Research article

Drug Testing and Analysis

Received: 6 December 2010 Revised: 8 March 2011 Accepted: 9 March 2011

(www.drugtestinganalysis.com) DOI 10.1002/dta.289

Single and mixed chemically modified carbon paste ion-selective electrodes for determination of ketotifen fumarate

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New modified carbon paste electrodes for determination of ketotifen fumarate in its pure and pharmaceutical preparations were constructed. The used modifiers are ketotifen phosphotungestate (Keto$_3$PT), and ketotifen tetraphenylborate (Keto-TPB). Single and mixed ion-associate electrodes were prepared. Both Keto-TPB and mixed (Keto-TPB and Keto$_3$PT) electrodes have a linearity range of 1.00×10^{-5}-1.00×10^{-2} mol L^{-1}. The slopes were 58.30 and 54.20 mV/decade for Keto-TPB and mixed chemically modified carbon paste electrodes (CMCPE), respectively. The limits of detection were 1.42×10^{-6} and 1.00×10^{-5} mol L^{-1} for Keto-TPB and mixed CMCPEs, respectively. The potential variation due to pH change is considered acceptable in the pH ranges 4.44–9.11 and 2.50–9.00 for Keto-TPB and mixed ion-exchanger CMCPE, respectively. The response time was $\leq$10 s for both electrodes. Selectivity coefficients values towards different inorganic cations, sugars, and amino acids reflect high selectivity of the prepared electrodes. Potentiometric titrations and standard addition methods were applied for the determination of ketotifen ion in its pure samples and pharmaceutical formulations (Zaditen tablet and syrup) using proposed electrodes. The electrodes were also tested in flow injection analysis (FIA). The results obtained from both methods were statistically treated by F- and *t*-tests. The carbon paste electrodes have the advantages of being more easily prepared and longer life span compared to the plastic membrane electrodes previously reported.

Keywords: ketotifen; flow injection analysis; ion-selective electrodes; chemically modified carbon paste.

Introduction

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

Ketotifen fumarate has been determined by several methods including, spectral,[3–9] chromatographic; which are time-consuming and involve sophisticated equipment,[10–16] and coulometric titration in which determination of ketotifen is based on oxidation with electrogenerated iodine.[17] Ketotifen was also determined using differential pulse polarography with a detection limit of 2.5 nM,[18] and ion-transfer voltammetry.[19] A carbon paste electrode (CPE) including ketotifen fumarate and hexacyanoferrate as ion-recognition species was used for cyclic voltammetric determination of the drug.[20] Ion-selective PVC membrane electrode for ketotifen fumarate was described based on its ion-pair with potassium tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate using 2-nitrophenyloctyl ether, 2-nitrophenyldodecyl ether, bis-(2-ethylhexyl)sebacate or 1-isopropyl-4-nitrobenzene as plasticizers.[21] PVC plastic membrane ion-selective electrodes were previously reported for the determination of ketotifen in drug formulations.[2] Coated graphite plastic membrane ion-selective electrode using Keto-TPB was reported by Ghoreishi *et al*.[22]

Ion-selective electrodes play an important role in pharmaceutical analysis due to their simplicity, rapidity, and accuracy over some other analytical methods.[23,25] Chemically modified carbon paste electrodes (CMCPEs) have found direct application in different analytical techniques such as amperometry, potentiometry, and voltammetry. CMCPEs were successful potentiometric sensors for determination of pharmaceutical compounds.[26,27]

In the present work, ketotifen fumarate-chemically modified carbon paste electrodes (Keto-CMCPEs) based on Keto-TPB and Keto$_3$PT as ion-exchangers were constructed. Potentiometric characterization in both batch and flow injection conditions was carried out. Potentiometric titrations and standard addition methods were applied for determination of ketotifen fumarate.[2,28] The proposed electrodes were successfully applied for the determination of ketotifen fumarate in the pure form and the pharmaceutical formulations.

