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Determination of pantoprazole by adsorptive stripping voltammetry at carbon paste electrode

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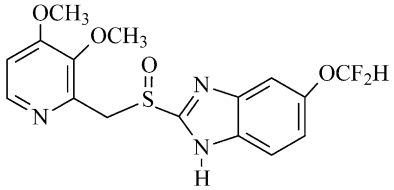
Abstract

A voltammetric method was described for the determination of pantoprazole by differential-pulse adsorptive stripping voltammetry at a carbon paste electrode. Accumulation of pantoprazole was found to be optimized in Britton–Robinson buffer (0.04 M, pH 4.0) solution following 5 min accumulation time at open circuit condition. Under optimized conditions, the current showed a linear dependence with concentration in the range 1.0×10^{-7}–1.0×10^{-5} M. The detection limit was 2.0×10^{-8} M. The method was applied successfully for the analysis of pantoprazole in tablet dosage form. The results of accuracy and precision were comparable to those obtained by spectrophotometry.

Keywords: Pantoprazole; Pharmaceutical analysis; Voltammetry; Carbon paste electrode

1. Introduction

Pantoprazole (**I**), 5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl}-1*H*-benzimidazole, is a highly gastric potent proton pump inhibitor (PPI) being introduced for the treatment of disorders of gastric acid hypersecretion, ulcer disease and relief of symptoms and healing of lesions in gastrooesophageal reflux disease (GERD) [1].



(I)

Pantoprazole is a substituted benzimidazole prodrug that requires an acid-induced activation. It is a weak base that is converted to the active form by gastric acid before acting on the proton pump [2]. Pantoprazole, as do all PPI, inhibits the final stage in gastric acid secretion through covalent binding and inhibition of the H^+/K^+/ATPase pump of the gastric parietal cell [3,4].

There have been relatively few reports for the determination of the drug in formulations or in biological media including spectrophotometry [5,6], high performance liquid chromatography [7–9] and capillary electrophoresis [10–13].

The electroanalytical techniques are well known as excellent procedures for the determination of drug dosage forms and drugs in biological fluids [14]. In recent years, the increasing use of carbon paste electrodes (CPEs) for electroanalytical measurement of a variety of organic species of biological and pharmaceutical importance has been reported [15–18]. The major advantages of carbon paste electrode are low background current; the ease of renewal of the whole electrode providing a fresh surface unaffected by electrode history and this electrode has a wide range of cathodic and anodic applicability [19].

The aim of the present study was to investigate the electrochemical oxidation of pantoprazole at carbon paste electrode and to develop a new differential-pulse adsorptive stripping voltammetric method for the determination of pantoprazole in pharmaceutical preparations. The developed method was applied to the analysis

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of two tablet dosage forms. The results were compared with those from spectrophotometric method [5].

2. Experimental

2.1. Reagents

Pantoprazole sodium sesquihydrate and Controloc® tablets were kindly supplied by Byk Golden (Kanstanz, Germany) batch no. 401971 and Pantoloc® tablets by MUP (Ismailia, Egypt) batch no. 020623. A stock solution of 1.0×10^{-3} M pantoprazole was prepared in methanol and more dilute solutions were prepared daily with methanol just before use. Britton–Robinson buffers (0.04 M, pH 2.0–11.0) were used as supporting electrolytes. Carbon paste was prepared containing 5 g of graphite powder (Aldrich, Milwaukee, WI) 1–2 μm and 1.8 ml of Nujol (Sigma) $d = 0.84$ g/ml. All chemicals used were of analytical-reagent grade. Ultra-pure water was used throughout.

2.2. Apparatus

Measurements were carried out using a computer driven AEW2 Analytical Electrochemical Workstation with ECprog3 Electrochemistry software, (both Sycopel, England) in combination with C-2 stand with a three-electrode configuration: a carbon paste working electrode (BAS model mf-2010, 3 mm diameter), an Ag | AgCl | 3 M KCl reference electrode (BAS model MF-2063) and a platinum wire counter electrode (BAS model MW-1032). Microcal Origin (ver. 4.10) 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.

