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Research Article

VOLTAMMETRIC AND CHROMATOGRAPHIC DETERMINATION OF NAPROXEN IN DRUG FORMULATION

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ABSTRACT

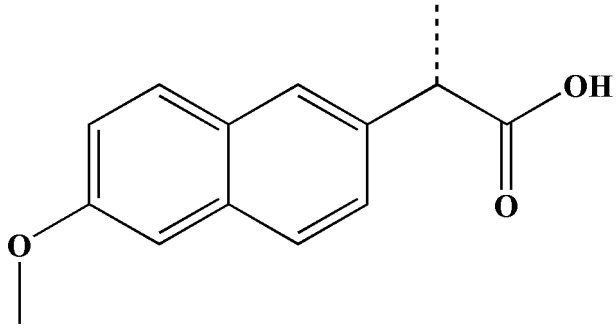
In this work, the electrochemical oxidation of naproxen (NAP) was studied at an ultra-trace graphite electrode (UTGE). The cyclic voltammetry (CV) technique was used to determine the optimum conditions and the effect of pH on the electrochemical oxidation of NAP. Acetate buffer (pH 4.50) was selected as the support electrolyte due to obtaining the highest electronic signal increase during oxidation of NAP at UTGE. The differential pulse voltammetry (DPV) technique was performed for electrochemical determination of NAP. In the optimum conditions, the limits of detection (LOD) and quantification (LOQ) were determined to be 8.66□10-8 M and 2.88□10-7 M. In addition, the amount of NAP was determined in drug tablets. The recovery studies of NAP from the drug tablet were completed in order to check the accuracy and precision of the applied voltammetric method. Furthermore, the determination of NAP was performed with the high-performance liquid chromatography (HPLC) method. These two methods were compared in terms of accuracy, precision and recovery studies.

Keywords: *naproxen; voltammetric method; differential pulse voltammetry; cyclic voltammetry; high performance liquid chromatography; ultra-trace graphite electrode; commercial drug tablets.*

1. INTRODUCTION

Naproxen, 2-(6-methoxynaphthalen-2-yl) (NAP), is a non-steroidal anti-inflammatory drug frequently used in the treatment of moderate or severe pain (**Figure 1**). It is also widely used for the reduction of stiffness caused by kidney stones, rheumatoid arthritis and other inflammatory diseases [1]. NAP, which needs a larger amount of tablet than non-steroidal anti-inflammatory drugs, strongly binds to albumin. Therefore, it has a longer half-life in blood than other drugs. Non-steroidal anti-inflammatory drugs have been associated with many cardiovascular events. However, according to recent studies, it was stated that naproxen is the least harmful non-steroidal anti-inflammatory for cardiovascular conditions [2].

Figure 1. Chemical formula of naproxen



Up to now, NAP was determined with different methods such as liquid chromatography [3], spectrophotometry [4], high-performance liquid chromatography [5,6], potentiometry [7], spectrofluorimetry [8] and electrochemical methods [9,10]. Sensitive, simple, rapid and economical methods are still needed. Therefore, electrochemical methods could be preferred to determine of NAP. The working electrodes such as a carbon paste electrode modified with activated carbon nanoparticles [11], a platinum electrode [12], a boron doped-diamond (BDD) electrode [13], ZnO nanoparticles and multi walled carbon nanotubes (MWCNTs) modified carbon paste electrode [14], a novel carbon paste electrode modified with NiO/CNTs nanocomposite and an ionic liquid (n-hexyl-3-methylimidazolium hexafluoro phosphate) [15], and graphite electrode [16] were used to determine NAP with electrochemical methods.

In this work, UTGE was used for voltammetric determination of NAP. A new electrochemical method for the determination of NAP using the DPV technique in 0.2 M acetate buffer (pH 4.50) media at UTGE was performed and used to determine the amount of NAP in drug tablets. In addition, the amount of NAP in pharmaceutical form was determined with the HPLC method. The results obtained from both methods were compared.

