Journal of Pharmaceutical & Biomedical Analysis
Vol. 11, No. 7, pp. 533–540, 1993
Printed in Great Britain

0731–7085/93 $6.00 + 0.00

Voltammetric study of salbutamol and application to its determination in a tablet dosage form and dissolution profiles for the dosage form

KAMAL A. SAGAR,† MALCOLM R. SMYTH*† and RAY MUNDEN‡

†*School of Chemical Sciences, Dublin City University, Dublin 9, Ireland*
‡*Glaxo Group Research Limited, Ware, Hertfordshire SG12 0DP, UK*

Abstract: The oxidative voltammetric behaviour of salbutamol at a glassy carbon electrode surface has been studied using cyclic voltammetry and differential pulse voltammetry. Oxidation of the drug was effected in a single irreversible, adsorption-controlled step in phosphate buffer. The process was found to be dependent on the ionic strength and the pH of the supporting electrolyte. The response was evaluated with respect to accumulation time, scan rate and other variables. Using differential pulse voltammetry following electrochemical pretreatment of the electrode surface, the drug yielded a well-defined voltammetric response in phosphate buffer, pH 5.0, at +0.75 V (vs SCE). This process could be used to determine salbutamol concentrations in the range 8×10^{-7} M to 8×10^{-5} M with a detection limit of 2×10^{-7} M. The method was applied, without any interferences from the excipients, to the determination of the drug in a tablet dosage form and in drug dissolution studies. The absolute recovery for salbutamol was greater than 95% at the concentration levels studied, and reproducible voltammetric signals were obtained with a relative standard deviation of 2.4% for $n = 7$ at a concentration level of 8×10^{-5} M.

Keywords: *Salbutamol; differential pulse voltammetry; glassy carbon electrode; cyclic voltammetry; coulometry; dissolution profile; formulation analysis.*

Introduction

Differential pulse voltammetric techniques have assumed an important place over the past 20 years in the armoury of analytical techniques as 'main' and 'secondary' methods for the identification and determination of trace concentrations, and physicochemical, thermodynamic and kinetic parameters of many drugs in pharmaceutical dosage forms [1, 2]. In general, voltammetric methods do not require time-consuming derivatization steps and can often be applied without prior separation of the active substance from the formulation matrix [3]. Sample preparation usually consists of dissolving the active ingredient from a particular formulation in a suitable solvent (aqueous or non-aqueous) and performing a direct analysis on an aliquot of this solution. Because of its low residual current in aqueous media [4] and a more extended range in organic solvents [5], glassy carbon has been used extensively as a working electrode for the determination of oxidizable drug substances [6, 7]. Salbutamol, 1-(4-hydroxy-3-hydroxymethylphenyl)-2-*tert*-butylamino-ethanol, also known as albuterol, is a sympathomimetic amine (or adrenergic drug) which affects those cell chemicals that mediate sympathetic nerve transmissions [8]. It has clinical application primarily as a bronchodilator and it is widely used in the prophylaxis of bronchospasms [9], where it has more prolonged actions than other bronchodilators and has been reported to have a more selective action [10]. The drug is also used in obstetrics for the prevention of premature labour [11] and as a nasal decongestant.

Methods for the assay of salbutamol in tablet dosage forms are usually based on spectrophotometric [12] or colorimetric determinations [13]. Liquid chromatographic methods have also been developed for determination of this sympathomimetic drug in pharmaceutical preparations [14]. For such applications, however, HPLC, while having the advantage of requiring minimal sample preparation, is relatively slow and expensive, requiring filtration, degassing and expensive grades of reagents, eluents and equipment. The objective of the work described in this paper was to investigate the electrochemical behaviour of salbutamol

*Author to whom correspondence should be addressed.

and devise a suitable differential pulse voltammetric method for the analysis of salbutamol in a tablet dosage form without employing a preliminary separation step, and to study the dissolution profile of the drug. The proposed direct method is rapid, requires less than 5 min to run a sample, and involves no sample preparation other than dissolving and transferring an aliquot to the supporting electrolyte consisting of 0.05 M sodium dihydrogen phosphate, pH 5.0. The method exhibits good recovery, is cost-effective, and offers the capability of selective and sensitive determination with no interferences from the excipients used in the dosage form.