A Shimadzu UV-160 double beam UV–Vis spectrophotometer was used for spectrophotometric analysis.

2.3. Procedures

Voltammetric analyses were carried out in 10 ml of BR buffers. The accumulation potential (usually open circuit condition) was applied for a selected time while the solution was stirred at 1600 rpm. The stirrer was then stopped, and after 5 s rest period, the drug was removed by stripping anodically using differential-pulse voltammetry (pulse height: 25 mV and scan rate 10 mV/s). After background voltammograms had been recorded, aliquots of the drug standard were introduced and the adsorptive stripping cycle was repeated using a new electrode surface. The peak current was evaluated as the difference between each voltammogram and the background electrolyte voltammogram. All data were obtained at ambient temperature.

2.3.1. Determination of pantoprazole in tablets

The average tablet weight was calculated from contents of ten tablets, the tablets were finely powdered and portion of this powder equivalent to 40 mg of pantoprazole was accurately weighed. The sample was shaken with 25 ml of methanol. Appropriate aliquot of the clear supernatant liquor was then transferred into a voltammetric cell containing 10 ml of BR buffer (0.04M, pH 4.0) to yield a final concentration of 5.0×10^{-6} M pantoprazole. The stripping differential-pulse voltammogram was subsequently recorded following 5 min accumulation time at open circuit condition. The content of the drug in tablet was determined referring to the calibration graph or regression equation.

3. Results and discussion

3.1. Differential-pulse voltammetry

Fig. 1 shows some of the differential-pulse voltammograms obtained for 1.5×10^{-6} M pantoprazole in Britton-Robinson buffers at carbon paste electrode (CPE) following accumulation time of 5 min at open circuit potential. In highly acidic medium, no signal appeared. When the pH increased to a value around pH 4.0, a single and well-defined signal could be seen. At pH > 6.0, two anodic waves appeared. The increase in pH produced a shift in the voltammogram to less positive potential, implying the involvement of protons in the current-limiting electrode process. As the best definition and maximum peak current were obtained for the voltammetric peak at pH 4.0, this pH was chosen for optimization of other variables and for the analytical determination.

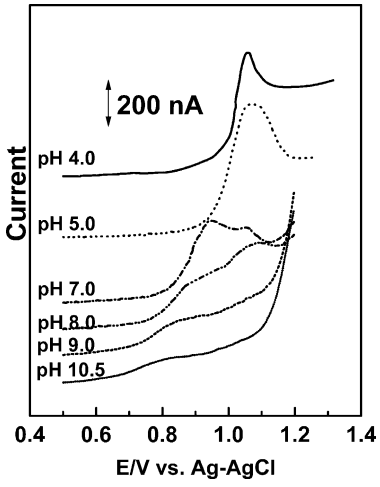

Fig. 1. Differential-pulse voltammograms for 1.5×10^{-6} M pantoprazole at different pH values. Pulse height: 25 mV, scan rate: 10 mV/s and t_{acc}: 5 min.

3.2. Linear sweep and cyclic voltammetry

Repetitive cyclic voltammograms for 5.0×10^{-5} M pantoprazole solution in Britton–Robinson buffer pH 4.0 are presented in Fig. 2. The cyclic voltammogram exhibits a single anodic peak, with no peak on the reverse scan, indicating that the drug is irreversibly oxidized at the carbon paste electrode. Continued scanning resulted in a positive shift of the oxidation potential and a decrease in the peak current. This behavior may be attributed to the formation of an adsorbed species on the electrode surface. After each scan, a thin sheet of carbon paste was discarded and the electrode surface was renewed by wiping on a filter paper.

Linear sweep voltammograms were obtained at different scan rates (25–500 mV/s). It was found that anodic peak potential E_p shifted from 1.080 V at 25 mV/s to 1.175 V at 250 mV/s, a further evidence for the irreversible nature of the electrode reaction [20]. The peak current (i_p) changed linearly with scan rate (v) as expected for adsorption–controlled reactions.

