

*Full Paper*

## **Voltammetric Investigation of Ketotifen Using Carbon Paste Electrode Modified by Magnetic Core-Shell Fe<sub>3</sub>O<sub>4</sub>@TMSPT Nanoparticles**

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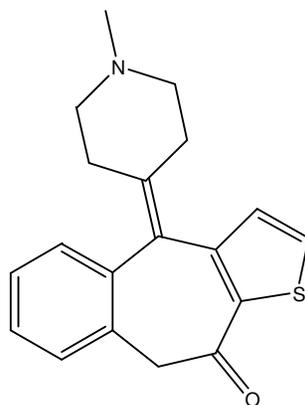
**Abstract-** A new carbon paste electrode was modified by Fe<sub>3</sub>O<sub>4</sub> magnetic nanoparticles coated by [3-(trimetoxysilil)-1-propanthiol] (TMSPT) with the help of permanent magnet and used for voltammetric investigation of ketotifen. The cyclic voltammetry indicated that Fe<sub>3</sub>O<sub>4</sub>@TMSPT modified electrode significantly enhanced the oxidation peak current of ketotifen than the bare electrode in a Britton Robinson buffer solution (pH 7). Cyclic voltammetric study at various scan rates and different pHs indicate that the mechanism of oxidation of ketotifen at the Fe<sub>3</sub>O<sub>4</sub>@TMSPT modified electrode is an irreversible with two electrons reaction in a diffusion process. Factors influencing the detection processes were optimized and heterogeneous rate constant ( $k^0$ ) was calculated. Under optimal conditions using differential pulse voltammetry, the modified electrode showed a linear response to the concentration of ketotifen in the range of  $2.5 \times 10^{-7}$ – $3.0 \times 10^{-5}$  M with a detection limit of  $4.5 \times 10^{-8}$  M. The method was utilized for the determination of ketotifen in ketotifen fumarate tablets with satisfactory results.

**Keywords-** Magnetic core-shell, Carbon paste electrode, Ketotifen, Nanoparticle, Voltammetry

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## 1. INTRODUCTION

Ketotifen, [4-(1-methyl-4-piperilidene)-4H-benzo-(4,5)-cyclohepta-(1,2-b)-thiophen-10(9H)-one] (Scheme 1) is a benzocycloheptathiophene derivative with multiple pharmacological actions [1]. It is used to prevent the development of allergic conjunctivitis [2,3], asthma [4,5], and it even showed an anti-wrinkle effect [6]. A number of methods, such as high performance liquid chromatography (HPLC) [7], liquid chromatographic–mass spectrometric (LC–MS) [8], atomic absorption spectrometry [9], and spectrophotometric [10] were employed for the determination of ketotifen. However, most of these methods have their shortcomings, such as time-consuming, low sensitivity, complicated process, and expensive devices. Consequently, the electrochemical techniques have attracted much attention because of their sensitivity, quick response, low cost, and short analysis time.



**Scheme 1.** The structure of ketotifen

$\text{Fe}_3\text{O}_4$  nanoparticles have attracted an increasing interest for application to sensors, because of high surface area, strong super-paramagnetic property, low toxicity, easy preparation, and high adsorption ability. Moreover,  $\text{Fe}_3\text{O}_4$  nanoparticles have a unique ability to promote fast electron transfer between electrode and the active site of the redox biological reaction [11]. In addition, magnetic nanoparticles are biocompatible and environmentally safe [12]. However, pure magnetic nanoparticles are intrinsically unstable over time, and small particles tend to form agglomerates to reduce the energy associated with ratio of surface area to volume. In addition, naked metallic nanoparticles are highly chemical active and easy to be oxidized in air, which results in poor magnetism and dispersibility. The functionalization of the magnetic nanoparticles is an important way to improve the stability and dispersibility.

In the recent years we used the modified magnetic nanoparticles for separation of some metal ions [13] and drugs [14], and in the modification of the carbon paste electrodes [15]. In this present work, magnetic nanoparticles were prepared by chemical co-precipitation of  $\text{Fe}^{3+}$  and  $\text{Fe}^{2+}$  ions. Following, the nanoparticles were directly coated and modified by

3-(trimethoxysilyl)-1-propanthiol (TMSPT). The  $\text{Fe}_3\text{O}_4$ @TMSPT magnetic nanoparticles were used as a modifier in carbon paste electrode ( $\text{Fe}_3\text{O}_4$ @TMSPT/MCPE). The possible applications of this material to the fabrication of stable and sensitive electrochemical sensor were investigated. The electrochemistry of ketotifen was studied in detail on the  $\text{Fe}_3\text{O}_4$ @TMSPT/MCPE, which indicates desirable electrocatalytic behavior toward the electrochemical redox of ketotifen. Based on this, a fast, simple, and sensitive detection method was developed for the determination of ketotifen.

