

Solid Contact Sensors For Determination of The Antihistaminic Drug Ketotifen Fumarate

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Abstract: Reliable potentiometric sensing devices with unique advantages were constructed for determination of ketotifen fumarate (keto-fuma). Five sensors based on Ag, Ag/Ag₂S, Ag/AgCl, graphite and glassy carbon solid beds were constructed. These sensors were constructed based on ketotifen-tetraphenylborate (keto-TPB) as ion pairing material and dibutyl phthalate as solvent mediators. The sensors showed high sensitivity and near Nernstian slope in batch and flow injection conditions (FIA). According to the results obtained, the best behavior observed for coated graphite sensor was with slope 60.10 mV·decade⁻¹, linear range 7×10^{-6} – 1×10^{-2} M, and limit of detection 3.9×10^{-7} M. Enhancement of the detection limit of the sensors was done by incorporating potassium tetraphenylborate (KTPB) and graphite in the membrane. The sensors were used for determination of keto-fuma in the pure form as well as in its pharmaceutical preparations. It was performed using potentiometric titration and standard addition methods with recoveries of 97.0–100.4 % and relative standard deviations of 0.13–1.42 %.

Keywords: Ketotifen fumarate; Sensors; Graphite; Solid contact.

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Introduction

Keto-fuma, 4-(1-methyl-4-piperidinylidene)-4H-benzo-[4,5]-cyclohepta-[1,2-b]thiophene-10-(9H)-one hydrogen fumarate, is used as an antihistaminic drug, it is a white, odorless, and crystalline powder [1].

Coated wire electrodes (CWEs) is a type of ISEs composed of electroactive species, incorporated in a thin polymeric support film and coated directly on a solid conductor. Different materials can serve as central conductors. It was shown in an extensive study that when the wire support did not react with the membrane component, it had no substantial influence on the potentiometric response of the electrode. The substrate in the wire type electrodes is usually platinum wire, but silver, glassy carbon and graphite rods have also been used [2].

Sometimes CWEs exhibited better selectivity than conventional type electrodes that have an internal solution. Among the advantages of CWEs is the simplicity of design, lower costs, mechanical flexibility of miniaturization and micro fabrication. These advantages made them widely used, especially in the fields of medicine and biotechnology [3].

Solid contact ISEs have been known for decades. In their original design, such electrodes lacked long-term stability. They were only useful in special applications, in which no need for long-term stability, like detectors for capillary electrophoresis or in flow injection analyzers. Potential instabilities of this type of sensors can be attributed to the lack of a well-defined redox couple at the membrane-metal interface. It was also assumed that an oxygen half-cell acts as a redox couple [3].

The specific response of every ion selective electrode (ISE) to the analyte ion is limited by constitutive parameters of all ion-selective electrodes selectivity and detection limit [4]. Detection limit has been an issue of interest since early stages in the history of ISEs and initially solid-state membranes were in focus [5, 6].

Keto-fuma used to be determined by several spectral methods [7-13], large number of chromatographic methods which are expensive methods [14-29], coulometric titration [30], differential pulse polarography [31], ion transfer voltammetry [32], cyclic voltammetry using carbon paste electrode based on ketotifen hexacyanoferrate as ion-recognition species [33] and some electroanalytical methods, which are simple in handling and relatively cheap. The electroanalytical methods seem to be good candidates for application in routine analysis in a

diagnostic laboratory. Also, PVC membrane electrode using ketotifen-tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate as ion sensing material [34], PVC membrane electrode incorporated with Keto-TPB [35] and coated graphite electrode [36] were reported to be utilized.

The quantization of ketotifen fumarate at low concentration is very important. The current study aims to enhance the sensitivity and the detection limit, using coated wire electrodes, Keto-TPB/Ag, Keto-TPB/Ag/AgCl, Keto-TPB/Ag/Ag₂S, Keto-TPB/GC and Keto-TPB/Graphite. They were characterized according to IUPAC recommendations. This work can be applied for both clinical and pharmaceutical fields. Also, it can be used for analysis of biological fluids (blood, serum and urine) for patients used this drug.

Experimental

Reagents

All reagents used were chemically pure grade. Doubly distilled water was used throughout all experiments. Keto-fuma (molecular weight 425.5 g·mol⁻¹), and its pharmaceutical preparations (*Zaditen* tablets, 1 mg·tablet⁻¹ and Syrup 1 mg·5 mL⁻¹) were provided by *Novartis PHARMA S.A.E.* Cairo, Egypt. Sodium tetraphenylborate (NaTPB) Na[C₂₄H₂₀B], dibutyl phthalate (DBP), poly (vinyl chloride) (PVC) of high relative molecular weight and tetrahydrofuran (THF), graphite, sodium hydroxide (NaOH), hydrochloric acid (HCl), and potassium chloride (KCl) were obtained from *Aldrich* chemical company. Potassium tetraphenylborate (KTPB) was prepared in our lab.