2. MATERIAL AND METHOD

2.1. Apparatus

A Model Metrohm 757 VA Trace Analyzer (Herisau, Switzerland) was used for the voltammetric measurements, with a three-electrode system consisting of UTGE as working electrode (UTGE; φ = 3 mm, Metrohm), a platinum wire as auxiliary electrode and Ag/AgCl (KCl 3 mol/L, Metrohm) as reference electrode. The UTGE electrode was polished with alumina (prepared from φ = 0.01 μm aluminum oxide) on an alumina polish pad before each experiment and then rinsed with ultra-pure deionized water and ethanol. Then, the deoxygenating process of the supporting electrolyte solution was carried out with argon gas for 5 min before all experiments. The argon gas was also passed through the solutions for 60 s after the addition of each sample solution during the experiments. All pH measurements were made with Model Metrohm 744 pH meter (Herisau, Switzerland) at ambient temperature of the laboratory (15 to 20 °C).

For the analytical applications, the following parameters were employed for differential pulse voltammetry (DPV); pulse amplitude 50 mV, pulse time 0.04 s and voltage step 0.009 V. Potential step 10 mV and scan rate in the range 100-750 mVs^{-1} for cyclic voltammetry (CV).

2.2. Reagents and materials

In this study, CH_3COOH (Riedel-de Haen, 99 %), CH_3OH (Merck, 99.5 %), NaOH (Merck, 99.8 %), acetonitrile (Merck 99 %), ethanol, and 0.05 μm sized Alumina powder (CH Instruments and metkom) were used. In addition, the drug active substance naproxen and drug dosage form Naprosyn was obtained from the Abdi Ibrahim Company. The stock solution of 1×10^{-2} M NAP was prepared by dissolving 4.3×10^{-3} mg NAP in 100 mL of ethanol. The working solutions for the voltammetric investigations were prepared by dilution of the stock solution. All solutions were protected from light and were used within 24 hours to avoid decomposition. 0.067 M phosphate buffer (pH 4.50-7.50), 0.2 M acetate buffer (pH 3.50- 5.50) and 0.04 M Britton-Robinson (B-R) buffer (pH 2.00-10.00) were selected as the support electrolyte solutions. The CV and DPV voltammograms of NAP were recorded to determine the support electrolyte type and optimum conditions. Ultra-pure water (UPW) obtained from Sartorius Arium model Ultra-Pure Water Systems was used to prepare the supporting electrolyte solutions. All chemicals used were analytical-reagent grade.

2.3. Calibration graph for quantitative determination

The diluted NAP solutions were obtained by diluting with water from the stock solution. In acetate buffer (pH 4.50) medium, a linear calibration curve for DPV analysis was constructed in the concentration range of NAP from 4×10^{-7} M to 1×10^{-5} M. The repeatability, accuracy and precision were checked.

2.4. Working voltammetric procedure for spiked tablet dosage forms

Five Naprosyn tablets were weighed and powdered to determine the amount of naproxen in Naprosyn tablets. Then, 5×10^{-6} M naproxen sample solution with an adequate amount of this powder was prepared and the DPV voltammogram of the sample was recorded.

The calibration curve was obtained from DPV voltammograms of NAP in the concentration range from 4×10^{-7} M to 1×10^{-5} M in 0.2 M acetate buffer (pH 4.50) at UTGE. The equation of the curve was $y = 8.87\times10^{4}\,x + 0.0045$. According to this equation, the amount of NAP in one tablet was determined to be 247 mg.

