ELSEVIER

Journal of Pharmaceutical and Biomedical Analysis
17 (1998) 349–355

JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

Determination of terbutaline based on oxidation by voltammetry[1]

N. Yilmaz [a], S.A. Özkan [a], B. Uslu [a], Z. Şentürk [b,*], İ. Biryol [a]

[a] *Department of Analytical Chemistry, Faculty of Pharmacy, Ankara University, 06100 Ankara, Turkey*
[b] *Department of Analytical Chemistry, Faculty of Pharmacy, Gazi University, 06330 Ankara, Turkey*

Received 3 November 1997; accepted 3 November 1997

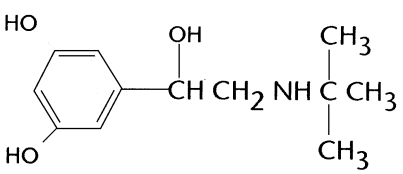
Abstract

A voltammetric study of the oxidation of terbutaline has been carried out at an activated glassy carbon electrode. The compound was oxidized irreversibly at high positive potential. The response was evaluated with respect to pH, scan rate, nature of the buffer and other variables. The peak current, at about 0.8 V (versus a saturated calomel electrode), was proportional to the terbutaline concentration in the range of 8×10^{-6}–8×10^{-4} M in phosphate buffer pH 6.0. This method was applied, without any interferences from the excipients, to determine the drug in a tablet dosage form. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Terbutaline; Voltammetry; Activated glassy carbon electrode; Formulation analysis

1. Introduction

Terbutaline [1-(3,5-dihydroxyphenyl-2-(*tert*-butylamino) ethanol], is a β_2 adrenoceptor agonist, primarily used in the treatment of bronchial asthma and other forms of allergic airway diseases [1].



The drug is given orally and/or by injection or inhalation [1]. In some respiratory diseases, it can often be taken in overdoses which can cause tremor, tachycardia, hypokalamia and sometimes fatal consequences [2]. It is for this reason that the analysis of terbutaline is important in pharmaceutical research and clinical chemistry.

High performance liquid chromatographic (HPLC) methods with ultraviolet [3], electrochemical [4–6] and fluorescence [7] detectors have been used mainly for the analysis of terbutaline in plasma. For such applications, however, the operations are time-consuming. There are few reported methods for the simultaneous determination of terbutaline and related compound, salbutamol, in plasma based on gas chromatography-mass spectrometry [8,9]. However,

* Corresponding author.

[1] Presented at the Fifth International Symposium on Pharmaceutical Science, June 1997, Ankara, Turkey.

0731-7085/98/$19.00
PII S0731-7085(97)00226-4

these methods require expensive instrumentation, and sample preparation is not available in clinical laboratories. Methods for the assay of terbutaline in pharmaceutical dosage forms are usually based on spectrophotometric determinations [10,11]. A flow injection analysis method with spectrophotometric detection has also been developed for the colorimetric determination of the drug [12]. The USA Pharmacopeia [13] recommends a spectrophotometric method with 4-aminoantipyrine and ferricyanide, whereas the British Pharmacopoeia [14] describes an HPLC method for the determination of terbutaline in drug formulations. Standard terbutaline can also be determined using the non-aqueous titrimetric method of both pharmacopeias [13,14]. In recent years, capillary zone electrophoresis has been applied to determine the compound in pharmaceutical formulations [15] and biological fluids [16].

The voltammetric characteristics of terbutaline have, to the best of our knowledge, not been reported previously. Owing to the presence of several electrochemically oxidizable groups in its molecular structure, confirmed by HPLC with electrochemical detector, it was decided to investigate voltammetric behavior of terbutaline at a glassy carbon electrode, which is in common use as a working electrode because of its low residual current in aqueous media. Further studies of this compound included the development of a simple and precise method for its determination in tablets.

2. Experimental

2.1. Apparatus

The voltammograms were recorded with a PRG-3 polarograph and an EPL-2 recorder (Tacussel Electronique). A saturated calomel electrode (SCE) and a platinum wire electrode were used as reference and counter electrodes, respectively. The working electrode was a glassy carbon stationary electrode (Tacussel XM 540, area 1.013 cm^2). For comparison studies, a platinum wire electrode (Tacussel, diameter 1 mm, height 15.7 mm) was used. A Wenking model HP 70 potentiostat and an exact-type 250 function generator were employed for the application of pretreatment to the glassy carbon electrode. Spectrophotometric measurements were carried out using a Shimadzu UV 160 spectrophotometer with a 1 cm quartz cell.

