Electrochemical Behavior of an Analgesic

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(Received on 12th August 2010, accepted in revised form 21st June 2012)

Summary: Electro-oxidation of naproxen sodium was carried out using cyclic, normal pulse and differential pulse voltammetry in a solvent mixture supporting electrolyte system, at platinum and glassy carbon electrode, respectively. Naproxen sodium exhibited well-defined and irreversible peaks in 90 % acetonitrile containing 0.1M sodium perchlorate. Naproxen sodium underwent one electron transfer resulting in the formation of cation radical for the first electro-oxidation step followed by other chemical and electrochemical steps involving removal of another electron and attack of nucleophile (ECEC mechanism). The influence of interference compounds namely α-naphthylamine was also investigated at platinum electrode only, versus silver/silver chloride saturated potassium chloride.

Introduction

Naproxen sodium is a nonsteroidal anti-inflammatory drug used in painful and inflammatory diseases. [1]. The characteristics, performance and application of an electrode, namely, Pt/Hg/Hg2 (naproxenate ion) 2/Graphite, were described. This electrode responds to naproxenate ion with sensivity of (58.1± 0.9) mV per decade over the range 5.0×10^{-5}–1.0×10^{-2} molL^{-1} at pH 6.0–9.0 and a detection limit of 3.9×10^{-5} molL^{-1}. The electrode is easily constructed at a relatively low cost with fast response time (within ten to thirty five seconds) and can be used for a period of six months without any considerable divergence in potentials. The proposed sensor displayed good selectivity for naproxen in the presence of several substances, especially concerning carboxylate and inorganic anions. It was used for the direct assay of naproxen in commercial tablets by means of the standard additions method. The analytical results obtained by using this electrode are in good agreement with those given by the United States Pharmacopeia procedure [2].

A combined enzymatic resolution and chemical polymerization strategy has been used to create optically active polymeric prodrugs. (*S*)-Naproxen, (*S*)-ketoprofen and (*S*)-ibuprofen derivatives were obtained in excellent optical purity and high yield by enzymatic resolution after optimization of reaction conditions. Each optically active monomer was subjected to free radical polymerization with methyl methacrylate. The obtained optically active polymeric prodrugs bearing (*S*) - naproxen, (*S*)-ketoprofen or (*S*)-ibuprofen residue were characterized by infrared, nuclear magnetic resonance and gel permeation chromatography. The effect of molar ratio of naproxen vinyl ester to methyl methacrylate on the polymerization was also investigated. This methodology is useful to provide a facile and clean route to optically active macromolecular prodrugs [3].

Electro-oxidation of naproxen was studied using boron-doped diamond electrode by cyclic and differential pulse voltammetry. A well-defined irreversible anodic peak was noted in the cyclic voltammetry at 1.44 V vs. silver/silver chloride, for naproxen in 0.1 M lithium perchlorate containing acetonotrile. The electrochemical process is diffusion controlled, and the number of electrons involved in the rate determining step is equal to one. A slop of 30.8 mV per decade was obtained from the plot of log peak potential vs. log of sweep rate, which indicates that the rate control is first order following electron transfer. Since differential pulse voltammetry offers the advantage of high sensitivity, and resulting signals obtained with this technique are very sharp and well defined, quantitative determination of naproxen was undertaken with this technique [4].

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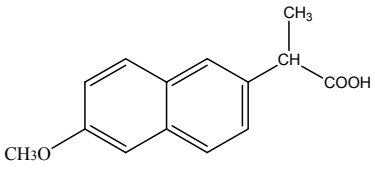
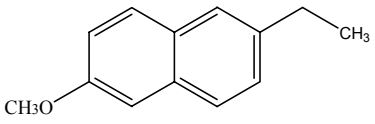
The electro-oxidation of naproxen was studied using boron-doped diamond electrode by cyclic and differential pulse voltammetry in non aqueous solvent supporting electrolyte system. The results were also compared with glassy carbon electrode under the same conditions. Naproxen undergoes one electron transfer resulting in the formation of cation radical for the first electro-oxidation step, which follows other chemical and electrochemical steps such as deprotonation, removal of another electrode and the attack of nucleophile electrochemical chemical electrochemical chemical mechanism. Boron-doped diamond electrode provided higher signal to background ratio, well resolved and highly reproducible cyclic voltammogram than the glassy carbon electrode. With a sweep rate of 50 mVs^{-1} and pulse height of 50 ms, respectively, the differential pulse voltammetry technique was able to determine the naproxen concentration in the range of 0.5 to 50 μM with a detection limit of 30 nM. The influence of interference compounds namely 2-acetyl-6-methoxynaphthalene on naproxen oxidation can also be followed successfully. Moreover, the percentage of 2-acetyl-6-methoxynaphthalene present in the standard chemical form of a mixture containing naproxen can be found accurately. Rapidly, precise and good selectivity were also found for the determination of naproxen in pharmaceutical formulations [5].

