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Differential Pulse Voltammetric Determination of Loperamide in a Pharmaceutical Dosage Form

A. Radi *, T. Elmogy

Department of Chemistry, Faculty of Science, Mansoura university, 34517 Dumyat, Egypt, e-mail: abdradi@yahoo.com

Abstract

A voltammetric study of the oxidation of loperamide has been carried out at the glassy carbon electrode. This compound exhibited a single peak in Britton-Robinson buffer solutions of pH 5.0-11.0, with a maximum current at pH 8.0. The electrochemical oxidation of loperamide is identified as an irreversible, diffusion-controlled process. Based on this study, a simple, rapid and sensitive voltammetric method was applied, without any interference from the excipients, to the determination of the drug in a capsule dosage form.

Keywords

Loperamide, Differential pulse voltammetry, glassy carbon electrode, electrochemical oxidation, pharmaceutical analysis

Introduction

Since it was introduced in 1973, loperamide (Fig.1, 4-(p-chlorophenyl)-4-hydroxy-N,N-dimethyl-α,α--diphenyl-1-piperidine butyramide) hydrochloride has been widely used as an effective drug for the control and symptomatic relief of acute non-specific diarrhea and chronic diarrhea associated with inflammatory bowel diseases [1]. Recently, loperamide has received attention as an anti hyperalgesic

agent that reduces pain without any central nervous system (CNS) side effects [2].

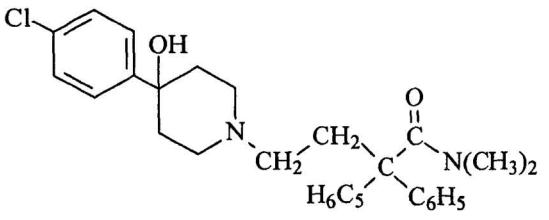

Fig.1. Chemical structure of loperamide.

Several methods have been reported for the quantification of the drug either in pure form or in its dosage forms including HPLC [3,4], GC-MS [5] colorimetry [6], spectrofluorimetry [7], nonaqueous titration [8] and spectrophotometry [9-12].

However, to our knowledge no information about the electrochemical redox properties of loperamide and its analytical application has appeared in the literature. In the present paper, details are given for voltammetric oxidation behaviour of loperamide on glassy carbon electrode and its determination by differential pulse voltammetry (DPV) in a capsule dosage form.

Results and Discussion

Effect of pH

The differential-pulse voltammetric behaviour of loperamide hydrochloride was investigated over a wide pH range pH 2.0-11.0. Loperamide gave rise to a single oxidation peak at the glassy carbon electrode in BR buffers of pH 5.0-11.0 using differential pulse voltammetry (DPV). The effect of pH on the peak potential (E_p) and peak current (i_p) of the oxidation peak of loperamide is shown in Fig. 2. The graph of E_p versus pH clearly indicates that the peak shifts to less positive potentials with increasing pH, as shown in Fig. 2a. Between pH

2 and 5 the slope of the graph was 45 mV pH. The effect of the solution pH on the peak enhancement is also shown in Fig. 2b. The best results with respect to signal enhancement accompanied by sharper response was obtained with Britton-Robinson buffer at pH 8.0. This supporting electrolyte was chosen for subsequent measurement experiments.

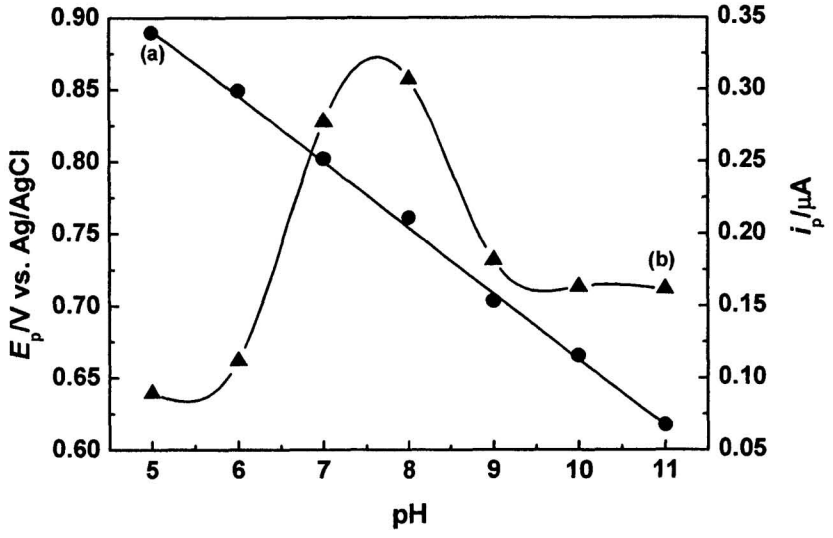

Fig. 2. Effect of pH on (a) peak potential and (b) peak current in Britton–Robinson buffer using differential pulse voltammetry at glassy carbon electrode. Loperamide hydrochloride concentration, 1.0×10^{-5}M; scan rate, 10 mVs-1; pulse amplitude, 50 mV; pulse width, 30 s

Cyclic Voltammetry

A typical cyclic voltammogram of 5.0×10^{-4}M loperamide hydrochloride at glassy carbon electrode in Britton–Robinson buffer at pH 8.0 is shown in Fig. 3. Loperamide has an anodic peak at 0.800 V. No peaks are observed in the cathodic branch indicating that the loperamide oxidation is an irreversible process.

