Journal of Pharmaceutical & Biomedical Analysis
Vol. 10, No. 1, pp. 17–21, 1992
Printed in Great Britain

0731–7085/92 $5.00 + 0.00

Differential pulse voltammetric determination of sumatriptan succinate (1:1) in a tablet dosage form

KAMAL SAGAR,* JOSE MARIA FERNANDEZ ALVAREZ,* CHI HUA,* MALCOLM R. SMYTH*† and RAY MUNDEN‡

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

Abstract: A voltammetric study of the oxidation of sumatriptan succinate (1:1) has been carried out at the glassy carbon electrode. This compound exhibited a single wave in Britton–Robinson buffer solutions of pH 2–11, with a maximum current at pH 5.0. The mechanism of oxidation was shown to be due to oxidation of the N—H group in the indole ring. Based on this study, a simple, rapid and sensitive voltammetric method was developed for the determination of the drug in a tablet dosage form.

Keywords: *Sumatriptan succinate (1:1); differential pulse voltammetry; glassy carbon electrode; formulation analysis.*

Introduction

Sumatriptan succinate (1:1) is a 5-hydroxytryptamine agonist under development for use in human medicine for the treatment of acute vascular headaches [1, 2]. Oral administration of the drug is an effective and well tolerated treatment for acute migraine, with a dose of 100 mg appearing optimal in terms of efficacy: side effect ratio [3]. A review of the animal pharmacology, bioavailability, metabolism and initial clinical studies using intravenous, subcutaneous and oral administration of the drug has been made by Oxford and Lant [4].

We have investigated the application of voltammetry for the analysis of this drug, with a view to developing a simple and precise method for its determination in a tablet dosage form. Voltammetric techniques have found widespread use in this regard in formulation analysis, since the procedures usually involve a simple dilution step, and most of the excipients used do not interfere in the subsequent determination step [5, 6]. Owing to the presence of several potentially oxidizable groups in its molecular structure, it was decided to investigate the voltammetric behaviour of this compound at a glassy carbon electrode.

Experimental

Reagents

Sumatriptan succinate (1:1) tablets (containing 100 mg of active ingredient) were obtained from Glaxo Group Research Ltd. A 1×10^{-3} M solution of sumatriptan succinate (1:1) was prepared in isotonic saline and stored in the dark under refrigeration. The graphite used in the construction of the carbon paste electrode was obtained from Aldrich Chemical Company. Deionized water was used to prepare all solutions. This water was obtained by passing distilled water through a Milli-Q water purification system. All other reagents were of analytical grade. A stock Britton–Robinson (BR) buffer solution was prepared which was 0.04 M in each of glacial acetic acid, orthophosphoric acid and boric acid. Buffer solutions of varying pH were then prepared by the addition of 0.2 M sodium hydroxide.

Apparatus

For voltammetric studies, a three-electrode cell was used in which a calomel electrode served as the reference electrode, a platinum wire served as the auxillary electrode, and a glassy carbon electrode was used as the working electrode. For coulometric studies, a carbon paste electrode was used as the working electrode.

The potential of the working electrode was controlled using an EG&G Princeton Applied Research (PAR) Model 264A potentiostat connected to an Omnigraph 2000 X–Y recorder. Rotating disc electrode experiments were carried out using a glassy carbon elec-

† Author to whom correspondence should be addressed.

trode connected to an analytical rotator and a PINE Model ASRE 416 speed controller.

Methods

Electrode activation procedures

The glassy carbon electrode was first hand polished on silicon carbide paper (No. 240), followed by polishing using an alumina slurry. Residual polishing material was removed from the surface by sonication of the electrode in a methanol bath for 15 min, during which the methanol was changed every 5 min.

As reported previously [7], activation of glassy carbon using a high anodic potential is highly effective. Activation of the glassy carbon working electrode used in this study was achieved by holding the electrode at +1.5 V under stirring for 90 s before recording each voltammogram. The appropriate initial potential was then selected and the electrode allowed to stabilize for 30 s; a scan was then initiated from 0 → +1.1 V using a scan rate of 10 mV s^{-1}.