In FIA measurements, doubly distilled water was used for preparing solutions and carrier stream. The carrier and reagent solutions were degassed by means of vacuum-suction. Sample solutions used for injections were freshly prepared prior to measurements. The samples were initially diluted with distilled water. The pH and ionic strength were adjusted in the interior of the manifold.

Apparatus

For Batch Measurement. Potential values were measured with a *Jenway* 3010 (Essex, England) digital pH/mV meter. A saturated Ag/AgCl electrode was used as the reference electrode. The pH of the sample solutions was monitored simultaneously with *Jenway* pH glass electrode. The temperature control system used was *Techne*, FTU-20 DE, Temp. Unit, England.

For Flow Injection Analysis. A single-stream FIA manifold as mentioned in our work [35] was used for this study.

Sensor Preparation

Keto-TPB ion-associate was prepared according to a previously reported method [35]. A mixture of PVC, DBP, and ion pair was dissolved in about 5 mL of THF. Then, they were mixed together at the following percentage 49 %, 49 %, and 2 %, respectively, to give a total mass of 200 mg forming the active membrane.

Spectroscopically pure silver (8 cm length and 2 mm diameter), graphite (8 cm length and 2 mm diameter) and glassy carbon (8 cm length and 3 mm diameter) rods were utilized. Ag/AgCl and Ag/Ag₂S beds were prepared by anodizing Ag wires (8 cm length and 2 mm diameter) in saturated KCl and Na₂S, respectively, using Pt wire as cathode. They were insulated by tight polyethylene tubes leaving 2 cm at one end for coating (sensitive area) and 1 cm at the other end for connection (Fig.1). Five types of sensors based on Ag, Ag/AgCl, Ag/Ag₂S, graphite and glassy carbon solid beds were constructed. The polished rod surface of each type was coated with the active membrane by dipping the exposed end into the coating solution and allowing the film to dry in air for about 1 min. The process was repeated until a plastic film of approximately 1.0 mm thickness was formed. The prepared electrodes were preconditioned by soaking for ~15 min in 10⁻³ M solution of keto-fuma. The electrochemical system in this case is: wire/membrane/test solution//Ag/AgCl.

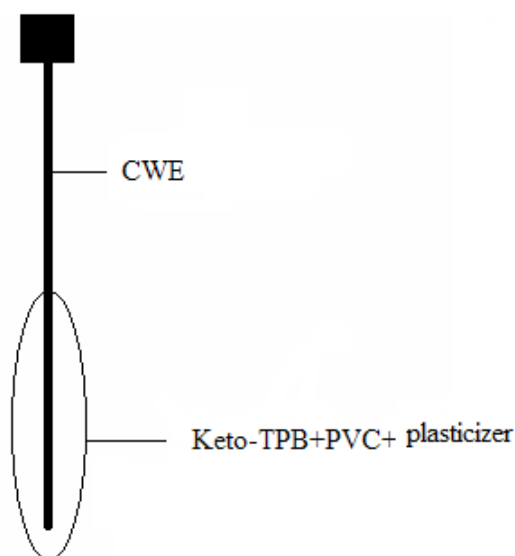


Fig. 1: Sensitive area of the coated wire.

Construction of Calibration Curves

For batch measurements, suitable increments of keto-fuma standard. Solution were added to 50 mL doubly distilled water to cover the concentration range 1×10^{-7} – 1×10^{-2} M at 25 °C, pH 2–8, and no control of ionic strength was needed. The sensor and the reference electrodes were immersed in the solution and the emf value was recorded at 25 ± 1 °C after each addition. The values obtained were plotted versus the negative logarithmic value of keto-fuma concentration ($-\log [\text{keto-fuma}]$).

A series of freshly prepared keto-fuma solutions, covering the range 1×10^{-6} – 1×10^{-2} M, were injected to the flow stream for FIA measurements. The corresponding peak heights were recorded and used to draw the calibration graphs.

Enhancement of the Electrode Behavior

The limit of detection in case of coated wire electrodes was improved by addition of 0.5 and 1 % KTPB or graphite powder to the mixture prepared for coating.

Potentiometric Determination of Ketotifen Fumarate

In batch measurements, potentiometric titrations were applied by transferring 2–10 mL 1×10^{-2} M keto-fuma into 100 mL titration cell. It was diluted to 50 mL by doubly distilled water. The resulting solutions were titrated against 1×10^{-2} M NaTPB using the corresponding electrode. The end points were determined from the conventional S-shaped and the first derivative plots. The standard addition technique was applied [37] by adding known volumes of standard drug solution to 50 mL solution containing different amounts of keto-fuma. The change in mV reading was recorded for each increment and used to calculate the concentration of the drug in the sample solution. The following equation was utilized:

$$C_x = C_s \left(\frac{V_s}{V_x + V_s} \right) \left[10^{n(\Delta E/S)} - \frac{V_x}{V_s + V_x} \right]^{-1} \quad (1)$$

where C_x is the concentration to be determined, V_x is the volume of the original sample solution, V_s and C_s are the volume and concentration of the standard solution added to the sample under test, respectively, ΔE is the change in potential caused by the addition, and S is the slope of the calibration graph.

