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Research Article

ELECTROCHEMICAL DETERMINATION OF KETOROLAC - A NON-OPIOID ANALGESIC AT GLASSY CARBON ELECTRODE

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ABSTRACT

Objectives: The study has been carried to investigate the electro-oxidation mechanism and to develop selective and sensitive methods for the determination of a non-opioid analgesic drug ketorolac (KTL).

Methods: A simple method was used for the determination of KTL using a glassy carbon electrode by cyclic and differential pulse voltammetric techniques. The effect of various experimental parameters such as accumulation time, pH, scan rate, on the voltammetric responses of KTL was evaluated.

Results: In the optimized conditions, variation of peak current with respect to concentration was studied and the calibration curve of the peak current versus KTL concentration was drawn with a linear range of 10–350 µM and an excellent detection limit of 8.08×10^{-8} M. The method was successfully applied for the determination of KTL in pharmaceuticals and human urine samples.

Conclusions: From the results, it has been observed that the selected method is rapid, sensitive, and low cost.

Keywords: Ketorolac, Glassy carbon electrode, Calibration curve, Detection limit, Pharmaceutical analysis.

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INTRODUCTION

In the past few decades, electrochemical techniques have been received considerable interest in the detection of small bio-molecules due to their high sensitivity, rapid response, simple operation, and low expense [1].

Ketorolac (KTL, as shown in Scheme 1) is a potent intravenous NSAID and a non-selective cyclo-oxygenase inhibitor which mediates pain, inflammation, and fever [2]. It has been evaluated and used for the treatment of moderate to severe pain including post-operative pain [3].

KTL crosses the placenta and is also excreted into breast milk in small quantities. The hydrophilicity and high protein binding of KTL prevent large concentrations of the drug from entering the breast milk. Administrations of KTL and other NSAIDs during the third trimester are contraindicated because they can cause premature closure of the ductus arteriosus.

A number of analytical methods have been investigated for the determination of KTL either alone or in its salt form or combination with other drugs, such as liquid chromatography-mass spectrometry (LC-MS/MS) [4], high-performance thin-layer chromatography [5], LC-MS [6], and high-performance liquid chromatography (HPLC) [7-11]. KTL has been determined in blood after a solid-phase extraction by gas chromatography-MS after derivatization using diazopropane [12]. Study in human serum has been performed by HPLC [13,14]. A flow injection analysis (FIA) method with spectrophotometric detection after derivatization with dichloronitrophenol in pharmaceutical formulations was published [15].

Most of the reported spectrophotometric methods based on derivative technique have shown poor selectivity, sensitivity, and required additional software's. Although the FIA and gas chromatographic methods have shown high sensitivities, they are expensive, involving the use of complex procedures with several sample manipulations and take longer analysis time. Hence, the development of an effective and efficient method for the determination of KTL in pharmaceutical preparation and biological fluids is an important task. To the best of our knowledge, only a few electrochemical methods have been reported for the determination of KTL in literature. The current study describes the determination of KTL in tablets and spiked human urine samples at glassy carbon electrode (GCE). The proposed method showed many advantages such as low detection limit, fast response, easy to apply, and economical for routine analysis. We believe that the proposed method would be a potential step forward in the determination of KTL in biological fluids.

METHODS

Reagents and materials

All chemicals and reagents were of analytical grade and used as received. KTL was purchased from Sigma-Aldrich. 0.2 M phosphate buffer solutions (pH 3.0–11.2) were prepared using H_3PO_4, Na_2HPO_4, and NaH_2PO_4, and double-distilled water was used throughout the experiment.

Instrumentation

All the voltammetric measurements (cyclic voltammetry and differential pulse voltammetry [DPV]) were carried out on CHI1112C (Version 9.03) using a 10 mL capacity electrochemical cell with the conventional three-electrode system: A platinum wire as a counter electrode, an Ag/AgCl electrode as the reference, and the GCE as working electrode. Solutions of various pHs were used, adjusted with H_3PO_4, Na_2HPO_4, and NaH_2PO_4 (different supporting electrolytes were also tested, such as Britton-Robinson buffer and acetate buffer). The pH of the buffer solution was measured using Elico model EI120 pH meter. All experiments were carried out at an ambient temperature of 25±0.1°C.

