compound in capsule dosage form. The spectrophotometric method was chosen as a comparative method in evaluating the proposed voltammetric technique. Electroanalytical methods are well known for their high sensitivity, fast analysis times, thus gaining increasing attention in the analysis of drugs [14, 15]. The SPEs, which are used as economical electrochemical substrates, have gone through improvements over the past few decades with respect to both their format and their printing materials. These electrodes can be easily replaced between each analysis, eliminating the need for electrode surface regeneration [16, 17]. The SPEs are characterized by simplicity of use, low cost and good reproducibility of each unit, with special attention to convenience associated with this type of electrode[18, 19], sometimes leading to more interesting devices than conventional electrodes. Thus, these interesting features have allowed their marketing as disposable electrodes. Several studies have shown that the use of SPE in electroanalysis ensures adequate sensitivity, selectivity, linearity, reproducibility and robustness for development of electroanalytical methodologies [20]. Finally, very little sample are generally required and the use of disposable electrodes, i.e. SPEs coupled with portable instrumentation, represents an attractive feature for electroanalytical method application in the field of pharmaceutical analyses.

2. Experimental

2.1. Reagents

Esomeprazole and its pharmaceutical dosage form (Esogerdazole capsules) were kindly provided by Al Rowad Pharm. Ind. (Egypt). Stock solution (1.0×10^{-2} mol L^{-1}) ESO was prepared in methanol and stored in a refrigerator at 4°C. Standard solutions were prepared daily by diluting of the stock solution with the selected supporting electrolyte. Orthophosphoric acid 85%, potassium dihydrogen phosphate KH_2PO_4, disodium hydrogen phosphate Na_2HPO_4, and sodium phosphate Na_3PO_4 were mixed in different amounts and diluted with distilled water to obtain the phosphate buffer solutions (0.2 mol L^{-1}) with the required pH. All other reagents purchased commercially were of analytical grade; double distilled water was used throughout.

2.2. Apparatus

Voltammetric measurements were carried out using Bio-logic SAS Electrochemical Analyzer, Model SP50, controlled by EC-Lab express Version 5.52 software (Bio-logic SAS, France). A three electrode configuration printed on the same strip, consisting of a disk working (geometric area 7.07 mm^2) and counter electrodes both printed using heat curing carbon-based ink, and a silver pseudo-reference electrode made from a silver-based ink; was employed. All pH-metric measurements were made on a CG 808 (Schott Gerate, Germany) digital pH-meter with glass combination electrode, which was previously standardized with buffers of known pHs. The UV spectra were performed by a PerkinElmer UV-vis double beam spectrophotometer equipped with a PC for data processing UV WinLab-ver 2.80.03 (PerkinElmer, USA). The spectra were recorded over the wavelength range from 200 to 500 nm. A quartz cell with a 1.0 cm path length was used.

2.3. Procedures

Aliquots of 200 µL of the supporting electrolyte solution and samples containing ESO were dropped on to the exposed area of the sensor, and the voltammograms initiated in the

positive direction were recorded directly without any accumulation time. The anodic potential sweep was carried under different operational parameters. To provide a reproducible active surface and improve the sensitivity and resolution of the voltammetric peaks, the electrodes were cleaning in a solution of 0.2 mol L^{-1} H_2SO_4 and a single voltammetric cycle was carried out between -1200 mV and 1500 mV at 100 mVs^{-1} *vs.* silver pseudo-reference electrode. A SPCE test strip was used for each measurement. DPV conditions were given as follows; step potential: 8 mV; modulation amplitude: 50 mV; modulation time: 0.07 s; interval time: 0.4s. All measurements were carried out at room temperature.

2.4. Analysis of capsule dosage form

The contents of 10 capsules were mixed and an amount containing the equivalent of 40 mg ESO was dissolved in 5 mL of methanol. The solution was sonicated for 15 min and diluted to 10 mL with the same solvent. A dilution of an appropriate aliquot of the clear supernatant liquor was performed using 0.2 PB pH 7.0 to obtain an ESO concentration of 5.0×10^{-5} mol L^{-1}. A 200 µL aliquot was then dropped directly on to the sensor surface and the DPV was subsequently recorded following the optimized conditions. The content of the drug in capsule was determined referring to the calibration graph or regression equation.

