

Feature Article

Triiodide Ion-Selective Polymeric Membrane Electrode Based on a Ketoconazole-Triiodide Ion Pair

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Received: July 18, 2001

Final version: October 11, 2001

Abstract

A new triiodide ion-selective PVC membrane sensor based on diprotonated ketoconazole-triiodide, as $(KCH_2)(I_3)_2$, ion pair, was proposed. The electrode has a linear dynamic range between 2.0×10^{-3} and 7.0×10^{-6} M with a Nernstian slope of -59.9 ± 1.6 mV per decade and a detection limit of 3.0×10^{-6} M. The potentiometric response is independent of the pH of the solution in the pH range 2–8.5. The electrode can be used for at least 3 months without any considerable divergence in potential. It was applied as indicator electrode in potentiometric titration of ascorbic acid, hydroquinone from pharmaceutical preparations and triiodide ions in solution. The proposed triiodide membrane sensor was also used in development of a new, simple, fast, inexpensive and precise method for the determination of Ketoconazole in formulations.

Keywords: Triiodide ion-selective electrode, PVC membrane, Ketoconazole, Potentiometry

1. Introduction

There has been a continued growth in the number of PVC membrane electrodes that are prepared for a variety of substances. These electrodes can be prepared by incorporating any of the many ion-exchanger or neutral-sequestering agents within a plasticized PVC matrix and used as very useful tools for clinical, chemical and environmental analysis [1, 2]. In recent years, search for anion carriers with the selectivity sequence different from the Hofmeister pattern (i.e., selectivity based solely on the lipophilicity of anions) [3] has been the subject of a series of investigations [4, 5]. Therefore, the design and synthesis of sensory molecules for anion-selective electrodes has been reported in recent years, based on quarternary ammonium salts [6–8], metal complexes [9, 10], organometallic compounds [11, 12] and metalloporphyrin derivatives [13, 14].

Despite the urgent need for a triiodide-selective sensor for direct determination of iodine or indirect determination of some important specific oxidizing substances, in many industrial, medical and environmental samples, there have been limited reports on I_3^- -ion selective electrode in the literature [15, 16]. Suzuki et al. [15] used a PVC membrane electrode based on (5,10,15,20-tetraphenyl porphyrinato) Manganese(III) to determine I_3^- ions. This electrode with a super-Nernstian response of -87 mV/decade to I_3^- ion, was applied for the indirect determination of some oxidizing agents. Recently, Shamsipur et al. [16] developed a triiodide PVC membrane sensor based on a charge-transfer complex of I_2 with 2,4,6,8-tetraazabicyclo[3.3.0] octane and used it as an indicator electrode in potentiometric titration of triiodide ions. We have recently studied the electrochemical

behavior and some chemical reactions of ketoconazole (KC) (an antifungal drug) in aqueous and non-aqueous media [17, 18]. Also, we have found that the protonated KC (as dication) is precipitated in the presence of I_3^- ions as $(KCH_2)(I_3)_2$ ion pair. Since the obtained ion pair is very stable and insoluble in aqueous solutions, we were interested in the preparation of a new solvent polymeric membrane sensor for selective monitoring of I_3^- ion based on a $(KCH_2)(I_3)_2$ ion pair complex. The characteristics as well as some analytical applications of the proposed electrode as a new indicator electrode in potentiometric titration of triiodide ion, ketoconazole, ascorbic acid and hydroquinone are studied in this article.

2. Experimental

2.1. Reagents

The plasticizers used were benzyl acetate (BA), 2-nitrophenyl octyl ether (NPOE), nitrobenzene (NB), acetophenone (AP) and didecyl sebacate (DDS) (all from Aldrich), while tetraphenylphosphonium chloride (TPPC), tetrabutylammonium bromide (TBAB), and sodium tetraphenyl borate(STPB) (all from Merck) were used as lipophilic cationic or anionic additives. High relative molecular weight PVC were purchased from Aldrich and used as received. Chloroform, tetrahydrofuran(THF), iodine and all of the anionic salts used (all from Merck) were of highest purity available and used without further purification. Triply distilled deionized water was used throughout. Reagent grade ketoconazole and its 200 mg-tablets as well as 2%-

cream samples were obtained from Behvazan Pharmaceutical Company, Rasht, Iran. Rouzdarou Laboratories, Tehran, Iran, supplied Vitamin C and Hydroquinone formulations.