The anodic oxidation of naproxen has been reported on a platinum electrode using cyclic, linear sweep and differential pulse voltammetry. Naproxen exhibited a single well defined and irreversible peak in acetonitrile/0.1 M lithium perchlorate with a peak potential at 1146 mV versus silver/silver chloride. This allowed the developed of a simple, selective and sensitive differential pulse voltammetric method for the determination of naproxen in pharmaceuticals. The calibration plot was linear (R^2=0.0998) over the range 1-25 μgmL^{-1}. the limit of detection (30/m) was 0.24 μgmL^{-1} and the relative standard deviation of the measurements was 1.2 % (n=6). Stability of naproxen in the raw material or in the final product could be altered under abnormal conditions such as: temperature, light, humidity and pH, which could yield different kinds of degradation products such as 2-methoxy-6-ethylnaphthalene. In addition, 2-acetyl-6-methoxynaphthalene was found to be a major impurity of the synthesis procedure. The strict international regulations obliged the pharmaceutical companies to control these compounds precisely in raw material and in final products.



Naproxen



2-methoxy-6-ethylnaphtalene (MEN)

Well defined peaks for two related compounds to naproxen 2-methoxy-6-ethylnaphthalene and 2-acetyl-6-methoxynaphthalene were detected, respectively, at 1096 and 1316 mV versus silver/silver chloride and no interference was measured during the determination of naproxen. The limits of detection of 2-methoxy-6-ethylnaphthalene and 2-acetyl-6-methoxynaphthalene were found to be respectively 0.28 and 0.21 μgmL^{-1}. The method was successfully applied to the determination of naproxen in commercial tablets and showed a good sensitivity and accuracy with mean recoveries between 99.8 and 101.2 % [6].

The retention behavior of nonsteroidal anti-inflammatory drugs using micellar mobile phases of sodium dodecylsulphate was studied and compared with that observed with micellar mobile phases of cetyltrimethylammonium bromide. A liquid chromatographic procedure for the determination of acemetacin, diclofenac, indomethacin, ketoprofen, naproxen and tolmetin in pharmaceutical preparations was also described using a Kromasil C18 analytical column and a solution of 0.15 M sodium dodecylsulphate at pH 3 with 10 % 1-propanol as mobile phase. [7].

Naproxen has a propensity to cause ulcers whereas zinc ions are known to possess an anti-ulcer and anti-inflammatory activity. Therefore, zinc complex of naproxen was prepared by adding zinc sulfate to an aqueous solution of sodium naproxen and its structure was characterized by infra red, proton nuclear magnetic resonance and carbon nuclear magnetic resonance, ultra violet, differential scanning calorimetry, atomic absorption spectro-scopy, and elemental analysis [8].

The purpose of this study was to examine the potential use of electrolytes to control naproxen sodium release from chitinosan tablets. An analysis

of variance was employed to evaluate the effects of molecular weight of chitinosan, electrolyte valence, and pH of the dissolution medium on naproxen sodium's release. The intrinsic dissolution rates and saturation solubility of naproxen sodium were determined at each of the pHs used. Directly compressed tablets were prepared from admixtures containing: naproxen sodium, sodium chloride, calcium chloride, or aluminum chloride, magnesium stearate, and chitinosan and were characterized for their dimensions, crushing strengths, friability, disintegration times, and in vitro dissolution profiles. The slopes of the log-log cumulative percent released time curves (time zero to five hours) were compared using analysis of variance [9].