## 2. EXPERIMENTAL SECTION

### 2.1. Apparatus

Electrochemical measurement carried out with a Palm Sense (EN 50081- 2, Netherland) potentiostat. A conventional three-electrode system was used consist of a work carbon paste electrode (unmodified or modified), an Ag/AgCl (KCl 3.5 M) as a reference electrode, and a platinum wire as a counter electrode. The pH values were determined using a Metrohm-827 pH/mV meter (Switzerland). All experiments performed at room temperature.

### 2.2. Reagents

A stock solution of  $1 \times 10^{-3}$  M ketotifen was prepared in doubly distilled water and stored at 4°C. All other standard solutions were prepared using this stock solution. All chemicals were of analytical reagent grade and used without further purification. Britton-Robinson (B-R) universal buffer of pH 2-11 was used as a supporting electrolyte and adjusting the pH with 0.2 M NaOH. Ketotifen tablets (1mg/ tablet) were purchased from Pharma Amin, (Tehran, Iran). All solutions were freshly prepared with doubly distilled water. The graphite powder and paraffin oil as the binding agent (both from Merck) were used for preparing the pastes.

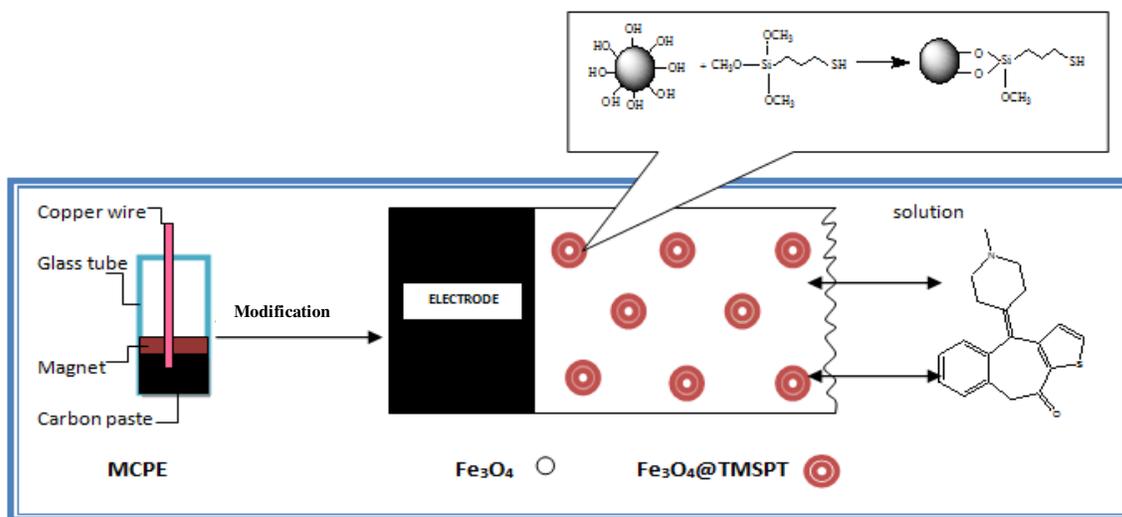
### 2.3. Synthesis of TMSPT coated magnetic nanoparticles

The magnetic nanoparticles (MNPs) were synthesized using the chemical co-precipitation method [13]. In brief,  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  (11.68 g) and  $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$  (4.30 g) were dissolved in 200 mL deionized water in the mole ratio of 2:1 under nitrogen atmosphere with vigorous stirring at 85 °C. Then, 45 mL of 25% ammonia solution was added. The clear orange solution turned to black immediately and the solution was stirred for 15 min at the same conditions. After cooling down to the room temperature, the magnetic precipitates were isolated by applying an external magnet at the bottom of the beaker and decantation of the supernatant. The magnetic precipitates were separated by magnet, which was washed twice with deionized water and once with 0.02 M sodium chloride. The washed magnetic nanoparticles were stored in

deionized water at the concentration of  $40 \text{ g L}^{-1}$ . The supernatant was removed and an aqueous solution of 10% (v/v) TMSPT (80 mL) was added followed by 60 mL glycerol. The mixture was stirred under nitrogen atmosphere at  $90 \text{ }^\circ\text{C}$  for 2 h. After cooling to room temperature, the deposit was removed again by a magnet and washed with deionized water ( $3 \times 200 \text{ mL}$ ), methanol ( $3 \times 100 \text{ mL}$ ), and deionized water ( $5 \times 200 \text{ mL}$ ), respectively. The TMSPT-MNPs composite was stored in deionized water at a concentration of  $40 \text{ g L}^{-1}$ .