2.2. Apparatus

All potentiometric and pH measurements were made at $25 \pm 1^\circ\text{C}$ with a digital WTW multilab 540 I analyzer (Germany). A LKB Model 4054-UV recording spectrophotometer with 10 mm quartz cells was employed for absorbance measurements. The infrared absorption and $^1\text{H-NMR}$ spectra were recorded using a Perkin-Elmer (Norwalk, CT, USA) 1430 ratio recording (IR) spectrometer and JEOL Model EX90A, respectively.

2.3. Preparation of Ion-Exchanger $(\text{KCH}_2)(\text{I}_3)_2$

To a 10 mL aliquot of 10^{-2}M aqueous ketoconazole solution containing a few drops of HCl (1 M), were slowly added 10^{-2}M triiodide solution with continuous stirring until precipitation was completed. The resulting brown KC-triiodide ion-pair precipitate was separated by filtration, washed thoroughly with demineralized water and dried at 40°C . The composition of the formed ion-pair was confirmed by the potentiometric titration of I_3^- with tetrabutylammonium periodate (TBAP) in chloroform [19] and also by determination of total iodide ion produced after the decomposition of ion-pair using the alkaline fusion method as well as UV-vis, $^1\text{H-NMR}$ and IR spectroscopy.

2.4. Electrode Preparation

The master membranes were fabricated according to compositions shown in Table 1, by dissolving some suitable powdered PVC, plasticizer, $(\text{KCH}_2)(\text{I}_3)_2$ ion pair complex in about 5 mL of THF. The resulting mixture was transferred into a glass dish of 2 cm diameter. The THF was evaporated slowly until an oily concentrated mixture was obtained. A Pyrex tube (3–5 mm o.d.) was dipped into the mixture for about 10 s so that a membrane of about 0.3 mm thickness was formed. The tube was then pulled out from the mixture and kept at room temperature for about 1 h. A $1.0 \times 10^{-2}\text{M}$ triiodide ion solution was used as an internal reference solution. The electrode was finally conditioned by soaking in $1.0 \times 10^{-2}\text{M}$ triiodide solution for 2 h. A silver/silver chloride wire was used as an internal reference electrode.

2.5. EMF Measurements

All EMF measurements were carried out with the following assembly:

$\text{Ag}/\text{AgCl}, \text{KCl} (3\text{ M}) \mid \text{internal solution } \text{KI}_3 (1.0 \times 10^{-2}\text{M}) \mid \mid \text{PVC membrane} \mid \text{test solution} \mid \text{Ag}/\text{AgCl}, \text{KCl} (3\text{ M})$

Activities were calculated according to the Debye-Hückel procedure [20].

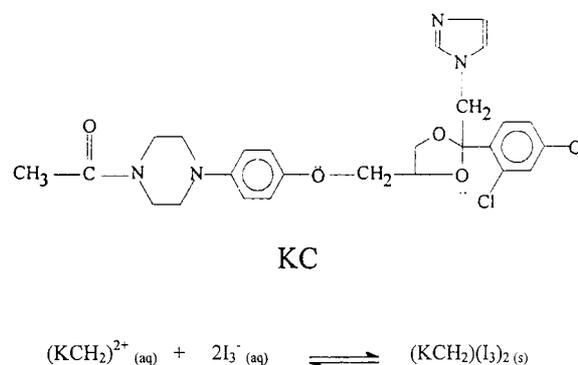
3. Results and Discussion

3.1. Study of Reaction Between KC and I_3^- Ions

Ketoconazole (KC), cis-1-acetyl-4-[4-[2-(2,4-dichlorophenyl)-2-(1 H-imidazole-1-yl methyl)-1,3-dioxolan-4-yl] methoxy piperazine, is an antifungal drug containing two basic piperazine and imidazole rings. Preliminary experiments showed that the protonated form of KC (as dication) is immediately precipitated in the presence of excess I_3^- ions. The obtained results from the determination of unreacted I_3^- ion in filtrated solution clearly indicated that each mole KC reacts with two moles of I_3^- ion as $(\text{KCH}_2)(\text{I}_3)_2$ ion pair (Scheme 1).