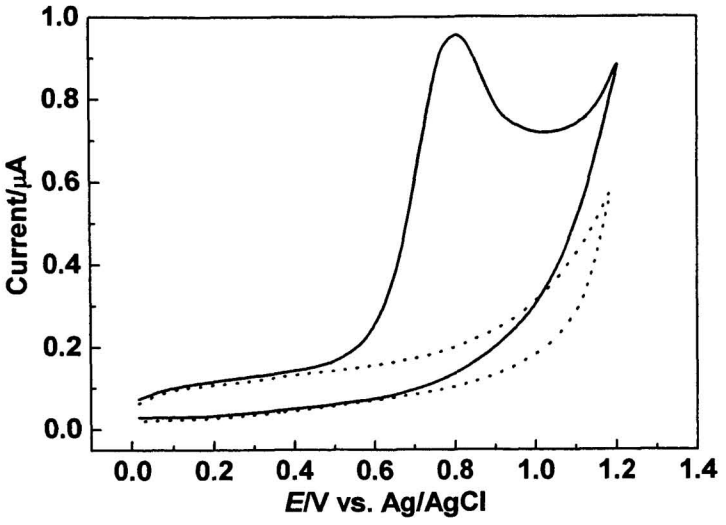

Fig. 3. Cyclic voltammograms of 5.0×10^{-4}M loperamide hydrochloride solution on glassy carbon electrode in Britton–Robinson buffer at pH 8.0. Scan rate, 100 mVs^{-1}. The dotted lines represent blank solution

Cyclic voltammograms were then recorded at different potential scan rates between 20 and 500 mVs^{-1}. A positive shift in the peak potential (E_p) was observed, which confirms the irreversibility of the process, with the simultaneous increase in peak current (i_p) when the scan rate (ν) was increased. The linear relationship existing between peak current and the square root of the scan rate (correlation coefficient 0.999) gave a slope of 0.87, close to the theoretical value of 1.0, which is expected for an ideal reaction of solution species [13], so in this case the oxidation process is predominantly diffusion-controlled in the whole scan rate range studied

On calculating the αn_a value (where α is the charge transfer coefficient and n_a is the number of electrons involved in the rate-determining step) for the loperamide oxidation step with the data from the linear-scan voltammograms at the stationary electrode and using

the expression: E_p-$E_{p/2}$ = 47.7/αn_a mV for the totally irreversible diffusion controlled process [14], a mean value of 49 is obtained for αn_a. The number of protons (p) transferred in the rate-determining step was calculated from the expression: $\Delta E_p/\Delta pH = 0.059\ p/\alpha\ n_a$. The αn_a and p values are consistent with one electron-one proton transfer involved in the rate-determining step. It seems reasonable to conclude that the nitrogen atom of the amide on 1 e^-, 1 H^+ oxidation gives a free radical species in the rate-determining step.

Effect of concentration

Using differential pulse voltammetry employing the optimum conditions (Pulse amplitude, 50 mV; pulse width 30 ms; scan rate, 10 mVs^{-1}), a linear calibration curve was obtained for loperamide hydrochloride in the range 3.0×10^{-6}M-5.0×10^{-5}M. The characteristics of this graph were slope 0.01179 μA μM^{-1}, current intercept 0.18964 μA and correlation coefficient r = 0.999. The limit of detection of the procedure was found to be 1.0×10^{-6}M, which were estimated as: LOD = $3S_{y/x}$/b [15], where $S_{y/x}$ is the standard deviation of y-residuals and b is the slope of the calibration plot. A set of voltammograms illustrating the variation of peak height with concentration is given in Fig. 4. The reproducibility of the measurement was calculated from five independent runs of 1.0×10^{-5}M loperamide hydrochloride solution. The relative standard deviations were calculated to be 0.35 and 1.25 % for peak potential and peak current, respectively.