3. RESULTS AND DISCUSSION

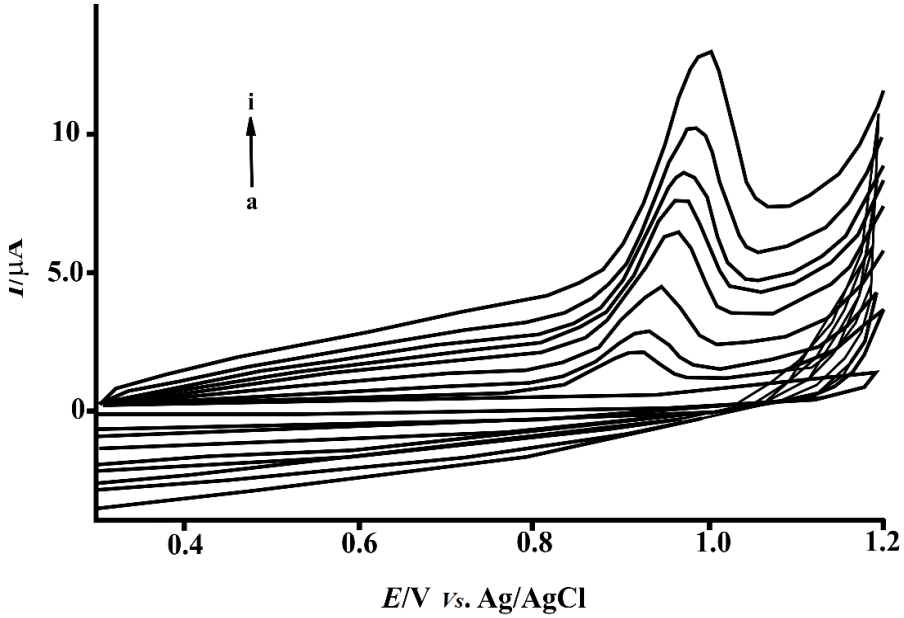
3.1. Electrochemical oxidation of naproxen

In order to determine the optimum conditions for the oxidation of NAP, 0.067 M phosphate buffer (pH 4.50 to pH 7.50), 0.2 M acetate buffer (pH 3.50 to 5.50) and 0.04 M B-R buffer (pH 2.00 to 12.00) were used as support electrolytes. DPV voltammograms of the NAP solutions of $5x10^{-5}$ M prepared in different electrolytes were recorded. Maximum peak current was obtained in the acetate buffer (pH 4.50) medium. Therefore, acetate buffer (pH 4.50) was chosen for further work.

3.2. The nature of the oxidation peak of naproxen

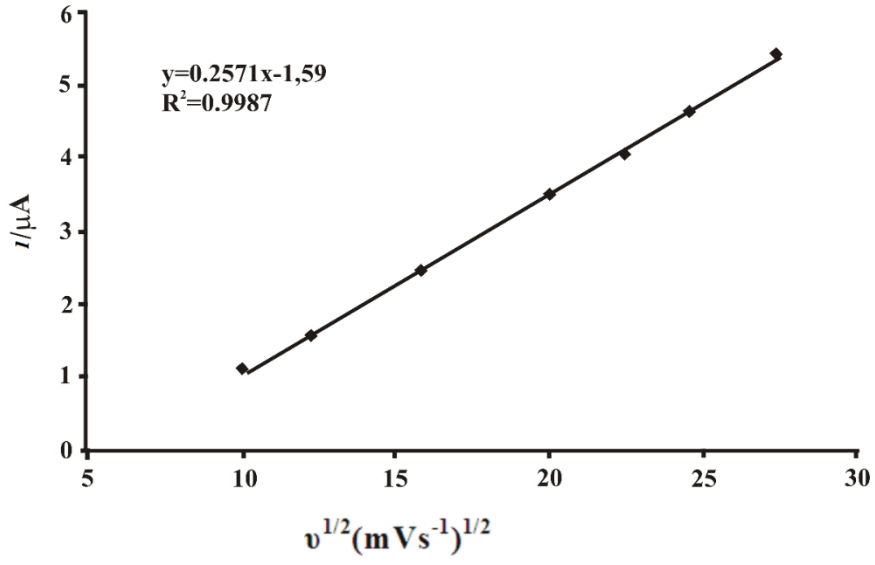
The cyclic voltammograms of $5x10^{-5}$ M NAP in 0.2 M acetate buffer (pH 4.50) at scan rates of 10-750 mVs^{-1} at UTGE were recorded (**Figure 2**).

Figure -2. CV voltammograms of 5×10^{-5} M NAP in 0.2 M acetate buffer (pH 4.50) at UTGE (Scan rates: a) the support electrolyte (0.2 M acetate buffer, pH=4.50), b) 100, c) 150, d) 250, e) 300 f) 400), g) 500, h) 600, j) 750 mVs^{-1}.