Area of the electrode

The area of the electrode was obtained by a cyclic voltammetric method using 1.0 mM $K_3Fe(CN)_6$ as a probe at different scan rates. For a reversible process, the following Randles–Sevcik formula [16] can be used to calculate the area of the electrode:

$$i_{pa} = (2.69\times10^{-5})n^{3/2}AD_0^{1/2}C_{0V}^{1/2}$$

Where i_{pa} refers to the anodic peak current, n is the number of electrons transferred, A is the surface area of the electrode, D_0 is diffusion coefficient, υ is the scan rate, and C_0 is the concentration of $K_3Fe(CN)_6$. For 1.0 mM $K_3Fe(CN)_6$ in 0.1 M KCl electrolyte, n=1, D_0=7.6×10^{-6} cm^2/s [16], then from the slope of the plot of i_{pa} versus $\upsilon^{1/2}$, the surface area of the electrode can be calculated. In our experiment, the slope was 14.15×10^{-6}μA $(Vs^{-1})^{-1/2}$ and the area of electrode was calculated to be 0.0212 cm^2.

Analytical procedure

For good reproducible results, the working electrode was carefully polished with 1 μm, 0.3 μm, and 0.05 μm α-alumina on smooth polishing cloth and then washed in double-distilled water. The three electrode systems consisting of a GCE (3 mm diameter) as the working electrode, an Ag/AgCl (3 M KCl) reference electrode, and a platinum wire as the auxiliary (counter) electrodes were used. The experimental conditions for DPV were: Initial potential: 1.1 V, final potential: 1.4 V, sensitivity: 1×10^{-6}A/V, pulse amplitude: 50 mV, sample width: 20 ms, pulse period: 500 ms, and scan rate: 50 mV/s.

Standard and pharmaceutical sample preparation

The commercially available tablets of KTL were weighed and powdered using pastel mortars. A portion of the powder equivalent to about 1.0 mM was weighed accurately, transferred to a 100 mL calibrated flask and completed the volume with double distilled water. It was then sonicated for 15 min to effect complete dissolution and diluted to volume with water. Suitable amounts of this solution were taken and analyzed. The amount of KTL in the tablet was calculated using a calibration graph or regression equation.

To study the accuracy of the proposed method, and to check the interference from excipients used in the dosage forms, recovery experiments were carried out by the standard addition method. This study was performed by addition of known amounts of KTL to a known concentration of the tablets. The resulting mixture was analyzed as in pure KTL.

Determination of KTL in spiked human urine samples

Using the calibration curve method, the application of the method for the determination of KTL in human urine was also investigated. The urine sample was diluted 100 times with 0.2 M PBS (pH=3.8) to fit the calibration curve and reduce the matrix effect. No other pre-treatment process was performed.

ESULTS AND DISCUSSION

Cyclic voltammetric investigation of KTL

The voltammetric behavior of KTL was investigated using cyclic voltammetry. Fig. 1 shows typical cyclic voltammograms of 0.1 mM of KTL, in PBS of pH 3.8 at scan rate 50 mV/s recorded at GCE. This shows two oxidation peaks at 0.982 V and 1.355 V. On scanning in the negative direction; no reduction peak was observed, showing that the oxidation of KTL is an irreversible process in this potential range. The peak intensity and peak current of the second oxidation peak are maximum, hence, selected the same for the analytical purpose.

Effect of pH

The electrochemical responses of 0.1 mM KTL at GCE in phosphate buffer of different pH (3.0–11.2) were investigated, and the corresponding voltammograms are shown in Fig. 2a. It was noticed that the oxidation peak shifted toward negative potentials with an increase in pH indicating the role of protons in the oxidation process [17]. For pHs comprised between three and seven, two well-defined voltammetric peaks were observed. At pH above seven these two peaks were fused into only one peak. The evolution of both peak potential and peak current with pH, for both peaks, is shown in Fig. 2b and c. Furthermore, both peaks potential showed a linear dependence with the pH variation confirms the transfer of electrons and protons during the electrochemical process [18-20]. The equations relating to them can be represented as:

$$E_p = -0.003pH+1.369 \ (R^2=0.974)$$

$$E_p = -0.003742pH+0.998251 \ (R^2=0.985)$$

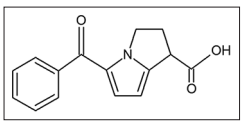
Effect of the time and potential of the accumulation

In the accumulation step, two important parameters are potential and time of accumulation, which can affect the sensitivity of determination via changing the amount of adsorbed KTL at the surface of modified electrode. Hence, influence of these parameters on the peak current was studied by the cyclic voltammetric method. It was found that by increasing the accumulation time, until 50 s, the peak current was increased; due to increasing the amount of the adsorbed analyte and it can be seen that after 50 s, the peak current stays nearly constant.