3. Results and discussion

Fig. 1 shows the resulting anodic cyclic voltammogram obtained for 5.0×10^{-4} mol L^{-1} solution of ESO at SPCE in 0.2 mol L^{-1}phosphate buffer (pH = 7.0) solution using a scan rate of 50 mVs^{-1}. It is clear that there is only a single anodic oxidation peak when the potential is scanned from 0.0 to 1.3 V (vs. Ag pseudo-reference electrode). On the return scan, the oxidation process is not accompanied by a reduction wave, which indicates that the oxidation reaction is totally irreversible.

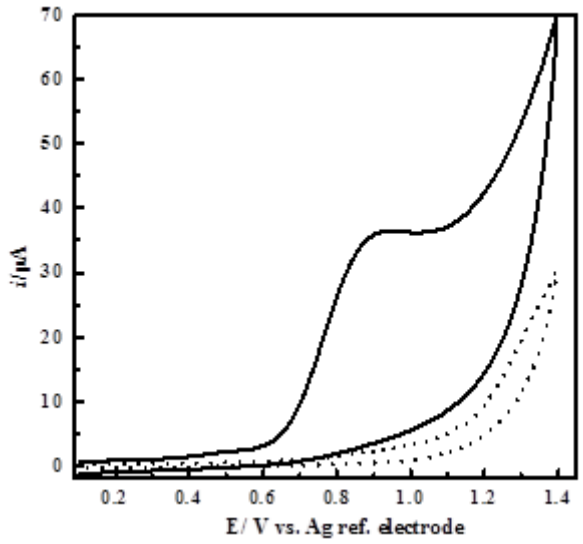

Fig.1: Cyclic voltammograms for 5.0×10^{-4} mol L^{-1} esomeprazole on screen printed carbon electrode in 0.2 mol L^{-1} phosphate buffer at pH 7.0. Scan rate: 50 mVs^{-1}; the dotted lines represent blank solution

The effect of scan rate on the anodic oxidation of 5.0×10^{-4} mol L^{-1} solution of ESO in 0.2 mol L^{-1} PB buffer at pH 2.00 at the SPCE was investigated by cyclic voltammetry. When the scan rate was varied between 5 mV/s and 150 mV/s, a linear dependence of the peak current measured and the square root of the potential scan rate ($\upsilon^{1/2}$) (mVs^{-1}) demonstrates the diffusion controlled nature of electrodic process. The dependence was linear and followed the

relationship: i_p (μA)=1.98 $\upsilon^{1/2}$ (mVs^{-1})+0.09, r=0.990 (n = 10). A plot of logarithm of peak current versus logarithm of scan rate gave a straight line with a slope of 0.59 very close to the theoretical value of 0.50, which is expressed for an ideal reaction for the diffusion-controlled electrode process.[21] However, the characteristic of adsorption controlled processes was corroborated by the linear dependence found between the peak current and the scan rate when the potential was scanned at increasing rates from 150-350 mVs^{-1}. The apparent change of mass transport nature with the scan rate can be related to each contribution in the total Faradaic current. At low scan rates, little contribution from the adsorptive component could be expected. Therefore, the Faradaic currents were mainly from diffusive mass transport and a linear dependence between peak currents and the square root of the potential scan rate are observed. On the other hand, the adsorptive component becomes the most important at high scan rates and therefore the peak currents were directly proportional to the potential scan rate. The peak potential was shifted to more positive values on increasing the scan rate, which confirms the kinetic limitation of the electrochemical reaction. The plot of ln (i_p) versus peak potential, E_p, at various scan rates, for a totally irreversible system, can be used for the evaluation of transfer coefficient (α).[21] The value of α determined by this method is 0.43. The value of the product of transfer coefficient (α) and number of electrons transferred (na) in the rate-determining step, αna, was also determined from Tafel treatment (log i vs. E) of the voltammetric curve.[21] Tafel plot was drawn, as derived from points in the Tafel region of the cyclic voltammogram. The slope of the Tafel plot was equal to n(1-α)F/2.3RT (where n is number of electron in steady state stage and α is charge transfer coefficient), which came up to 10.15 decade V. Therefore, we obtained the value of α equal to 0.39. The αn_a value obtained shows that two electrons are likely involved in the oxidation of ESO.