Experimental

Reagents and solutions

Salbutamol and the different excipients used in the interference studies were kindly supplied by Glaxo Group Research Limited (Park Road, Ware, Hertfordshire, UK). Analytical grade sodium dihydrogen phosphate was obtained from BDH Chemicals Limited (Poole, Dorset, UK). The compound and the supporting electroyte were used without further purification. Stock solutions (1.0×10^{-3} M) of salbutamol were prepared by dissolving the compound in deionized water obtained by passing distilled water through a Milli-Q water purification system (Millipore). The solutions were stored in the dark under refrigeration to minimize decomposition. More dilute solutions were prepared daily from the stock solution. The supporting electrolyte used for all the voltammetric studies was prepared from a 0.1 M stock solution of sodium dihydrogen orthophosphate. This was subsequently diluted with deionized water to give the required concentration and adjusted to the required pH with 0.2 M sodium hydroxide.

The standard polishing kit and the glassy carbon electrode were supplied by EG&G Princeton Applied Research (PAR). The saturated calomel electrode was obtained from Metrohm (Herisau, Switzerland). For chromatographic experiments, the mobile phase used was 0.067 M sodium phosphate (pH 5.0)–methanol–40 g l^{-1} sodium dodecyl sulphate (SDS)–diethylamine (DEA) in a ratio of 45:55:0.5:0.02 (v/v/v/v). The drug was separated on a LC column (2.5 cm × 4.6 mm i.d.), packed with reversed-phase octadecylsilane, (10 μm spherical particles) obtained from HPLC Technology (Macclesfield, Cheshire, UK).

Apparatus

For voltammetric studies, the experiments were carried out in an all-glass cell designed for a three-electrode potentiostatic circuit. A platinum wire and a saturated calomel electrode were used as auxilliary and reference electrode, respectively. The potential of the working electrode was controlled using an EG&G Princeton Applied Research (PAR) Model 264A potentiostat connected to a JJ Instruments Model PL4 X–Y recorder. Rotating disc electrode experiments were carried out using a glassy carbon electrode connected to an analytical rotator and a PINE Model ASRE 416 speed controller. For coulometric studies, a carbon paste electrode was used as the working electrode. Chromatographic experiments were carried out using a Waters Model 501 liquid chromatograph. The dissolution test was performed in a basket-stirrer recommended by the United States Pharmacopeia (USP) [15].

Activation of glassy carbon electrode

The electrode surface was first polished successively with small-particle-size silicon carbide paper containing a light covering of distilled water to lubricate the glassy carbon-paper interface, wet and dry emery paper (1200 grade) and finally with slurries prepared from 3, 1 and 0.03-μm aluminium oxide on a felt polishing mat. Residual polishing material was removed from the surface after each polishing step by sonication of the electrode in a water bath for 15 min, during which the deionized water was changed every 5 min. Prior to use, the electrode surface was washed with a jet of deionized water and dried with tissue paper. This polishing procedure was followed by electrochemical pretreatment involving cyclic voltammetry where the electrode was cycled between −1 and 0.6 V for 5 min at a scan rate of 100 mV s^{-1}.

Preparation of carbon paste electrode

The carbon paste electrode used for potentiostatic coulometry was made by pressing the active paste into the well of the body of plastic syringe (20 mm in diameter, 5 mm deep). The paste surface was manually smoothed by polishing it on clean paper and a new surface

was prepared for each experiment by removing the paste from the electrode body, which was washed with absolute methanol and water, then dried with tissue paper, and subsequently packed with a fresh portion of the required carbon paste. To simplify this procedure, the syringe plunger provided a screw system to slide the brass disk in and out which thus pushed the paste out of the electrode body for surface renewal. Unmodified carbon paste was prepared by careful hand-mixing of 5 mg of UCP carbon graphite powder (Spectro pure grade, Fluka Chemical Co.) and 3 mg of Nujol oil (McCarthy Scientific Co., Fullerton, CA) using a glass mortar and pestle, and blending the mixture into a paste. In its design the paste was in direct contact with a disk made of brass which was attached to a copper wire of about 3 mm o.d. providing electrical contact to the measuring circuit. The carbon paste electrode was stored in 0.05 M sodium dihydrogen phosphate, pH 5.0, at room temperature and at open circuit.

