Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Pharmaceutical and Biomedical Analysis 37 (2005) 195–198
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Short communication

Differential pulse voltammetric determination of the dopaminergic agonist bromocriptine at glassy carbon electrode

A. Radi*, M.S. El-Shahawi, T. Elmogy

Department of Chemistry, Faculty of Science, Mansoura University, 34517 Dumyat, Egypt

Received 2 May 2004; received in revised form 6 October 2004; accepted 10 October 2004
Available online 23 November 2004

Abstract

The electrochemical oxidation of bromocriptine at glassy carbon electrode has been carried out in Britton–Robinson (B–R) buffer solutions in the pH range 2.0–11.0 employing cyclic, linear sweep and differential pulse voltammetry (DPV). Bromocriptine showed one well-defined oxidation peak accompanied by a smaller one. The oxidation process was found irreversible. For analytical purposes, the well-resolved diffusion controlled voltammetric peak at pH 5 was critically investigated. The linear relationship between peak current height and bromocriptine concentration allowed the differential pulse voltammetric determination of the drug over a wide concentration range, from 0.04 to 5.00 $\mu g\,ml^{-1}$ with a detection limit of 0.01 $\mu g\,ml^{-1}$. A relative standard deviation of 1.44% at 0.1 $\mu g\,ml^{-1}$ level was obtained. The proposed DPV method was successfully applied for the individual tablet assay to verify the uniformity content of bromocriptine in commercial tablets.

Keywords: Bromocriptine; Differential pulse voltammetry; Glassy carbon electrode; Electrochemical oxidation; Pharmaceutical analysis

1. Introduction

The semi-synthetic ergot alkaloid bromocriptine [1] exhibits several therapeutic effects [2–6]: (i) it has a beneficial effect in severely disabled patients suffering from Parkinson's disease, (ii) it is used, like other ergot alkaloids, in the treatment of migraine, and (iii) it is a strong inhibitor of prolactin formation and have therapeutic potency in the treatment of hyperprolactinaemia. These effects have been related to its ability to block dopamine receptors and to its interaction with calmodulin-induced activation of phosphodiesterases in human brain [7,8].

Several analytical procedures have been published for quantification of bromocriptine levels in biological fluids. Radioimmunoassay methods have been used to measure bromocriptine in rat tissue and in human plasma [9,10]. Gas chromatographic, mass spectrometric and liquid chromatographic techniques have been described for the determinations of bromocriptine in human plasma [11–14]. High-performance liquid chromatographic (HPLC) methods with UV or MS detector have also been reported [15–16]. Few reports for the determination of the drug in formulations including X-ray fluorescence spectroscopic analysis [17] and high-performance liquid chromatography [18] have been published.

So far, it seems that, no report has been appeared in the literature on the electrochemical redox properties of bromocriptine. Electroanalytical techniques, especially modern pulse techniques, such as differential pulse have been used for the determination of a wide range of pharmaceuticals [19]. Thus, the present paper describes the electrochemical behavior of bromocriptine at a glassy carbon electrode using cyclic, linear sweep and differential pulse voltammetry and the analytical determination of the title drug in tablets by differential pulse voltammetry.

* Corresponding author. Tel.: +20 57 403 866; fax: +20 57 403 868.
E-mail address: abdradi@yahoo.com (A. Radi).

0731-7085/$ – see front matter © 2004 Published by Elsevier B.V.
doi:10.1016/j.jpba.2004.10.013

2. Experimental

2.1. 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 (BAS model MF-2012, Ø = 3 mm) working electrode, an Ag–AgCl–3 M KCl (BAS model MF-2063) reference electrode and a platinum wire (BAS model MW-1032) counter electrode. OriginPro 7.0 software was used for the transformation of the initial signal. A Schott Geräte CG 808 digital pH meter with H 61 pH combination electrode (Mainz, Germany) was used for the pH measurements.

2.2. Reagents

Bromocriptine mesylate and Lactodel® tablets were obtained from (Amoun Phar., Cairo, Egypt). Stock solution of bromocriptine was prepared by dissolving the drug in methanol. Stock solution was stored under refrigeration and was stable for at least eight weeks. Working solutions of bromocriptine were obtained by serial dilution of the stock solution into methanol. Britton–Robinson buffers (0.04 M in each of acetic, orthophosphoric, and boric acids, adjusted to the required pH with 0.2 M sodium hydroxide) were used as supporting electrolytes. All solutions were prepared from AnalaR-grade reagents in double distilled water.