2.2. Reagents

Terbutaline sulphate (generously provided by Eczacibaşi, İstanbul, Turkey) was used without further purification. All other chemicals used were of analytical reagent grade. All solutions were prepared with doubly distilled water. Stock solutions were prepared by dissolving appropriate amounts of terbutaline sulphate in selected supporting electrolytes, namely acetate buffer (pH 3–6, 0.2 M), phosphate buffer (pH 4.5–7.5, 0.2 M) and Britton–Robinson buffer (pH 2–12, 0.2 M). For the spectrophotometric study, working solutions of tris(hydroximethyl)aminomethane (pH 9.5), 4-aminoantipyrine and ferricyanide were used.

2.3. Pretreatment of working electrodes

After polishing with 0.3 μm aluminium oxide, the glassy carbon electrode was pretreated by cycling a square wave potential with a frequency of 350 Hz between the potential limits of ± 6 V, followed by the application of a triangular potential sweep between ± 6 V (frequency 3500 Hz) in 0.1 M potassium nitrate solution. Finally, this procedure was followed by electrochemical treatment involving an application of $+1.25$ V for 5 min, followed by -1.0 V for 2 s in 0.1 M potassium nitrate solution. These steps were repeated until reproducible voltammetric signals were obtained. At the end of these procedures, the electrode surface was so stable that for ca. 40 measurements, the above mentioned electrochemical treatment alone was sufficient prior to each analysis [17].

When a platinum electrode was utilized, it was electrochemically pretreated with an application of $+1.25$ V for 5 min and then maintained at a potential of $+0.15$ V for 5 min in deaerated 0.5 M sulphuric acid.

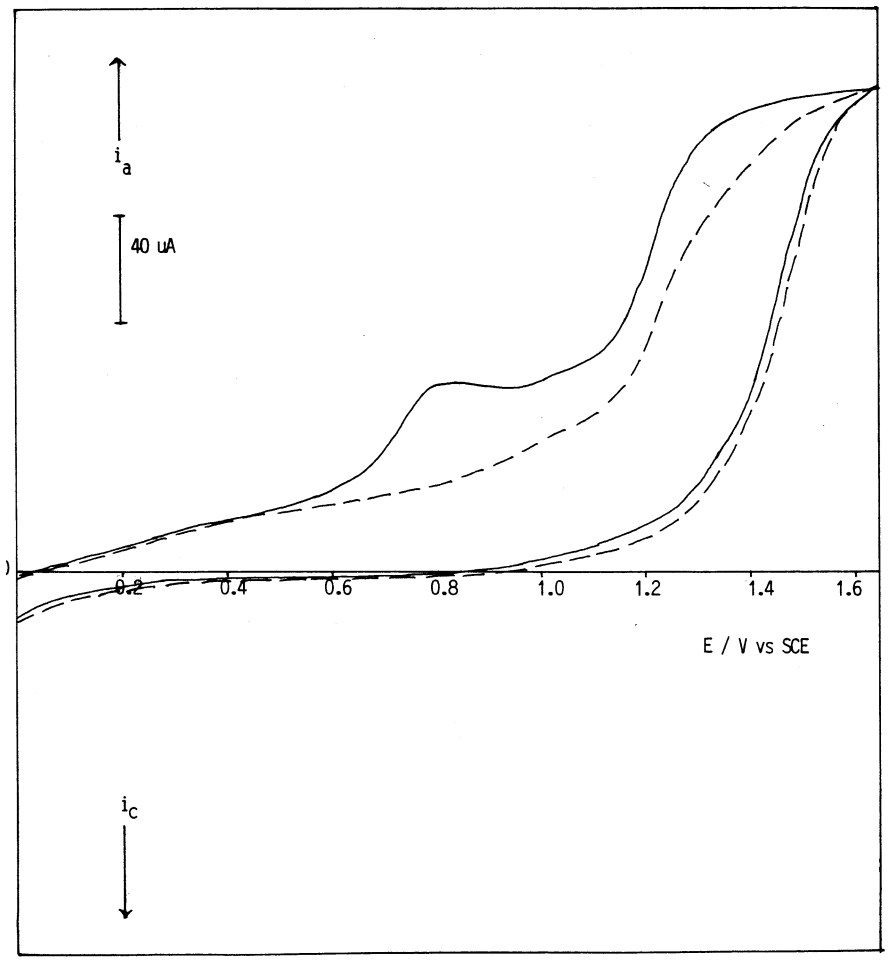


Fig. 1. Cyclic voltammogram of terbutaline (concentration 4×10^{-4} M) at an activated glassy carbon electrode (phosphate buffer pH 6.0, scan rate 100 mV s^{-1}). The dashed line represents the blank scan.