3.3. Effect of accumulation parameters

The effect of accumulation potential was investigated at a potential range from -0.3 to $+0.3$ V or at open circuit potential. The adsorptive behavior at carbon paste electrode was essentially independent of the accumulation potential. This may be due to the non-electrochemical nature of the adsorptive process. The dependence of the stripping peak current on the accumulation time was tested at two concentration levels: 1.0×10^{-5} and 5.0×10^{-5} M using linear sweep voltammetry. The resultant curves are shown in Fig. 3. For 1.0×10^{-5} M pantoprazole solution, the peak current increased linearly with the accumulation time in the whole range of the accumulation times tested, while for 5.0×10^{-5} M solution, a rectilinear relation up to accumulation time of 10 min was obtained. Above this time, saturation of the electrode surface was observed. Hence, the choice of the accumulation time depends on the range of the analyte concentration being determined. An accumulation time of 5 min was chosen as a compromise between sensitivity and speed.

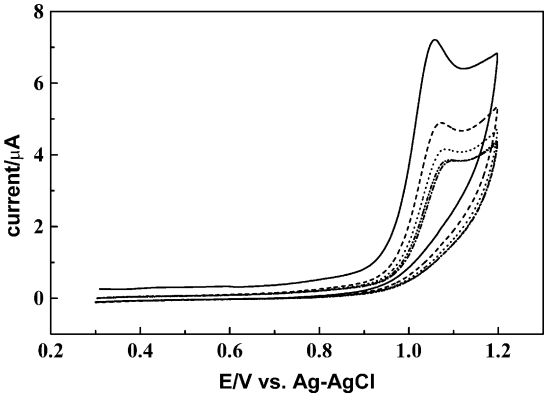

Fig. 2. Repetitive cyclic voltammograms of 5.0×10^{-5} M pantoprazole in Britton–Robinson buffer (0.04 M, pH 4.0). Scan rate: 100 mV/s.

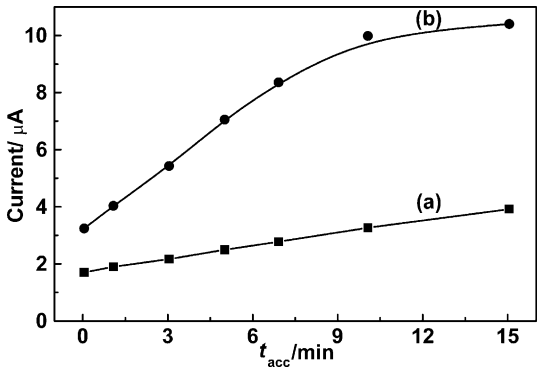

Fig. 3. Stripping peak current-accumulation time plots for (a) 1.0×10^{-5} M and (b) 5.0×10^{-5} M pantoprazole in BR buffer (0.04 M, pH 4.0). Scan rate: 100 mV/s.

3.4. Analytical characteristics

3.4.1. Calibration curve

The influence of pantoprazole concentration on peak current in Britton–Robinson buffer at pH 4.0 using differential pulse voltammetry (pulse height: 25 mV and scan rate: 10 mV/s) following 5 min at open circuit condition is shown in Fig. 4. A linear range was observed for concentration between 1.0×10^{-7} and 1.0×10^{-5} M; then the plot leveled off at higher concentration, as expected for a process that is limited by adsorption of analyte. The regression equation was i_p (nA) $= 182 + 200c$ (μM) with $r = 0.998$. The detection limit, calculated following the expression $a + 3S_{yx}$ [21], where a = intercept and S_{yx} = error standard deviation, was 2.0×10^{-8} M.

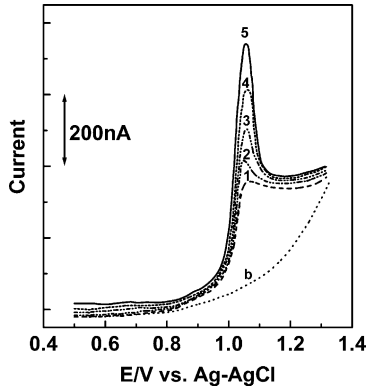

Fig. 4. Differential-pulse voltammograms for different pantoprazole concentrations in BR buffer (0.04 M, pH 4.0), (1) 5.0×10^{-7} M (2) 1.0×10^{-6} M (3) 1.5×10^{-6} M (4) 2.0×10^{-5} M and (5) 2.5×10^{-6} M. (b) The blank response.