Experimental

Reagents and materials

All chemicals used were of analytical grade. Doubly distilled water was used throughout all experiments. Pure grade ketotifen fumarate (keto-fuma., M.wt=425.5 g/mol), and its pharmaceutical preparations (Zaditen tablets, 1 mg/tablet and syrup 1 mg/5 ml) were supplied by Novartis PHARMA SAE (Cairo, Egypt). Sodium tetraphenylborate (NaTPB) Na[$C_{24}H_{20}B$], Phosphotungstic acid (PTA) $H_3[PW_{12}O_{40}]$, dibutyl phthalate (DBP), dioctyl phthalate (DOP), tricresyl phosphate (TCP), ethylhexyl adipate (EHA) and graphite were obtained from Aldrich Chemical Company (Taufkirchen, Germany).

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Apparatus

The potentiometric and pH measurements in batch mode were carried out with a Jenway 3010 (UK) digital pH/mV meter. A Techne circulator thermostat Model C-100 (Cambridge, England) was used to control the temperature of the test solution. Ag/AgCl/KCl_{sat} was used as an external reference electrode.

For flow injection analysis, a single-stream FIA manifold is composed of a four-channel peristaltic pump (Ismatei, ISM 827), (Zurich, Switzerland) and an injection valve model 5020 with exchangeable sample loop from Rheodyne (Cotati, CA, USA). The electrodes were connected to a WTW micro-processor pH/ion-meter pMx 2000 (Weilheim, Germany) and interfaced to a strip chart recorder model BD 111 from Kipp and Zonn (Deflt, the Netherlands). In this flow system, a wall-jet cell, providing low dead volume, fast response, good wash characteristics, ease of construction and compatibility with electrodes of various shapes and sizes, was used where a homemade teflon cup with axially positioned inlet polypropylene tubing is mounted at the sensing surface of the electrode body. The optimized distance between nozzle and the sensing surface of the electrode was 5 mm; this provides the minimum thickness of the diffusion layer and consequently, a fast response.

The system permitted analyses to be carried out using a low dispersion FIA manifold and a carrier stream that is 0.033 mol L^{-1} with respect to Na_2SO_4 and 1.00×10^{-7} mol L^{-1} with respect to Ketotifen fumarate. The optimized factors of the FIA analysis along with the response characteristics of the electrode under these conditions were evaluated according to the IUPAC recommendations.[28] The dispersion coefficient, the optimum injection volume and the flow rate were 1.13, 75.0 µL, and 12.50 ml/min, respectively.

Preparation of the ion-exchanger

Keto-TPB and $Keto_3PT$ were prepared by addition of 100 ml of 10^{-2} mol L^{-1} Keto-fuma. solution to 100 ml 0.01 mol L^{-1} of NaTPB and 100 ml 0.0033 mol L^{-1} of PTA. The resulting precipitates were left in contact with their mother liquors overnight to assure complete coagulation. The precipitates were then filtered and washed thoroughly with distilled water, dried at room temperature, and ground to fine powders. The ion-pairs with NaTPB and PTA where 1 : 1 and 1 : 3, respectively, as confirmed by elemental analysis using automatic CHN analyzer (Perkin-Elmer model 2400) in the Micro Analytical Center, Faculty of Science, Cairo University.

The C, H, and N percentages are 82.20, 6.20 and 2.24% and 17.80, 1.50 and 0.35% the corresponding calculated ones are 82.19, 6.20 and 2.23% and 17.90, 1.49 and 0.37%, for Keto-TPB and $Keto_3PT$, respectively.