A high performance liquid chromatographic method for simultaneous determination of naproxen, nabumetone and its major metabolite, 6-methoxy-2-naphthylacetic acids, was developed for the application to pharmaceuticals and human urine. The calibration curves of naproxen and nabumetone showed good linearity in the concentration range 32 to 160 μgmL^{-1} with ultra violet detection (270 nm) for pharmaceuticals. In the low concentration ranges (8 to 96 ng of naproxen per mL, 24 to 288 ng of nabumetone per mL and 5.6 to 67.2 ng of 6-methoxy-2-naphthylacetic acid per mL) [10].

A simple, selective and sensitive heavy atom induced room temperature phosphorimetric method has been described for the determination of naproxen in pharmaceutical preparations. The phosphorescence signals were a consequence of intermolecular protection when analytes were, exclusively, in presence of a heavy atom salt and sodium sulfite as an oxygen scavenger to minimize room temperature phosphorimetric quenching. These variables selection constituted the basis of a heavy atom induced room temperature phosphorimetric method for the determination of naproxen (detection limit 17.6 $ngmL^{-1}$; 1.71 % relative standard deviation at 250 $ngmL^{-1}$). The method has been applied satisfactorily to the analysis of pharmaceutical preparations [11].

A very simple, rapid and highly sensitive method was described for determining naproxen in serum and urine. This method is based on room temperature phosphorescence of naproxen in sodium dodecylsulphate micelles, with thallium(I) providing the external heavy atom and sodium sulphite acting as the oxygen scavenger. The most relevant characteristic of this method was its great selectivity, e.g. naproxen could be determined in the presence of other nonsteroidal anti-inflammatory drugs. The analytical recoveries and inter and intra assay precision data obtained demonstrate the usefulness of this procedure when used with very complex samples [12].

The efficacy and safety of single doses of naproxen sodium 440 mg and ibuprofen 400 mg were evaluated in a randomized, parallel, double blind, placebo controlled study conducted at a single site. Naproxen sodium was significantly better ($P \leq 0.026$) than ibuprofen at hours eight through twelve for pain relief and categorical pain intensity scores. There were no serious adverse events or deaths [13].

A simple and sensitive liquid chromatographic method with electrochemical detection is described for the quantitative determination of the nonsteroidal anti-inflammatory drugs diflunisal, indomethacin, naproxen, piroxicam and sulindac in human plasma. Isolation of the drug from the biological fluid is achieved using a Sep-pak RP18 cartridge. Separation of plasma components occurs on a reversed phase C18 column with a mobile phase consisting of methanol-water-phosphate buffer. For the amperometric detection the potential of +0.9 V was set on the working electrode. The detection limit of the assay is 10–20 $ngmL^{-1}$. The method showed good concordance for plasma samples containing the drugs (R^2 = 0.999) and can be readily utilized for clinical pharmacokinetic studies [14].

A unique detector for a specific ionic drug has been fabricated. This sensor has been used to quantitatively determine naproxen in either tablet or capsule form. Detector sensitivity for naproxinate ion was $\leq 10^{-5}$ M. with very good selectivity in the presence of most inorganic ions. Assay times were short and appeared amenable to automation [15].

Results and Discussion

Voltammetry of Naproxen Sodium at Platinum Electrode

A typical cyclic voltammogram was obtained for 1.0 mM naproxen sodium in 90 % acetonitrile/10 % water containing 0.1 M sodium perchlorate as a supporting electrolyte, reported in Fig. 1. Two well-defined anodic peaks were observed with no associated cathodic peak in the reverse scan which indicated that oxidation of naproxen sodium at platinum electrode to be an irreversible process. The anodic peak current of the irreversible peak of naproxen sodium was observed to shift anodically with increasing sweep rate as shown in Fig. 2. The value of transfer co-efficient was found to be approx-

imately 0.5, which suggested one electron transfer in the rate-determining step for the electro-oxidation of naproxen sodium for irreversible processes, data was represented in Table-1.