Subsequent scans on the positive going direction using the same voltammetric conditions for 5.0×10^{-4} mol L^{-1} at scan rate of 50 mVs^{-1} are shown in Fig. 2. Repetitive CVs did not show any alternation on the number of peaks showing that the oxidation product formed at the SPCE surface in these conditions is electroinactive. Successive scans exhibit a gradual decrease of the anodic peak by increasing the number of scans and this process is due to the adsorption of oxidation product of ESO at the SPCE surface which reduced the available electrode surface area.

The pH of the supporting electrolyte generally affects the voltammetric behaviour of organic substances; we decided to test and repeat the previous study in 0.2 mol L^{-1} phosphate buffer at different pHs (in the range 2.0–11.0) as supporting electrolytes (Fig. 3). Cyclic voltammetric studies of 1.0×10^{-4} mol L^{-1} ESO exhibited a well-defined oxidation peak over the entire pH range at a sweep rate of 50 mVs^{-1}, when the sweep was initiated in the positive direction. No reduction peak was observed on reversal of the sweep; Fig. 3A. Clearly, the oxidation peaks are shifted towards less positive potentials which is consistent with both protons and electrons being involved in the electrode reaction. The electrochemical oxidation of ESO was also studied over the pH range using DPV; Fig. 3B. The results showed that the potential of anodic peak of ESO is shifted again linearly towards less positive values with increase in the pH. The results showed that the slope (Ep/pH) is 58.6 mV/pH unit over a pH range from 2.0 to 7.0. This slope was close to the Nernstian value of 59.2 mV for a 2-electron, 2-proton process. However, such a process can be regarded as a simple reaction with 2 successive 1-electron exchanges as indicated for the conditions at which the transfer coefficients of the electrochemical reactions are about 0.5 and protonations are at equilibrium. The slope of the 25.0 mV/pH unit was anticipated for pH values more than 7.0, which is very close to the Nernstian value of 29.6 mV for a 2-electron, 1-proton process. [21] The change in the slope for pH values above 7.0 can be attributed to the deporotonation of the ESO. The peak current increased along with an increase of the pH value, and reached to a maximum response

at pH 7.0–7.5; at pH > 7.5, the peak current decreased. Thus, a solution of 0.2 mol L^{-1} PB pH 7.0 was used in the following experiments as ESO produced the best response.

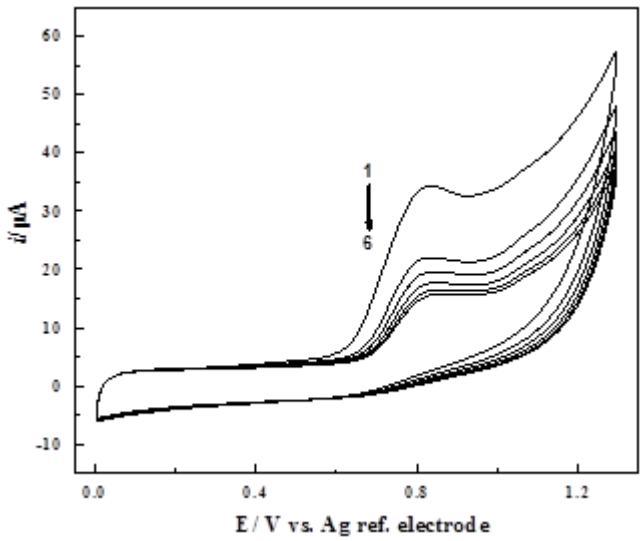

Fig. 2: Successive voltammograms for 5.0×10^{-4} mol L^{-1} Mesomeprazole on screen printed carbon electrode in 0.2 mol L^{-1} phosphate buffer at pH 7.0. Scan rate: 50 mVs^{-1}

