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Voltammetric Determination of Salbutamol Based on Electrochemical Oxidation at Platinum and Glassy Carbon Electrodes

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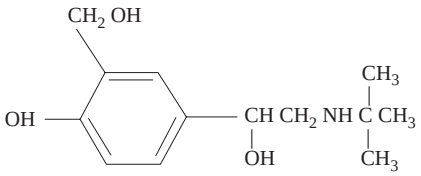
The oxidative behavior of salbutamol was studied as a function of pH at platinum and activated glassy carbon electrodes. Between pH 1.9 and 12.0, the drug was characterized by a single oxidation step at both electrodes. The process was found to be dependent on the nature and the pH of the supporting elctrolyte. The procedure yielded a linear concentration range of 1×10^{-4} to 1×10^{-3} M and 2×10^{-5} to 1×10^{-3} M in 0.2 M sulphuric acid and a phosphate buffer of pH 6, at platinum and glassy carbon electrodes, respectively. The method was used for the determination of salbutamol in pharmaceutical dosage forms.

Keywords: Salbutamol, platinum and glassy carbon electrodes, pharmaceutical dosage forms, voltammetry.

Introduction

Salbutamol, [1-(4-hydroxy-3-hydroxymethyl phenyl)-2-(t-butylamino) ethanol], also known as albuterol, is a β_2 adrenergic receptor agonist, primarily used in the treatment of bronchial asthma and other forms of allergic airways disease. The drug is also used in obstetrics for the prevention of premature labour and as a nasal decongestant[1,2].



The pharmacokinetics following a therapeutic dose and the analysis of salbutamol are important in pharmaceutical research and in clinical chemistry because, since the drug is widely prescribed, it can sometimes be taken in overdose.

This compound has been determined by spectrophotometry[3,4], liquid chromatography[5–7], high-performance liquid chromatography[8–10], gas chromatography[11], mass spectrometry[12], and fluorimetry[13].

There is very little data available on its electrochemistry, however. A voltammetric study of salbutamol and two structurally related compounds, fenoterol and metaproterenol, reported that at the carbon paste electrode, they produce two oxidation processes, the first probably due to oxidation of the hydroxy groups on the aomatic ring, and the second, which cannot be observed in asidic media, due to oxidation of the amino group[14]. To date, voltammetric determination in pharmaceutical preparations based on electrooxidation has been reported only in a recent study by Sagar et.al.[15] on the differential pulse voltammetric techniques at carbon based electrodes.

The investigation of the electrooxidation of salbutamol yielded information on clinical activities. The explanation of the electrode reaction may provide information on drug receptor interaction.

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. Sample preparation usually consists of dissolving the active ingredient from a particular formulation in a suitable solvent and performing a direct analysis on an aliquot of this solution.

In the present study, experimental conditions were established for the electrochemical oxidation of salbutamol at platinum and glassy carbon electrodes, which are very commonly used as solid electrodes, and for determination in pharmaceutical dosage forms.

Experimental

Apparatus

The voltammetric studies were carried out with a Tacussel type PRG-3 polarograph coupled with an EPL-2 recorder (Tacussel). A platinum wire and a saturated calomel electrode were used as axiliary and reference electrodes, respectively. Two working electrodes were used: a platinum wire (Tacussel; diameter: 1mm, length: 15.7 mm) and a glassy carbon electrode. (Tacussel XM 540; area: 1.013 sq.cm). For the application of pretreatment to the glassy carbon electrode, a Wenking model HP 70 potentiostat and an exact-type 250 function generator were used.

Reagents

Salbutamol sulphate (generously provided by ILSAN-ILTAŞ Drug Ind. Inc. Istanbul, Turkey) was used without further purification. All other reagents were of analytical grade. Stock solutions were prepared daily by dissolving salbutamol in selected supporting electrolytes, namely sulphuric acid (0.2 M), acetate buffer (pH 3-6; 0.2M), phosphate buffer (pH 4.5-7.5; 0.2 M) and Britton-Robinson buffer (pH 1.9-12; 0.2 M). Double-distilled water was used to prepare the solutions.