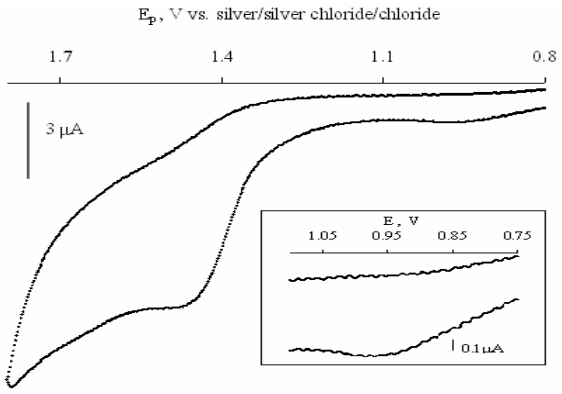


Fig. 1: Cyclic voltammogram of 1.0 mM naproxen sodium in 90 % acetonitrile/10 % water containing 0.1 M sodium perchlorate at platinum electrode ($8x10^{-4}$ cm^2). Sweep rate 0.8 Vs^{-1}. The first peak is shown as an inset with different current scale on lower right.

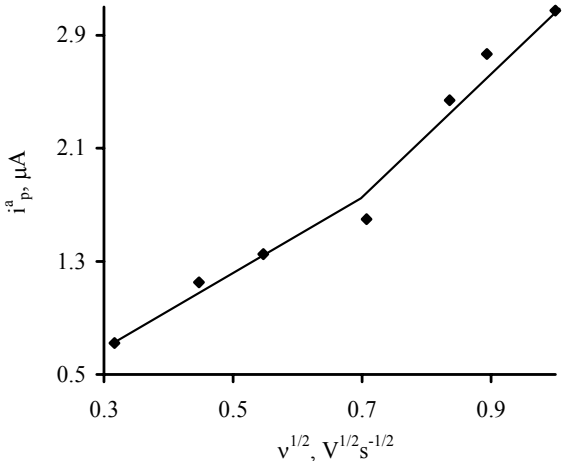


Fig. 2: Influence of square root of sweep rate on anodic peak current for 0.8 mM naproxen sodium in 90 % acetonitrile/10 % water containing 0.1 M sodium perchlorate at platinum electrode ($8x10^{-4}$ cm^2).

A typical normal pulse voltammogram was recorded for 0.3 mM naproxen sodium in 9:1 acetonitrile:water containing supporting electrolyte system. A broad peak was obtained, shown in Fig. 3. Increasing the concentration of naproxen sodium a proportional increase in corresponding normal pulse voltammetric current was also observed, Fig. 4.

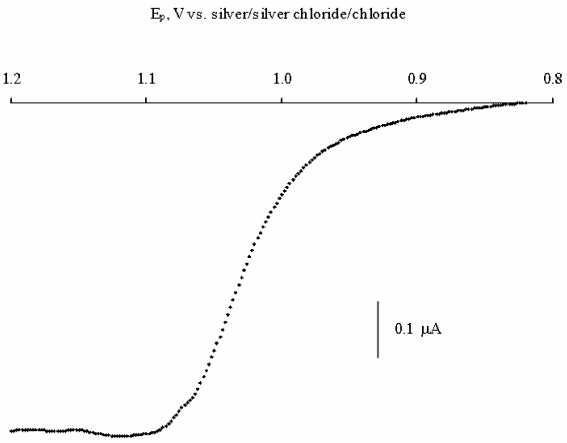


Fig. 3: Normal pulse voltammogram of 0.3 mM naproxen sodium in 90 % acetonitrile/10 % water containing 0.1M sodium perchlorate at platinum electrode ($8x10^{-4}$ cm^2) at sweep rate, ν = 0.01 Vs^{-1}. Pulse width, t_p = 50 ms, Step time, τ= 0.2 s.

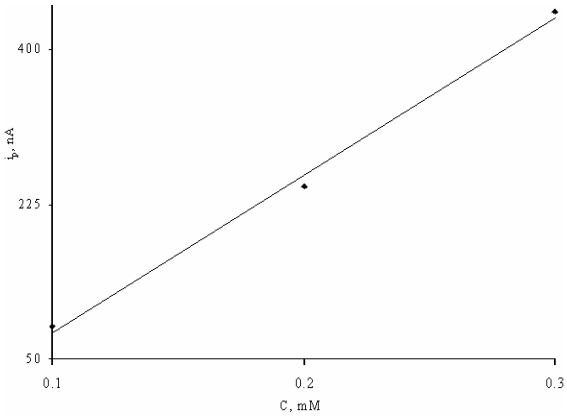


Fig. 4: Normal pulse voltammetric current vs. concentration of naproxen sodium in 90 % acetonitrile/10 % water containing 0.1 M sodium perchlorate at platinum electrode ($8x10^{-4}$ cm^2). y = 1778.8x – 97.133; R^2 = 0.9956.