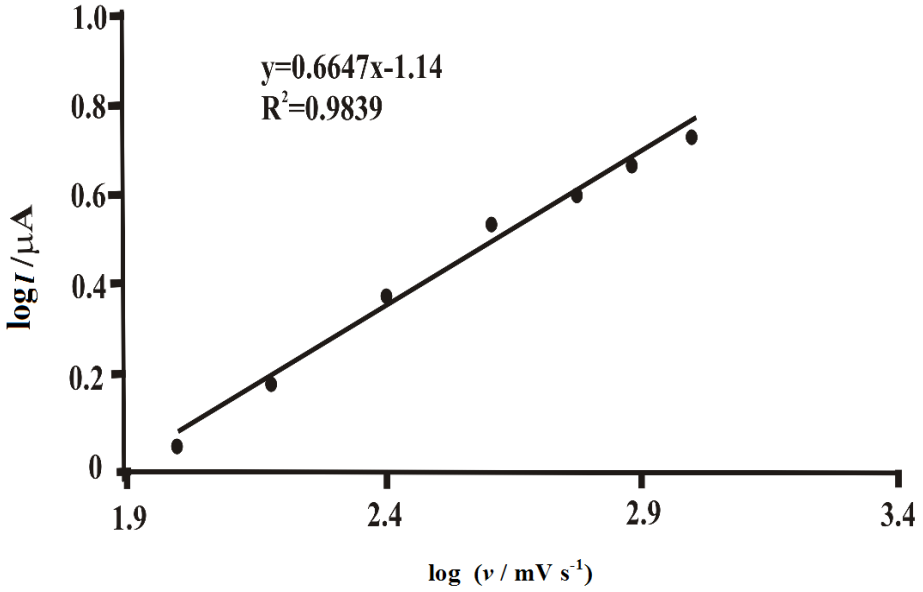
The peak current values increase with the increase in the scan rate. In addition, the peak potential values shift to more positive values when the scan rate increases. The peak current values plotted against $v^{1/2}$ are shown in **Figure 3.**

Figure - 3. The peak current values plotted against $v^{1/2}$ obtained from the CV voltammograms of 5×10^{-5} M NAP in 0.2 M acetate buffer (pH 4.50) at UTGE (Scan rates: a) 100, b) 150, c) 250, d) 400), e) 500, f) 600, g) 750 mVs^{-1}).



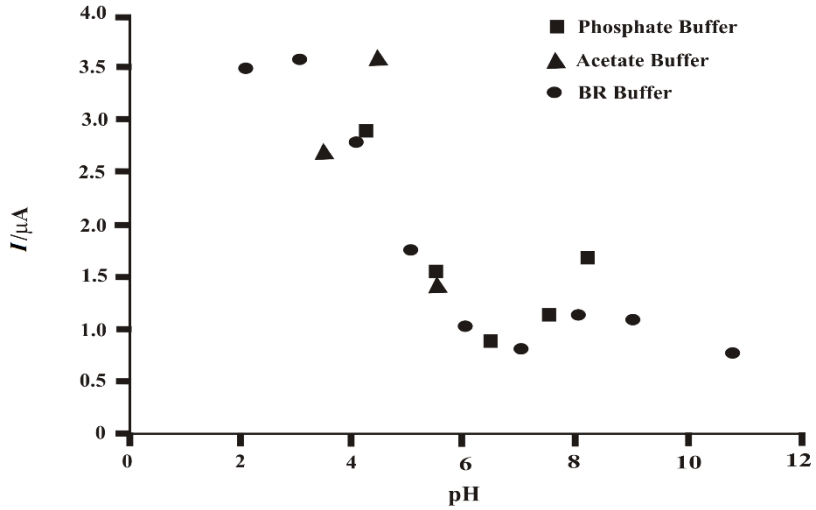
The peak current values plotted against $v^{1/2}$ was obtained with good linearity in the scan rate range of 100-750 mVs^{-1}. The linear regression equation was $Ip(\mu A) = 0.2571\upsilon^{1/2}-1.59$ with correlation coefficient (r=0.996). The correlation coefficient is very close to 1.0. Consequently, it is understood that the electrochemical-oxidation is diffusion controlled [12,17,18]. The logarithm of peak current (log *I*) against the logarithm of scan rate (log *v*) is shown in **Figure 4.**