Pretreatment of working electrodes

Pretreatment of the platinum electrode was performed by anodising the electrode at +1.25 V for 5 min and, after washing it thoroughly with doubly distilled water, allowing it to stand at +0.05 V until the current became zero in decreated 0.5 M sulphuric acid.

The glassy carbon electrode was pretreated principally by the application of high frequency square wave potential with a frequency of 350 Hz between the potential limits of ±6V and triangular potential signals between ± 6 V(frequency of 3500 Hz) in 0.1 M potassium nitrate solution repeatedly until an active and permanent surface state was obtained. The response of the activated glassy carbon electrode and its

surface structure completely changed after this treatment. Scanning electron micrographs taken before and after the activation procedure showed great differences, and when the active surface state was reached, the ratio of the peak currents of the substances under investigation to the background current was highly increased. At the end of this treatment, the electrode was pretreated, only by applying a potential of +1.5 V for 5 min and -1.0 V for 2-3 s in 0.1 M potassium nitrate solution before each experiment. A detailed description of this pretreatment has been given elsewhere.[16]

Analysis of the pharmaceutical dosage forms

Salbutamol tablets were assayed by voltammetry. For this purpose, ten tablets were accurately weighed and ground to a fine powder. The required amount of sample corresponding to a stock solution of a concentration of $ca10^{-3}$ M was accurately weighed and transferred into a 100-ml calibrated flask containing 80 ml of selected supporting electrolyte. The contents of the flask were stirred magnetically for 15 min to effect complete dissolution and then diluted to volume with the same buffer and filtered through a fine-pore filter paper. Appropriate solutions were prepared by taking suitable aliquots of the clear filtrate and then diluting with the supporting electrolyte.

Salbutamol syrup and i.m. injection solution were assayed by the same method. The required amount of sample corresponding to a stock solution of a concentration of $ca10^{-3}$ M was accurately pipetted and transferred into a 100- ml calibrated flask. Appropriate solutions were prepared by taking suitable portions of these solutions and diluting them with the supporting electrolyte. Voltammograms were recorded with the final solutions, as in standard salbutamol solutions.

Results and Discussion

Experiments on platinum electrode

Figure 1 shows the cyclic voltammograms recorded in 0.2 M sulphuric acid having 4×10^{-4} M salbutamol solution.

On the anodic branch of the voltammogram of salbutamol, two steps beginning at about 1.0 and 1.15 V are seen. The first one is also seen on the curve of supporting electrolyte solution and must be related to the surface layers of platinum. The second one at 1.15 V is well defined and represents the oxidation of salbutamol. The cathodic peak at about 0.30 V is related to the reduction of the surface oxides of platinum, as the current intensities of this peak on the voltammograms of 0.2 M sulphuric acid solution and salbutamol solution have the same value. The oxidation of salbutamol seems to be irreversible in the range of scan rates of between 10 and 100 mVs^{-1}.

In the case of Britton-Robinson buffer of pH 1.9, the same oxidation steps were observed at nearly the same potentials (0.95, 1.15 V) as in Figure 1. These steps shifted to less positive potentials in solutions of pH higher than 5. In acetate and phosphate buffers with a pH of 6, the oxidation steps were ill defined, and in buffers with a pH higher than 6 the current decreased and the difference between the faradaic and background currents grew smaller.

Experiments on activated glassy carbon electrode

In a previous paper of ours[16], a new pretreatment procedure was described for treating the glassy carbon electrode which offered improved responses in drug analysis[17–22].

In 0.2 M sulphuric acid solution, a well defined peak at 1.1 V was observed (Figure 2).