2.3. Procedure

A 10 ml of the electrolyte solution was transferred into the voltammetric cell. After measurement of the blank solution, the appropriate amount of bromocriptine solution was 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 glassy carbon electrode was polished manually with alumina (Ø = 0.01 μm) in the presence of bidistilled water on a smooth polishing cloth prior to each measurement.

2.3.1. Tablets assay procedure

One finely ground tablet of Lactodel® (amount declared 2.5 mg bromocriptine mesylate per tablet) was dissolved in 5 ml methanol. The contents were sonicated for 10 min to insure complete dissolution. A suitable amount of the supernatant liquor was diluted to 10 ml with 0.04 M B–R buffer solution at pH 5.0 to obtain a bromocriptine concentration of 0.10 μg ml^{-1}. The sample solution was transferred to a voltammetric cell and recorded at least twice following the optimized experimental conditions. The amount of bromocriptine (mg) in the sample solution was calculated from the prepared standard calibration plot.

3. Results and discussion

Preliminary differential pulse voltammetry experiments of 1.0 μg ml^{-1} bromocriptine in B–R buffer over the pH range 2.0–11.0 at glassy carbon electrode were carried out. Representative differential pulse voltammograms are shown in Fig. 1. At the investigated pH, one well-defined peak was observed accompanied by a smaller one. Thus, in the subsequent work the study was focused mainly on the first oxidation peak because of its analytical interest. The plot of E_{p1} versus pH showed two straight lines (Fig. 2a), which can be expressed by the following equations in differential pulse voltammetry in B–R buffer: E_{p1} (V) = 1.011 + 0.070 pH, r = 0.996 and E_{p1} (V) = 0.070 + 0.025 pH, r = 0.997. The intersection observed in the plot at pH 7 is most likely attributed to a change in protonation–deprotonation process of the electroactive indolic moiety in the molecular structure of bromocriptine. The best results with respect to signal enhancement (Fig. 2b) accompanied by sharper response was obtained with B–R buffer at pH 5.0. Thus, this supporting electrolyte was chosen for subsequent measurement experiments.

Cyclic voltammetry was also used to investigate the anodic oxidation of bromocriptine. A typical cyclic

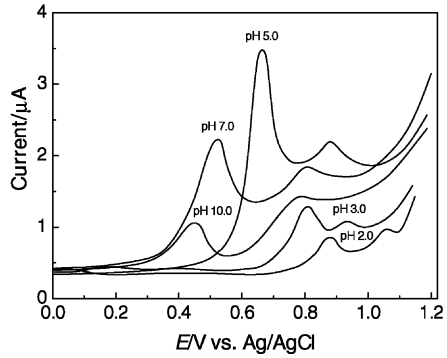

Fig. 1. Differential pulse voltammograms for 1.0 μg ml^{-1} bromocriptine in B–R buffers of different pH values, at glassy carbon electrode. Scan rate, 10 mV s^{-1}; pulse amplitude, 50 mV; pulse width, 30 ms.

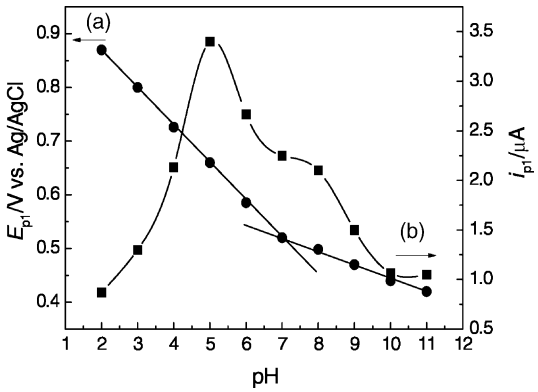

Fig. 2. Effect of pH on (a) peak potential and (b) peak current in B–R buffer using differential pulse voltammetry at glassy carbon electrode. Bromocriptine concentration, 1.0 μg ml^{-1}; scan rate, 10 mV s^{-1}; pulse amplitude, 50 mV; pulse width, 30 s.