Preparation of carbon paste electrodes

The assembly of the CPE was previously reported.[27] The modified paste of each electrode was prepared by dissolving the appropriate weight(s) of ion-exchanger(s) in acetone; then high purity carbon was added to the mixture to ensure homogeneity of the mixture, and this mixture was left to evaporate acetone. After evaporation of acetone, the calculated amount of plasticizer was added. Very intimate homogenization is then achieved by careful mixing with a glass rod in agate mortar and afterwards rubbed by intensive pressing with a pestle. The ready-prepared paste is then packed into the hole of the electrode body. The carbon paste surface was smoothed onto paper until it had a shiny appearance and was used directly for potentiometric measurements without preconditioning requirements. The electrochemical system is represented as follows: CMCPE/test solution//Ag/AgCl, KCl_{sat}.

Calibration curves

For batch measurements, suitable increments of standard Keto-fuma solution were added to 50 mL doubly distilled water so as to cover the concentration range 1.0×10^{-6}-1.0×10^{-2} mol L^{-1}. The sensor and the reference electrodes were immersed in the solution and the emf values were recorded at 25 ± 1 °C, after each addition, and plotted versus the negative logarithmic value of the drug concentration (pDrug).

For FIA measurements, a series of freshly prepared solutions of the drug covering the range $1.0 \times 10^{-6} - 1.0 \times 10^{-2}$ mol L^{-1} was injected to the flow stream and the corresponding peak heights were recorded and used to draw the calibration graphs.

Effect of pH on the electrode potential

The stability of the proposed electrodes at different pH values was tested on different drug concentrations (1.0×10^{-3}, 1.0×10^{-4} and 1.0×10^{-5} mol L^{-1}). 50 ml of the drug solution was transferred to 100-ml titration cell and the tested ion-selective electrode in conjunction with the Ag/AgCl, KCl_{sat} reference electrode, and a combined glass electrode were immersed in the same solution. The mV and pH readings were simultaneously recorded. The pH of the solution was varied over the range of 2.0–12.0 by addition of very small volumes of (0.10–1.00) mol L^{-1} HCl and/or NaOH solutions. The mV-readings were plotted against the pH-values for the different concentrations.

Selectivity of the electrodes

In batch measurement, potentiometric selectivity coefficients of the Keto-fuma – CMCPs were evaluated using the separate solutions (SSM)[29] and matched potential methods (MPM).[30]

In FIA, 1.0×10^{-3} mol L^{-1} solutions of the interfering ions were prepared and the corresponding peak heights were measured. The peak heights were converted to millivolts and then compared to that obtained from the standard drug of the same concentration at the same conditions.

Potentiometric determination of ketotifen fumarate

In batch measurements, the standard addition technique was applied[30] 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 sample solution, using the following equation:

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

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. Also potentiometric titrations were applied by transferring 2–10 mL

Table 1. Composition and slope of calibration curves for ketotifen fumarate carbon paste electrodes at 25.0 ± 0.1 °C, Response time (t_{resp}) $\leq$10 s

Ion-exchanger%	Plasticizer%	Slope (mV/decade)	Linear range (mol L^{-1})	LOD (mol L^{-1})
Keto-TPB				
1.00	49.50 DBP	46.8	1.00×10^{-5}-1.00×10^{-2}	3.46×10^{-6}
2.00	49.00	53.2	1.00×10^{-5}-1.00×10^{-2}	3.46×10^{-6}
3.00	48.50	57.9	1.00×10^{-5}-1.00×10^{-2}	3.46×10^{-6}
5.00*	47.50	58.3	5.60×10^{-6}-1.00×10^{-2}	1.42×10^{-6}
7.00	46.50	60.6	1.00×10^{-5}-1.00×10^{-2}	4.99×10^{-6}
5.00	47.50 DOP	54.0	9.30×10^{-6}–1.00×10^{-2}	6.16×10^{-6}
5.00	47.50 EHA	42.0	1.00×10^{-5}–1.00×10^{-2}	1.14×10^{-6}
5.00	47.50 TCP	50.2	5.60×10^{-6}–1.00×10^{-2}	3.80×10^{-6}
$Keto_3PT$				
1.00	49.50 DBP	35.0	3.50×10^{-5}-1.00×10^{-2}	1.42×10^{-5}
3.00	48.50	28.7	4.64×10^{-5}-1.00×10^{-2}	1.59×10^{-5}
5.00	47.50	30.5	1.58×10^{-5}-1.00×10^{-2}	1.00×10^{-5}
7.00	46.50	38.0	2.93×10^{-5}-1.00×10^{-2}	1.00×10^{-5}
Keto-TPB + $Keto_3PT$				
1.00 + 2.00	48.50 DBP	40.4	1.00×10^{-5}-1.00×10^{-2}	1.00×10^{-5}
2.50 + 2.50	48.50	54.2	1.00×10^{-5}-1.00×10^{-2}	1.00×10^{-5}