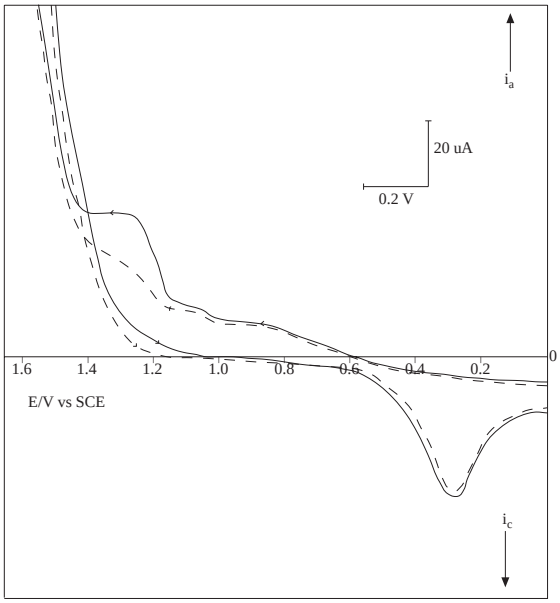


Figure 1. Cyclic voltammogram of 4×10^{-4} M salbutamol in 0.2 M H_2SO_4 at platinum electrode. Scan rate: 100 mVs^{-1}. Dashed line represents the residual current.

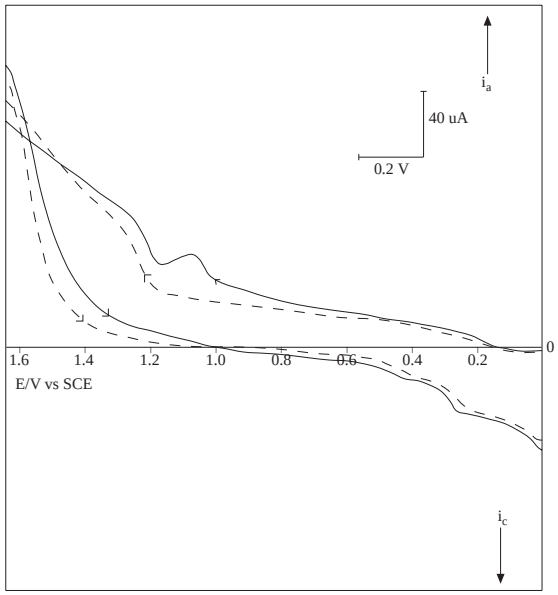


Figure 2. Cyclic voltammograms of 4×10^{-4} M salbutamol in 0.2 M H_2SO_4 at activated glassy carbon electrode. Scan rate: 100 mVs^{-1}. Dashed line represents the residual current.

In reverse scan, a small single cathodic peak appeared at 0.25 V, which may have been due to the reduction of the oxidized product. Cyclic voltammetry demonstrated the total irreversibility of this system at scan rates from 10 mVs^{-1} to 100 mVs^{-1}. In phosphate and Britton-Robinson buffers having the same pH, the shapes of the curves were nearly the same, but the current intensity in phosphate buffers was higher than in Britton-Robinson buffers. In acetate buffers, no clear oxidation step was obtained.

The examination of the data obtained with the glassy carbon electrode in all of the solutions given above revealed that the best results with respect to peak shape and peak current intensity were obtained in a phosphate buffer of pH 6.

The use of the activated glassy carbon electrode in the measurements caused a dramatic increase in current response in comparison with that obtained by non-activated electrode (Figure 3). (In the case of the non-activated glassy carbon electrode, the surface of the electrode was polished on 0.3 μm alumina after each scan). The values of the ratio of faradaic current at about 0.75 V to background current for activated and non-activated electrodes in Figure 3 were found to be 2.00 and 1.33, respectively. The oxidation process of salbutamol can be attributed to the oxidation of the phenolic hydroxy group, which can be observed in both acidic and basic media[14,23,24]. Figure 4a shows the relationship between peak potential and pH in the oxidation process of salbutamol at the glassy carbon electrode. Linearity was observed in the pH range 2-8, giving a negative slope of 77.5 mV per pH unit, except for a small inflection between pH 5.5 and 7. Because of the poor peak definition above pH 8, quantification was unreliable. The peak current related to phenolic hydroxy group oxidation was also pH-dependent (Figure 4b). Increasing the pH from 1.9 to 4 resulted in a sharp increase in the peak height, which then decreased to pH 8.

The effects of potential scan rate on the peak current and potential were evaluated for salbutamol. A 180-mV positive shift in the peak potential as well as an increase in peak current was observed when the

scan rate was increased from 10 to 100 mVs^{-1}. A plot of the logarithm of peak current versus the logarithm of scan rate gave a straight line with a slope of 0.79 (correlation coefficient 0.997). Slopes of 1.00 and 0.50 are expected for ideal reactions of surface and solution species, respectively. The linear relationship existing between peak current and the square root of the scan rate (correlation coefficient 0.997) showed that the process was diffusion controlled.