2.4. Analysis of tablets

Ten tablets were weighed and their average value was determined. The tablets were then reduced to a homogeneous fine powder in a mortar, an accurately weighed quantity of powder, corresponding to a stock solution of concentration ca. 1×10^{-3} M, was dissolved in phosphate buffer pH 6.0 and transferred to a 100 ml volumetric flask. The resulting mixture was stirred magnetically for 15 min to ensure that terbutaline was dissolved completely. Appropriate solutions were prepared by taking suitable aliquots of the clear supernatant liquor and diluting them with the same supporting electrolyte. Each solution was transferred to a voltammetric cell and recorded in a similar way to the pure drug.

3. Results and discussion

This article is one of a series about electroanalytical behavior of several organic molecules [18–26] at glassy carbon electrode, activated by applying a new pretreatment and carried out in our department.

The voltammetric oxidation of terbutaline at the activated glassy carbon electrode was investi-

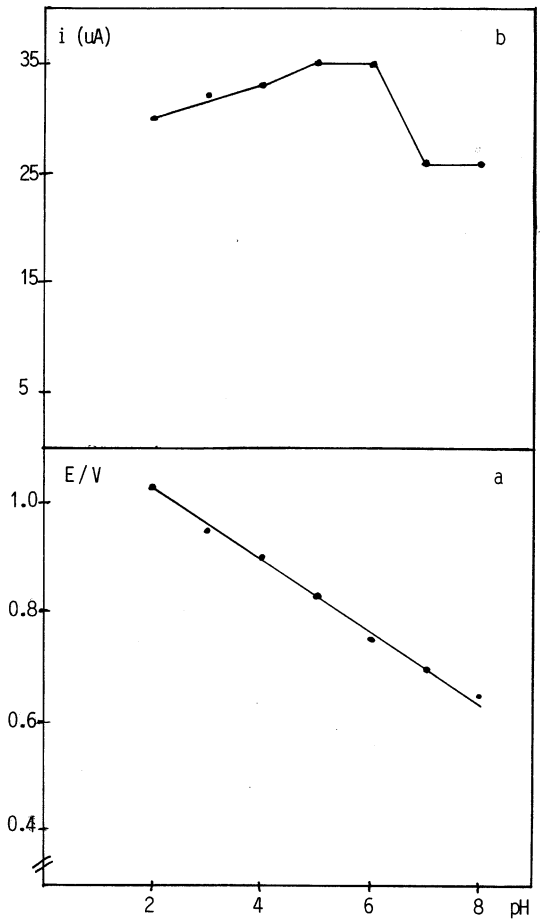


Fig. 2. Effects of pH on the terbutaline peak potential (a) and peak current (b). Terbutaline concentration 4×10^{-4} M, scan rate 100 mV s^{-1}.

gated in the pH range 2–12.0. The cyclic voltammetric behavior of the compound yielded a single oxidation process in all cases. Fig. 1 shows the cyclic voltammogram of 4×10^{-4} M terbutaline in phosphate buffer (pH 6). At pH > 8, this process became smaller, together with a poor peak definition. In reverse scan, a small single cathodic peak was observed, which may be due to the reduction of the oxidized product (e.g. at ca. −0.1 V in phosphate buffer pH 6; not shown in Fig. 1). Cyclic voltammetry demonstrated the total irreversibility of this system at scan rates from 10 to 100 mV s^{-1}.

The relationship between peak potential and pH for the oxidation process of terbutaline is shown in Fig. 2a. Linearity was observed in the pH range 2–8, giving a negative slope of 65.5 mV per pH unit. Such behavior was also reported for the oxidation of other related compounds: salbutamol, fenoterol and metaproterol on carbon paste electrode [27]. The measurement became unreliable above pH 8 due to distortion of the response. The peak current was also pH dependent (Fig. 2b). The maximum peak current value was obtained at pH 6.0, hence why this pH value was chosen to carry out the electroanalytical study.