The evolution of the UV-vis spectrums of the resulting ion-pair and KC in chloroform is shown in Figure 1. As is seen, while the KC solution is colorless and has no absorption in the visible region, the ion-pair is a pale yellow solution possessing two sharp peaks at 292 and 364 nm which is characteristic of triiodide free (or solvent separated) ion [21, 22].

For further investigations, the $^1\text{H-NMR}$ spectroscopy was used for the study of the structure of the ion pair. The $^1\text{H-NMR}$ spectrum of the ion pair exhibits a sharp peak in acidic region ($\delta = 9$ to TMS), due to pyridine type proton of the



Scheme 1.

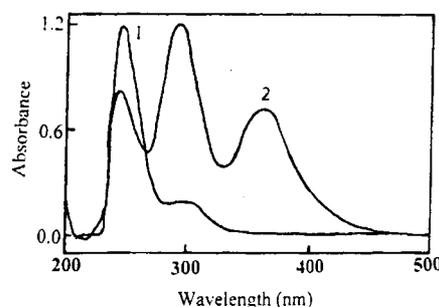


Fig. 1. UV-vis spectrums of KC (1) and $(\text{KCH}_2)(\text{I}_3)_2$ (2) in chloroform.

imidazole ring [23], while a KC solution has no peak in this region. The existence of another proton in the structure of ion pair was confirmed by the appearance of broad peaks in the range ($\delta = 6.5-8$) of the ion pair spectrum, probably due to a tertiary amine salt hydrogen type [23]. Therefore, it can be stated that the formation of triiodide ion-pair in an acidic aqueous medium is due to the protonation of imidazole (pyridine type nitrogen of imidazole, $pK_b = 6.92$) [24] and piperazine rings of KC. It is interesting to note that, the product of the reaction between protonated clotrimazole (a compound containing a imidazole ring) and triiodide ion was a lemon yellow ion-pair with ratio of 1:1. This is also in support of the idea that KC is protonated from the two mentioned sites.

On the other hand, the presence of KC as dication form in the structure of the resulting ion-pair was studied by IR spectroscopy. The IR spectrum of the ion pair displays a set of strong and broad N-H stretching vibration peaks in the $2700-2250\text{ cm}^{-1}$ region, which is characteristic of tertiary amine salts [23]. Furthermore, no considerable shifts in stretching vibration bands of C=O amide type in $(KCH_2)(I_3)_2$ in comparison to KC, confirmed that probably the nitrogen atom of the piperazine ring attached to methoxy residue was protonated in the ion pair.

3.2. Triiodide Ion Selective Electrode

In preliminary experiments, $(KCH_2)(I_3)_2$ was used as an ionophore to prepare PVC membrane ion-selective electrode for variety of anions. The potential responses of various anion-selective membrane based on ion-pair are shown in Figure 2. As seen, with the exception of I_3^- ion, all anions tested show negligible responses in the concentration range of $4.0 \times 10^{-6} - 1.0 \times 10^{-2}\text{ M}$, due to their very weak interactions with the membrane. Noteworthy, among these anions, I^- shows higher potential responses at the mentioned concentration range. This is most probably due to specific interaction between I^- and protonated imidazole ring of KC. Similar behavior has been reported for vitamin