Differential pulse and cyclic voltammetry

The voltammetric conditions for a typical anodic differential-pulse scan were as follows: initial potential, 0.0 V; scan rate, 10 mV s^{-1}, and final potential, 1.0 V. From the voltammetric data, the optimum supporting electrolyte was found to consist of 0.05 M sodium dihydrogen phosphate. The following operational conditions gave rise to the best sensitivity and selectivity for the determination of salbutamol: pulse amplitude 25 mV, scan rate 10 mV s^{-1} and pulse interval 0.25 s. A blank solution without addition of salbutamol was used to obtain the base current. Standard cyclic voltammetry experiments were performed on plain 0.05 M sodium dihydrogen phosphate, pH 5.0, solutions and those containing 4×10^{-5} M salbutamol using a glassy carbon electrode and the instruments described above. The voltammetric conditions were as follows: initial potential 0 mV; final potential 1.0 V, and sweep rate 20 mV s^{-1}.

Salbutamol determination in commercial preparations

(a) *Bulk drug.* Four and 8 mg portions of bulk drug were accurately weighed and transferred to two separate 100 ml volumetric flasks. The drug was dissolved and diluted to volume in deionized water. The prepared solutions were used within 2 days.

(b) *Tablet dosage form.* Ten 8 mg tablets were selected at random, weighed, and the average value was determined. The tablets were then ground into a fine powder, an accurately weighed quantity of powder equivalent to the average mass was dissolved in deionized water, and transferred to a 100 ml volumetric flask. The resulting mixture was shaken for 15 min to ensure that salbutamol was completely dissolved. A 200 μl aliquot of the dissolved sample was placed in an electrolytic cell containing 25 ml of 0.05 M sodium dihydrogen phosphate, pH 5.0, and the voltammogram was recorded by employing a scan rate of 10 mV s^{-1}. To quantify the unknown amount of salbutamol, successive 50 μl aliquots of a standard 1×10^{-3} M salbutamol solution were added to the cell and the voltammograms were recorded.

Dissolution-profile studies using glassy carbon electrode

The dissolution test was carried out according to the USP XXII method [15] with use of a USP basket stirrer type of apparatus in 900 ml of 0.05 M sodium dihydrogen phosphate, pH 5.0, at a stirring rate of 50 rpm. The temperature of the cell was controlled at 37 ± 0.05°C by use of a thermostatic bath (AGB Ltd, Ireland). The tablet was placed in the basket which was rotated at 50 rev min^{-1}. Using the voltammetric technique, the current values were recorded at appropriate time intervals, and the amount of salbutamol released was determined from a calibration graph.

Results and Discussion

Study of the differential pulse voltammetric behaviour of salbutamol

The discharge current of the background electrolyte in the potential region close to salbutamol oxidation gave rise to inaccurate measurements of the currents using linear sweep voltammetry (LSV). The differential-pulse voltammetric (DPV) signals were preferred in order to determine salbutamol in real dosage forms. Of the four electrolytes investigated, i.e. 0.05 M boric acid, 0.9% sodium chloride, 0.05 M sulphuric acid and 0.05 M sodium dihydrogen phosphate, the last gave rise to the best response with regard to oxidation peak current sensitivity, morphology, etc. Thus for further investigations, a solution of sodium dihydrogen phosphate at

constant ionic strength (U = 0.05 M) was used.

Effect of pH

The differential-pulse voltammograms of the drug were investigated at various pH values. The glassy carbon working electrode was rinsed with deionized water prior to each analysis. The results obtained indicated that the peak potential (E_p) is strongly influenced by the pH. The peak shifts towards negative potentials with an increase in pH, in such a way that two straight lines with different slopes can be observed. The two lines intersect at pH 9.0, which coincides with the pK_a value of salbutamol (Glaxo Group Research Data). The slopes above or below this pH were 0.004 and 0.002 V pH^{-1}, respectively. The peak obtained at pH 5.0 was found to be symmetrical in shape and easily measurable, and could be used to determine low concentrations of the drug. Hence, a pH of 5.0 was chosen for further study.

Variation of peak current with pulse amplitude and interval

The peak obtained for salbutamol at pH 5.0 was found to vary with pulse amplitude and interval. Differential pulse voltammograms recorded at various pulse intervals and with various pulse amplitudes showed that the peak current increased as the pulse interval and pulse amplitude increased. The application of the differential-pulse wave form (pulse amplitude = 25 mV) yielded voltammograms in which the peak currents were on average twice as sensitive as those obtained by linear sweep voltammetry (LSV). A pulse amplitude of 100 mV provided the most sensitive signal. However, the use of this pulse amplitude resulted in an increased capacitive current and the analytical signal merged to a certain extent with the electrolyte discharge current. Optimum conditions of pulse amplitude and pulse interval were found to be 25 mV and 0.2 s, respectively.