At the optimum value of accumulation time (50 s), the effect of accumulation potential was investigated form 0.2 to −0.2 V. The results showed that changing the potential of accumulation step from open circuit condition has no effect on the peak current. Therefore, 50 s of accumulation time in an open circuit condition was chosen for the accumulation step in all voltammetric determinations.

Effect of the potential scan rate

Cyclic voltammetric studies at different potential scan rates (25–400 mV/s) for 0.1 mM solution of KTL were performed on the surface of GCE in a PBS of pH 3.8 as shown in Fig. 3a. It was found that the peak current has a linear relationship with the square root of scan rate as it is shown in Fig. 3b. This linear relationship confirms the diffusion-controlled process [21] for the electro-oxidation of KTL at the electrode. Further, the plots of log I_{pa} versus log υ gave the slope of 0.39 for peak 1 and 0.31 for peak 2(logI_{pa1}=0.391log υ+1.296 R^2=0.943; log I_{pa2}=0.317 log υ+0.749, R^2=0.969) confirming the diffusion controlled electrode process [21,22].



Scheme 1: Chemical structure of ketorolac

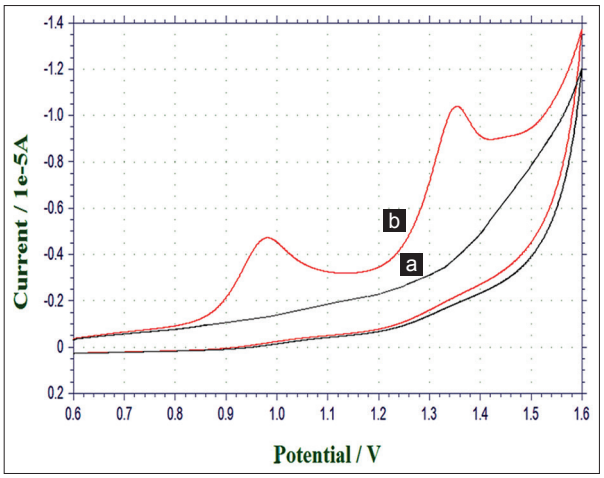


Fig. 1: Cyclic voltammogram of 0.1 mM KTL at (a) bare glassy carbon electrode, (b) glassy carbon electrode + KTL; scan rate 50 mV/s; phosphate buffer of pH 3.8 as supporting electrolyte