* Selected composition
Plasticizer: graphite is 1 : 1.

10^{-2} mol L^{-1} Keto-fuma into 100-mL titration cell and diluting to 50 mL by doubly distilled water, the resulting solutions were titrated against 10^{-2} mol L^{-1} NaTPB using the corresponding electrode. The end points were determined from the conventional S-shaped curves and the first derivative plots.

Phamaceutical analysis

For analysis of Zaditen tablets, 20 tablets were weighed and ground to fine powder and an appropriate weight from this powder was taken and dissolved in 60% ethanol, the solution was filtered in a 50-mL measuring flask and completed to the mark by doubly distilled water, then 5 mL of this solution was diluted to 50 mL using doubly distilled water. It was observed that there is no effect on the response of the proposed electrode in presence of the small percentage of ethanol (6%). In case of syrup, it was taken directly to the titration cell.

In FIA, 4.7×10^{-4} mol L^{-1} of Keto-fuma, Zaditen tablet 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

Effect of the paste composition

It is well known that the sensitivity and linearity for a given CMCPE depend significantly on the nature and the amount of the modifier in the paste. For this reason, several pastes of varying nature and ratios of ion-exchanger(s)/graphite/plasticizer were prepared for the systematic investigation of each paste composition.[22] The slopes given by the electrodes containing different percentages of single and mixed ion-exchanger are listed in Table 2. The best result was obtained from the paste modified with 5.00% Keto-TPB as it has a Nernastian slope of 58.30 mV/decade and the lowest limit of detection 1.42×10^{-6} mol L^{-1}. For $Keto_3PT$, the maximum slope was 38.00 mV/decade and the detection limit was 1.00×10^{-5} mol L^{-1}. However, the slope was improved to 54.20 mV/decade by using 2.50% Keto-TPB and 2.50% Ket_3PT as modifiers, with no effect on the detection limit.

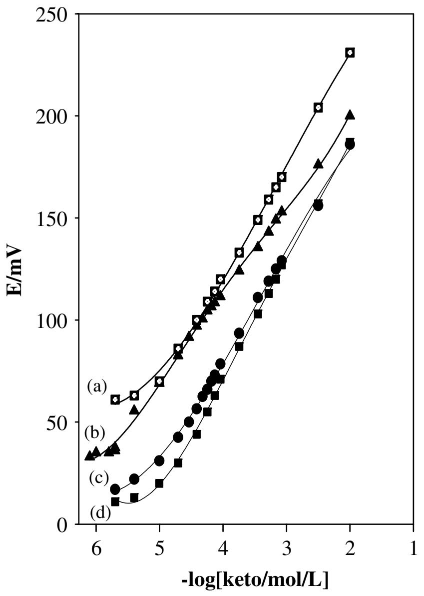

Figure 1. Effect of different plasticizers on the potential response of Keto-TPB CMCPE, TCP (a), EHA (b), DOP (c), DBP (d).