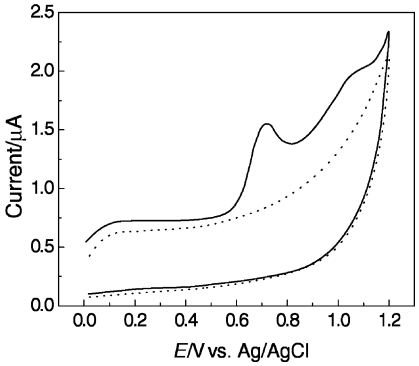

Fig. 3. Cyclic voltammograms of 10.0 μg ml^{-1} bromocriptine solution on glassy carbon electrode in B–R buffer at pH 5.0. Scan rate, 100 mV s^{-1}. The dotted lines represent blank solution.

voltammogram of 10.0 μg ml^{-1} bromocriptine at glassy carbon electrode in Britton–Robinson buffer at pH 5.0 is shown in Fig. 3. Bromocriptine showed a main anodic peak followed by a smaller one. No reduction peaks were obtained in the reverse scans at any scan rate used (until 500 mV s^{-1}), suggesting the irreversible character of the overall process involved at the glassy carbon electrode.

Cyclic voltammograms recorded at different potential scan rates showed a positive shift in the peak potential, which confirms the irreversibility of the process, with a simultaneous increase in the peak current height when the scan rate 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 0.90. The plot of logarithm of peak current versus logarithm of scan rate (ν) also gave a straight line (correlation coefficient $r = 0.998$) with a slope of 0.55, close to the theoretical value of 0.5, which is expected for an ideal reaction of solution species [20], indicating that the oxidation process is predominantly diffusion-controlled in the whole range of scan rate studied.

The plot of the anodic peak potential (E_p) versus the logarithm of scan rate (ν) was found linear, with a slope value $b = 2.303RT/\alpha n_a F$ of 0.082, where α is the charge transfer coefficient and n_a the number of electrons involved in the rate-determining step. The dependence of E_p on pH is $\partial E_p/\partial \mathrm{pH} = mb$ [21], where m is the electrochemical reaction order with respect to the H^+ ion. The experimental value was found around 0.070 V per pH unit, meaning that $m = 1$. These data are actually as expected for a one proton, one electron transfer process from the nitrogen atom of the indolic moiety in the rate-determining step.

3.1. Analytical application

In order to develop a voltammetric method for the determination the drug, we selected the differential pulse mode. Differential pulse mode yielded voltammogram in which the peak currents were greater than those obtained by cyclic and linear sweep voltammetry. The DP voltammograms (pulse amplitude, 50 mV; pulse width 50 ms; scan rate, 20 mV s^{-1}) showed successive enhancement of peak current on increasing bromocriptine concentration. An excellent calibration curve over a wide range 0.04–5.00 μg ml^{-1} was obtained. The calibration graph fitted the equation: i_{p1} (μA) = (0.0289 ± 0.0151) + (3.3997 ± 0.0306) C (μg ml^{-1}), with a correlation coefficient $r = 0.9995$. The limit of detection (LOD) of the developed procedure was calculated to be 0.01 μg ml^{-1}, based upon the definition: LOD = $3S_{y/x}/b$ [22], where $S_{y/x}$ is the standard deviation of y-residuals and b is the slope of the calibration plot. The reproducibility of the measurement was calculated for five independent runs of 1.0 μg ml^{-1} bromocriptine solution. The relative standard deviations were calculated to be 0.72 and 1.44% for peak potential and peak current, respectively.

The effect of various inactive ingredients (colloidal silicon dioxide, gelatin, lactose, magnesium stearate, silicon dioxide, sodium lauryl sulfate, starch, titanium dioxide, yellow iron oxide) in the bromocriptine tablets was examined carrying out the determination of 1.0 μg ml^{-1} bromocriptine by the developed method in the presence of each inactive ingredient at concentrations that can be found in the tablet dosage form. A deviation of more than 2% from the peak current of the solution containing no inactive ingredients was taken as a sign of interference. The results showed that the inactive ingredients in the bromocriptine tablets do not cause positive or negative error in the measurements, indicating that there was no interference to the method.

The proposed DP voltammetry method was applied for the individual tablet assay in order to verify the uniformity content of bromocriptine in tablets. The bromocriptine was commercially provided by Amoun Phar. (Cairo, Egypt) presentation named Lactodel® tablets containing 2.5 mg of bromocriptine. High-performance liquid chromatography (HPLC) with UV [18] detector was chosen as a comparison method to evaluate the validity of the proposed voltammetric procedure. The results obtained by the proposed DPV were compared to those of the HPLC method utilizing certain statistical evaluations. The results of the statistical evaluations are demonstrated in Table 1. The results of F- and t-tests showed that there were insignificant differences between the two techniques. Moreover, The content for all assayed tablets falls within the claimed amount, fulfilling the

Table 1
Application of the proposed voltammetric method to the determination of bromocriptine analysis in single Lactodel® tablets

	Proposed voltammetric method	Reference HPLC method [18]
Labeled amount (mg)	2.50	2.25
n	6	6
$\bar{x}$	2.48	2.51
s	0.040	0.011
CL	±0.042	±0.012
t-test of significance	1.91 (2.23[a])	
F-test of significance	0.075 (5.05[a])	

[a] The tabulated t- and F-values, respectively, at $P = 0.05$.

criteria of acceptance set according to the USP23 Uniformity of the Dosage Units [23]. Content uniformity test allows not a single one of the assayed tablets to deviate more than 10%.