## 2.4. Fabrication of sensor

The magnetic carbon paste electrodes (MCPEs) were prepared by the following method (Scheme 2). Paraffin oil (0.132 mg) was added into 0.268 mg of graphite powder, and the resulting mixture was stirred thoroughly. A magnet (10 mm in diameter and 2 mm in depth) was fixed in a polyethylene syringe (10 mm diameter and 45 mm in depth), and then a portion of paste was put on the magnet. For electrical contact, a copper wire was inserted into the carbon paste. The obtained magnetic carbon paste electrode (MCPEs) was dried and stored for a day at  $4 \text{ }^\circ\text{C}$  in refrigerator. Finally, the electrode tip was carefully rubbed on a fine paper to produce a flat surface and cleaned with doubly distilled water, then dipped into a  $\text{Fe}_3\text{O}_4$ @TMSPT nanoparticles suspension at  $4 \text{ }^\circ\text{C}$  for 4 h.



**Scheme 2.** Schematic illustration of the  $\text{Fe}_3\text{O}_4$  @TMSPT/MCPE sensor

## 2.5. Procedure for pharmaceutical analysis

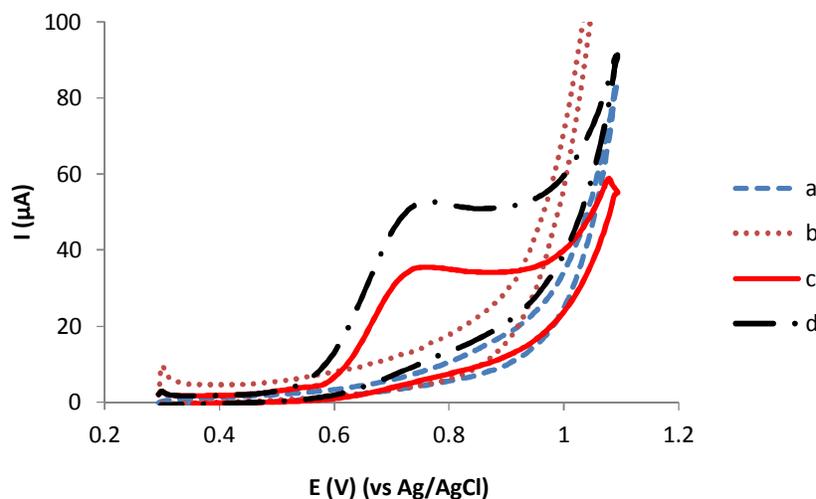
In order to analysis the tablets, ten tablets were powdered and homogenized in a mortar. An appropriate amount of the homogenous powder corresponding to a stock solution of

$4.0 \times 10^{-4}$  M ketotifen was transferred to a 50 mL beaker and dissolved in distilled water. Then, the solution was filtered and diluted in a 50.0 mL calibrated flask and completed to the volume with distilled water. Appropriate working solutions were prepared by taking suitable aliquots for the voltammetric determination of them by DPV techniques in the standard addition mode, and diluted with buffer to achieve final concentrations in the range of calibration graph.

### 3. RESULTS AND DISCUSSION

#### 3.1. Electrochemical behavior of ketotifen at $\text{Fe}_3\text{O}_4@\text{TMSPT}/\text{MCPE}$

Fig. 1 shows cyclic voltammograms recorded in B–R buffer solution with pH 7.0 as supporting electrolyte in the absence and presence of  $1.5 \times 10^{-5}$  M of ketotifen at bare CPE and  $\text{Fe}_3\text{O}_4@\text{TMSPT}/\text{MCPE}$  at a scan rate of  $100 \text{ mV s}^{-1}$ . Under these experimental conditions, the oxidation of ketotifen at the bare and modified electrode is an irreversible process. As seen, in the blank solution no peak is observing at these electrodes (curves a and b).

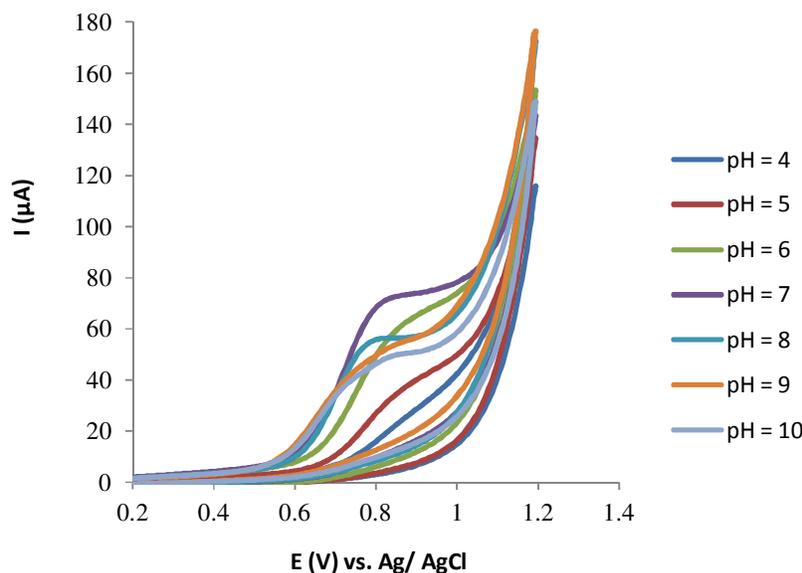


**Fig. 1.** Cyclic voltammograms of bare CPE and  $\text{Fe}_3\text{O}_4@\text{TMSPT}/\text{MCPE}$  recorded in B–R buffer solution with pH 7.0 in the absence (a and b) and presence (c and d) of  $1.5 \times 10^{-5}$  M ketotifen at a scan rate of  $100 \text{ mV s}^{-1}$