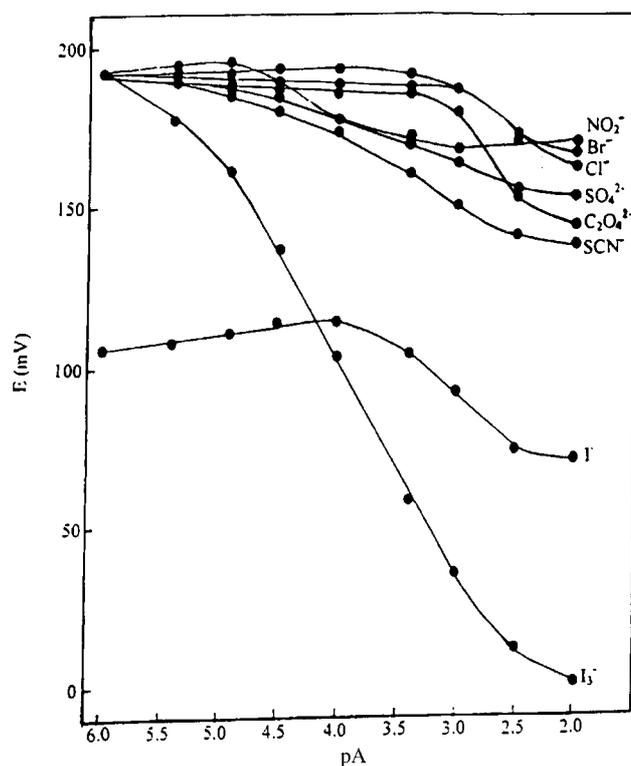


Fig. 2. Potential response of various anion-selective membranes based on $(KCH_2)(I_3)_2$.

B_{12} analogue with an imidazole ring [25, 26]. The observed potential changes at high concentration of I^- are most probably due to the oxidation of iodide, to a limited extent, resulting in the form of a low level amount of I_3^- ion in the solution [27]. However, the triiodide ion shows a Nernstian potential response at a wide concentration range.

It has been previously shown that, plasticizer and organic additives can affect the ion selectivities of PVC-membrane ion selective electrodes [28], especially in cases where non-cyclic neutral carriers are used. This was proved through the study of lipophilic additives in the PVC-matrix ion-selective

Table 1. Optimization of membrane ingredients

No.	Composition (%) PVC	Plasticizer	Ionophore	Additive	Slope (mV/decade)[a]	Linear range (M)
1	30.9	68.1, AP	1.0	—	-21.7	$8.0 \times 10^{-5} - 1.3 \times 10^{-3}$
2	29.8	69.2, DDS	1.0	—	-30.4	$1.0 \times 10^{-4} - 1.0 \times 10^{-3}$
3	30.0	69.0, BA	1.0	—	0	—
4	29.8	69.2, NB	1.0	—	46.3	$4.0 \times 10^{-5} - 3.0 \times 10^{-3}$
5	30.7	68.3, NPOE	1.0	—	-60.5	$7.0 \times 10^{-6} - 2.0 \times 10^{-3}$
6	28.0	71.4, NPOE	0.6	—	-55.4	$9.0 \times 10^{-6} - 4.2 \times 10^{-3}$
7	33.8	64.9, NPOE	1.2	—	-73.7	$1.0 \times 10^{-5} - 1.5 \times 10^{-3}$
8	29.5	65.7, NPOE	4.8	—	-86.1	$9.0 \times 10^{-5} - 3.0 \times 10^{-3}$
9	30.0	68.5, NPOE	1.0	0.5, TPPC	-67.5	$8.0 \times 10^{-5} - 1.3 \times 10^{-3}$
10	30.0	68.5, NPOE	1.0	0.5, TBAB	-65.5	$2.0 \times 10^{-5} - 1.0 \times 10^{-3}$
11	29.1	70.2, NPOE	1.0	0.6, STPB	-39.6	$1.0 \times 10^{-4} - 1.0 \times 10^{-3}$
12	30.0	70.0, NPOE	—	—	-12.1	$1.0 \times 10^{-4} - 1.0 \times 10^{-3}$
13	30.5	68.5, NPOE	—	1.0, TPPC	-24.5	$2.0 \times 10^{-5} - 5.0 \times 10^{-4}$
14	30.5	68.5, NPOE	—	1.0, TBAB	-30.6	$2.0 \times 10^{-5} - 5.0 \times 10^{-4}$

[a] RSD on the values lies within ± 1.1 .