Assay of sumatriptan in a tablet dosage form

A single tablet was dissolved in 900 ml of isotonic saline solution. A series of serial dilutions was then performed to give a nominal final concentration of 6×10^{-4} M. An aliquot of this solution was then transfered to the voltammetric cell containing 20 ml of BR buffer (pH 5.0) to yield a final concentration of 2×10^{-6} M sumatriptan. The differential pulse voltammogram was subsequently recorded by employing a scan rate of 10 mV s^{-1}. To quantify the unknown amount of sumatriptan in solution, a multiple standard addition procedure was employed.

Results and Discussion

Activation procedure

Glassy carbon electrodes have found common usage as working electrodes for numerous electroanalytical applications [8], particularly relating to the analysis of compounds undergoing oxidation reactions. The main problem arising from the use of this electrode material, however, is in the fouling of the surface due to adsorbed products of such oxidation processes. It has been found necessary by many authors [9–12], therefore, to employ an activation procedure prior to analysis. This can be best achieved using an electrochemical pretreatment regime [9–11]. For this particular application, we found that good reproducibility could only be achieved by holding the potential of the working electrode at a potential more positive than the oxidation potential of the drug.

The optimum conditions were found to be at +1.5 V for 90 s under stirring. The precision (expressed as the relative standard deviation) of the signal obtained for a 8×10^{-6} M solution of sumatriptan in Britton–Robinson buffer (pH 5) under these conditions was 1.1% (n = 10).

Effect of pH

Sumatriptan gave rise to a single oxidation process at the glassy carbon electrode in BR buffers of pH 2–11 using differential pulse voltammetry (DPV). The effect of pH on the peak potential (E_p) and peak current (i_p) of the oxidation peak of sumatriptan is shown in Figs 1 and 2, respectively. The graph of E_p versus pH clearly indicates that the peak shifts to more negative potentials with increasing pH. Between pH 2 and 5 the slope of the graph was 95 mV pH^{-1}. A break in the graph then occurred at pH 5.0, and the slope of the graph subsequently became 50 mV pH^{-1} between pH 5 and 11. The position of this break is close to the pK_{a1} and pK_{a2} values of succinic acid at pH 4.16 and 5.61 [Glaxo Group Research, personal communication].

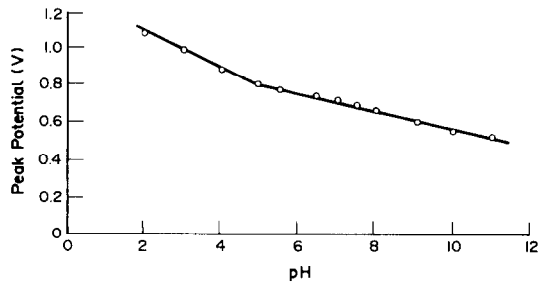

Figure 1
Influence of pH on peak potential of sumatriptan succinate (1:1) (1×10^{-3} M). Scan rate = 10 mV s^{-1}.

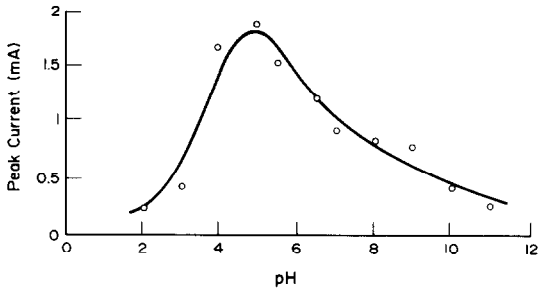

Figure 2
Influence of pH on peak current of sumatriptan succinate (1:1) (1×10^{-3} M). Scan rate = 10 mV s^{-1}.

Sumatriptan succinate (1:1) has pK_a values (determined by UV spectroscopy) associated with the succinic acid ion pair at 4.21 and 5.67, with the tertiary amino group at 9.63 and the sulphonamide group at pH > 12.

The effect of pH on i_p shows a maximum peak current at pH 5.0, which coincides exactly with the polarographic pK_a value obtained from the plot of E_p vs pH. Below pH 4.0, the drug exists mainly in a protonated form, since the succinic acid will be mostly in the diprotonated state and the drug will be protonated at the tertiary amino group. On approaching the pK_{a1} value of succinic acid, the acid begins to dissociate into the hemisuccinate form which forms a neutral ion pair with the monoprotonated form of the drug. As the pH is increased beyond 5.0, and nears the pK_{a2} value of succinic acid, the ion pair becomes negatively charged as the concentration of succinate increases in solution. Only one polarographic pK_a value was seen because of the relative closeness of the pK_{a1} and pK_{a2} values of succinic acid. The highest current value was therefore obtained for the neutral species over either the positively or negatively charged moieties.