For analysis of tablets, 20 tablets were weighed and ground to fine powder. Then, an appropriate weight from this powder was taken and dissolved in 60% ethanol. After that, the solution was filtered in a 50 mL measuring flask and completed to the mark by doubly distilled water. A volume of 5 mL from this solution was diluted by doubly distilled water and titrated against NaTPB. In case of syrup, it was taken directly after dilution to the titration cell.

In FIA, 4.7×10^{-4} M solutions of keto-fuma, *Zaditen* tablets, and syrup were prepared according to the manufacture claim for concentration. The peak heights were measured and then used for calculating the recovery percent in tablets and syrup.

Results and Discussion

Calibration of the Sensors

Several membrane compositions were investigated previously by varying the ratio of PVC, DBP and Keto-TPB. The maximum sensitivity was observed with 1:1 PVC:DBP by weight. It was also observed that the potentiometric response of the electrode toward Ketotifen ion was achieved by using 2 % Keto-TPB incorporated within the membrane [35].

After conditioning, the electrodes were examined by plotting the calibration curve in the concentration range 1×10^{-6} – 1×10^{-2} M of the drug (Fig. 2). The dynamic range of concentration and the limit of detection for each electrode were estimated according to the IUPAC recommendations [38]. It seems that the detection limits and dynamic ranges for coated wire electrodes are influenced by the nature of the bed. The detection limit decreases with increasing the chemical affinity of the electro active ingredient towards the bed matrix, and is also influenced to some extent by its resistivity (Table I). In batch conditions, the lowest limit of detection was observed for graphite sensor, 3.9×10^{-7} M with the highest slope $60.1 \text{ mV} \cdot \text{decade}^{-1}$ as shown in Table I and Figure 2.

FIA is carried out at 75 μL sample volume and flow rate $12.5 \text{ mL} \cdot \text{min}^{-1}$. In potentiometric detection, the electrode potential depends on the activity of the main sensed ion. This can be considered as a principle advantage of this method. In flow measurements the dependence is semi-logarithmic over a wide analyte activity range according to the Nickolsky-Eisenman equation. The main unfavorable feature of this detection is the slow

response of the electrode potential to concentration change [37]. This slow response is a quite good reason for the super-Nernstian sensitivities obtained in FIA measurements using the investigated electrodes. The potentiometric response of Ag, graphite and glassy carbon sensors were studied by FIA. It was observed that the readings were stable after less than 10 sec and remained stable for 1 min. The average slopes from five replicate measurements are higher than the batch ones (Table I, Fig. 3).