Figure - 4. The logarithm of peak current (log *I*) against the logarithm of scan rate (log *v*) obtained from the CV voltammograms of 5×10^{-5} M NAP in 0.2 M acetate buffer (pH 4.50) at UTGE (Scan rates: a) 100, b) 150, c) 250, d) 400), e) 500, f) 600, g)750 mVs^{-1}).



The plot of logarithm of peak current (log *I*) versus logarithm of scan rate (log *v*) has a slope of 0.6647 (theoretical value of 0.50-0.75) indicate that the peak is diffusion controlled [12,17,18]. The peak current values of the oxidation peak obtained from the DPV voltammograms of the solutions of 5×10^{-5} M NAP prepared with different support electrolytes in the range from pH 2.0 to 10.0 are showed in **Figure 5**.

Figure - 5. Oxidation peak current values obtained from DPV voltammograms of 5×10^{-5} M NAP in the range from pH 2.0 to 10.0 in 0.2 M acetate, 0.067 M phosphate and 0.04 M B-R buffers at UTGE

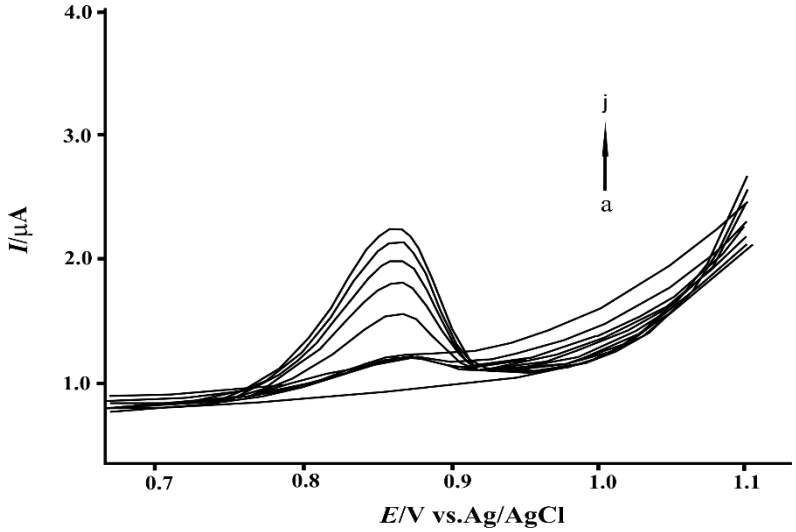


As seen in Figure 5, the oxidation peak current of NAP in 0.2 M acetate buffer reached the maximum value at pH 4.50. In addition, the anodic peak potential shifts towards lower positive values.

3.3. Determination of the analytical concentration range of NAP using the DPV technique

The assay of NAP at UTGE was performed using the DPV technique in 0.2 M acetate buffer (pH 4.50). The DPV voltammograms recorded in the potential range from + 0.6 V to +1.1 V for the different concentration of NAP are shown in **Figure 6.**