Optimization of operating parameters

Variation of peak current with pulse amplitude. The application of the differential pulse waveform (pulse amplitude = 50 mV) yielded voltammograms in which the peak currents were on average twice as sensitive as those obtained by linear sweep voltammetry (LSV).

The peak current intensity increased as the pulse amplitude was increased and 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 process merged to a certain extent with the electrolyte discharge. A value of 50 mV was therefore used for further studies.

Variation of peak current with pulse interval. Differential pulse voltamograms recorded at various 'pulse intervals' showed that the peak current increased as the pulse interval was increased. A pulse interval of 0.25 s gave rise to the sharpest and most symmetrical peak shape.

Variation of peak current with scan rate. The oxidation process was studied using DPV at different scan rates from 2 mV s^{-1} → 100 mV s^{-1}. The optimum scan rate was found to be 10 mV s^{-1}. Higher scan rates gave rise to broader peaks and resulted in the oxidation process merging with the electrolyte discharge. The following operational conditions therefore gave rise to the best sensitivity and selectivity for the determination of sumatriptan: pulse height 50 mV, scan rate 10 mV s^{-1} and pulse interval 0.25 s.

Mechanism of oxidation process

The cyclic voltammetric behaviour of sumatriptan succinate at a glassy carbon electrode in Britton–Robinson buffer is shown in Fig. 3, indicating that the drug is irreversibly oxidized at the glassy carbon electrode. Studies were then undertaken to investigate the rate-controlling step of this process. Linear sweep voltammograms obtained for increasing values of the scan rate showed the existence of a linear dependence of the peak intensity upon the unit power of the scan rate between 5 and 100 mV s^{-1}. The characteristics of this graph were slope 4.00 μA mV s^{-1}, current intercept 0.25 μA, and correlation coefficient r = 0.9992. When this data was plotted vs the 1/2 power of the scan rate, a non-linear fit was obtained. These considerations pointed to an adsorption-controlled process, rather than a diffusion-controlled one. In order to further support this finding, hydrodynamic voltammograms were obtained for concentrations ranging from as low as 5×10^{-7} up to 1.5×10^{-6} M sumatriptan at rotation speeds between 200 and 1000 r.p.m. The resulting voltammograms failed to show the typical plateaux expected. Instead, peaks were obtained throughout, whose magnitude did not depend markedly on the rotation speed applied to the electrode. This evidence constituted

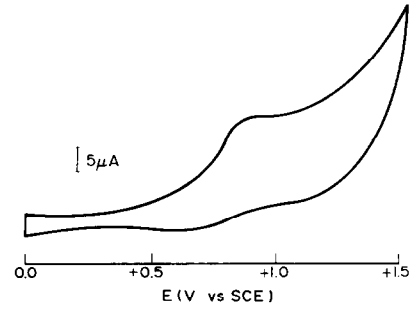

Figure 3
Cyclic voltammogram of sumatriptan succinate (1:1) (1×10^{-3} M). Scan rate = 200 mV s^{-1}.

further proof of a non diffusion-controlled oxidation process.

Potentiostatic coulometry experiments were than carried out for a 1×10^{-3} M solution of sumatriptan succinate in Britton–Robinson buffer pH 5.0 using a carbon paste macroelectrode (diameter 2 cm) at a fixed potential of + 0.90 V. The number of electrons involved in the oxidation process was found to be 0.80, indicating that one electron was transferred in the oxidation process. A comparison with the oxidation wave obtained for indole-3-acetic acid, which occurred at a similar potential to that of sumatriptan, indicated that the oxidation occurred at the nitrogen atom in the indole ring of the molecule.