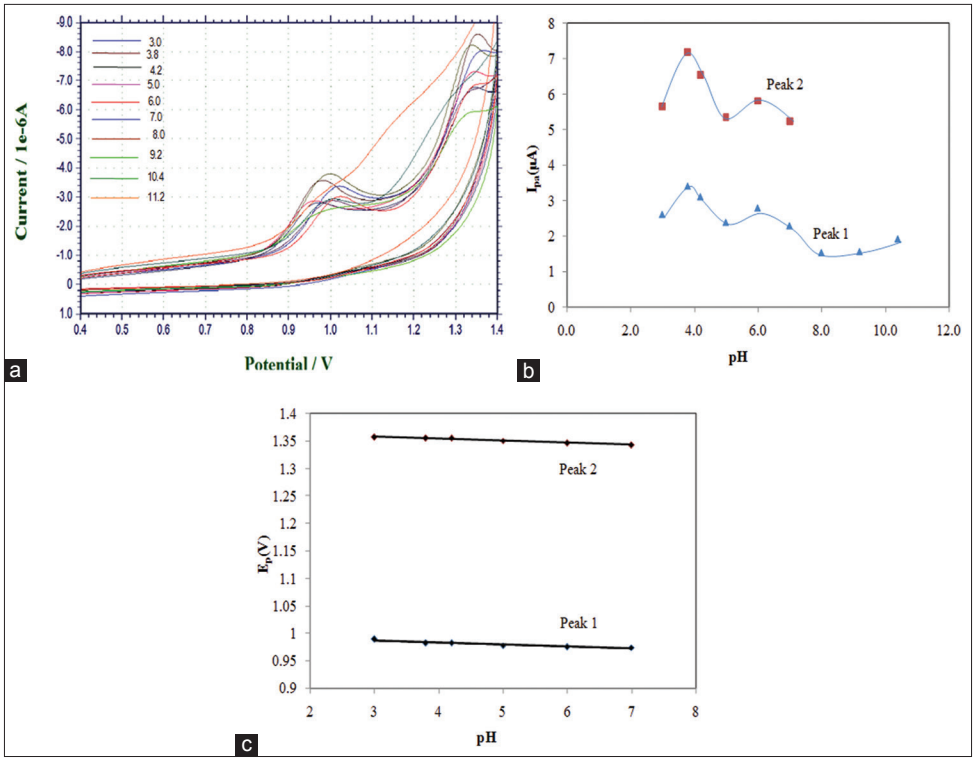


Fig. 2: (a) Influence of pH on the shape of the anodic peak, pH: 3.0–11.2. (b) Variations of peak currents I_{pa} (μA) of KTL with pH. (c) Influence of pH on the peak potential E_p (V) of KTL. Other conditions as shown in Fig. 1

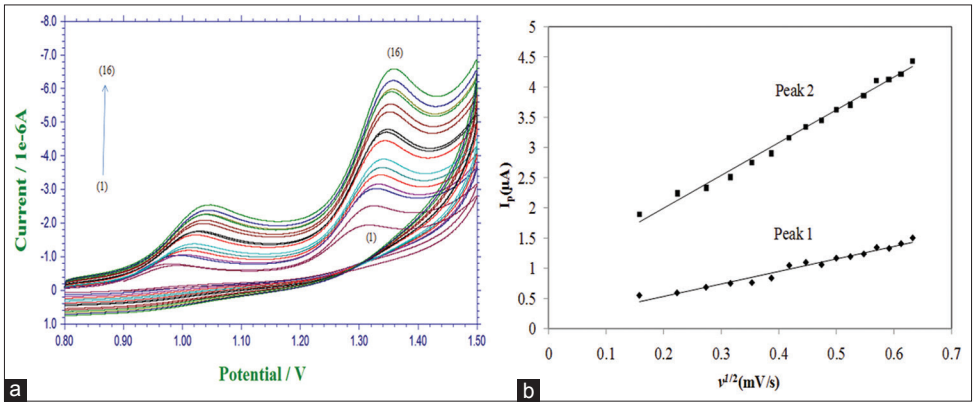


Fig. 3: (a) Cyclic voltammograms for the oxidation of KTL at different scan rates (1)–(16): 25 m v/s - 400 m v/s. (b) Dependence of oxidation peak current on the square root of scan rate

As for an irreversible electrode process, according to Laviron [23], E_{pa} is defined by the following equation:

$$E_{pa} = E^{0'} + \left(\frac{2.303RT}{\alpha nF}\right)\log\left(\frac{\vec{R}Tk^0}{\alpha nF}\right) + \left(\frac{2.303RT}{\alpha nF}\right)\log v \qquad (1)$$

Where α is the transfer coefficient, k^0 the standard heterogeneous rate constant of the reaction, n the number of electrons transferred, υ the scan rate, and $E^{0'}$ is the formal standard redox potential. Other symbols have their usual meaning. Thus, the value of αn can be easily calculated from the slope of E_p versus log υ plot. In this system, the slope is 0.054 and 0.030 for peak 1 and peak 2, respectively. Taking α=0.5 for irreversible electrode process, T=298 K, R=8.314 JK/mol, and F=96480 C/mol, the number of electrons (n) transferred in the electro-oxidation of KTL was calculated to be 1.24~1.0 and 2.23~2.0 for first and second peak, respectively. The value of k^0 can be determined from the intercept of the previous equations, if the value of $E^{0'}$ is known. The value of $E^{0'}$ in eqn. (1) can be obtained from the intercept of E_p versus υ curve by extrapolating to the vertical axis at υ=0 [24]. In our system, the intercept for E_p versus log υ plot was 1.065 and 1.368 for peak 1 and

Table 1: Characteristics of KTL calibration plot using differential pulse voltammetry at a glassy carbon electrode

Linearity range	10–350 μM
Slope of the calibration plot	340.0
Intercept	3.677
Correlation coefficient (r)	0.987
RSD of slope (%)	0.26
RSD of intercept (%)	1.33
Number of data points	12
LOD (M)	8.08×10^{-8}
LOQ (M)	2.69×10^{-7}

RSD: Relative standard deviation, LOD: Limit of detection, LOQ: Limit of quantitation