Table 1
Accuracy and precision data for pantoprazole obtained by differential-pulse voltammetric (DPV) method

Added (μM)	Found (μM) $\bar{x}$	Precision			Accuracy (% relative error)
		Standard deviation, s	Relative standard deviation, s_r	Confidence limit ($n = 5$, $P = 0.05$) CL	
0.13	0.127	0.013	2.65	0.016	−2.0
0.65	0.655	0.024	0.95	0.030	0.80
1.30	1.310	0.054	1.07	0.067	−0.80
2.60	2.592	0.109	1.09	0.136	−0.30
3.90	3.843	0.381	2.28	0.474	−1.47

3.4.2. Accuracy and precision

In order to determine the accuracy and precision of the method, solutions containing five different concentrations of pantoprazole were prepared and analysed in quintuplicate. The measured standard deviations (s), relative standard deviation (s_r), the confidence limit (CL) and the percentage relative error (Table 1) can be considered satisfactory, at levels of concentrations examined.

3.4.3. Interference

The voltammograms obtained with the synthetic samples of pantoprazole are in fact the same as those obtained with pure pantoprazole. The presence of tablet excipients causes no interference with the pantoprazole.

3.4.4. Application to pharmaceuticals

The differential-pulse voltammetric technique (DPV) has been applied to determine pantoprazole in two tablet dosage forms containing 40 mg of drug per tablet, Pantoloc (MUP, Egypt) and Controloc (Byk Gulden, Konstanz, Germany). The results of the proposed technique have been evaluated statistically as compared to results of spectrophotometeric method (Table 2). The spectrophotometric method is based on the absorption of pantoprazole in methanol at 290 nm [5]. There was no significant difference between the mean values and precision of the two methods at 95% confidence level.

Table 2
Data of differential-pulse voltammetric (DPV) and UV-spectrophotometric methods for determination of pantoprazole

Technique Preparations	DPV		UV–spectrophotometric	
	Pantoloc	Controloc	Pantoloc	Controloc
n	5	5	5	5
$\bar{x}$	40.13	39.88	40.25	39.79
s	0.53	0.61	0.67	0.77
s_r	1.32	1.53	1.66	1.94
CL	0.66	0.76	0.83	0.96
t-test significance	0.31	0.20	t ($P = 0.05$) = 2.78	
F-test significance	0.63	0.63	F ($P = 0.05$) = 6.39	

4. Conclusion

It can be concluded that pantoprazole is irreversibly oxidized in a pH-dependent reaction on the carbon paste electrode with adsorption characteristics. The adsorptive differential-pulse voltammetric method described here, is sensitive, rapid, reliable and simple to perform, and thus suitable for analysis of pharmaceutical preparations. Preparation of the samples is easy and no extraction procedure is required.