Differential pulse voltammetric analysis of sumatriptan succinate (1:1) in a tablet dosage form

Effect of excipients. The effect of excipients on the DPV behaviour of sumatriptan succinate (1:1) was investigated by adding the relative concentration of each excipient into a pure solution of the drug in BR buffer pH 5.0. The magnitude of the peak current for sumatriptan succinate increased after the addition of each additive. Interference was found to be caused by cellulose, lactose and magnesium stearate. A cumulative effect for these compounds was also noticed when the analysis was carried out using placebo tablets (Fig. 4). This effect could be nullified using the activation procedure described in the Experimental section.

Effect of concentration. Using the optimum conditions described, a linear calibration curve was obtained for sumatriptan in the range 1–8 $\times 10^{-6}$ M. The characteristics of this graph were slope 1.75 μA mol^{-1} dm^3, current intercept 0.23 μA and correlation coefficient r = 0.999. The limit of detection of the procedure was found to be 5×10^{-7} M.

Assay of sumatriptan in a tablet dosage form. Nine samples from different dissolved tablets were analysed using the proposed voltammetric method. Appropriate dilution to produce solutions within the linear range of the calibration curve was used in the analysis. The values found ranged from 96 to 99 mg per tablet. The relative standard deviation for the analysis of nine tablets was 1.86%.

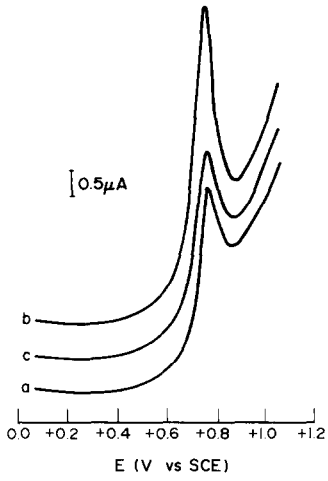

Figure 4
Effect of the excipients on the DPV determination of sumatriptan succinate (1:1) (1.5×10^{-6} M). (a) 1.5×10^{-6} M sumatriptan succinate (1:1); (b) 1.5×10^{-6} M sumatriptan succinate (1:1) in presence of dissolved placebo tablet with no pretreatment; (c) 1.5×10^{-6} M sumatriptan succinate (1:1) in presence of dissolved placebo tablet following electrode pretreatment.

Conclusion

A method has been developed for the determination of sumatriptan in a tablet dosage form. The proposed method is rapid, requiring less than 5 min to run a sample, and involves no sample preparation other than dissolving and transferring an aliquot to the supporting electrolyte. The activation procedure used in this study allowed us to estimate the concentration of the drug without any interferences from the additives present in the dosage form.

References

[1] W. Paulus, K. Butzel, H. Plendl and A. Straube, *Lancet* **335**, 51 (1990).
[2] P. Schoeffter and D. Hoyer, *Arch. Pharmacol.* **340**(1), 135–138 (1989).
[3] C. Dahlof, P. Winter and S. Ludlows, *Cephalalgia* **9**(suppl. 10), 351–352 (1989).
[4] J. Oxford and M.S. Lamt, *Drugs of the Future* **15**(1), 104–105 (1990).
[5] A. Ivaska and W.F. Smyth, in W.F. Smyth (Ed.), *Electroanalysis in Hygiene, Environmental, Clinical and Pharmaceutical Chemistry*, pp. 337–347. Elsevier, Amsterdam (1980).
[6] P.T. Kissinger and W.R. Heineman (Eds), *Laboratory Techniques in Electroanalytical Chemistry*, p. 573. Marcel Dekker, New York (1980).
[7] J. Wang and L. Hutchins, *Analyt. Chim. Acta* **167**, 325–334 (1985).
[8] W.E. Van Der Linden and J.W. Dieker, *Analyt. Chim. Acta* **119**, 1–24 (1980).

[9] H.E. Zittel and F.J. Miller, *Anal. Chem.* **37**, 200–203 (1965).
[10] K.J. Stutts, P.M. Kovach, W.G. Kuhr and R.M. Wightman, *Anal. Chem.* **55**, 1632–1634 (1985).
[11] J. Zak and T. Kuwana, *J. Am. Chem. Soc.* **104**, 5514–5515 (1982).
[12] N. Cenas, J. Rozgaite, A. Pocius and J. Kulys, *J. Electroanal. Chem.* **154**, 121–128 (1983).

[*Received for review 4 July 1991; revised manuscript received 16 September 1991*]