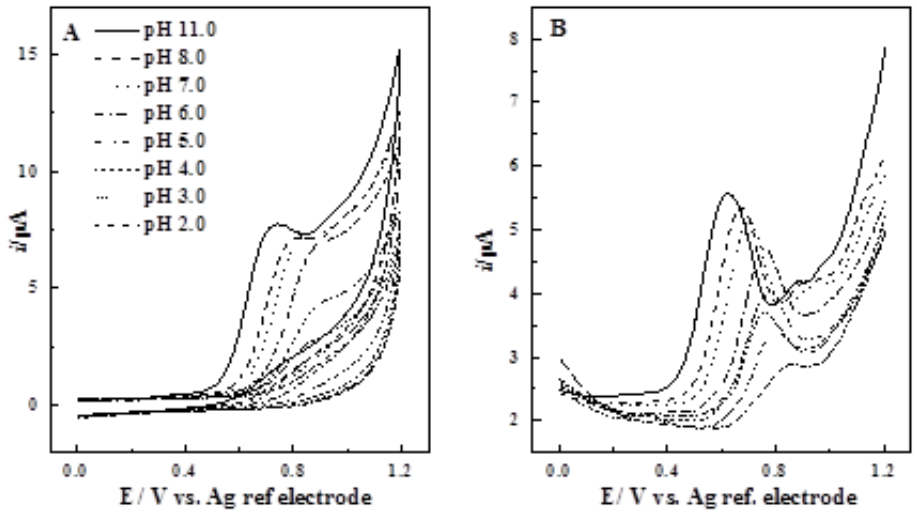

Fig. 3: (A) Cyclic voltammetric studies of 1.0×10^{-4} mol L^{-1} ESO; (B) The electrochemical oxidation of ESO over the pH range using DPV

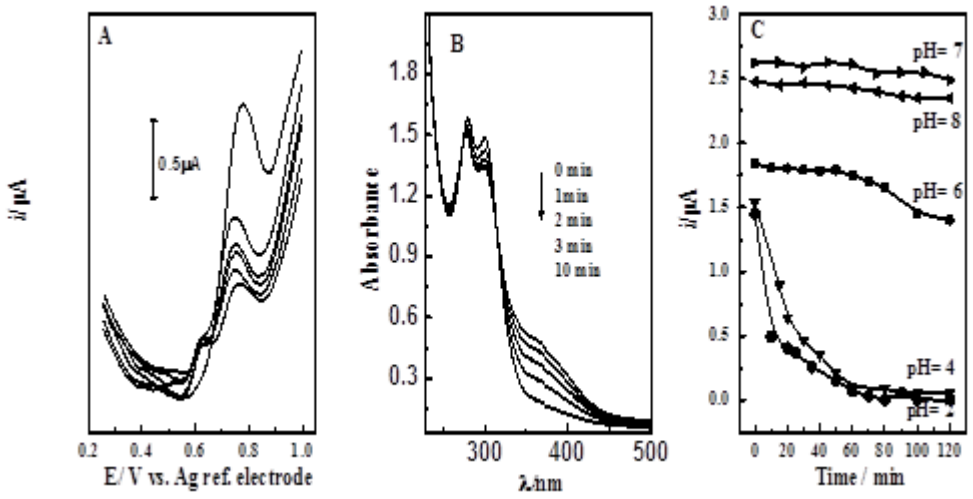

Fig. 4: (A) Differential-pulse voltammograms (B) UV–vis spectra of 1.0×10^{-4} mol L^{-1} esomeprazole solution in 0.2 mol L^{-1} phosphate buffer pH 2.0 after degradation. (C) Stability profile of esomeprazole as measured by differential-pulse voltammetry at different pH values: 2.0; 4.0; 6.0; 7.0 and 8.0.

The results obtained enabled to propose the mechanism of proton and electron exchanges between the redox moiety of the ESO molecule, the electrode surface and the medium, Scheme 2. The results indicate that ESO sulfinyl is electrochemically oxidized to ESO sulfone [22] by a mechanism involving the conversion of sulfinyl group to sulfone by a 2 electrons and 2 protons process as sulfoxide with sulfur in oxidation state of 0 is oxidized to sulfone with sulfur in oxidation state of +2.

3.1. Degradation of Esomeprazole

The degradation of 1.0×10^{-4} mol L^{-1} ESO in 0.2 mol L^{-1} PB buffer, pH 2.0, as monitored by DPV is shown in Fig.4A. It shows that the anodic peak at +0.864 V, which corresponds to oxidation of the parent ESO drug, decays over time, with the appearance of a new peak at +0.612 V. This new peak may be attributed to the electro-oxidation of the degradation product by a mechanism involving $2e^{-}/2H^{+}$ process, as sulfide group yielding a sulfinyl function, as sulfide group with sulfur in oxidation state of -2 is oxidized to sulfinyl with with sulfur in oxidation state of 0.