A representative differential pulse voltammogram was shown for 1.0 mM naproxen sodium in Fig. 5. It was observed by increasing the concentration of naproxen sodium anodic peak current was also increased as exhibited by Fig. 6.

Cyclic voltammogram for α–naphthylamine was recorded to investigate its interference with naproxen sodium as revealed in Fig. 7.

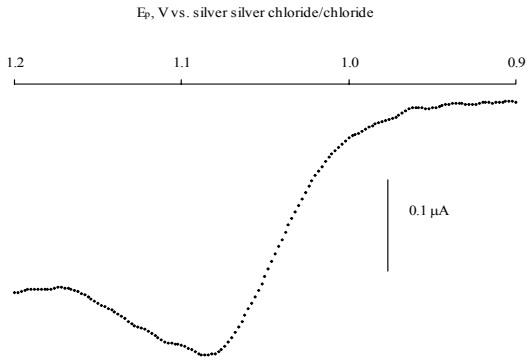


Fig. 5: Differential pulse voltammogram of 1.0 mM naproxen sodium in 90 % acetonitrile/10 % water containing 0.1M sodium perchlorate at platinum electrode ($8x10^{-4}$ cm^2). Sweep rate, ν =0.01 Vs-1. Pulse width, tp= 50 ms, step time, τ = 0.2 s and pulse height, ΔE = 75 mV.

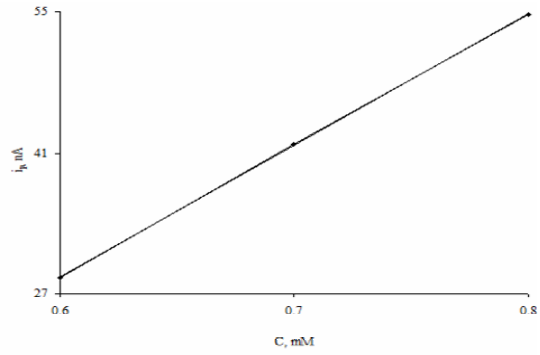


Fig. 6: Variation of differential pulse voltammetric current with concentration of naproxen sodium in 90 % acetonitrile/10 % water containing 0.1 M sodium perchlorate at platinum electrode ($8x10^{-4}$ cm^2). y = 130.85x- 49.835; R^2 = 0.9999.

Voltammetry of Naproxen Sodium at Glassy Carbon Electrode

A characteristic cyclic voltammogram was obtained for 1.0 mM naproxen sodium in 90 % acetonitrile/10 % water, Fig. 8. Two well-defined anodic peaks were observed with no associated cathodic peak in the reverse scan. The anodic peak currents for the irreversible peaks of naproxen sodium were observed to shift anodically with increasing sweep rate as shown in Fig. 9 variation of half peak potential with square root of sweep rate was represented in Fig. 10.

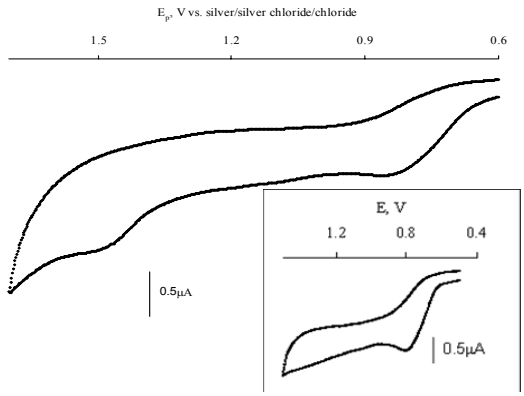


Fig. 7: Cyclic voltammogram of α-naphthylamine and naproxen sodium in 90 % acetonitrile/10 % water containing 0.1 M sodium perchlorate at platinum electrode ($8x10^{-4}$ cm^2). Sweep rate 0.1 Vs^{-1}. Cyclic voltammograme of α-naphthylamine is shown as an inset.