Compared with bare electrode the background current of  $\text{Fe}_3\text{O}_4@\text{TMSPT}/\text{MCPE}$  was enhanced, indicating that magnetic  $\text{Fe}_3\text{O}_4$  modified the bare electrode coated TMSPT nanoparticles. The oxidation current of ketotifen (curve d) was higher than that at bare CPE. On the basis of these results,  $\text{Fe}_3\text{O}_4@\text{TMSPT}$  was increased the available surface area of the electrode.

### 3.2. Influence of pH

The influence of pH value on the response of  $\text{Fe}_3\text{O}_4\text{@TMSPT/MCPE}$  to  $1.5 \times 10^{-5}$  M of ketotifen in the pH range of 4.0-10.0 at a scan rate of  $100 \text{ mV s}^{-1}$  was investigated (Fig. 2).



**Fig. 2.** Cyclic voltammograms of  $1.5 \times 10^{-5}$  M ketotifen recorded from pH 3.0–10.0 at a scan rate of  $100 \text{ mV/s}^{-1}$

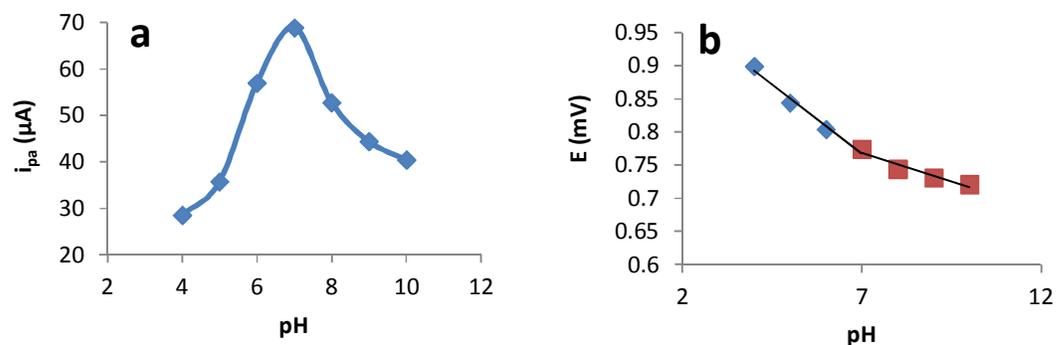
With increasing pH (up to pH 7.0) oxidation peak current increased and then decrease at higher pH values (Fig. 3a). Thus, B-R buffer solution (pH 7) was selected and used in the following experiments. The relationship between the oxidation peak potential ( $E_{\text{pa}}$ ) and pH was also shown in Fig. 3b. As seen, there are two linear regions, one between pH 4.0 to 7.0 with a slope of  $-41.5 \text{ mV/pH}$  and another between pH 7.0 to 10.0 with a slope of  $-17.2 \text{ mV/pH}$ . The lines equations are

$$E_{\text{pa}} (\text{V}) = 1.058 - 0.0415 \text{ pH} \quad \text{for pH range of 4.0–7.0}$$

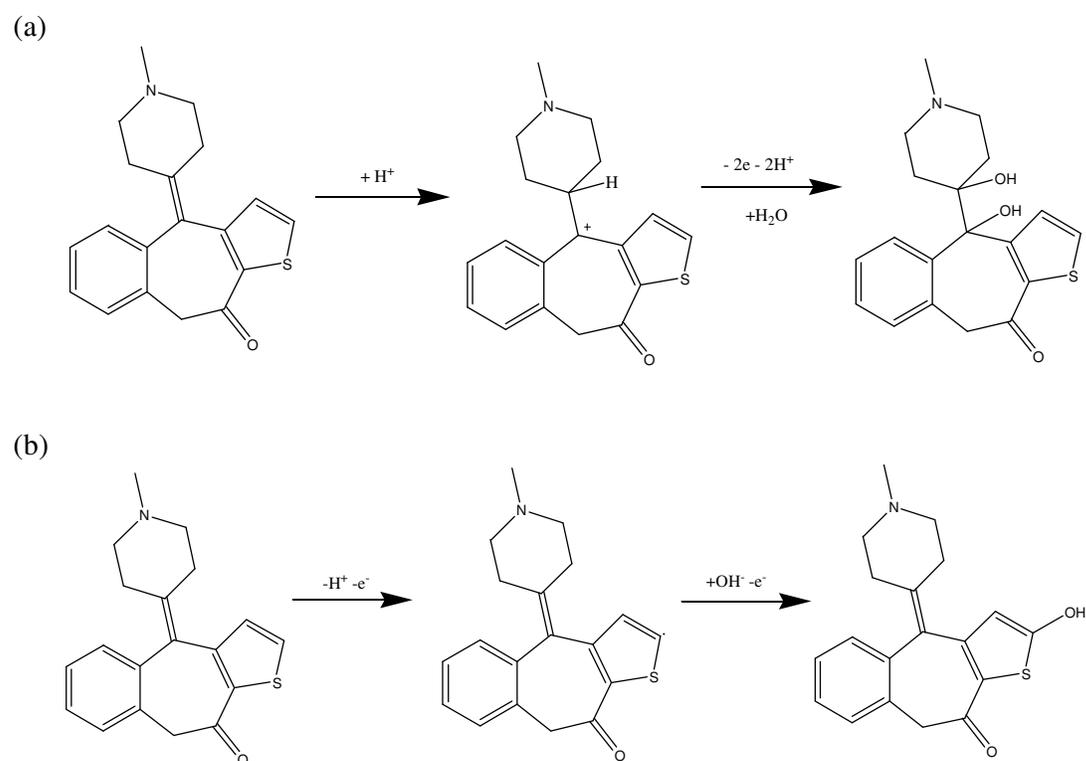
$$E_{\text{pa}} (\text{V}) = 0.888 - 0.0172 \text{ pH} \quad \text{for pH range of 7.0–10.0.}$$