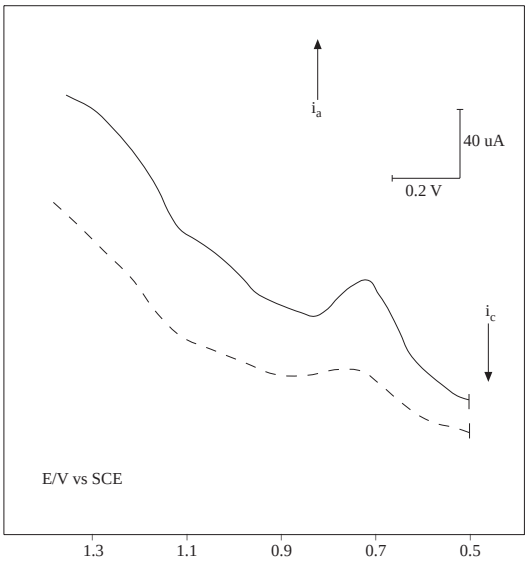


Figure 3. Voltammograms of 4×10^{-4} M salbutamol in phosphate buffer pH 6. Scan rate: 100 mVs^{-1}. Full line: Activated glassy carbon electrode. Dashed line: Non activated glassy carbon electrode.

Quantitative determination

The results of the voltammetric investigation of salbutamol showed electrooxidation at platinum and activated glassy carbon electrodes to be suitable for the determination of the drug. The supporting electrolytes selected for platinum and glassy carbon electrodes were 0.2 M sulphuric acid and a phosphate buffer of pH 6, respectively. Satisfactory results (with respect to peak current enhancement) were obtained with a scan rate of 100 mVs^{-1} at both electrodes. The reproducibility of peak potential and peak current was tested by repeating 4 experiments on 4×10^{-4} M salbutamol. The relative standard deviations were calculated to be 1.01 and 1.68 % for peak potential and 1.17 and 1.27 % for peak current on platinum and glassy carbon electrodes, respectively. In order to propose a new quantitative method for salbutamol dosage forms, a linear current/concentration relation was established. By choosing the optimum conditions mentioned above, calibration plots were drawn by spiking the blank solution with different amounts of the drug. The characteristics of these plots are listed in Table 1. The detection limit is 8×10^{-5} M and 1×10^{-5} for platinum and glassy carbon electrodes, respectively.

Table 1. Characteristics of salbutamol calibration plots.

Electrode	Medium	Concentration Ranges, M	Slope μA/M	Intercept μA	Correl. Coeff.	S.e. of Slope μA/M	S.e. of Intercept, μA
Platinum	0.2 M H_2SO_4	$1 \times 10^{-4} - 1 \times 10^{-3}$ M (n=6)	1.16×10^4	0.33	0.9996	1.56×10^2	9.45×10^{-2}
Glassy Carbon	Phosphate buffer (pH 6)	$2 \times 10^{-5} - 1 \times 10^{-3}$ M (n=10)	6.65×10^4	12.87	0.9997	5.86×10^2	0.28

On the basis of these results, the proposed method was applied to the direct determination of salbutamol in pharmaceutical dosage forms (Table 2). As far as we know, there is no official method in pharmocopeias related to pharmaceutical preparations of salbutamol. For this reason, only the results of the proposed method for salbutamol tablets were compared with those obtained by the non-aqueous titration procedure described for the salbutamol standard sample[25] (Table 2). Statistical analysis of the data of salbutamol tablets obtained by the official and the proposed methods using student's t test showed no significant difference between the performances of the two methods with regard to the accuracy and precision.