Variation of peak current with scan rate

Figure 1 shows the effect of the potential scan rate on salbutamol differential-pulse peak heights at a glassy carbon electrode at different scan rates from 2 to 100 mV s^{-1}. The response was increased markedly upon increasing the scan rate until it started to level off at 50 mV s^{-1}. The increase in peak height was accompanied with broadening and distortion of the response (see inset). As a result, the optimum scan rate was found to be 10 mV s^{-1}, and this was subsequently used throughout the study.

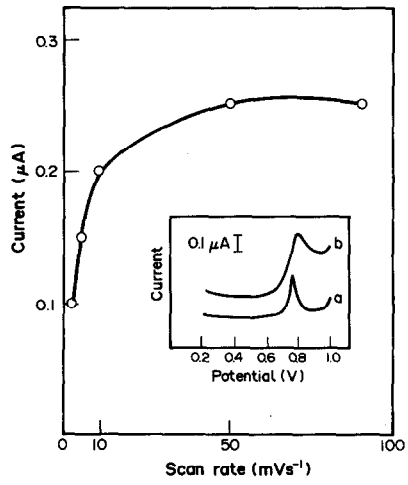

Figure 1
Dependence of peak current on the scan rate of the differential pulse wave form. Also shown (inset) typical voltammograms of salbutamol at 10 (a) and 100 mV s^{-1} (b).

Mechanism of oxidation process

The cyclic voltammetric behaviour of salbutamol at an activated glassy carbon electrode in 0.05 M sodium dihydrogen phosphate, pH 5.0, is shown in Fig. 2, illustrating a single voltammetric oxidation peak. On the reverse sweep, no distinct reduction wave was observed, indicating that the drug is irreversibly oxidized at the glassy carbon electrode.

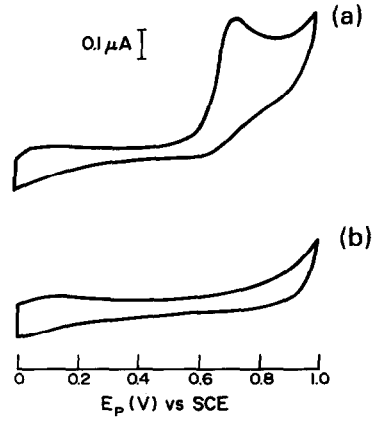

Figure 2
Cyclic voltammogram of (a) 4 × 10^{-5} M solution of salbutamol in 0.05 M sodium dihydrogen phosphate, pH 5.0, obtained at a glassy carbon electrode and (b) blank scan; initial potential, 0.0 V; final potential, +1.0 V; reference electrode SCE; scan rate, 10 mV s^{-1}.

Studies were then undertaken to investigate the rate-controlling step of the process, in order to determine whether the oxidation process was adsorption or diffusion controlled. Linear sweep voltammograms were obtained at different scan rates, and plots of i_p versus $v^{1/2}$, where v is the scan rate (mV s^{-1}), were constructed. The dependence of the peak current (i_p) on the square root of the scan rate ($v^{1/2}$) was found to be non-linear in the range 1–50 mV s^{-1}. When the peak current was plotted versus the unit power of the scan rate (v) it was found to be linear in the range 1–50 mV s^{-1}, according to the equation:

$$i_p\ (\mu A) = 0.004\ \mu A\ (mV\ s^{-1}) + 0.046 \quad (r = 0.9996,\ n = 6).$$

These considerations pointed to an adsorption-controlled process rather than a diffusion-controlled one. In order to further investigate this, studies were carried out under hydrodynamic conditions and hydrodynamic voltammograms were obtained for concentrations ranging from as low as 9×10^{-7} M up to 1×10^{-5} M at different rotation speeds between 200 and 1000 rpm. The resulting voltammograms failed to show the typical plateaus expected for a diffusion-controlled process and to increase linearly with the ½ power of the rotation speed ($w^{1/2}$). Instead, peaks were obtained throughout whose magnitude did not depend markedly on the rotation speed applied to the electrode. This evidence constituted a further proof of a non-diffusion-controlled oxidation process. The effect of accumulation time is shown in Fig. 3.