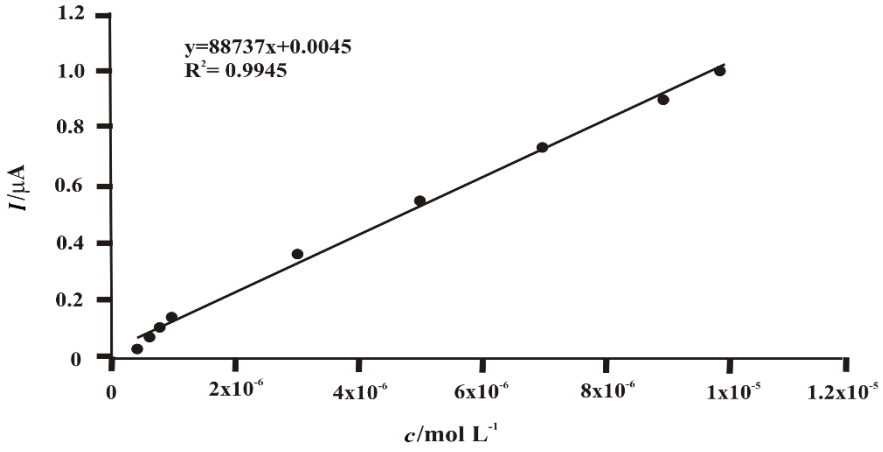
Figure - 6. DPV voltammograms recorded at UTGE for increasing concentrations of NAP in 0.2 M acetate buffer (pH 4.50). a) the support electrolyte (0.2 M acetate buffer, pH=4.50); b) 4.0×10^{-7}; c) 6.0×10^{-7}; d) 8.0×10^{-7}; e) 1.0×10^{-6}; f) 3.0×10^{-6}; g) 5.0×10^{-6}; h) 7.0×10^{-6}; i) 9.0×10^{-6} ; j) $1.0\text{x}10^{-5}$ M naproxen.



A linear calibration curve was constructed for NAP in the range 4×10^{-7} to 1×10^{-5} M in 0.2 M acetate buffer (pH 4.50) supporting electrolyte (**Figure 6**).

The plot of concentration versus current obtained from DPV voltammograms of NAP is given in **Figure 7.**

Figure - 7. Plot of concentration versus current obtained from DPV voltammograms of NAP in the concentration range from 4×10^{-7} to 1×10^{-5} M in 0.2 M acetate buffer (pH 4.50) at UTGE.



As shown in Figure 7, the plot was linear in the concentration range of 4×10^{-7} to 1×10^{-5} M NAP. For the regression plot of the peak current versus NAP concentration, the slope was 8.87×10^{4} μA/M, the intercept was 0.0045μA and the correlation coefficient was R^2=0.9945.

Limit of detection (LOD) and limit of quantification (LOQ) values were calculated using the following equations [12,17,18].

LOD = 3 s/m and LOQ = 10 s/m

Where, s is the standard deviation of the peak currents (for five runs) and m is the slope of the calibration curve. To determine LOD and LOQ values, the standard deviation of peak currents for five measurements recorded at 6×10^{-7} M, which is the concentration above the lowest concentration in the calibration graph, was determined to be 4.46×10^{-3}. The LOD and LOQ obtained were 8.66×10^{-8} M and 2.88×10^{-7} M at UTGE, respectively.

The different detection limits, pH, linear range and potential values for determination of NAP with several electrochemical methods were recorded in the literature. The results obtained in this study and the other references for the determination of TNX are given in Table I with different parameters.

Table - 1. The reported electrodes and analytical parameters for determination of NAP by voltammetric technique.

WE	Technique	Linear range	LOD	Ref.
MCPE	DPV	0.1-120 μM	0.0234 μM	11
PE	DPV	1.0-25 μg mL^{-1}	0.24 μg mL^{-1}	12
BDDE	DPV	0.5-50 μM	30 nM	13
MCPE	SWV	1.0×10^{-6}- 2.0×10^{-4} M	2.3×10^{-7} M	14
MCPE	SWV	7.5×10^{-7}- 8.0×10^{-4} M	1.2×10^{-7}	15
GBE	DPV	1.96-28.18 μg mL^{-1}	0.68 μg mL^{-1}	16
UTGE	DPV	4.0×10^{-7}- 1.0×10^{-5} M	8.66×10^{-8} M	This work

WE: Working electrode; MCPE: Modified carbon paste electrode; PE: platinum electrode; BDDE; GBE: graphite bar electrode; UTGE: Ultra trace graphite electrode; DPV: Differential pulse voltammetry; SWV: Square wave voltammetry

As can be seen in Table I, the quantitative determination of NAP by using several working electrodes was performed with different voltammetric techniques.