For the oxidation process, the effect of the potential scan rate on the peak current and potential were investigated at a scan rate range 10–100 mV s^{-1}. When the scan rate increased, the peak current increased and shifted in the positive direction. The diffusion control of this process was demonstrated by the linear relation of peak current and the square root of the scan rate (correlation coefficient 0.996). The optimum scan rate was found to be 100 mV s^{-1} with regard to oxidation peak current sensitivity, and subsequently, this was used throughout the study. The influence of different supporting electrolytes is shown in Table 1. The experimental results showed that the

Table 1
Voltammetric characteristics of terbutaline in the buffer systems

Buffer	Studied pH range	Selected pH	E_p/V	I_p/μA
Britton–Robinson	2–12	4	0.90	33
		6	0.75	35
Acetate	3–6	4	0.85	24
Phosphate	4.5–7.5	6	0.80	38

Terbutaline concentration 4×10^{-4} M.

Table 2
Statistical analysis of current–potential dependence of terbutaline at an activated glassy carbon electrode

Medium	Concentration range (M)	Slope (μA/M)	Intercept (μA)	Correlation coefficient	S.E. of the slope (μA/M)	S.E. of the intercept (μA)
Phosphate buffer pH 6	8×10^{-6}–8×10^{-4} ($n=11$)	8.88×10^{4}	2.52	0.999	1.14×10^{3}	0.38

Table 3
Comparative studies for terbutaline tablets

	Voltammetry	Spectrophotometry [13]
Amount found[a](mg)	2.55	2.56
R.S.D. (%)	1.2	0.8
$t_{calculated}$	0.717	$t_{theoretical}$: 2.306 ($P = 0.05$)

Declared amount 2.5 mg per tablet.
[a] The mean of five measurements.

shapes of the curves were nearly the same in all cases, however, the current intensity in phosphate buffer was higher than in Britton–Robinson and acetate buffers. A phosphate buffer (pH 6) was the best compromise with respect to sharper response and reproducibility for analytical application.

To provide a reproducibly active surface, and to improve the sensitivity, the glassy carbon electrode was pretreated as described in Section 2. The surface chemistry, including scanning electron microscopic imaging of this modified electrode, was discussed in our previous paper [17]. From the terbutaline voltammograms, it appeared that the use of the activated glassy carbon electrode caused higher faradaic currents than those achieved at nonactivated electrodes polished on 0.3 μm aluminium oxide after each scan. The ratio of faradaic current (at approximately $+0.8$ V for 4×10^{-4} M terbutaline in phosphate buffer pH 6) to the background current for activated and nonactivated surfaces were found to be 2.52 and 1.82, respectively.

Comparative study on resorcinol, by cyclic voltammetry at the activated and non-activated glassy carbon electrodes, as a function of pH, permitted identification of the oxidation site of terbutaline. Taking into account that the oxidation of resorcinol closely resembles the oxidative process of terbutaline, we assume that the oxidation step of terbutaline is located on the aromatic ring and attributed to the oxidation of phenolic hydroxy groups, which are electroactive in both acidic and basic media [18,28]. This mechanism is in agreement with reported data concerning other β-agonist drugs [27,29].

Oxidation of terbutaline could also be observed on a platinum electrode at all pHs studied. However, the oxidation occurred less readily and the oxidation process was ill-defined, giving rise to inaccurate measurements of the currents.

3.1. Quantitative determination

From a quantitative point of view, the activated glassy carbon electrode was well suited for the determination of terbutaline. The quantitative determination of the drug was performed in phosphate buffer (pH 6) with a scan rate of 100 mV s^{-1}. The reproducible voltammetric signals were obtained with a RSD of 1.31% for four replicate measurements of 4×10^{-4} M terbutaline. Table 2 summarizes the characteristics of calibration curves established in proposed supporting electrolytes. The activation of the glassy carbon surface resulted in the bringing the limit of detection for the compound down to 6×10^{-6} M.

In order to check the application of the proposed method, terbutaline was analysed in tablets. The results were compared with the spectrophotometric procedure, which is recommended by USP XXII [13] (Table 3). In comparison to the official method, the proposed method is less sensitive, but simpler and faster. The UV spectrophotometric measurements requires a number of manipulations including a precisely controlled reaction for color formation and careful timing due to the color product being unstable. On the other hand, as Table 3 shows, the calculated t value did not exceed the theoretical value. This result indicates that there is no significant difference between the population means for the two procedures. Moreover, in order to know whether the excipients show any interference with the analysis, known amounts of the pure drug were added to the same aliquot portions of the same powdered tablets and the mixtures were analyzed by the proposed method. The mean percentage recovery obtained after five repeated experiments was $98.3 \pm 2.4\%$, which demonstrates the accuracy and repeatability of the proposed voltammetric method for the determination of terbutaline in tablets.