Data obtained by UV-Vis spectrophotometry showed that there are differences between the absorbance values before and after degradation of the drug. This decomposition is shown by a decrease of absorption signal intensity. However, it can be observed that this change in absorbance is small compared to the high decrease in anodic signal for the same samples and degradation times. The difference between UV-Vis spectrophotometry and DPV as regards sensitivity for monitoring the degradation process of ESO is evident. These results demonstrated that DPV is a useful technique for the rapid analysis of ESO in an aqueous solution during stability. These results allowed considering this procedure as useful for the rapid analysis of ESO in stability studies since there was no interference with its decomposition products.

The dependence of the current height on degradation time for 1.0×10^{-4} mol L^{-1} ESO in 0.2 PB solutions of several pH values as measured by DPV is shown in Fig. 4C. The kinetics of degradation can be followed by the decrease in height of the anodic peak at different pH values. In order to interpret the degradation of esomeprazole, the logarithm of the percentage anodic peak current (log *i* %), which was proportional to the concentration of the parent drug

in the solution, was plotted vs. time. This made it possible to determine the rate law of this reaction. This plot [i.e. log *i* % vs. *f*(t)] is straight line, indicting a first-order reaction. The rate constants were calculated from the slopes, and the half-life can be readily calculated using the following relation: ks $0.693/t_{1/2}$. After the drug has degraded, depending on the proton concentration, a curvature appears in the originally linear logarithmic plot and the reaction obeys a different rate law. The degradation kinetics is strongly pH dependent. ESO was unstable in acid solution, although it was rather stable in neutral and alkaline solutions. The half-life of ESO was: 15 min at pH 2.0; 23 min at pH 4.0; 150 min at pH 6.0; 24 h at pH 6.0; and 36 h at pH 8.0.

3.2. Analytical Determination

The analytical determination of ESO was investigated by DPV and UV-VIS spectrophotometry. On the basis of the electrochemical oxidation of ESO at SPCE, an electroanalytical method was developed involving DPV for the determination of the drug. DP voltammograms were recorded for standard additions of ESO corresponding to bulk concentrations between 1.0×10^{-6} and 1.0×10^{-4} mol L^{-1} in PB pH = 7.0, Fig. 5A. The peak current increased linearly with increasing concentration. UV–VIS spectra were recorded for standard additions of ESO corresponding to bulk concentrations between 1.0×10^{-5} and 5.0×10^{-5} mol L^{-1} in pH = 7.0, Fig. 5B. ESO has shown well-defined absorption band at 300 nm was used as analytical signal for the determination of the calibration curve. Calibration graphs were obtained by least-square regression method. LOD and LOQ were calculated from the calibration curve. The limits of detection (LOD) and the limits of quantification (LOQ) were calculated from the calibration plots using the equations: LOD=3 s/m and LOQ=10 s/m (where s is the standard deviation of the intercept and m is the slope of the calibration plot) .[23]