3.4. Determination and recovery of the amount of NAP in the drug form at UTGE

Five tablets of Naprosyn were weighed and powdered to determine the amount of NAP in Naprosyn tablets using the DPV technique in 0.2 M acetate buffer at UTGE. Then, $5x10^{-6}$ M naproxen solution was prepared. The DPV voltammogram of this solution was recorded. The amount of NAP in the sample was calculated by using the equation y= 88737x+0.0045 obtained from the calibration curve and the amount of NAP in one tablet was found to be 247.40 mg. This value was compared with the value indicated on the tablet (Table 2).

Table2. The assay of NAP in Naprosyn tablets with the DPV technique and recovery of NAP

Parameters	**Results**
Labeled NAP, mg	250
Amount found, mg	247
Relative Standard deviation (*RSD* / %)	0.81
Bias, %	1.04
Added NAP, mg	40.00
Found NAP, mg	39.64
Average recovery, %	99.10
Relative standard deviation of recovery (*RSD* / %),	2.17
Bias, %	0.90

3.5. Interference Studies NAP was formulated either in pure form or with some additives in drug tablets.

In present study, Naprosyn tablets contained only 250 mg NAP. Therefore, we observed only one peak without interferences. So, in order to investigate the effect of co-formulated substances such as glucose, starch, citric acid and magnesium stearate acid on the voltammetric response of NAP was carried out. Differential-pulse voltammetric experiments were carried out $1x10^{-6}$ M NAP in the presence of $1x10^{-4}$ M of each of the interferents (concentration ratios,1:100) are given Table 3.

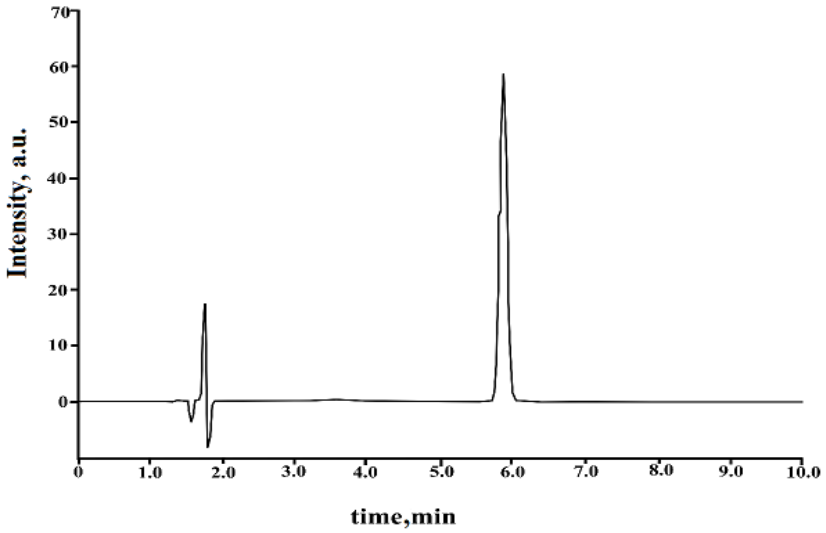
Table - 3. Influence of potential interferents on the voltammetric responses of $1x10^{-6}$ M NAP

Interferent	Concentration (M)	Current signal change, %
Glucose	1×10^{-4}	-1.12
Starch	1×10^{-4}	-1.40
Citric acid	1×10^{-4}	+ 1.25
Magnesium stearate	1×10^{-4}	+ 1.35