Besides the critical role of the nature and the amounts of ion-associates in preparing CMCPEs, some other important features, such as the nature of the solvent mediator, the plasticizer/graphite ratio and the nature of any additives used, are known to significantly influence the sensitivity and selectivity of prepared electrode.[30]

The influence of the plasticizer type and concentration on the characteristics of the studied electrodes was investigated by using four plasticizers with different polarities including DBP, DOP, TCP,

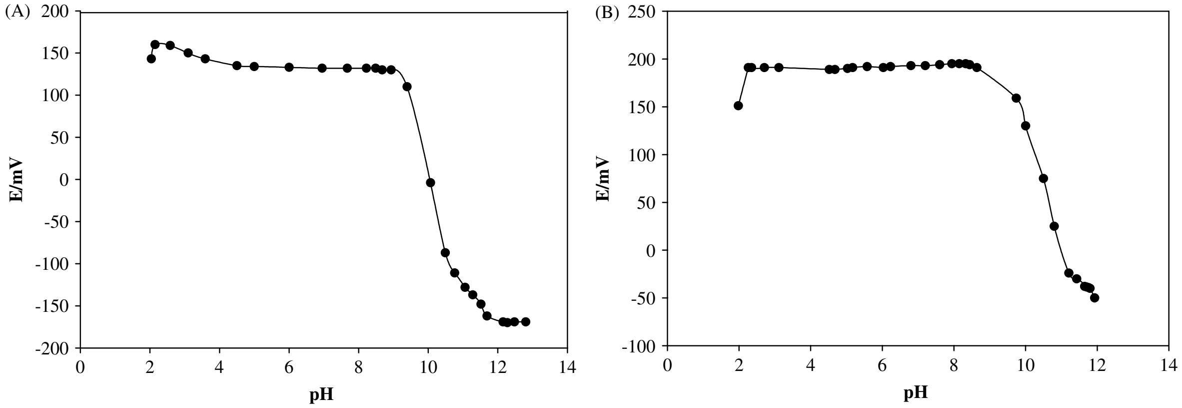

Figure 2. Effect of pH on 10^{-3} mol L^{-1} of Keto-fuma. solutions on the potential response of Keto-TPB (A) and mixed CMCPE (B).

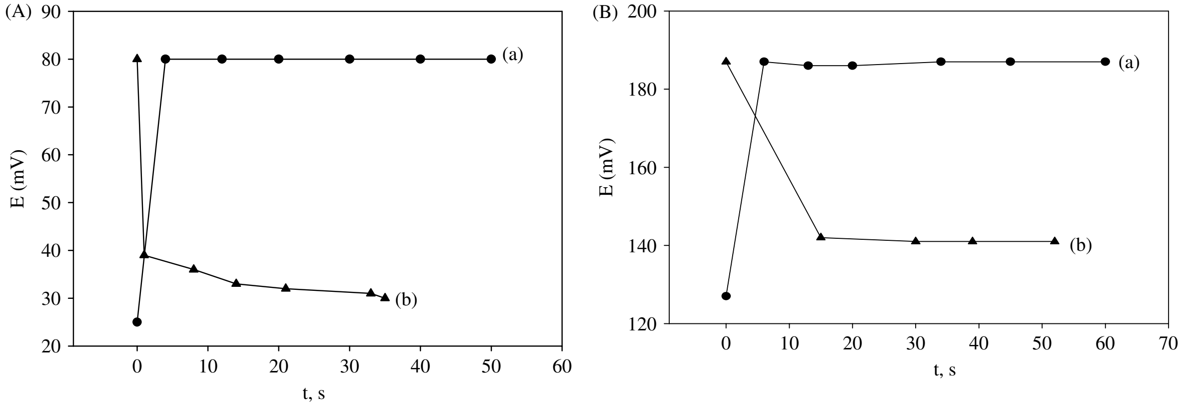

Figure 3. Potential-time plots for the response of (A) Keto-TPB and (B) mixed CMCPE: (a) from 1×10^{-5} to 1×10^{-4} mol L^{-1}, (b) from 1×10^{-4} to 1×10^{-5} mol L^{-1}.

and EHA. Different plasticizer/graphite (*w*/*w*) ratios were studied, and the optimum composition for each electrode was given in Table 1 and Figure 1. The results obtained in Table 1, support the use of DBP (the most polar plasticizer) resulting Nernestian slope of 58.3 mV/decade, linear range 5.60×10^{-6}-1.00×10^{-2} mol L^{-1} and lower detection limit 1.42×10^{-6} mol L^{-1} Although EHA shows the lowest detection limit 1.14×10^{-6} mol L^{-1}, it has small slope which is far than Nernestian value, 42.0 mV/decade.