4. Conclusions

The developed voltammetric method provides the advantage of simplicity, precision and reliability. It allows direct determination of bromocriptine by skipping several tedious sample preparation steps. The proposed method is free from the interferences of inactive ingredients used in the drug formulation. In this study, the glassy carbon electrode was selected, as it is very commonly used as electrochemical detector for HPLC and FIA techniques.

References

[1] US Pharmacopoeia, twenty seventh ed., US Convention, Rockville, MD, 2004, p. 266.
[2] D. Parkes, in: N.J. Harper, A.B. Simmonds (Eds.), Advances in Drug Research, Academic Press, New York, 1977, pp. 247–344.
[3] H.P. Weber, in: M. Goldstein (Ed.), Ergot Compounds and Brain Function: Neuroendocrine and Neuropsychiatric Aspects, Raven Press, New York, 1980, pp. 25–34.
[4] K.Y. Ho, M.O. Thorner, Drugs 36 (1988) 67–82.
[5] F. Marzatico, C. Cafe, M. Taborelli, G. Benzi, Neurochem. Res. 18 (1993) 1101–1111.
[6] E. Del Pozo, L. Varga, H. Wyss, G. Tolis, H. Friesen, R. Wenner, L. Vetter, A. Uettwiler, J. Clin. Endocrinol. Metab. 39 (1974) 18–26.
[7] C.Q. Earl, W.C. Prozialeck, B. Weiss, Life Sci. 35 (1984) 525–534.
[8] B. Weiss, W.C. Prozialeck, T.L. Wallace, Biochem. Pharmacol. 31 (1982) 2217–2226.
[9] J.S. Bevan, D. Baldwin, C.W. Burke, Ann. Clin. Biochem. 23 (1986) 686–693.
[10] D. Valente, E. Ezan, C. Creminon, M. Delaforge, H. Benech, P. Pradelles, J.M. Grognet, J. Immunoassay 17 (1996) 297–320.
[11] N-E. Larsen, R. Ohman, M. Larsson, E.F. Hvidberg, J. Chromatogr. 174 (1979) 341–349.
[12] K.H. Schellenberg, M. Linder, A. Groeppelin, F. Erni, J. Chromatogr. 394 (1987) 239–251.
[13] N. Haering, Z. Salama, H. Jaeger, Arzneim. Forsch. 38 (1988) 1529–1532.
[14] L.M. Nyholm, P.J.R. Sjoberg, K.E. Markides, J. Chromatogr. A. 755 (1996) 153–164.
[15] D.G. Phelan, N.H. Greig, S.I. Rapoport, T.T. Soncrant, J. Chromatogr. 533 (1990) 264–270.
[16] Y.J. Choi, M.K. Seo, I.C. Kim, Y.H. Lee, J. Chromatogr. B 694 (1997) 415–420.
[17] M.A. Raggi, F. Lucchini, P. Da-Re, Collect. Czech. Chem. Commun. 56 (1991) 2229–2233.
[18] N.H. Foda, F. El-Shafie, J. Liq. Chromatogr. Relat. Technol. 19 (1996) 3201–3209.
[19] M.A. Brooks, in: P.T. Kissinger, W.R. Heineman (Eds.), Laboratory Techniques in Electroanalytical Chemistry, second ed., Marcel-Dekker, New York, 1996.
[20] D.K. Gosser Jr., Cyclic Voltammetry. Simulation and Analysis of Reaction Mechanisms, VCH, New York, 1993, p. 43.
[21] J.M. Rodriguez-Mellado, M. Blazquez, M. Dominguez, J.J. Ruiz, J. Electroanal. Chem. 195 (1985) 263–270.
[22] J.C. Miller, J.N. Miller, Statistics for Analytical Chemistry, Ellis Horwood Series, PTR Prentice Hall, New York, London, 1993, p. 119.
[23] US Pharmacopoeia, twenty-seventh ed., US Convention, Rockville, MD, 2004, p. 2396.