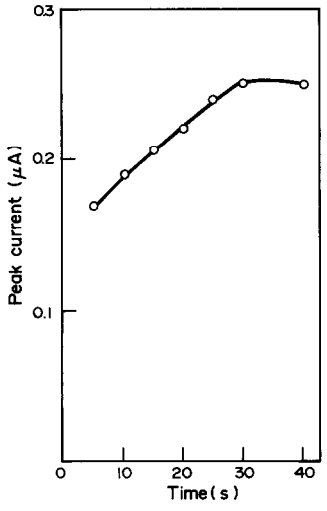

Figure 3
Plot of peak current (μA) versus accumulation time (s).

Greater sensitivity was achieved by using a 30 s accumulation time. This points to adsorption of the drug compound on the surface of the electrode. Longer times of accumulation time gave rise to the same response. A potentiostatic coulometry experiment [16] was then carried out for a 1×10^{-3} M solution of salbutamol in 0.05 M sodium dihydrogen phosphate, pH 5.0, using a carbon paste macroelectrode (diameter 2 cm) at a fixed potential of +0.85 V. The coulometric analysis of the drug showed that two electrons were involved in the oxidation process.

Electrode activation

Glassy carbon electrodes used in electrochemical analysis are often pretreated in some way before measurements are performed. The voltammograms shown in Fig. 4(b), (c) and (d) represent the formation of an adsorbed film by the reaction product. Accordingly, a gradual loss in the electrode activity is observed on successive use. The reason for the low activity may result from the lack of functional groups on the surface or formation of passivating film [17], gradually blocking the access of analyte to the surface and hindering the oxidation reaction. To provide a reproducibly active surface, and to improve the sensitivity and resolution, the glassy carbon electrode was polished to a mirror finish with a 1 μm diamond paste, carbide paper, and alumina and then rinsed with ethanol and deionized water. The electrode was then cleaned by ultrasonication. The effect of electrochemical pretreatment was systematically evaluated with respect to the scan range, scan rate, and the duration of pretreatment. The pretreatment

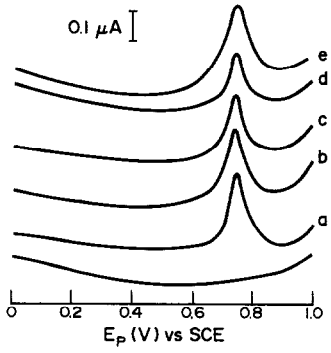

Figure 4
The effect of the pretreatment of glassy carbon electrode on the DPV curves. (a) Original response, (b) response after three scans (c) response after five scans, (d) response after six scans, (e) response after pretreatment.

procedure found to give rise to the optimum response for salbutamol was cyclic voltammetry scanning between −1.0 and +0.6 V for 5 min at a scan rate of 100 mV s^{-1}. During this time, the electrode was kept in a quiescent solution. The current was then switched off, and the solution then stirred for 30 s. Before potential scanning the current was stabilized for 30 s at the required initial potential. Under this electrochemical pretreatment, no loss of electrode activity was observed [Fig. 4(e)] for similar analyses. Clearly, the 'poisoning' effect appears to have been eliminated and the peak current was restored to its original height [Fig. 4(a)]. The electrode pretreated in this way also exhibited a dramatic reduction in the background charging current. Some possible reasons for enhancement of the heterogenous electron transfer rates and the increase of the apparent rate of the electrode process are: (a) surface cleanliness or lack of impurities to adsorb on the surface blocking active sites; (b) surface roughness causing the effective area for electron transfer to be greater than the geometric area; (c) formation of 'oxide' layers on the surface. The voltammetric experiments, described below, were performed with no further polishing to avoid the likelihood of drastically changing the physicochemical characteristics of the carbon surface, and the electrochemical treatment was performed daily prior to use of the electrode, whereas the polishing procedure was performed weekly. Precautions were taken to keep potential limits at which the electrode was operating, to within the range −1.0 to +1.0 V versus SCE, which ensured that significant alteration of the carbon surface did not take place. Background cyclic voltammograms were routinely run between experiments to check the state of the surface. From these voltammograms it appeared that the glassy carbon surface remained reasonably constant throughout the entire course of the experiments. The electrode was soaked overnight in distilled, deionized water. When the above-mentioned pretreatment procedures were followed, reproducible voltammetric signals were obtained. Seven successive voltammograms of 8×10^{-5} M salbutamol in NaH_2PO_4, pH 5.0, had a standard deviation of 2.4%. In view of the simplicity and speed of the pretreatment procedure step, it is recommended that the pretreatment is carried out at the beginning of each analysis.