The slope of  $-41.5 \text{ mV/pH}$  for ketotifen oxidation in the pH range of 4.0-7.0 indicates that the number of electrons and protons involved in the reaction mechanisms are the same. On the other hand, the obtained slope at pH range of 7.0–10.0 ( $-17.2 \text{ mV/pH}$ ) demonstrates that the electrode process in this pH range is transfer of two electrons, which is associated with one-proton transfer. These results indicate that the solution pH influenced the peak current considerably and protons were involved in the electrochemical oxidation of ketotifen.

Thus, we were proposed Scheme. 3 as a possible mechanism to explain the electrochemical oxidation of ketotifen on Fe<sub>3</sub>O<sub>4</sub>@TMSPT/MCPE in B-R buffer solution.



**Fig. 3.** Effect of pH of ketotifen solutions on the peak current (a) and peak potential (b)



**Scheme 3.** Mechanism for electrooxidation of ketotifen at: (a) pH < 7 and (b) pH > 7

### 3.3. Scan rate effect

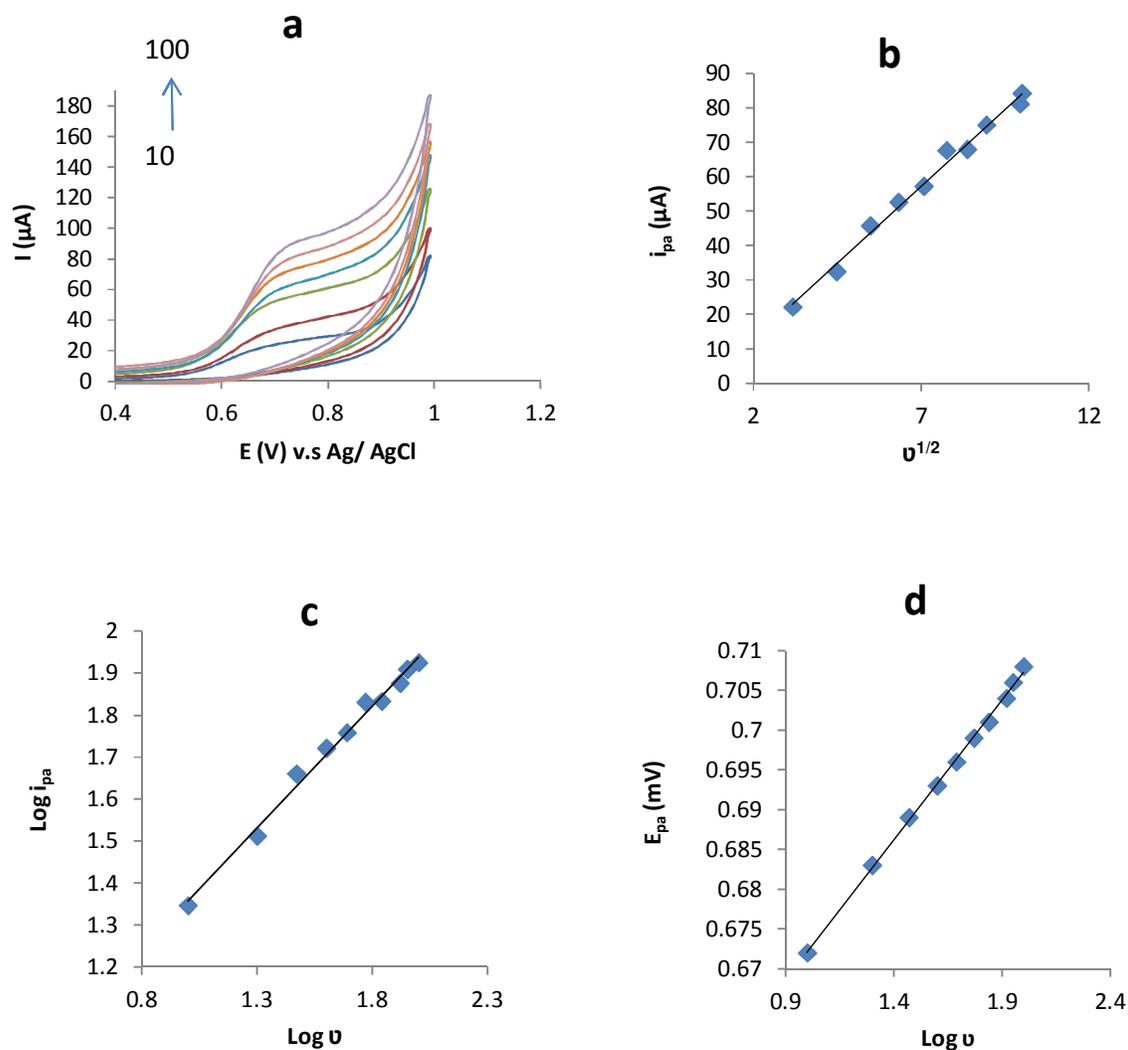
The effect of scan rate ( $\nu$ ) on the peak current and peak potential of ketotifen was also investigated. Fig.4a showed cyclic voltammograms of  $1.5 \times 10^{-5}$  M ketotifen at  $\text{Fe}_3\text{O}_4/\text{TMSPT}/\text{MCPE}$  with different scan rates. As seen in Fig. 4b, the influence of the square root of the scan rate on the oxidation peak current showed a linear relation rate in the range of 10 to 100  $\text{mV s}^{-1}$ , which indicate that the oxidation of ketotifen on  $\text{Fe}_3\text{O}_4/\text{TMSPT}/\text{MCPE}$  is a diffusion controlled