Table 2: Comparison of detection limits for KTL to different classical methods

Method	LOD	References
RP-HPLC method	3.97×10^{-7} M (0.116 µg/mL)	8
LC and LC-MS	7.19×10^{-7} M (0.21 µg/mL)	28
Spectrophotometric method	1.18×10^{-7} M	25
Differential pulse polarographic determination	4.04×10^{-6} M	27
Zero-crossing derivative spectrophotometry	1.13×10^{-6} M (0.33 µg/mL)	29
Ratio spectra derivative spectrophotometry	2.23×10^{-6} M (0.65 µg/mL)	29
Ratio difference spectrophotometry	1.71×10^{-6} M (0.50 µg/mL)	29
HPLC-DAD	2.74×10^{-6} M (0.80 µg/mL)	29
Voltammetric method	8.08×10^{-8} M	Present method

HPLC: High-performance liquid chromatography, LOD: Limit of detection, LC-MS: Liquid chromatography-mass spectrometry

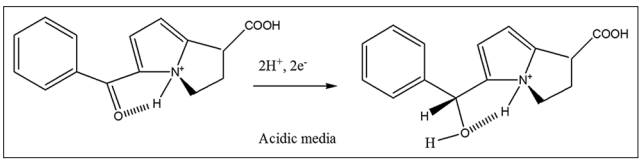
Table 3: Influence of potential excipients on the voltammetric response of 1.0×10^{-6} M KTL

Excipients (1.0 mM)+Drug KTL (1.0×10^{-6})	Potential observed (V)	Signal change (%)
Only Ketorolac	1.280	0
Tartaric acid+KTL	1.271	−0.703
Citric acid+KTL	1.255	−1.95
Glucose+KTL	1.270	−0.78
Gum acacia+KTL	1.314	2.65
Lactose+KTL	1.244	−2.81
Dextrose+KTL	1.265	−1.17
Sucrose+KTL	1.268	−0.93
Starch+KTL	1.276	−0.31

Table 4: Analysis of KTL tablet by DPV and recovery studies

Ketorol (10 mg)	DPV
Labeled claim (mg)	10.00
Amount found (mg)[a]	9.981
RSD (%)	01.35
Bias (%)	−00.19
Added (mg)[a]	03.00
Found (mg)	02.89
Recovered (%)	96.63
RSD (%)	03.31
Bias (%)	03.36

[a]Average of three determinations. DPV: Differential pulse voltammetry, RSD: Relative standard deviation



Scheme 2: Probable electro-oxidation mechanism of KTL

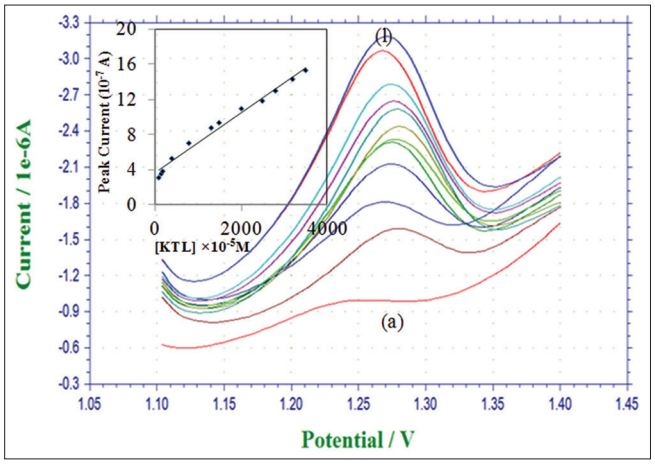


Fig. 4: Differential pulse voltammograms for increasing concentration of KTL at GCE: (a)-(l): 10 µM–350, inset: Plot of current against the concentration of KTL

peak 2, respectively, and $E^{0'}$ were 0.992 and 1.326, respectively. From the above, calculated k^0 values were 140.73/s and 269.63/s.

Electro-oxidation mechanism

Exact oxidation mechanism was not determined for KTL, but some conclusions about the electroactive group can be reached. Two pK values were reported for KTL, a pK value of 3.5 due to the carboxylic group [25] and another 6.2, due to protonation of the tertiary nitrogen in the pyrrole nucleus, from polarographic determination [26]. As the oxidation peaks were observed till pH 7.0 and after that the peaks were vanishes, it can be concluded that heterocyclic nitrogen is directly involved as the electro-oxidable group. Based on all the experimental results and the reported works [26-28] electro-oxidation mechanism for KTL in the acidic medium can be given as shown in Scheme 2.