In conclusion, this electrochemical method has the advantage of being simple, rapid and practical

without any interferences from the additives in tablet dosage form.

References

[1] A. Goodman-Gilman, L.S. Goodman, T.W. Rall, F. Murad, The Pharmacological Basis of Therapeutics, 7 ed., Macmillan, New York, 1985, p. 145.
[2] Pharmaceutical Codex, Pharmaceutical Press, London, 1979, pp. 800, 917.
[3] J.E. Kountourellis, C. Markopoulou, J. Liq. Chromatogr. 12 (1989) 3279–3286.
[4] B.M. Kennedy, A. Blomgren, L.E. Edholm, C. Ross, Chromatographia 24 (1987) 895–899.
[5] K.A. Sagar, M.T. Kelly, M.R. Smyth, J. Chromatogr. 577 (1992) 109–116.
[6] K.A. Sagar, M.T. Kelly, M.R. Smyth, Biomed. Chromatogr. 7 (1993) 29–33.
[7] P.T. Mc Carthy, S. Atwal, A.P. Sykes, J.G. Ayres, Biomed. Chromatogr. 7 (1993) 25–28.
[8] J.G. Leferink, J. Dankers, R. Maes, J. Chromatogr. 229 (1982) 217–221.
[9] C. Lindberg, S. Joensson, Biomed. Mass Spectrom. 9 (1982) 493.
[10] M. El-Sadek, H. Abel Latef, A. Aboul Khier, Anal. Lett. 22 (1989) 2511–2519.
[11] M. El-Sadek, H. Abel Latef, A. Aboul Khier, J. Pharm. Biomed. Anal. 9 (1981) 83–86.
[12] S. Tanabe, T. Togawa, K. Kawanabe, Anal. Sci. 5 (1989) 513–516.
[13] The United States Pharmacopoeia, 22nd revision, Mack Printing, Easton PA, 1990, pp. 1320–1322.
[14] British Pharmacopoeia, 1988. H.M.S.O., London, 1993, pp. 653, 1122.
[15] M.T. Ackermans, J.L. Beckers, F.M. Everaerts, I.G.J.A. Seelen, J. Chromatogr. 590 (1992) 341–353.
[16] M.H. Lamoree, N.J. Reinhoud, U.R. Tjaden, W.M.A. Niessen, J. van der Greef, Biol. Mass. Spectrom. 23 (1994) 339–345.
[17] S. Özkan, İ. Biryol, Z. Şentürk, Turk. J. Chem. 18 (1994) 34–40.
[18] S. Özkan, İ. Biryol, Z. Şentürk, Acta Pol. Pharm. 52 (1995) 365–371.
[19] S. Özkan, İ. Biryol, S.T.P. Pharm. Sci. 5 (1995) 347–350.
[20] S.A. Özkan, Z. Şentürk, Analusis 24 (1996) 73–75.
[21] S.A. Özkan, Analusis 25 (1997) 130–131.
[22] Z. Şentürk, S.A. Özkan, Acta Pol. Pharm. 54 (1997) 243–245.
[23] İ. Biryol, S.A. Özkan, J. Pharm. Biomed. Anal. 15 (1997) 1695–1701.
[24] B. Uslu, İ. Biryol, S.T.P. Pharm. Sci. 7 (1997) 248–253.
[25] Z. Şentürk, S.A. Özkan, Y. Özkan, J. Pharm. Biomed. Anal., 1997 (in press).
[26] S.A. Özkan, Z. Şentürk, İ. Biryol, Int. J. Pharm., 157 (1997) 137–144.
[27] D. Boyd, J.R.B. Rodriquez, A.J.M. Ordieres, P.T. Blanco, M.R. Smyth, Analyst 119 (1994) 1979–1984.
[28] E. Bishop, W. Hussein, Analyst 109 (1984) 627–632.
[29] K.A. Sagar, M.R. Smyth, R. Munden, J. Pharm. Biomed. Anal. 11 (1993) 533–540.