process [16] and the equation could be expressed as:  $i_{\text{pa}} = 8.928 \nu^{1/2} - 5.157$ . As shown in Fig.4c was also a linear relation between  $\log i_{\text{pa}}$  and  $\log \nu$  with a slope of 0.5805, corresponding to the equation:  $\log i_{\text{pa}} = 0.5805 \log \nu - 0.7768$ . This slope (0.5805) is close to the theoretically expected value of 0.5 for diffusion-controlled process [17]. This indicates that the electrode process was controlled by diffusion rather than adsorption. In addition the anodic peak potential ( $E_{\text{pa}}$ ) with increasing the scan rate shifted to positive values. The linear relation between  $E_{\text{pa}}$  and  $\log \nu$  could be expressed as:  $E_{\text{pa}} = 0.0352 \log \nu + 0.6369$ . This behavior was consistent with the electrochemical nature of the reaction in which the electrode reaction is coupled with an irreversible follow-up chemical step [18]. According to Laviron [19], for an irreversible electrode process  $E_{\text{pa}}$  is defined by this equation:

$$E = E^0 + (2.303RT/\alpha nF) \log (RTk^0/\alpha nF) + (2.303RT/\alpha nF) \log \nu$$

Where  $\alpha$  is the transfer coefficient,  $\nu$  the scan rate,  $n$  the number of electron transferred,  $k^0$  the standard heterogeneous rate constant of the reaction and  $E^0$  is the formal redox potential. And  $R$ ,  $T$  and  $F$  have their usual meanings. Thus  $\alpha n$  was easily calculated to be 1.162 from the slope of  $E_{\text{p}}$  versus  $\log \nu$ . According to Bard and Faulkner [20],  $\alpha$  can be given as:

$$\alpha = 47.7 / (E_{\text{p}} - E_{\text{p}/2}) \text{ mV}$$

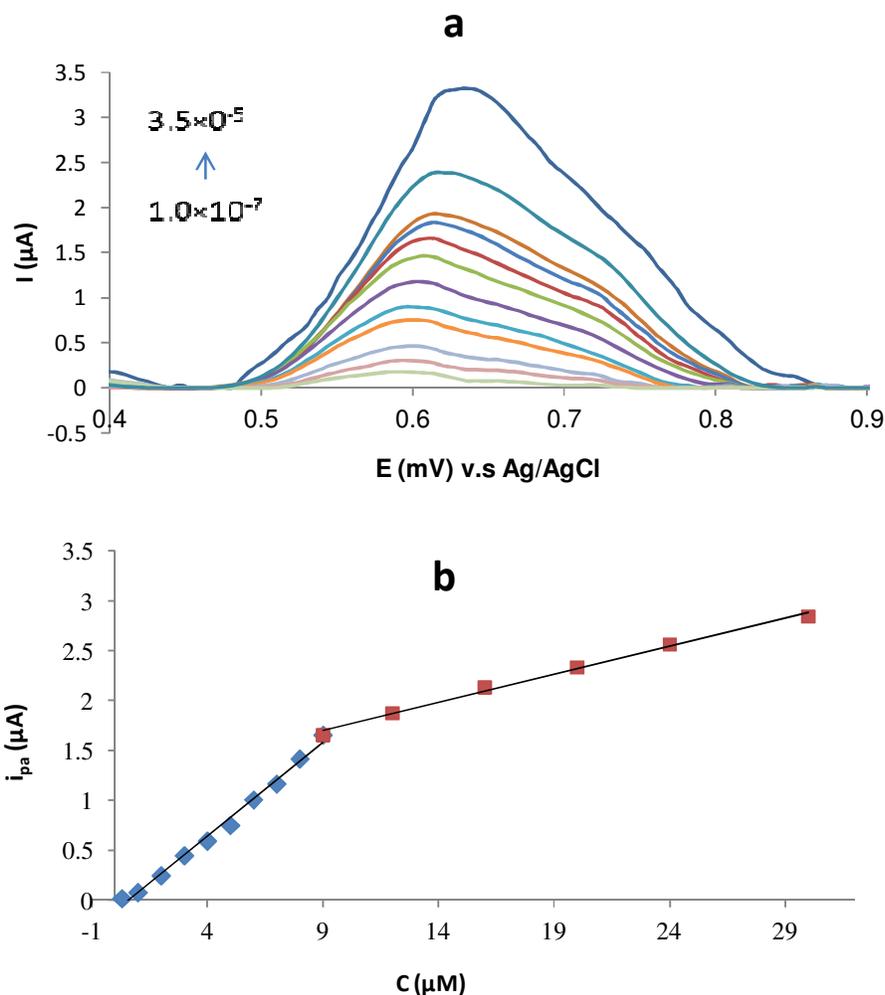
where  $E_{\text{p}/2}$  is the potential where the current is at half the peak value. Thus the value of  $\alpha$  was calculated to be 0.596 and the number of electron transferred ( $n$ ) in the oxidation of ketotifen  $2.82 \approx 3$ . If the value of  $E^0$  is known, the value of  $k^0$  could be obtained from the intercept of the  $E^0$  of the Laviron equation. From the intercept of  $E_{\text{p}}$  versus  $\log \nu$  curve, the value of  $E^0$  could be obtained by extrapolating to the vertical axis at  $\nu=0$  [21]. In our system the intercept for  $E_{\text{p}}$  versus  $\log \nu$  plot was 0.6369 and  $E^0$  was calculated obtained to be 0.6822 mV, the  $k^0$  was determined to be  $3.37 \text{ s}^{-1}$ .



**Fig. 4.** (a) CVs of Fe<sub>3</sub>O<sub>4</sub>NP-MCPE in B-R buffer solution (pH 7.0) containing  $1.5 \times 10^{-5}$  M ketotifen at various scan rates; from inner to outer scan rates of 5, 20, 40, 60, 80, 100 and 120  $\text{mVs}^{-1}$ , respectively; (b) Variation of anodic peak current versus  $v$ ; (c)  $\log i_{pa}$  vs.  $\log v$ ; (d) peak potential vs.  $\log v$

### 3.4. Calibration curve

The differential pulse voltammetry was used as a very sensitive and low detection limit for determination of ketotifen. Fig. 5a shows the DPVs curve of ketotifen at the Fe<sub>3</sub>O<sub>4</sub>@TMSPT/MCPE at various concentrations from  $1 \times 10^{-7}$  to  $3.5 \times 10^{-5}$  M in B-R buffer at pH 7.0.



**Fig. 5.** (a) Differential pulse voltammograms of  $\text{Fe}_3\text{O}_4\text{NP-MCPE}$  in various ketotifen concentrations in the range  $1.0 \times 10^{-7}$ – $3.5 \times 10^{-5}$  M. (b) Plots of  $i_p$  versus ketotifen concentration in the ranges  $2.5 \times 10^{-7}$ – $3.0 \times 10^{-5}$  M

As shown in Fig. 5b the oxidation peak current of ketotifen enhanced linearly with increasing concentration in the range from  $2.5 \times 10^{-7}$  to  $3 \times 10^{-5}$  M. As can be seen in the inset of Fig. 5b, two linear ranges can be obtained in the range of  $2.5 \times 10^{-7}$ – $9 \times 10^{-6}$  M and  $9 \times 10^{-6}$ – $3 \times 10^{-5}$  M. The corresponding regression equation can be expressed as  $I_{pa} (\mu\text{A}) = 0.1868 C (\mu\text{M}) - 0.1132$  ( $R^2 = 0.9924$ ) and  $I_{pa} (\mu\text{A}) = 0.0563 C (\mu\text{M}) + 1.1989$  ( $R^2 = 0.994$ ). The limit of detection (LOD) was calculated  $4.5 \times 10^{-8}$  M by  $3\sigma$  method. In Table 1, responses of the proposed method are compared with those obtained by other reported methods [8-10, 22, 23]. The LOD values calculated by the present method are better compared to some reported works.