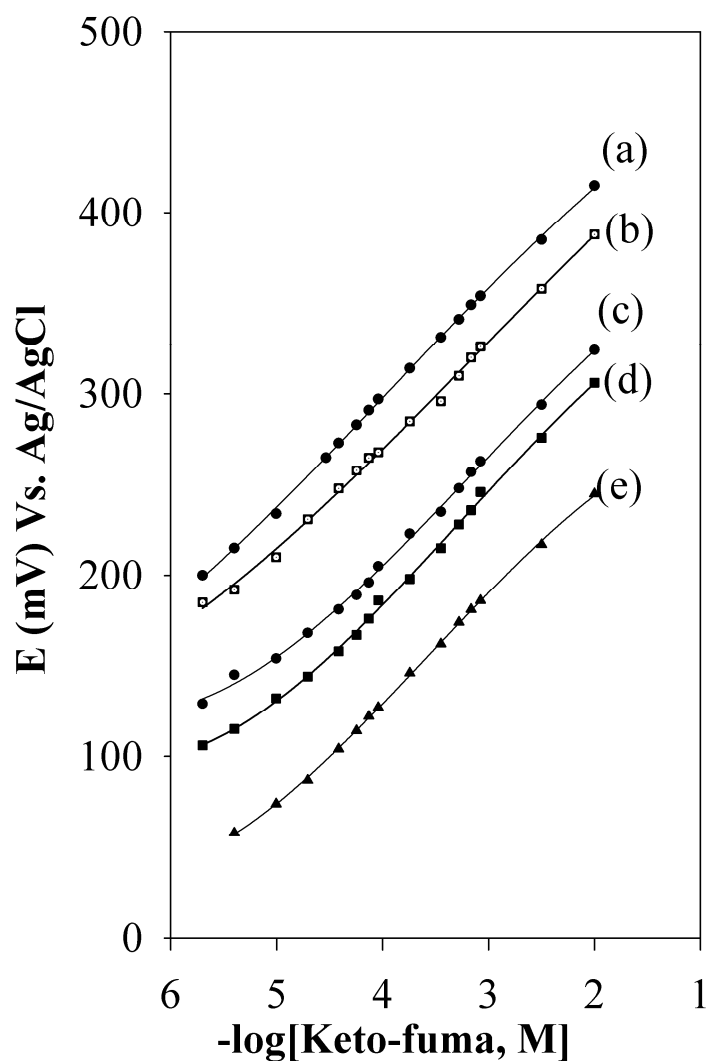


Fig. 2: Calibration graphs for coated wire electrodes. Keto-TPB/G (a), Keto-TPB/Ag/AgCl (b), Keto-TPB/GC (c), Keto-TPB/Ag/Ag₂S (d), and Keto-TPB/Ag (e).

Table I: Analytical characteristics of various Keto-TPB coated wire electrodes prepared by using the optimized membrane mixture.

| Sensor | Batch | | | FIA | | |
|----------------------|--|----------------------------------|-----------------------|--|----------------------------------|----------------------|
| | Linear range (M) | Slope (mV·decade ⁻¹) | LOD (M) | Linear range (M) | Slope (mV·decade ⁻¹) | LOD (M) |
| Silver | 1.0×10 ⁻⁵ – 1.0×10 ⁻² | 58.0 | 5.01×10 ⁻⁶ | 1.0×10 ⁻⁵ – 1.0×10 ⁻² | 69.40 | 5.5×10 ⁻⁶ |
| Ag/AgCl | 5.6×10 ⁻⁵ – 1.0×10 ⁻² | 57.1 | 4.40×10 ⁻⁶ | | | |
| Ag/Ag ₂ S | 1.0×10 ⁻⁵ – 1.0×10 ⁻² | 59.1 | 6.60×10 ⁻⁶ | | | |
| Graphite | 1.0×10 ⁻⁵ – 1.0×10 ⁻² | 60.1 | 3.90×10 ⁻⁷ | 7.0×10 ⁻⁶ – 1.0×10 ⁻² | 70.40 | 5.6×10 ⁻⁶ |
| Glassy– carbon | 1.0×10 ⁻⁵ – 1.0×10 ⁻² | 59.5 | 2.50×10 ⁻⁶ | 1.0×10 ⁻⁵ – 1.0×10 ⁻² | 80.35 | 4.9×10 ⁻⁶ |

Selectivity of the Sensor

The selectivity coefficients of the previous study on the membrane behavior [35], indicated that, Keto-TPB electrode is highly selective to ketotifen cation. Most inorganic cations do not interfere because of the difference in their mobility and permeability as compared to ketotifen cation. In the case of sugars and amino acids the high selectivity has been related to the difference in polarity and lipophilic nature of their molecules relative to ketotifen cation.

Enhancement of the Sensor Response

Coated wire electrodes with optimal detection limit must not contain an internal water film which may cause primary ions to accumulate during conditioning [41]. Additionally, a redoxactive internal layer must be present in order to avoid interference from O₂. The presence of graphite in PVC membrane could help ion-to-electron transduction between the membrane and the internal solid contact.

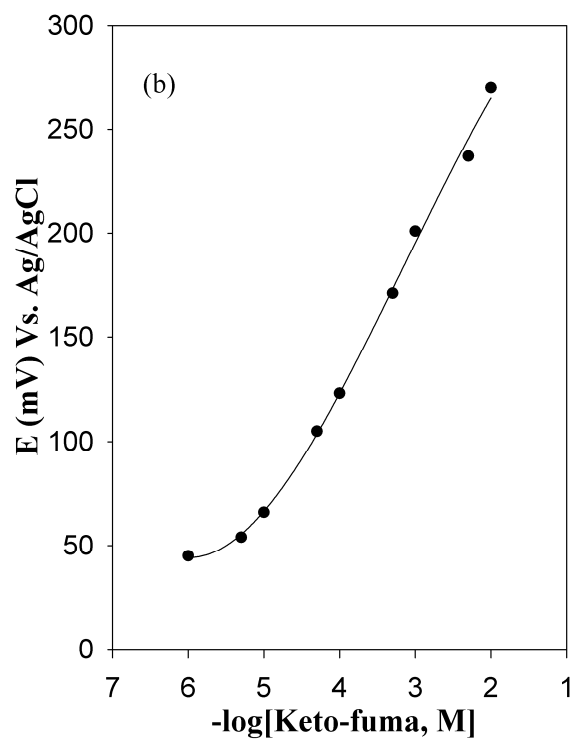
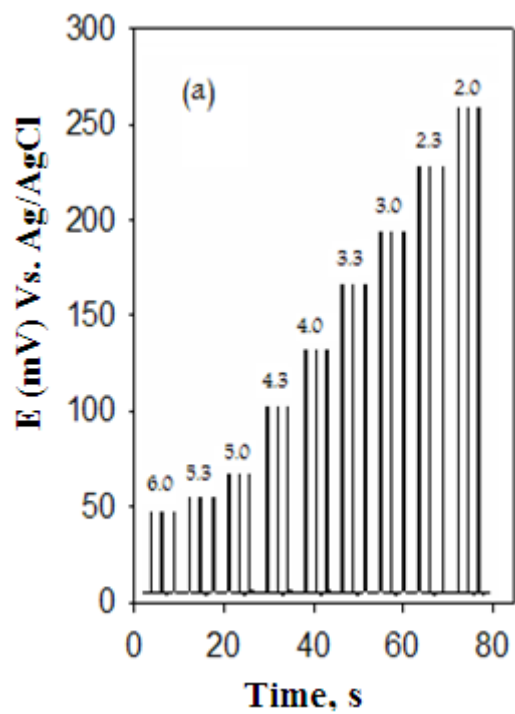