Analytical determinations

Under the optimized experimental conditions, GCE was used for the determination of KTL by means of DPV. DPV is having better resolving power and higher sensitivity than CV. Fig. 4 shows the DPVs of KTL at different concentrations. The results showed that the peak current (I) has a linear relationship with the concentration of KTL in the range of 10.0–350.0 µM with the following linear characteristics, which is shown in Fig. 4 inset: $I_{pa}(10^{-5}A)=340.0$ KTL+3.677(R^2=0.987). In these measurements, a theoretical detection limit (S/N=3) of 8.08×10^{-8} M was obtained for KTL.

As mentioned in the introduction, only a few analytical methods have been reported for the determination of KTL in pharmaceutical or urine samples. Thus, Table 1 shows the analytical parameters obtained in this work and Table 2 shows the parameters obtained using other reported analytical techniques. It can be observed that the analytical parameters obtained, in terms of LOD, herein are better than those based in usual analytical methods [8,25,28-30]. Besides that, HPLC-MS and GC–MS methods require high consumption of organic solvent are time-consuming for sample pre-treatment, on the other hand, our method requires minimal sample pre-treatment and the instrumentation is inexpensive.

Interference study

Under the optimized conditions, the influence of various common interferences in pharmaceutical samples for the determination of KTL was studied. 1000-fold Glucose, Gum Acacia, Sucrose, Citric acid, Dextrose, Lactose, Tartaric acid, and Starch had no obvious interference with the current response of KTL (signal change <10%). The results are as shown in Table 3.

Determination of KTL in pharmaceutical preparations

To demonstrate the electrocatalytic oxidation of KTL in pharmaceutical preparations, we examined this ability in DPV for determination of KTL concentration in tablet sample.

Table 5: Application of DPV to the determination of KTL in a spiked human urine sample

Sample	Added (×10^6 M)	Found[a] (×10^6 M)	Recovery (%)	RSD (%)	Bias (%)
1	2	1.9786	98.93	0.524	−1.07
2	5	5.016	100.32	1.608	0.32
3	6	6.203	103.38	2.625	3.38
4	8	7.954	99.425	0.778	−0.575

[a]Average of three determinations

The tablets were grounded to powder, dissolved in water and then further diluted so that KTL concentration falls in the range of calibration plot. DPV were then recorded under exactly identical conditions that were employed while recording differential-pulse voltammograms for plotting calibration plot. Based on the repeated DPV responses (n=3) of the diluted analytes and the samples that were spiked with a specified concentration of KTL and using the calibration plot measurements were made of KTL concentrations in the pharmaceutical preparations and the recovery rate of the spiked samples. The results are listed in Table 4.

Recovery study of KTL in a urine sample

The developed DPV method for the KTL determination was applied to urine samples. The recoveries from urine were measured by spiking drug-free urine with known amounts of KTL. A quantitative analysis can be carried out by adding the standard solution of KTL into the detection system of urine samples. The calibration graph was used for the determination of spiked KTL in urine samples. The detection results of four urine samples obtained with recovery percentage and RSD are listed in Table 5.

Repeatability and reproducibility of the electrode

The precision of the method was evaluated by repeating five experiments on the same day and in the same standard condition (repeatability) and over 2 days from the different standard solutions (reproducibility). For these studies, 1.0×10^{-6} M KTL standard solution was used. The corresponding RSD of the peak current of 2.49% and 2.44% confirms that the electrode has good repeatability and reproducibility.

CONCLUSIONS

In this study, the voltammetric determination of KTL is carried out by GCE in a phosphate buffer solution of pH 3.8. pH effects showed the role of proton transfer in the electrochemical process. Effect of potential scan rate was examined, and the results show that the electrochemical process is diffusion controlled. The number of electrons transferred during the process was calculated. Under the optimum condition, KTL shows a linear response in the concentration range from 10 to 350 μM and a detection limit of 8.08×10^{-8} M, besides presenting good intra- and inter-day repeatability. The method has been successfully applied to the determination of KTL in pharmaceutical samples and recovery study in urine sample successively.

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AUTHOR'S CONTRIBUTIONS

Author Rohini M. Hanabaratti contributed substantially toward the study starting from literature survey, the conception of the problem, its design, data collection, optimization of the experimental conditions, and conduct of experiments. Author Jayant I. Gowda involved in analysis, interpretation of data, preparing of graphs, manuscript writing. Suresh M. Tuwar involved in writing the manuscript, editing, and finalized findings.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest.

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