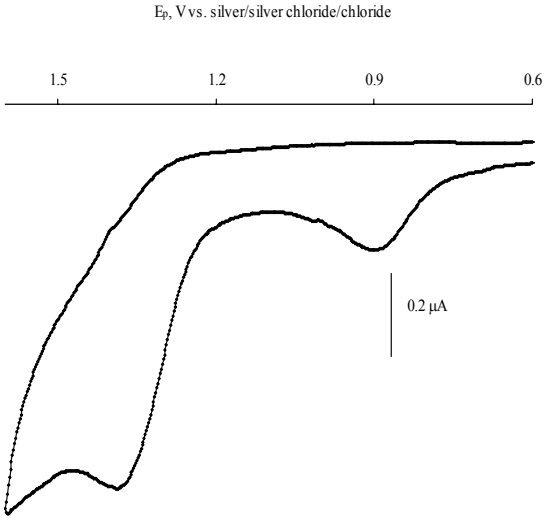


Fig. 8: Cyclic voltammogram of 1.0 mM naproxen sodium in 90 % acetonitrile/10 % water containing 0.1 M sodium perchlorate at glassy carbon electrode (0.125 cm^2). Sweep rate 0.1 Vs^{-1}.

A differential pulse voltammogram for electro-oxidation of 0.5 mM naproxen sodium comprised of two peaks at around 0.8 V and 1.3 V, respectively, illustrated in Fig. 11. Variation of anodic peak current with increasing concentration of naproxen sodium was shown in Fig. 12.

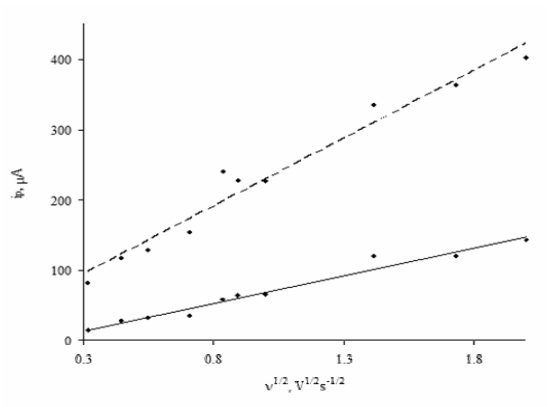


Fig. 9: Variation of anodic peak current with square root of sweep rate for cyclic voltammetric oxidation of 0.8 mM naproxen sodium in 90 % acetonitrile/10 % water containing 0.1 M sodium perchlorate at glassy carbon electrode (0.125 cm^2). Solid line is for first peak (y = 78.344x - 8.6228; R^2 = 0.970) and broken line is for second peak (y = 192.49x + 37.594; R^2 = 0.963)

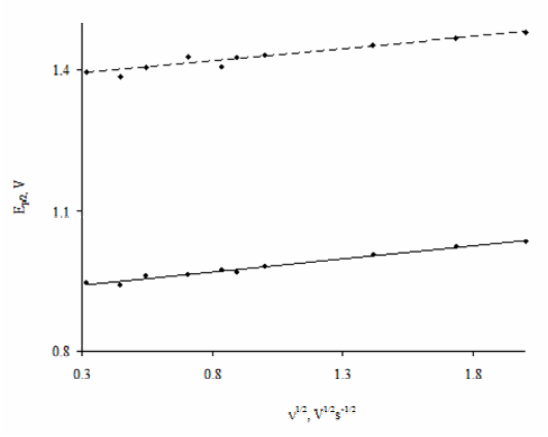


Fig. 10: Variation of half peak potential with square root of sweep rate for cyclic voltammetric oxidation of 0.8 mM naproxen sodium in 90 % acetonitrile/10 %water containing 0.1 M sodium perchlorate at glassy carbon electrode (0.125 cm^2). Solid line is for first peak (y = 0.0558x + 0.9264; R^2 = 0.9798) and broken line is for second peak (y = 0.0527x + 1.376; R^2 = 0.9258)

The electrochemical reaction might be expressed as an electrochemical chemical electrochemical chemical (ECEC) type mechanism where one electron oxidation of naproxen proceeded with the formation of a cation radical intermediate at the aromatic nuclei, which resulted in a rapid deprotonation from the side chain and it was possibly further oxidized irreversibly with the loss of a second electron followed by the attack of solvent/water molecule to produce acetamide derivative of naproxen [5. The cation radical was supposedly highly unstable and it was not possible to detect it by the ex-situ analytical techniques available in the laboratory. Mechanism was depicted in Scheme 1.