Fig. 3: The recordings (a) and their corresponding calibration graph (b) obtained for Keto-TPB graphite sensor at optimum FIA conditions.

In addition, the reducing characteristics of carbon minimize the interference from oxygen. The sensor response was improved by addition of KTPB or graphite powder to the mixture prepared for coating.

Graphite or KTPB addition affect on the limit of detection of different types of coated wire electrodes. The enhancement was investigated by addition of different percentages of them. From the results listed in Table II, it was shown that the addition of different percentages of KTPB and graphite affect the limit of detection, the slope and the linear range.

Limit of Detection (LOD)

The practical limit of detection can be calculated by plotting a calibration graph using several standards at the lower end of the concentration range, and below it. We have to define the linear slope and to show the position of the horizontal section below the limit of detection, where the electrode is unresponsive to concentration change. The limit of detection is then defined by the crossing point of the two straight lines drawn through these points (Fig. 4) [42]. The LOD of glassy carbon based sensor decreased to 3.1×10^{-7} M upon addition of 0.5 % graphite or 0.5 and 1.0 % KTPB and to 5.0×10^{-7} M upon addition of 1.0 % graphite compared with 2.5×10^{-6} M for the untreated electrode.

Small improvement of the detection limit was observed with graphite based sensor upon addition of 1 % graphite and 0.5–1 % KTPB and it was 2.0×10^{-7} M upon addition of 0.5 % graphite. In case of silver based sensor, the improvement in the detection limit was dramatic reaching a ten-fold decrease upon addition of 0.5 and 1 % KTPB. Upon addition of 0.5 and 1 % graphite, it was 1.2×10^{-6} and 3.9×10^{-6} M, respectively as shown in Table II. Figure 5 is a representative example to show this enhancement.

Table II: Effect of different percentage of KTPB or graphite powder on GC, graphite and silver sensors.

| Sensor | Graphite or KTPB (%) | LOD (M) | Slope (mV·decade ⁻¹) | Linear range (M) |
|---------------------|-------------------------|----------------------|-------------------------------------|--|
| GC CWE | | | | |
| 1 | – | 2.5×10^{-6} | 59.6 | 1.0×10^{-5} – 1.0×10^{-2} |
| 2 | 0.5 graphite | 3.1×10^{-7} | 59.0 | 1.0×10^{-6} – 1.0×10^{-2} |
| 3 | 1.0 | 5.0×10^{-7} | 59.7 | 1.0×10^{-6} – 1.0×10^{-2} |
| 4 | 0.5 KTPB | 3.1×10^{-7} | 55.0 | 1.0×10^{-6} – 1.0×10^{-2} |
| 5 | 1.0 | 3.1×10^{-7} | 54.0 | 1.0×10^{-6} – 1.0×10^{-2} |
| Graphite CWE | | | | |
| 6 | – | 3.9×10^{-7} | 60.1 | 7.0×10^{-6} – 1.0×10^{-2} |
| 7 | 0.5 graphite | 2.0×10^{-7} | 61.2 | 1.0×10^{-6} – 1.0×10^{-2} |
| 8 | 1.0 | 3.1×10^{-7} | 56.4 | 1.0×10^{-6} – 1.0×10^{-2} |
| 9 | 0.5 KTPB | 3.1×10^{-7} | 51.2 | 1.0×10^{-6} – 1.0×10^{-2} |
| 10 | 1.0 | 3.1×10^{-7} | 60.3 | 1.0×10^{-6} – 1.0×10^{-2} |
| Silver CWE | | | | |
| 11 | – | 5.0×10^{-6} | 58.0 | 1.0×10^{-5} – 1.0×10^{-2} |
| 12 | 0.5 graphite | 1.2×10^{-6} | 60.3 | 3.9×10^{-6} – 1.0×10^{-2} |
| 13 | 1.0 | 3.9×10^{-6} | 63.7 | 1.0×10^{-5} – 1.0×10^{-2} |
| 14 | 0.5 KTPB | 6.3×10^{-7} | 58.6 | 1.0×10^{-5} – 1.0×10^{-2} |
| 15 | 1.0 | 6.3×10^{-7} | 57.7 | 1.0×10^{-5} – 1.0×10^{-2} |