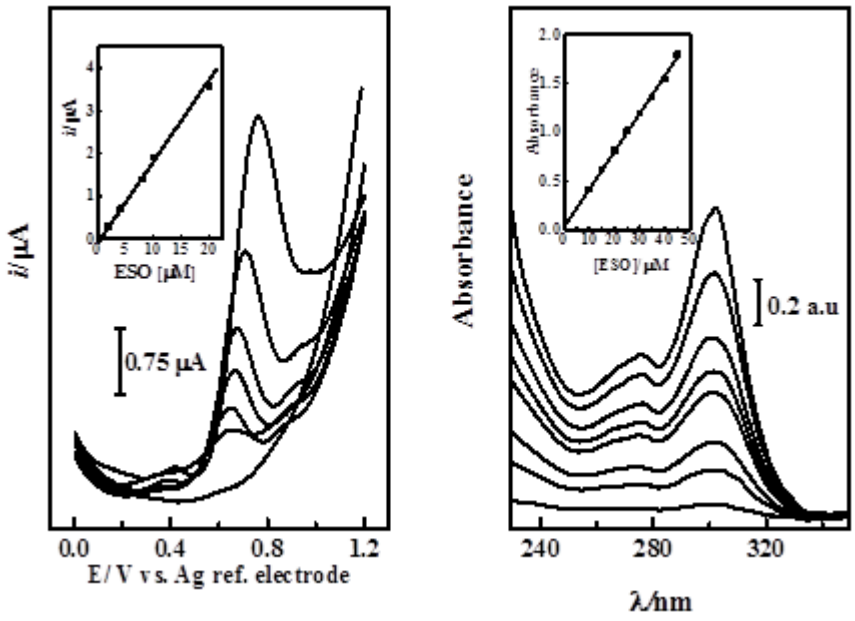

Fig. 5: (A) Differential-pulse voltammograms for increasing concentrations of esomeprazole from 1.0×10^{-6} to 1.0×10^{-4} mol L^{-1} in 0.2 mol L^{-1} PB buffer at pH 7.0 buffer solution on screen printed carbon electrode. (B) UV-vis spectra of esomeprazole for increasing concentrations from 1.0×10^{-5} to 1.0×10^{-4} mol L^{-1} in 0.2 mol L^{-1} PB buffer at pH 7.0 buffer solution. Insets: calibration plots

The repeatability (intraday precision) was evaluated by assaying during the same day 5 samples containing 5.0×10^{-5} mol L^{-1} drug and the reproducibility (interday precision) on two different days. The analytical parameters are summarized in Table 1. The relative standard

deviation (RSD) and Bias values can be considered satisfactory at levels of concentrations examined.

3.3. Interference Studies

Each Esogerdazole capsule® contains 40 mg of ESO (present as 44.5 mg esomeprazole magnesium trihydrate), in the form of enteric-coated pellets granules. The inactive granules are composed of the following ingredients: glyceryl monostearate 40-55, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, and triethyl citrate. DPV experiments were carried out for 5.0×10^{-5}M ESO in the presence of the different excipients at concentrations that can be found in the capsule dosage form. The voltammetric behavior even in the presence of excipients present in capsule shows the same voltammetric signal anodic activity as a standard substance with negligible decreasing of current maximums values; indicating that excipients are electrochemically inactive at the potential of electrooxidation of ESO. Therefore, the proposed method can be used as a selective method and the voltammetric responses provide a means of conducting measurements of ESO capsules without the need for extensive sample preparation.

3.4. Determination of esomeprazole in capsule

The analytical performance of the developed methods was evaluated by quantifying ESO in commercial pharmaceutical dosage forms (labeled values 40 mg). The proposed method was used without prior separation of the excipients. The corresponding DP voltammogram was recorded and the nominal content of the tablet amount was calculated from the related regression equation of the previously plotted calibration curve. The obtained results are presented in Table 2. The mean results was found to be very close to the declared value of 40 mg, indicating that the developed method could be applied with great success to ESO assay in capsules without any interference from the excipients. Furthermore, the reliability of this method was tested by analyzing ESO through a spectrophotometric technique. For the DPV and spectrophotometric methods, five different independent measurements were carried out. These results are summarized in Table 2. The *F*- and t-test were carried out on the data and statistically examined the validity of the obtained results. For a confidence level of 95%, the values of *t*- and F-tests were less than those of theoretical values, showing that there is no significant difference between the DPV technique and the spectrophotometric comparative method with regard to accuracy and precision. Furthermore, the recovery, as an average value of 5 replicates, was calculated after addition of a standard drug solution of ESO to commercial formulations. Recovery in commercial capsules showed the accuracy of the methodology and its comparability with spectrophotometric method. The proposed approaches are thus precise and accurate and they can be applied directly to the analysis of ESO in commercial formulations.

4. Conclusion

The anodic voltammetric behavior of ESO at the SPCE was an irreversible and diffusion-adsorption controlled driven process. The ESO was oxidized by a mechanism involving $2/2H^+$ process. It is clear that SPCE using sample volumes of only 200 µL; has great potential for practical sample analysis. The optimized electroanalytical method was successfully applied for determination of ESO in capsule dosage form with no tedious extraction or filtration procedures have been applied during sample preparation and only dilution of aliquot from the supernatant layer with the supporting electrolyte is required before measurement. The proposed DPV method proved to be a very useful tool in monitoring the degradation of ESO and might be preferred to other reported methods.

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