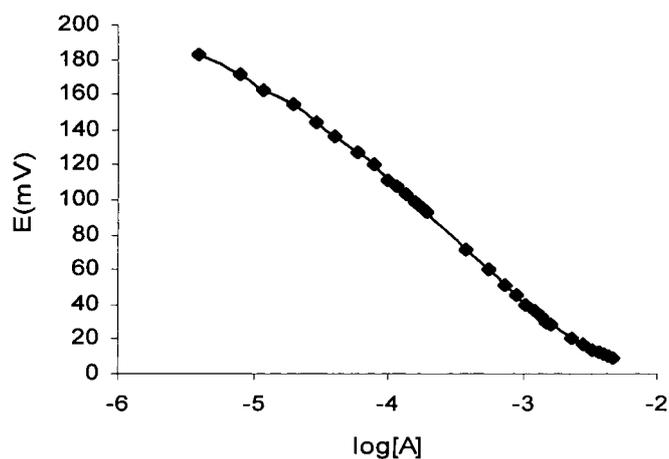


Fig. 3. Calibration graph for the I_3^- ion-selective electrode.

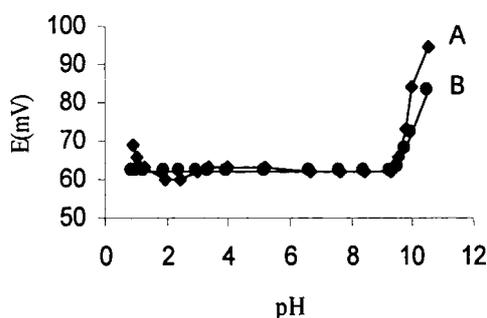


Fig. 4. Effect of pH of test solution on the potential response of the I_3^- ion-selective electrode, based on A) observed and B) calculated values.

electrodes [29]. Thus, the influence of the amount of ionophore, nature of plasticizer and nature of additive on potential response of the membrane sensor was investigated while keeping the PVC: plasticizer ratio of about 1:2 [30]. The results are summarized in Table 1.

As exhibited in Table 1, among five different plasticizers used, NPOE results in the best sensitivity and the widest linear range. Replacing the plasticizer NPOE by AP, BA, DDS and NB will diminish the slope of the potential-pA plot from expected Nernstian value (No. 1–5). On the other hand, the increased amount of ionophore from 0.6 to 4.8% results in an increase in the slope of e.m.f. versus log concentration plot with any considerable change in linear range (electrodes No. 5–8). Finally, the data given in Table 1 reveal that, the presence of TPPC and TBAB as lipophilic cationic additives had no significant effect on the sensitivity but decreases the linear range (electrodes No. 9–10). On the other hand, the incorporation of STPB as a lipophilic anionic additive (electrode No. 11) indicate a sub-Nernstian behavior with a narrow linear range probably due to strong interaction between the tetraphenylborate (TPB) anion and protonated KC resulting in ion-pair formation [31]. Thus, due to Nernstian behavior and wide linear range a membrane with a PVC:NPOE:(KCH₂)(I₃)₂ ratio of 30:69:1 was chosen for further studies. This membrane

displays remarkable selectivity and sensitivity for I_3^- ion over most common anions. While, the membrane without ionophore (electrodes No. 12–14) resulted in no significant selectivity and sensitivity toward I_3^- ion and other anions.

The critical response characteristics of the electrode were assessed according to the IUPAC recommendations [32]. The e.m.f. response of the membrane at varying concentration of I_3^- ion (Fig. 3) indicate a linear range from 2.0×10^{-3} to 7.0×10^{-6} M. The detection limit of I_3^- ion, as determined from the intersection of the two extrapolated segments of the calibration plot is 3.0×10^{-6} M.