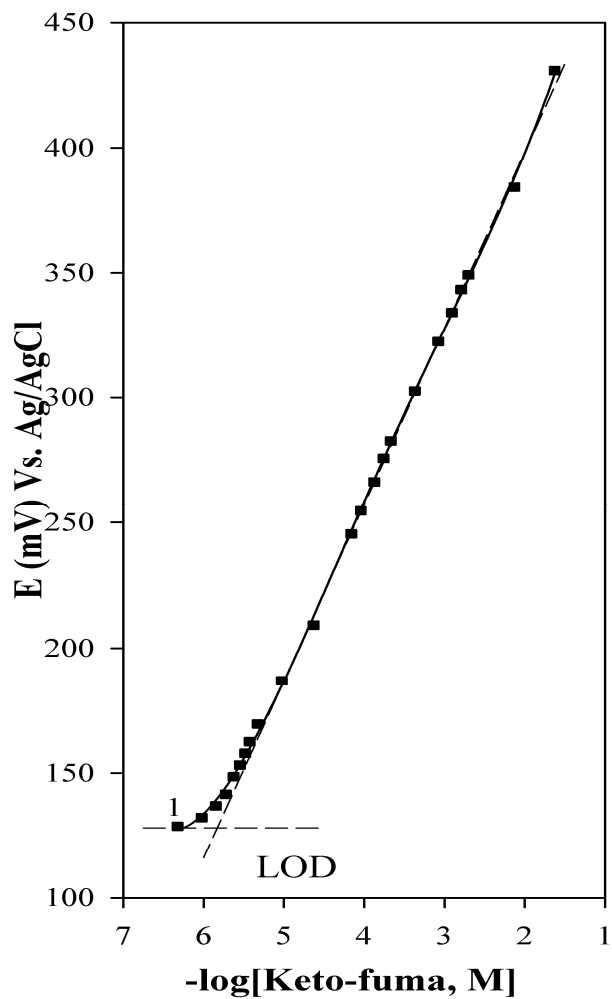


Fig. 4: *Determination of detection limit.*

Potentiometric determination of ketotifen fumarate

The potentiometric titration technique usually offers the advantage of high accuracy and precision despite, the cost of increased consumption of titrants. A further advantage is that the potential break at the titration end-point is well defined, but the response of the used electrode does not require being reproducible or Nernstian. Also, the actual potential value at the end point is of secondary interest.