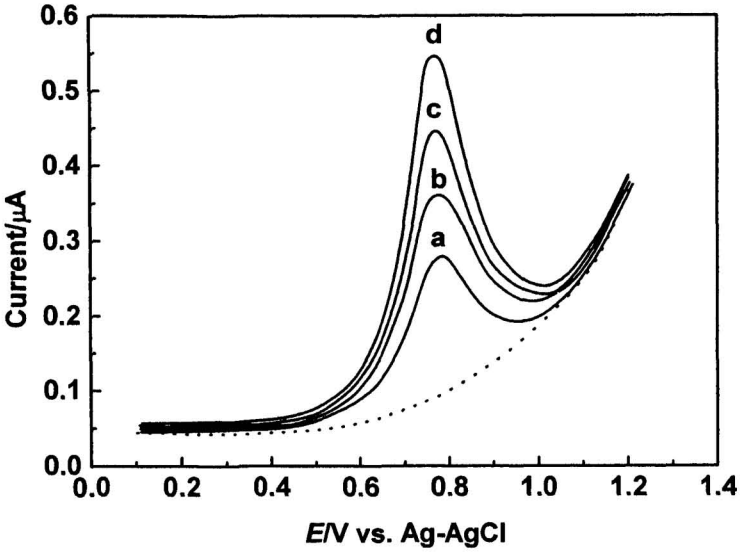

Fig. 4. Differential pulse voltammograms for increasing concentrations of loperamide hydrochloride in Britton–Robinson buffer at pH 8.0 on glassy carbon electrode. Scan rate, 10 mVs.1; pulse amplitude, 50 mV; pulse width, 30 ms. Loperamide hydrochloride concentration: (1) 7.5×10^{-6}M, (2) 1.5×10^{-5}M, (3) 2.25×10^{-5}M and (4) 3.0×10^{-5}M; the dotted lines represent blank solution.

Interference studies

The effect of inactive ingredients (pregelatinized corn starch, iron oxides, lactose monohydrate, magnesium stearate, and titanium dioxide) present in capsules on the DPV behaviour of loperamide was investigated by adding the relative concentration of each ingredient into a pure solution of the drug in BR buffer pH 8.0. The magnitude of the peak current for loperamide hydrochloride showed no deviation of more than 3 % from the peak current of the solution containing no inactive ingredient, indicating that there were no interferences to the method.

Application of the method to pharmaceutical capsules

The proposed method was applied in the case of Imodium capsules containing 2 mg of loperamide hydrochloride. The capsules were processed as described in the Experimental section and the optimum voltammetric conditions were employed for the analysis. No interference was observed from the inactive ingredients. The official colorimetric method served as a comparison method. The results of the methods were compared to each other at the 95% probability level. The results of the statistical evaluations are given in Table 1. According to the results of *t*- and *F*-tests, insignificant differences appeared between the two methods.

Tab. 1. Application of the proposed voltammetric method to the determination of loperamide hydrochloride in Imodium capsules (2 mg / capsule)

Item	DPV	Official colorimetric method [6]
Mean (%)	101.32	102.79
S.D.	1.17	1.56
N	5	5
t-value	1.69 (2.78)	
F-value	1.778 (6.388)	

Figures in parentheses are the corresponding theoretical *t*- and *F*-values (P = 0.05).

In conclusion, the proposed method is sensitive, accurate, rapid and involves no sample preparation other than dissolving and transferring an aliquot to the supporting electrolyte. The voltammetric procedure used in this study allowed us to estimate the concentration of the loperamide drug without any interference from the inactive ingredients present in the dosage form.

Experimental

Reagents

Loperamide hydrochloride obtained from Solchem Italiano S.P.A certified to contain 100.12% was used. Imodium capsules (Galaxo Wellcome Egypt- S.A.E., Cairo, Egypt under license from Janssen Pharmaceutica, Beerse, Belgium labeled to contain 2 mg of active ingredient per capsule) were purchased from local pharmacies. All the other chemicals used in the experiments were of analytical grade. Double distilled water was used for preparation of the solutions. Stock solution of Loperamide hydrochloride was prepared in methanol. Dilutions were made from this solution to the final concentrations with water. A stock Britton-Robinson (BR) buffer solution was prepared which was 0.04 M in each of glacial acetic acid, ortho-phosphoric acid and boric acid. Buffer solutions of varying pH were then prepared by the addition of 0.2 M sodium hydroxide.

Apparatus

The voltammetric measurements were performed using a PC controlled AEW2 analytical electrochemical workstation with ECprog3 electrochemistry software (Sycopel, UK) connected to C-2 stand with a three-electrode configuration: a glassy carbon (Φ=3mm) working electrode, an Ag-AgCl-3M KCl reference electrode and a platinum wire counter electrode. OriginPro 7.0 software was used for the transformation of the initial signal. A CG 808 (Schott Geräte, Germany) digital pH meter with glass combination electrode served to carry out the pH measurements.

Procedure

10 mL of the supporting electrolyte solution was placed in the voltammetric cell. After measurement of the blank solution, the appropriate amount of loperamide hydrochloride solution is added and

the anodic potential sweep was carried under different operational parameters. All measurements were carried out at room temperature. The peak heights were evaluated by means of the tangent method. The electrode surface was hand-polished with 0.5 μm particle size alumina; then it was rinsed with distilled water and dried with a non-abrasive tissue paper before each experiment.

Analysis of pharmaceutical dosage form

The mixed powder of twenty Imodium capsules was weighed. An amount of capsules powder corresponding to 2 mg Loperamide hydrochloride was accurately weighed, transferred to a 10-mL flask, and methanol was added to dissolve the active material. The solution was magnetically stirred for 10 min and made up to the final volume with methanol. An aliquot of clear supernatant liquor was then transferred to the voltammetric cell containing 10 ml of BR buffer (pH 8.0) to yield a final concentration of 1.0×10^{-5}M loperamide. The differential pulse voltammogram was subsequently recorded employing the optimized conditions. To quantify the unknown amount of loperamide hydrochloride in solution, a multiple standard addition procedure was employed.

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