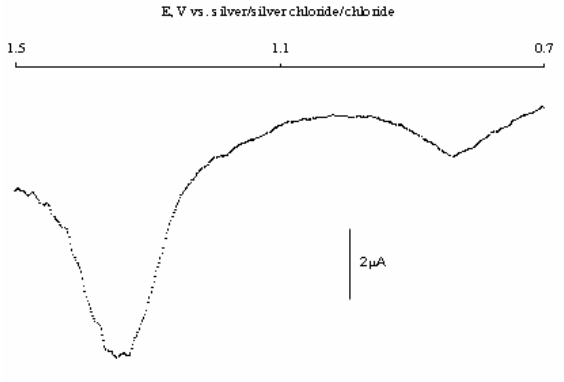


Fig. 11: Differential pulse voltammogram of 0.5 mM naproxen sodium in 90 % acetonitrile/10 % water containing 0.1 M sodium perchlorate at glassy carbon electrode (0.125 cm^2) at sweep rate, ν = 0.01 Vs-1. Pulse width, tp= 50 ms, Step time, τ =0.2 s and pulse height, ΔE = 75 mV.

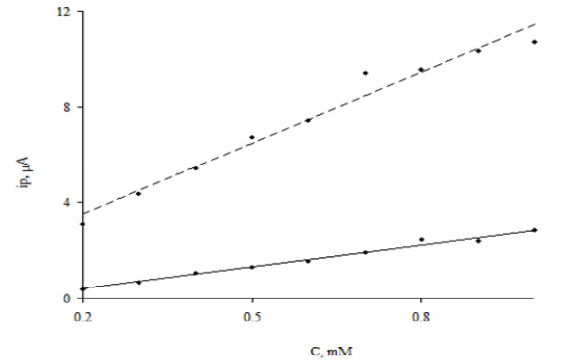


Fig. 12: Variation of anodic peak current with concentration for differential pulse voltammetric oxidation of naproxen sodium in 90 % acetonitrile/10 % water containing 0.1 M sodium perchlorate at different concentrations at glassy carbon electrode (0.125 cm^2). Solid line is for first peak (y = 3.0762x – 0.2248; R^2 = 0.9828) and broken line is for second peak (y = 9.9228x + 1.5042; R^2 = 0.9726).

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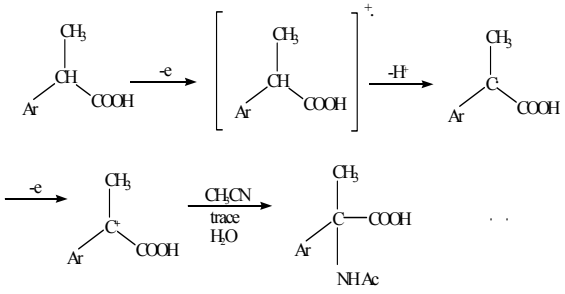

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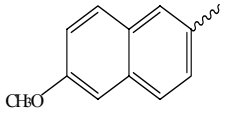

Scheme 1: The electrochemical reaction for naproxen expressed by an electrochemical chemical electrochemical chemical type mechanism.

Table-1: The value of transfer co-efficient. Data was obtained by using cyclic voltammetry of 0.6 mM naproxen sodium at platinum electrode ($8x10^{-4}$ cm^2) vs. silver/silver chloride, chloride.

ν mVs^{-1}	E_p mV	$E_{p/2}$ mV	*E mV	$\alpha = 47.7/*E^a$
100	**1455**	**1365**	**90**	**0.53**
200	**1450**	**1359**	**91**	**0.52**
300	**1447**	**1356**	**91**	**0.52**

*E = E_p-$E_{p/2}$

*E = (1.85 + RT$_y$ αF = 47.7/α

Experimental

Voltammetry of 0.1 mM Naproxen Sodium at Platinum and Glassy Carbon Electrode in 9:1 Acetonitrile Water Mixture

Chemicals and Materials

Specification of chemicals and materials used were used as follows:

a. Naproxen sodium($C_{14}H_{13}O_3Na$) was obtained as a gift.
b. Acetonitrile(CH_3CN) E-Merck Germany.
c. Sodium perchlorate($NaClO_4$) E-Merck Germany.
d. α–Nephthylamine ($C_{10}H_9N$) BDH.
e. γ-alumina (0.05micron) Mesoporous (moleculer sieve alumina) EG&G.