Effect of pH

The effect of pH of the test solution on the potential readings of the developed electrodes was studied in batch conditions as

Table 2. Selectivity coefficient values

	$-\log K^{Pot}_{keto,JZ+}$					$-\log K^{Pot}_{keto,JZ+}$	
Interferent	Batch		FIA			Batch	
	Keto-TPB elrctrode	Mixed electrode	Keto-TPB elrctrode	Mixed electrode	**Interferent**	Keto-TPB elrctrode	Mixed electrode
Na^+	1.16	0.54	1.77	1.58	Fructose	3.50	2.84
$NH_4{}^+$	1.34	1.13	1.97	1.84	Sucrose	3.00	2.84
K^+	1.36	0.58	1.82	1.58	DL-Threonine	2.30	2.91
Ni^{2+}	4.60	4.17	3.61	3.41	Glycine	4.00	2.61
Mg^{2+}	1.70	2.95	2.72	3.99	D-Alanine	2.07	3.60
Cr^{3+}	4.86	4.26	2.37	4.07	L-Arginine	2.00	1.60
Cu^{2+}	1.62	1.80	2.70	3.95	L-cysteine HCl	0.30	1.30
Glucose	2.10	2.78	…….	…….	DL-Histidine	4.00	2.60
Lactose	2.04	2.80	…….	…….	DL-Asparagine	2.30	3.05
Maltose	2.20	2.15	…….	…….	…….	…….	…….

$-\log K^{Pot}_{keto,JZ+}$: Selectivity coefficient.

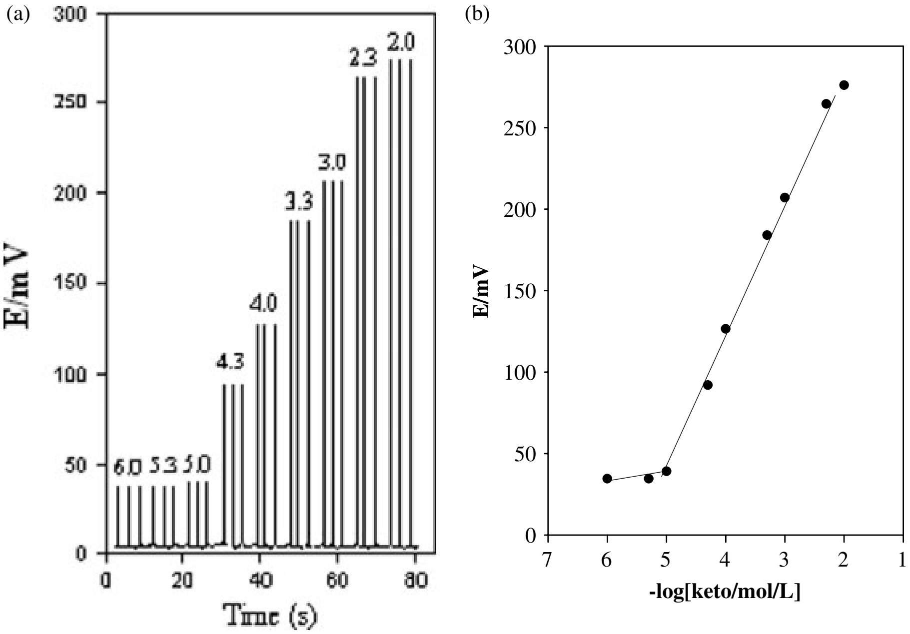

Figure 4. The recordings (a) and their corresponding calibration graph (b) obtained for Keto-TPB electrode at optimum FIA conditions.