3.6. Determination of the amount of NAP in pharmaceutical form with the HPLC method

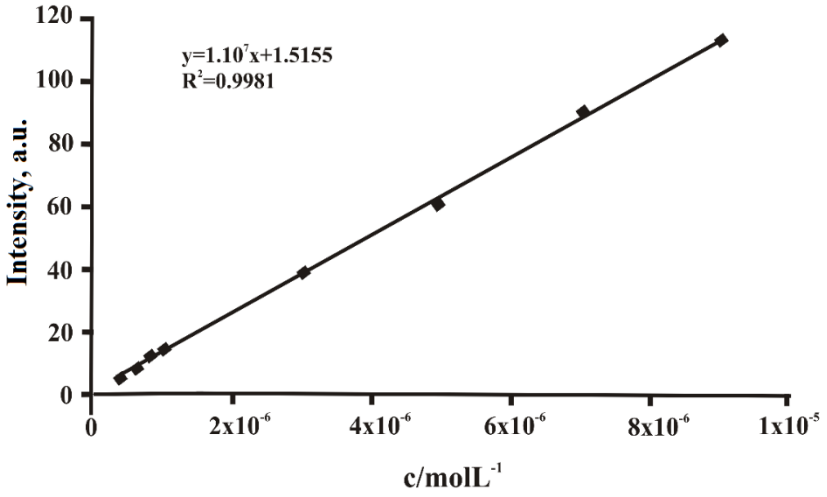
With 1% acetic acid as mobile phase, methanol and acetonitrile (40:20:40 v/v) as a detector, the retention time (t_R) for naproxen was 6.35 minutes, using the Diode-Array Detector (DAD) and the C18 Thermo Acclaim (3) M; 4.6 mm x 150 mm) column. The chromatogram of $5x10^{-6}$ M naproxen is given in **Figure 8**.

Figure - 8. The HPLC chromatogram of 5×10^{-6} M NAP



Different concentrations of naproxen were used to determine the analytical concentration range. A calibration graph was created from the peak-peak values of these chromatograms (**Figure 9**).

Figure - 9. Calibration line of naproxen standard obtained by HPLC with DAD detector



3.7. Statistical comparison of the results obtained with voltammetry and HPLC techniques

In order to verify the validity of the applied voltammetric method, the same analysis was performed with HPLC and the results were compared with each other (Table 4).

Table - 4. Comparison of parameters for Analysis applied voltammetry and HPLC techniques

Parameters	**Voltammetry**	**HPLC**
Linearity range of concentration, M	$4x10^{-7}$–$1x10^{-5}$	$4x10^{-7}$ – $1x10^{-4}$
LOD (M)	$8.66x10^{-8}$	$1.55x10^{-7}$
LOQ (M)	$2.88x10^{-7}$	$5.16x10^{-7}$
Amount of Naproxen indicated on tablet, mg	250.00	250.00
Amount of Naproxen found (mg)	247.00	253.00
Added Naproxen (mg)	40.00	40.00
Found in Naproxen (mg)	39.64	40.61
Recovery, %	99.10	101.52

LOD and LOQ values obtained by the voltammetry method are lower than those obtained by the HPLC technique. Therefore, the voltammetric technique is more advantageous.

Voltammetry and HPLC techniques were compared statistically. Accordingly, the t-test was applied in order to determine whether there were any differences between the means of analysis of the two techniques and to show the validity of the voltammetric technique. N = 6 degrees of freedom and 95% confidence interval based on the calculated value is greater than the calculated value ($t_{calculated}<t_{critical}$, 0.0085 <2.45). There were no differences found between the results of the two methods.[19, 20]

The F test was used to compare the accuracy of the measurement results of the two methods. With 6 degrees of freedom, $F_{critical}> F_{calculated}$ was 4.28> 0.057. Thus, it was concluded that there was no significant difference between the accuracy of these two methods [19, 20].

4. CONCLUSIONS

Ultra-trace graphite electrode was used for determination of NAP. A simple, sensitive and selective determination was performed with the DPV technique based on the electrochemical oxidation of NAP. It is understood that the electrode reaction process is irreversible and pH dependent from the CV and DPV measurements. NAP in pharmaceutical preparations was successfully determined using the DPV technique in 0.2 M acetate buffer (pH 4.50). In addition, the amount of NAP in pharmaceutical form was determined with the HPLC method. When the results obtained from both methods are compared, it is understood that the results obtained from the voltammetric method are more sensitive.

The differential pulse voltammetry technique can be used for the determination of NAP in pharmaceutical preparations in optimum conditions with UTGE as the working electrode and 0.2 M acetate buffer (pH=4.50) as the supporting electrolyte.

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