References

[1] A. Dettmer, R. Vogt, F. Sielaff, R. Luhmann, A. Schneider, R. Fischer, Pantoprazole 20 mg is effective for relief of symptoms and healing of lesions in mild reflux oesophagitis, Aliment. Pharmacol. Ther. 12 (1998) 865–872.
[2] R.J. Playford, T. Podas, I. Modlin, Pantoprazole, prout and the proton pump, Hosp. Med. 60 (1999) 500–504.
[3] P.W. Jungnickel, Pantoprazole: a new proton pump inhibitor, Clin. Ther. 22 (2000) 1268–1289.
[4] L.S. Welage, R.R. Berardi, Evaluation of omeprazole, lansoprazole, pantoprazole and raberazole in treatement of acid-related diseases, J. Am. Pharm. Assoc. 40 (2000) 52–62.
[5] A.A.M. Moustafa, Spectrophotometric methods for the determination of lansoprazole and pantoprazole sodium sesquihydrate, J. Pharm. Biomed. Anal. 22 (2000) 45–58.
[6] A.M. Wahbi, O. Abdel-Razak, A.A. Gazy, H. Mahgoub, M.S. Moneeb, Spectrophotometric determination of omeprazole, lansoprazole and pantoprazole in pharmaceutical formulations, J. Pharm. Biomed. Anal. 30 (2002) 1133–1142.
[7] A. Ekpe, T. Jacobsen, Effect of various salts on the stability of lansoprazole, omeprazole and pantoprazole as determined by high-performance liquid chromatography, Drug Dev. Ind. Pharm. 25 (1999) 1057–1065.
[8] M. Tanaka, H. Yamazaki, H. Hakushi, Direct HPLC separation of enantiomers of pantoprazole and other benzimidazole sulfoxides using cellulose-based chiral stationary phases in reversed-phase mode, Chirality 7 (1995) 612–615.
[9] M. Tanaka, H. Yamazaki, Direct determination of pantoprazole enantiomers in human serum by reversed-phase high-performance liquid chromatography using a cellulose-based chiral stationary phase and column-switching system as a sample clean up procedure, Anal. Chem. 68 (1996) 1513–1516.
[10] D. Eberle, R.B. Hummel, R. Kuhn, Chiral resolution of pantoprazole sodium and related sulfoxides by complex formation with bovine serum albumin in capillary electrophoresis, J. Chromatogr. 759 (1997) 185–192.

[11] N. Masubuchi, H. Yamazaki, M. Tanaka, Stereoselective chiral inversion of pantoprazole enantiomers after separate doses to rats, Chirality 10 (1998) 747.
[12] A. Tivesten, S. Folestad, V. Schonbacher, K. Svensson, Nonaqueous capillary electrophoresis for the analysis of labile pharmaceutical compounds, Chromatographia 49 (1999) S7–S11.
[13] Q.B. Cass, A.L.G. Degani, N.M. Cassiano, J. Pedrazolli, Jr, Enantiomeric determination of pantoprazole in human plasma by multidimensional high-performance liquid chromatography, J. Chromatogr. B 766 (2001) 153–160.
[14] M.A. Brooks, Application of electrochemistry to pharmaceutical analysis, in: P.T. Kissinger, W.R. Heineman (Eds.), Laboratory Techniques in Electroanalytical Chemistry, 2nd ed., Marcel Dekker, New York, 1996.
[15] M.A. Garcia-Fernandez, M.T. Fernandez-Abedul, A. Costa-Garcia, Voltammetric study and determination of buprenorphine in Pharmaceuticals, J. Pharm. Biomed. Anal. 21 (1999) 809–815.
[16] G.J. Volikakis, C.E. Efstathiou, Determination of rutin and other flavonoids by flow-injection: adsorptive stripping voltammetry using nujol–graphite and diphenylether–graphite paste electrodes, Talanta 51 (2000) 775–785.
[17] R.F. Torres, M.C. Mochon, J.C.J. Sanchez, M.A.B. Lopez, A.G. Perez, Electrochemical oxidation of cisatracurium on carbon paste electrode and its analytical applications, Talanta 53 (2001) 1179–1185.
[18] A.R. Fiorucci, E.T.G. Cavalheiro, The use of carbon paste electrode in the direct voltammetric determination of tryptophan in pharmaceutical formulations, J. Pharm. Biomed. Anal. 28 (2002) 909–915.
[19] R.L. McCreery, Carbon electrodes, Structural effects on electron transfer kinetics, in: A.J. Bard (Ed.), Electroanalytical Chemistry, vol. 17, Marcel Dekker, New York, 1991.
[20] R.S. Nicholson, I. Shain, Theory of stationary electrode polarography single scan and cyclic methods applied to reversible, irreversible, and kinetic systems, Anal. Chem. 36 (1964) 706–723.
[21] J.C. Miller, J.N. Miller, Statistics for Analytical Chemistry. Ellis Horwood Series, Prentice Hall, New York, 1993, p. 119.