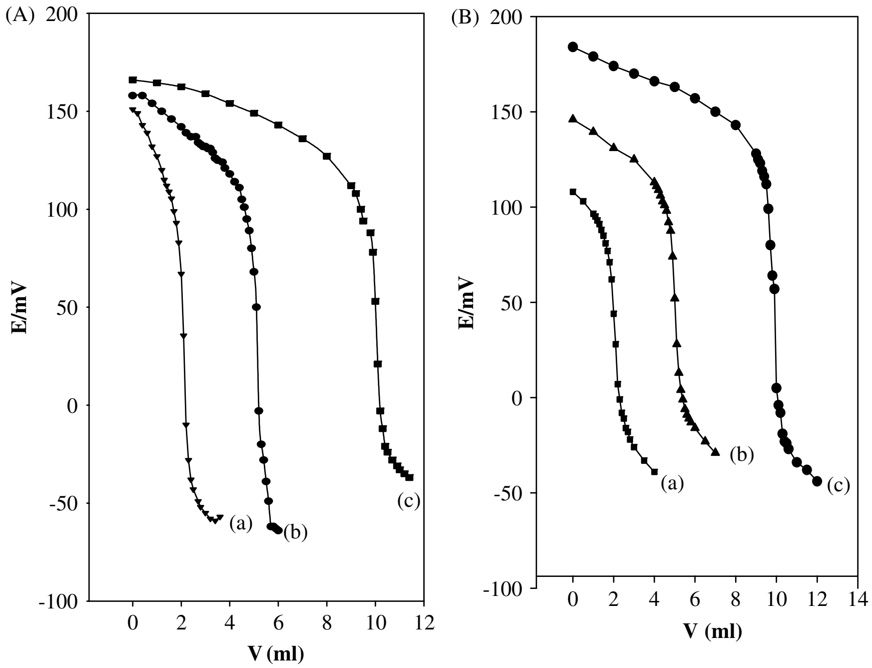

Figure 5. Potentiometric titrations of 8.51 (a), 21.27 (b), 42.55 mg (c) of Keto-fuma. against 10^{-2} mol L^{-1} NaTPB solution using Keto-TPB CMCPE (A), Mixed CMCPE (B).

described previously.[2] The potential variation due to pH change is considered acceptable in the pH ranges 4.44–9.11 for Keto-TPB CMCPE, and 2.50–9.00 for mixed ion-exchanger electrode as iillustrated in Figure 2 using 10^{-3} mol L^{-1} Keto-fuma.

At pH values lower than the previously mentioned pH ranges, the potential readings increase which can be related to interference of hydronium ion. While at pH higher than the given ranges, the potential readings decrease gradually which can be attributed to the formation of the free base of the drug and decrease of the protonated species in the test solutions.

Response time

The response time of each electrode was tested by measuring the time required to achieve a steady potential (within ±1 mV) after successive immersion of the electrode in a series of the drug solution, each having a 10-fold increase in concentration from 1.00×10^{-5} to 1.00×10^{-2} mol L^{-1}.[2,30] The electrode yielded steady potential within 5–10 s. The potential readings stay constant, to within ±1 mV, for at least 4 min. From Figure 3, the electrode potential doesn't return to its value when it is

Table 3. Determination of Ketotifen fumarate in pure solutions and pharmaceutical preparations applying the standard addition method and potentiometric titrations in batch conditions