The electrode potential is independent of the pH in the range 2–8.5 (Fig. 4A). Over this range, the potential does not vary more than ± 1.0 mV for 10^{-4} – 10^{-3} M I_3^- . In pH > 9, the potential increases sharply most probably due to the disproportionation reaction of I_3^- [27]. The potentials based on the true activity of the triiodide species with known disproportionation equilibrium are shown in Figure 4B. As seen, the actual response of the proposed electrode is different from the calculated values at alkaline pH. This behavior is probably related to serious interferences from OH^- on the protonated KC in the membrane. At low pH (<2), the slight increase in potential may be due to interference of the H_3O^+ ions, resulting in a diminished activity of I_3^- in the solution.

The influence of the concentration of the internal solution on the potential response of the I_3^- ion-selective sensor was studied. The I_3^- concentration was changed from 1.0×10^{-4} to 1.0×10^{-2} M and e.m.f. vs. $-\log [I_3^-]$ plot was determined. It was found that the variation in the concentration of the internal solution did not cause any significant difference in the potential response, except for an expected change in the intercept of the resulting plots. A 1.0×10^{-2} M portion of the reference solution was quite appropriate for smooth functioning of the system. For analytical applications, the response time of a membrane sensor is of critical importance. The average time required for the I_3^- selective membrane electrode to reach a potential within ± 1 mV of the final equilibrium value after successive immersion of a series of I_3^- ion solutions, each having a 10 fold difference in concentration was measured. The static response time of the PVC-membrane thus obtained was less than 5 s over all the linear concentration range, and the potentials remained constant for more than 5 minutes. The standard deviation of ten replicate measurements was ± 0.3 mV. The sensing behavior of the membrane remained unchanged when the potentials recorded from low either to high concentration or vice versa. The ion-selective membrane prepared could be used for 3 months without any measurable divergence in potential.

The selectivity is clearly one of the most important characteristics of a sensor, as it often determines whether a reliable measurement in the target sample is possible. This is usually expressed in terms of potentiometric selectivity coefficient ($K_{B,A}^{pot}$). In this work, the potential response of the proposed I_3^- ion-selective sensor to other anions was investigated by the matched potential method (MPM) [33–35]. This is a recently recommended method by IUPAC

Table 2. Selectivity Coefficient $\log (K_{A,B}^{\text{pot}})$ of Various Interfering Anions.

Anions	$(\log K_{A,B}^{\text{pot}}) [a]$	Anions	$(\log K_{A,B}^{\text{pot}}) [a]$
Br^-	-3.10	SO_4^{2-}	-4.10
Cl^-	-2.80	$\text{C}_2\text{O}_4^{2-}$	-3.71
NO_2^-	-2.55	SCN^-	-2.30
NO_3^-	-2.74	IO_3^-	-2.45
CH_3COO^-	-2.65		

[a] SD on the values lies within ± 0.10 .

[33], which gets rid of the restrictions of the corresponding methods based on the Nicolsky-Eisenman equation for the determination of potentiometric selectivity coefficients (including the fixed interference ions and the mixed solution methods) [36]. These limitations include the non-Nernstian behavior of interfering ions and inequality of charges of primary and interfering ions. According to MPM, the selectivity coefficient is defined as the activity ratio of the primary ion (A) and the interfering ion (B) that gives the same potential change in a reference solution [33]. Thus, one should measure the change in potential upon changing the primary ion activity. Then, the interfering ion would be added to an identical reference solution until the same potential change is obtained. The selectivity coefficient, $K_{A,B}^{\text{pot}}$, is determined as $K_{A,B}^{\text{pot}} = \Delta A/a_B$, where $\Delta A = a'_A - a_A$, a_A is the initial primary ion activity and a'_A the activity of A in the presence of interfering ion, B. It should be noted that the concentration of I_3^- used as a primary ion in this study was 1.0×10^{-4} M. The resulting selectivity coefficient values thus obtained for the proposed I_3^- ion-selective electrode are summarized in Table 2. As seen, much of diverse anions used cannot significantly disturb the functioning of the I_3^- ion-selective membrane electrode. It is interesting to note that the observed selectivity pattern (i.e., $\text{I}_3^- > \text{SCN}^- \sim \text{IO}_3^- > \text{NO}_2^- \sim \text{CH}_3\text{COO}^- > \text{Cl}^- \sim \text{NO}_3^- > \text{Br}^- > \text{C}_2\text{O}_4^{2-} > \text{SO}_4^{2-}$) considerably differs from the so-called Hofmeister selectivity sequence [3].