Effect of concentration

The peak current at +0.75 V was found to increase linearly over two orders of magnitude from 8×10^{-7} M to 8×10^{-5} M. The characteristics of the calibration graph of peak current versus concentration obtained by linear regression were: slope = 0.027 μA μM^{-1}; current intercept = 0.002 μA; and correlation coefficient = 0.9998. The minimum detectable concentration for salbutamol at the pre-treated glassy carbon electrode was found to be 2×10^{-7} M.

Interference studies

In order to investigate the analytical application of this method, the effect of the excipients present in the dosage form was examined by carrying out the determination of 3×10^{-5} M salbutamol in the presence of each of the different excipients at concentrations that can be found in the tablet dosage form. Analysis of salbutamol was also carried out in presence of a placebo tablet. A deviation of more than 2% from the peak current of the solution containing no interfering additives was taken as a sign of interference. These studies showed that none of the excipients at the concentration level existing in the dosage form caused a positive or a negative error indicating that there were no serious interferences to the method.

Assay of salbutamol in bulk drug and tablet dosage form

Differential pulse voltammetry for the determination of pharmaceutical products is by far the most common electroanalytical technique employed in pharmaceutical analysis. The proposed procedure described under the Experimental section was used for salbutamol determination in 4 and 8 mg tablets and for the bulk drug. Such determinations yielded mean values of 3.87 and 7.80 mg of salbutamol for 4 and 8 mg tablets with relative standard deviations of 1.4 and 2.5% (n = 7), respectively. The results for the bulk drug samples showed mean values of 3.91 and 7.85 mg of salbutamol with relative standard deviations of 2.0 and 2.9% (n = 7), respectively. The recovery was in excess of 95% at the concentration levels studied. This is in a good agreement with official methods using high-performance liquid chromatography with UV detection [18, 19].

Table 1
Comparative results for the determination of salbutamol in tablet and bulk preparations with voltammetric assay and HPLC

Sample	Voltammetric assay*		HPLC*	
	Tablet, % found	Bulk, % found	Tablet, % found	Bulk, % found
1	96	97	98	97
2	97	96	97	96
3	95	95	96	98

* Results are the means of three replicate determinations.

Comparison studies

Three different samples were analysed using a standard addition procedure and the proposed voltammetric method was checked by HPLC with carbon fibre electrochemical flow cell detection. This detection method [20] was developed in our laboratory for determination of salbutamol in human plasma. The results obtained by both methods are summarized in Table 1. As can be seen, the results obtained with the voltammetric method are in good agreement with those given by LC–EC. However, the voltammetric method is simpler, faster and requires less expensive equipment than the chromatographic method.

Dissolution studies using glassy carbon electrode

Figure 5 shows the dissolution profiles of salbutamol tablets obtained using the differential pulse voltammetric method. The glassy carbon electrode used in the monitoring of the drug from the tablet dosage form was pretreated between analyses while it was immersed in the dissolution medium. This procedure showed the advantage of continuously monitoring the concentration of the active ingredient in the standard dissolution cell without the need for withdrawing aliquots for analysis purposes, as it is the case in UV detection.

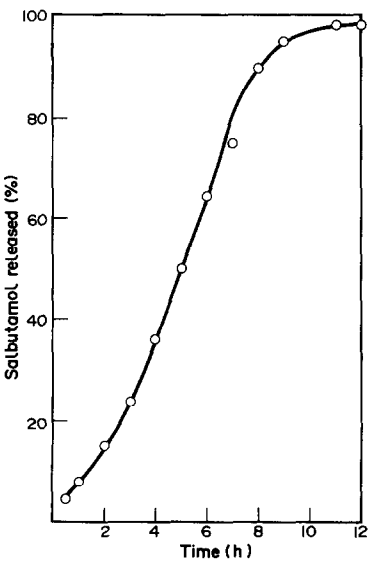

Figure 5
Dissolution profile obtained with glassy carbon electrode for salbutamol tablets.

Conclusions

Using differential pulse voltammetry, a method for determination of the drug in a tablet dosage form and the dissolution rate of salbutamol tablets has been described. The analyses were performed without any interferences from the additives present in the dosage form. The proposed method is rapid, involves no sample preparation other than dissolving and transferring an aliquot to the supporting electrolyte, and does not require filtration, degassing and expensive grades of solutions that are needed for HPLC procedures. The method also has the advantage of good recovery and is able to continuously monitor the concentration of the active ingredient in the standard dissolution cell without the need of withdrawing aliquots for analysis purposes.

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[*Received for review 2 September 1992; revised manuscript received 15 December 1992*]