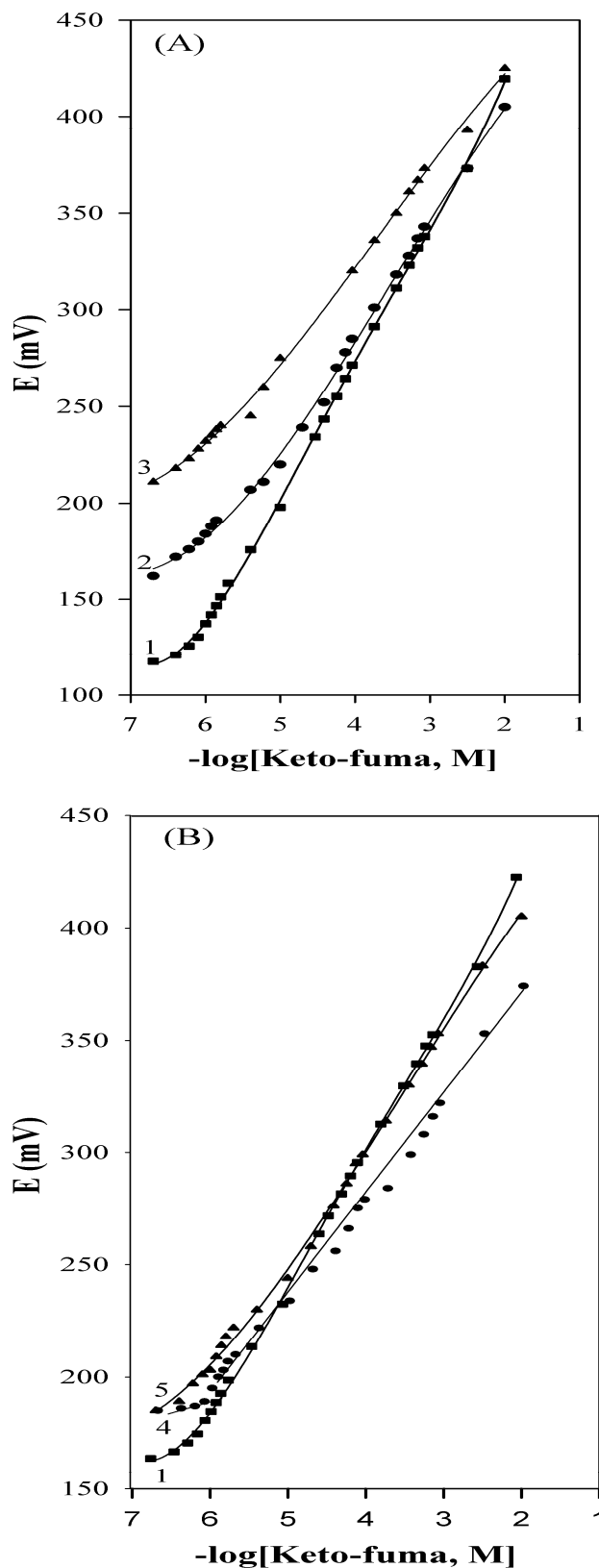


Fig. 5: Effect of addition of KTPB (A) and graphite (B) on the performance of Keto-TPB graphite CWE. 1) Keto-TPB graphite CWE; 2) Keto-TPB graphite CWE (1% KTPB); 3) Keto-TPB graphite CWE (0.5% KTPB); 4) Keto-TPB graphite CWE (1% graphite); 5) Keto-TPB graphite CWE (0.5% graphite).

In this case, using Keto-TPB coated graphite sensor, the titration process was carried out manually in aqueous solution containing 2.13–42.55 mg keto-fuma, with average recoveries of 99.8–100.8 % and the relative standard deviation values ranging from 0.13–0.80 %, as shown in Table III. The potential jump at the vicinity of end point amounts to 80–145 mV (Fig. 6). The magnitude and the potential breaks at the vicinity of the endpoint increases by increasing the concentration of keto-fuma, reaching 145 mV on titrating 42.55 mg of keto-fuma. The sharpness of the potential breaks reflects very high degree of completeness of the titration reactions [38, 41].

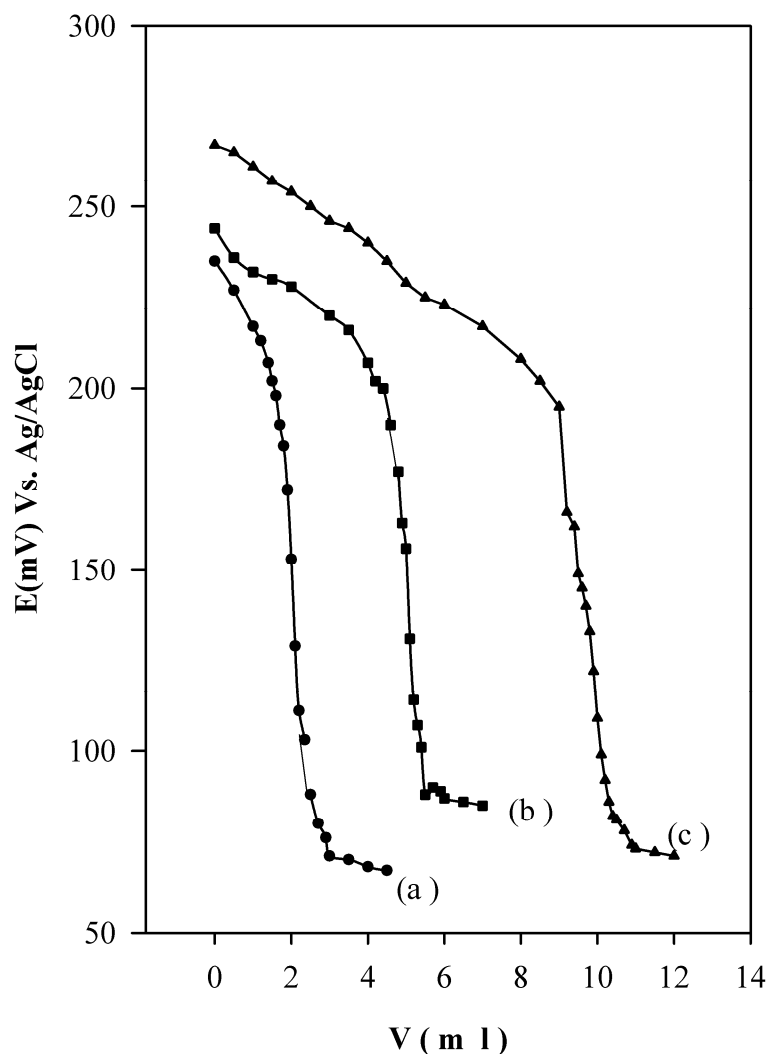


Fig. 6: Potentiometric titrations of 8.51 mg (a), 21.27 mg (b), and 42.55 mg (c) of Ketotifen fumarate against 1×10^{-2} M NaTPB solution using coated graphite sensor.