**Table 1.** Comparison of LOD and LR of the proposed electrode with some other methods

Method	Linear range (M)	LOD (M)	Ref.
Liquid chromatographic–mass spectrometric (LC–MS)	$6.5 \times 10^{-8}$ – $1.6 \times 10^{-9}$	Not reported	[8]
Spectrophotometric	$3.1 \times 10^{-4}$ – $1.3 \times 10^{-6}$	$5.2 \times 10^{-7}$	[9]
Atomic absorption spectrometry	$3.07 \times 10^{-4}$ – $3.9 \times 10^{-5}$	$7.1 \times 10^{-6}$	[10]
Potentiometric	$1.0 \times 10^{-2}$ – $5.6 \times 10^{-6}$	$2.4 \times 10^{-6}$	[22]
Adsorptive stripping voltammtric (AdSV)	Not reported	$2.5 \times 10^{-9}$	[23]
Carbon paste electrode modified with Fe <sub>3</sub> O <sub>4</sub> magnetic nanoparticles	$3.0 \times 10^{-5}$ – $2.5 \times 10^{-7}$	$4.5 \times 10^{-8}$	This Work

### 3.5. Reproducibility, repeatability, and stability

The repeatability and the stability of a sensor are two important parameters. Ketotifen was repeatedly determined 5 times in  $1.5 \times 10^{-5}$  M ketotifen solution with the same modified electrode, and the relative standard deviation was found 3.6%. This indicates that the good repeatability of the response of the modified electrode. The ketotifen solution was then determined with three different electrodes fabricated independently, and the relative standard deviation was found 3.9%. Thus, the reproducibility was acceptable. Additionally, under the same conditions; the modified electrode was stable for 25 days. The electrode retained 97.0% of its initial peak current response with a standard deviation of 3.5%. The results indicate that the modified electrode has well repeatability and reproducibility in both the preparation procedure and the voltammetric determinations with good stability.

### 3.6. Interference studies

The influences of various foreign species (organic compounds commonly existed in pharmaceuticals and biological samples) on the determination of ketotifen were investigated. The tolerance limit was defined as the concentration ratio of interference/ketotifen causing less than  $\pm 5.0\%$  relative error. The results indicated as follows: the tolerance limit of additives to  $1.5 \times 10^{-5}$  M ketotifen was  $\sim 18$  times for glucose,  $\sim 20$  for uric acid,  $\sim 9.0$  for glycine,  $\sim 20$  for sucrose,  $\sim 16$  for valine,  $\sim 9.5$  for galactose, and  $\sim 5.0$  for malic acid.

### 3.7. Analytical application

In order to demonstrate the applicability of the proposed method in the pharmaceutical preparation, a commercial medical sample containing ketotifen i.e., ketotifen fumarat (1 mg per tablet) was used. By the procedure described in the experimental section, 10 tablets of ketotifen fumarat were powdered. In order to minimize the matrix effect the determination of ketotifen was carried out by using the standard addition method. As shown in Table 2, the recoveries obtained ranged from 96.6% to 103.1%, indicating that the method could provide satisfactory result for the quantitative determination of ketotifen in tablets.

**Table 2.** Determination of ketotifen in ketotifen fumarat tablet

No.	Sample ( $\mu\text{M}$ )	Added ( $\mu\text{M}$ )	Found ( $\mu\text{M}$ )	Recovery (%)
1	7.5	0.0	7.73 $\pm$ 0.30	103.1
2	7.5	4.0	11.61 $\pm$ 0.28	101.0
3	7.5	6.0	13.26 $\pm$ 0.33	98.2
4	7.5	8.0	15.69 $\pm$ 0.31	101.2
5	7.5	10.0	16.9 $\pm$ 0.26	96.6

### 4. CONCLUSION

A new modified carbon paste electrode as  $\text{Fe}_3\text{O}_4@\text{TMSPT}/\text{MCPE}$  for detection of ketotifen was reported. CV investigated the electrochemical behavior and oxidation mechanism of ketotifen at a  $\text{Fe}_3\text{O}_4@\text{TMSPT}/\text{MCPE}$  in B-R buffer solution (pH 7.0). The oxidation of ketotifen was found to be an irreversible and diffusion controlled process. The electrochemical response was involving two electron accompanied by a transfer of two protons in the pH range of 4.0 to 7.0 and two electrons transfer which is associated with one proton transfer in the pH range of 7.0 to 10.0. The voltammetric response was linear in the  $2.5 \times 10^{-7}$ – $3.0 \times 10^{-5}$  M concentration range. The high sensitivity and low detection limit, together with the ease of preparation are the advantages of the studied modified electrode. This method has been successfully used to determined ketotifen in the pharmaceutical sample. The proposed method offered the advantages of accuracy and time saving as well as simplicity of reagents and apparatus.

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