	Keto-TPB electrode			Mixed electrode	
Sample	Taken (mg)	Recovery %	RSD %	Recovery %	RSD %
Standard addition method					
Pure solution					
	0.212	100.1	0.63	100.2	0.33
Zaditen tablet (1 mg/tablet)					
	0.212	98.7	0.83	99.0	0.84
Zaditen syrup (1 mg/5 ml)					
	0.212	98.0	0.48	99.6	0.86
Potentiometric titration					
Pure solution					
	2.13	96.5	0.42	104.0	0.41
	4.26	......	......	101.0	0.44
	8.51	100.0	0.13	100.0	0.13
	21.27	100.0	0.19	100.0	0.13
	42.55	99.0	0.19	98.0	0.51
Zaditen tablet (1 mg/tablet)					
	2.13	97.5	0.80	102.0	0.58
Zaditen syrup (1 mg/5 ml)					
	2.00	98.0	0.65	103.0	0.46

Table 4. Statistical treatment of data obtained for the determination of Ketotifen fumarate applying the standard addition method and potentiometric titration using Keto-TPB elrctrode in comparison with official methods

	Official	Keto-TPB elrctrode		
		Pure solution	Zaditen tablet	Zaditen syrup
Standard addition method				
x±S.E%	100.2 ± 0.96	102.1 ± 0.33	98.9 ± 0.41	98.6 ± 0.23
RSD%	0.95	0.63	0.84	0.48
t-test		3.0	3.01	2.70
F-test		2.40	1.80	2.44
Potentiometric titration				
X± S.E%	100.2 ± 0.96	99.2 ± 0.22	97.6 ± 0.34	98.2 ± 0.32
RSD%	0.95	0.21	0.77	0.65
t-test		2.24	2.65	2.27
F-test		4.84	1.50	2.79

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.

transferred from higher to lower concentration of the drug and this can be attributed to memory effect of the electrode.

Selectivity of the electrodes

The selectivity coefficients presented in Table 2 indicate that single and mixed CMCPEs are 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 is related to the difference in polarity and lipophilic nature of their molecules relative to ketotifen cation.

Optimization of the electrodes response in FIA conditions

Flow injection analysis (FIA) is a widespread type of methodology characterized by its versatility, high sampling frequency, and minimum sample treatment prior to injection into the system, reduced time of analysis, and low consumption of reagents compared to the conventional manual procedure.[31,32]

The FI manifold was used to evaluate the working characteristics of the constructed electrodes, and to make the applicability of the developed system viable for the determination of the studied drug in different samples. Following this, the optimization of several physicochemical and hydrodynamic parameters of the system was conducted using a univariated method, namely, the dispersion coefficient, the carrier composition, the injection volume and the flow rate. The slope, linear range and limit of detection were 80.37 mV/decade, 1.00×10^{-5}-1.00×10^{-2} mol L^{-1} and 7.24×10^{-6} mol L^{-1}, respectively. Figure 4 represents the recording obtained by the studied electrode at optimum FIA conditions and its corresponding calibration graph.

Analytical applications

The proposed electrodes were used as sensors for determination of ketotifen fumarate in pure solutions and pharmaceutical preparations applying the standard addition method and potentiometric titration (Figure 5). Table 3 shows the results obtained, which are in good agreement with those obtained by the official method.[1] The present method has the advantage that it does not need any extraction or separation. In potentiometric titration, the end-point was determined from zero and first derivative curves.

A new method is often compared with a standard method in order to find if there is any significant difference between the two methods and to find the extent to which this difference can affect the applicability of this method rather than an already used method. In order to decide the difference between the results obtained by the two methods, paired *t*- and F-tests were calculated (Table 4). Comparing the F- and *t*- values with the tabulated ones, it is clear that the obtained values were lower than the 5% critical values (95% confidence level), i.e. the method does not exhibit significant differences in comparison with the official one, which reflects the high accuracy and precision of our method.

Conclusion

The proposed CMCPEs based on Keto-TPB and $Keto_3PT$ ion-exchangers as electro-active compounds might be useful detector in batch and FI systems. These sensors show high sensitivity and accuracy for the determination of ketotifen fumarate in its pure and pharmaceutical preparations. The reported methods are very simple, sensitive, highly specific and advantageous over the previously described procedures for ketotifen fumarate determinations, since the interference of the excipients, impurities are nullified.

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