It is noteworthy that, despite the sensitivity of the proposed electrode does not change by incorporation of lipophilic cationic additives (see Table 1), the selectivity coefficient values for I_3^- -ion and other anions used show a slight variation. Based on these observations and also, anti-Hofmeister selectivity of the membrane it may be stated that, in addition to ion-exchange behavior, a specific interaction between I_3^- ion and protonated KC in membrane control the response mechanism of the electrode. Detecting details of this mechanism requires studies that are more specific.

4. Analytical Applications of Triiodide Ion Selective Electrode

4.1. Direct Potentiometric Titration of Iodine

The practical utility of the proposed triiodide membrane sensor was initially tested by its use as indicator electrode for

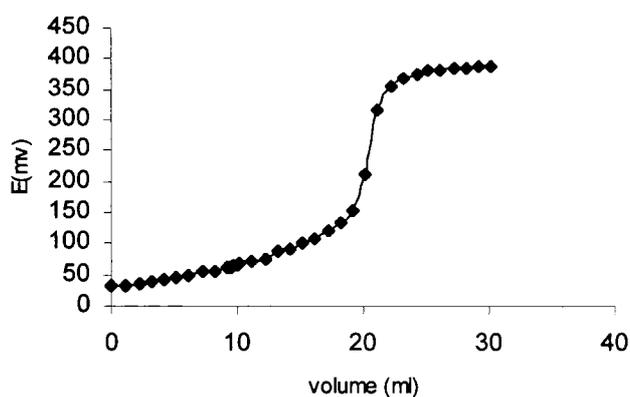


Fig. 5. Potentiometric titration curve for 50 mL of 2×10^{-3} M triiodide solution with 0.01 M sodium thiosulfate, using the proposed sensor as an indicator electrode.

the titration of 50 mL of 2×10^{-3} M triiodide solution with 0.01 M sodium thiosulfate. The resulting titration curve is shown in Figure 5. As shown, the amount of I_3^- ions in solution can be accurately determined by using the proposed electrode.

4.2. Indirect Potentiometric Titration of Ketoconazole

Due to vital importance of ketoconazole in a pharmaceutical preparation and biological fluids [37], in this work, we have reported a new accurate, precise and inexpensive potentiometric method for the determination of KC in formulations. The method is based on the reaction of KC (as diprotonated form) with excess triiodide ions and subsequent potentiometric titration of the remaining triiodide ions with a standardized thiosulfate solution using the proposed triiodide ion selective electrode. The proposed method was successfully applied for the determination of KC in cream and tablet samples. The results are summarized in Table 3.

4.3. Determination of Ascorbic Acid and Hydroquinone

The proposed triiodide membrane electrode was also used as an indicator electrode for the direct potentiometric titration of ascorbic acid and hydroquinone with a standardized solution of iodine. Typical potentiometric titration curve obtained from the titration of 50 mL of 1.5×10^{-3} M ascorbic acid (pH 3.65) and 50 mL of 10^{-3} M hydroquinone (pH 8) with a 0.01 M iodine solution are shown in Figures 6 and 7, respectively. As seen, the amount of ascorbic acid and/or hydroquinone in solutions can be accurately determined from the resulting titration curve providing a sharp end point. Assays of ascorbic acid in its powder, tablets and effervescent tablets and hydroquinone in its cream samples were carried out using the proposed method and the official method [38] (Table 3). The data given in Table 3 clearly

Table 3. Results of determination of ketoconazole, ascorbic acid and hydroquinone in their formulations.