These chemicals were of analytical grade and were used without further purification. Polishing of the working electrode was done on a nylon-texture synthetic cloth pad soaked with slurry of γ-alumina powder (0.05 micron) in water.

Instrumentation and Techniques

Cyclic and pulse voltammetry were carried out using EG&G, Princeton Applied Research Corp, VersaStat II potentiostat. All experiments were performed in a three electrode cell containing platinum ($8x10^{-4}$ cm^2) and glassy carbon ($1.25x10^{-1}$ cm^2) working electrode, a platinum short wire as counter electrode and silver/silver chloride, saturated potassium chloride reference electrode. 90 % acetonitrile/10 % water solution containing 0.1 M sodium perchlorate was used as background. Data were acquired using M270 electrochemistry research software on a dedicated PII microprocessor coupled to the potentiostat. All experiments were carried out at room temperature.

Procedure

The cyclic and pulse voltammetry were carried out in a three electrode voltammetric cell working, counter and reference electrode containing 0.1 M sodium perchlorate in 90 % acetonitrile/10 % water solution. Working electrodes were polished prior to each scan. The electrodes were thoroughly washed with distilled water and dried then they were introduced in to the cell.

Connections for the three electrodes were made between the potentiostat and the electrodes through cell cable connector. The parameters for cyclic and pulse voltammetry were adjusted in Model M270 electrochemistry research software and voltammograms were recorded.

Voltammetry at Platinum Electrode

Cyclic and pulse voltammograms were recorded for the background electrolyte at sweep rate 0.1 Vs^{-1} and 0.01 Vs^{-1}. 25 mL of 1.0 mM solution of naproxen sodium was added to the electrochemical cell and cyclic voltammograms were recorded at different sweep rates. Normal pulse voltammograms were recorded at different concentrations 0.1 mM, 0.2 mM, 0.3 mM, 0.4 mM, 0.5 mM at sweep rate 0.01 Vs^{-1} and pulse width 50 ms. Differential pulse voltammogrames were recorded at concentrations 0.4 mM, 0.5 mM, 0.6 mM, 0.7 mM, 0.8 mM, 0.9 mM and 1.0 mM at sweep rate 0.01 Vs^{-1} and pulse width 50 ms. Cyclic voltammogramms of the interference compound namely α–naphthylamine has also been checked at platinum electrode only and well-defined

peak for it was detected versus silver/silver chloride saturated potassium chloride.

Voltammetry at Glassy Carbon Electrode

Cyclic and pulse voltammograms were recorded for the background electrolyte at sweep rates $0.1Vs^{-1}$ and $0.01Vs^{-1}$. 25 mL of 1.0 mM solution of naproxen sodium was added to the electrochemical cell and cyclic voltammograms were recorded at different sweep rates. Cyclic voltammograms were recorded at different concentrations from 0.2 mM to 1.0 mM at sweep rate $0.1\ Vs^{-1}$. Normal and differential pulse voltammograms were also recorded at different concentrations from 0.2 mM to 1.0 mM at sweep rate $0.01\ Vs^{-1}$ and pulse width 50 ms.

Conclusion

Two irreversible anodic peaks were obtained during cyclic voltammetry indicating that oxidation of naproxen sodium was not reversible. It was reported [6] that two related compounds to naproxen 2-methoxy-6-ethylnaphthalene and 2-acetyl-6-methoxynaphthalene gave pre and post peaks to naproxen respectively. During our investigations relating to voltammetry of naproxen sodium for its estimation in analgesics tablets, it was found that all samples contained an impurity, namely: 2-methoxy-6-ethylnaphthalene and interference studies showed that the same compound interfered with α–naphthylamine.

The application of this method for the analysis of naproxen sodium in drug samples indicated that the method was precise, straight forward and accurate.

Acknowledgment

Authors are indebted to Japan International Co-operation Agency (JICA) for the gift of the potentiostat, and to the University of Engineering and Technology Lahore for facilitation. I U H thanks Prof Dr E Bouwman for kind hospitality.

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