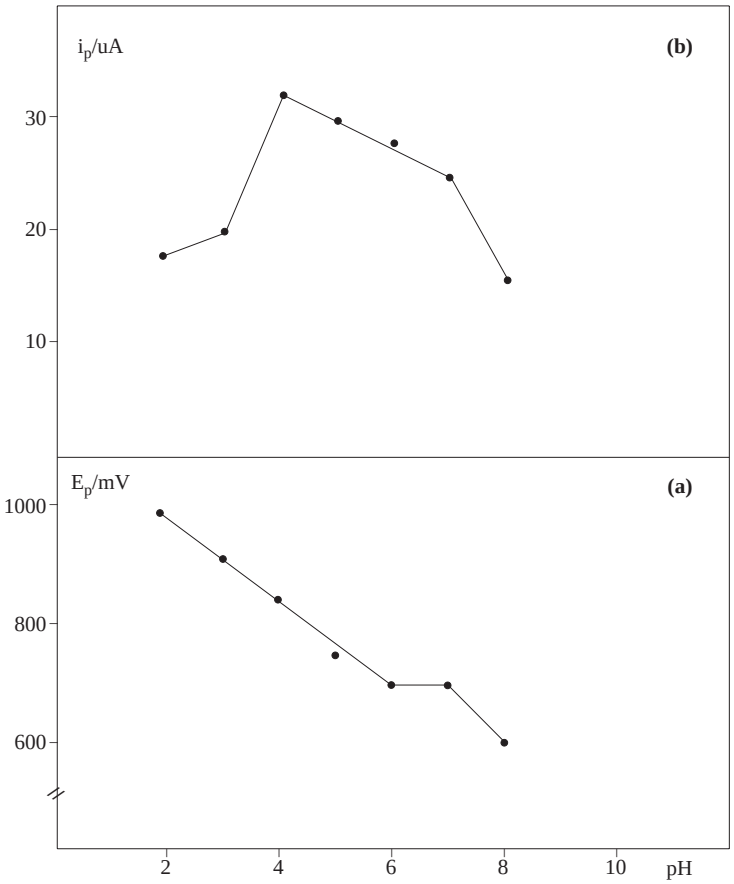


Figure 4. Effects of the pH on the salbutamol peak potential (a) and peak current (b) Salbutamol concentration 4×10^{-4} M. Scan rate: 100 mVs^{-1}.

Table 2. Assay of salbutamol pharmaceutical preparations and comparative studies for salbutamol tablets.

	Voltammetric Assay						Titrimetric Assay (USP XXII)
Electrode	Platinum (0.2 M H_2SO_4)			Glassy Carbon (Phosphate buffer pH 6)			
	Tablet	Syrup	Injection	Tablet	Syrup	Injection	Tablet
Labelled Claim	2 mg	2 mg/5 ml	1 mg/5 ml	2 mg	2 mg/5 ml	1 mg/5 ml	2 mg
Amount Found*	2.08 mg	2.15 mg/5 ml	1.03 mg/5 ml	2.03 mg	2.07 mg/5 ml	1.04 mg/5 ml	2.11 mg
s.d	0.060	0.026	0.060	0.069	0.029	0.044	0.096
t/test of significant	0.673			1.520			(p=0.05, t=2.306)

* Each value is the mean of 5 experiments.

The accuracy of the proposed method was evaluated by recovery studies after the addition of known amounts of pure drug to various pre-analysed formulations of salbutamol and the application of the procedure specified under the Experimental section. As Table 3 shows, the results demonstrate the validity of the proposed method for the determination of salbutamol in commercial dosage forms. The proposed method was proved to have precision and accuracy adequate for the reliable analysis of salbutamol. Moreover, no treatment of the sample is required before voltammetric analysis. Excipients present in tablet or syrups do not interfere with the analysis.

Table 3. Recovery studies by proposed method for both electrodes.

	Platinum Electrode (0.2 M H_2SO_4				Glassy Carbon Electrode (Phosphate buffer pH 6)			
Pharmaceutical Formulations	Added (mg)	Found (mg)*	Recovery %	r.s.d %	Added (mg)	Found (mg)*	Recovery %	r.s.d %
Tablets	10.0	9.84	98.4	1.08	10.0	9.89	98.9	0.99
Syrup	10.0	9.86	98.6	1.75	10.0	9.97	99.7	1.58
Injection	10.0	9.88	98.8	0.73	10.0	9.85	98.5	0.82

* Each value is the mean of 5 experiments.

Finally, the voltammetric method developed is not time-consuming, as the characteristics mentioned above indicate. This method is recommended as a useful tool for the analysis of salbutamol in pharmaceutical preparations.

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