Analogous results were obtained when keto-fuma content in *Zaditen* tablets and syrup were titrated. The results of applying the above methods shown in Table III reveal that the constructed sensors can be used successfully as indicator electrodes in potentiometric titrations of keto-fuma in different sample solutions with very high percentage recovery. Statistical treatment of the data was carried out, F- and t-tests were used to compare the experimental data obtained with the official method [1] (Table IV) with the tabulated ones and it was found that values were lower than the 5 % critical values (95 % confidence level).

Table III: Determination of Ketotifen fumarate in pure solutions and pharmaceutical preparations applying the standard additions method and potentiometric titrations in batch condition using GC based sensor.

| Sample | Standard addition method | Potentiometric titration |
|--|---------------------------------|-------------------------------------|
| Pure solution | | |
| Taken (mg) | 0.212 | 2.13; 4.26; 12.76; 21.27; 42.55 |
| Recovery (%) | 97.8 | 100.8; 100.0; 100.0; 99.8; 100.0 |
| RSD (%) | 1.42 | 0.80; 0.42; 0.13; 0.13; 0.16 |
| Zaditen tablet (1 mg·tablet⁻¹) | | |
| Taken, mg | 0.212 | 2.13 |
| Recovery% | 104.0 | 101.0 |
| RSD% | 1.24 | 0.71 |
| Zaditen syrup (1mg·5 ml⁻¹) | | |
| Taken, mg | 0.212 | 2.00 |
| Recovery% | 99.8 | 100.0 |
| RSD% | 0.61 | 0.80 |

Table IV: Statistical treatment of data obtained for the determination of Ketotifen fumarate applying the standard addition method and potentiometric titration in comparison with the official method.

| | Official method [1] | GC sensor | | |
|---------------------------------|---------------------|---------------|----------------|---------------|
| | | Pure solution | Zaditen tablet | Zaditen syrup |
| Standard addition method | | | | |
| x ± S.E. (%) | 100.2 ± 0.96 | 97.6 ± 0.7 | 103.5 ± 0.6 | 99.6 ± 0.3 |
| RSD (%) | 0.95 | 1.42 | 1.24 | 0.61 |
| T-test | | 4.90 | 3.15 | 1.09 |
| F-test | | 2.12 | 1.81 | 2.43 |
| Potentiometric titration | | | | |
| x ± S.E. (%) | 100.2 ± 0.96 | 99.8 ± 0.1 | 101.5 ± 0.4 | 100.4 ± 0.5 |
| RSD (%) | 0.95 | 0.13 | 0.40 | 0.48 |
| T-test | | 0.95 | 3.20 | 0.24 |
| F-test | | 3.20 | 5.40 | 3.90 |

X ± S.E – recovery ± standard error. F-tabulated is 9.82 at 95.0% confidence limit. T-tabulated is 3.14 at 99.0 % confidence limit and 6 degrees of freedom.

Table V: Comparison between the present and published ISE for Keto-fuma.

| Parameter | Present work | Reference [35] | Reference [36] | |
|----------------------------------|--|--|--|--|
| | | Plastic membrane | Plastic membrane | Coated wire |
| Slope (mV·decade ⁻¹) | 61.20 ± 0.27* | 58.40 ± 0.18 | 57.50 ± 1.07 | 59.00 ± 0.91 |
| LOD (M) | 1.99 × 10 ⁻⁷ | 2.37 × 10 ⁻⁶ | 1.0 × 10 ⁻⁵ | 5.0 × 10 ⁻⁶ |
| Linear range (M) | 1.00 × 10 ⁻⁶ – 1.00 × 10 ⁻² | 2.5 × 10 ⁻⁶ – 1.0 × 10 ⁻² | 1.0 × 10 ⁻⁵ – 1.0 × 10 ⁻² | 5.0 × 10 ⁻⁶ – 1.0 × 10 ⁻² |
| RSD (%) | 0.88 | 0.61 | 1.04 | 1.04 |

*Mean of five replicates.

Conclusion

The present study shows that sensors modified with graphite and inner solid contacts with low resistivity are very promising platforms to reach low detection limits. The sensors were used successfully as indicator electrodes in the titration of keto-fuma. with NaTPB. Also, it can be employed for keto-fuma. estimation in pharmaceutical preparations. The addition of graphite or KTPB to the cocktail used for coating increases the linear range of the calibration curve and decreases the detection limit. The present electrode are considered a better sensor than those previously reported using graphite coated PVC membrane electrode [36], and plastic membrane using Keto-TPB [35] (Table V), the reading were calculated from five replicate measurments. The membranes incorporating Keto-TPB carrier has many advantages including ease of preparation, low cost, wide dynamic range, low detection limit, Nernstian behavior and good reproducibility in both batch and FIA methods.

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