Sample	Labeled	Found[a] Proposed method	Official method
<i>Ketoconazole</i>			
Tablet(KC)	200 (mg/tablet)	202.2 ± 2.3	202.0 ± 1.3
Cream(KC)	2% (wt% drug)	2.06 ± 0.04	1.99 ± 0.01
<i>Hydroquinone</i>			
Cream	2% (wt% drug)	2.06 ± 0.04	1.99 ± 0.01
<i>Ascorbic acid</i>			
Tablet	250 (mg/tablet)	246.4 ± 2.3	246.5 ± 3.0
Powder	500 (mg/sachet)	503.5 ± 2.8	503.8 ± 2.7
Eff. Tablet	1000 (mg/eff. tablet)	986.0 ± 2.7	986.0 ± 2.9

[a] Average of five replicate measurements ($X \pm SD$).

indicated a reasonably fair agreement between the present and official methods.

It is worth mentioning that the proposed membrane electrode may be used for the determination of some

important environmental as well as pharmaceutical organic molecules in a field related to the chemist, such as clinical and drug analysis. The use of I_3^- ion selective electrode for this purpose may be simple and more accurate than the use of the usual chromatographic, spectrophotometric, non-aqueous titration and other electrochemical methods.

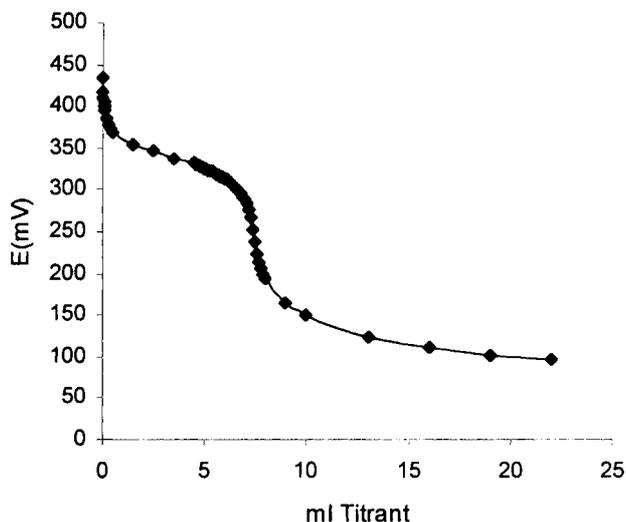


Fig. 6. Potentiometric titration curve for 50 mL of 1.5×10^{-3} M ascorbic acid with 0.01 M triiodide standard solution.

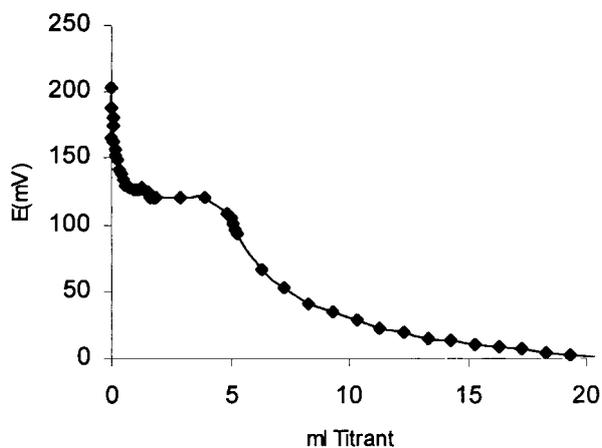
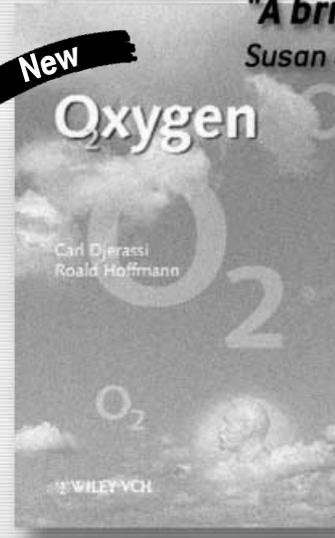


Fig. 7. Potentiometric titration curve for 50 mL of 10^{-3} M hydroquinone with 0.01 M triiodide standard solution.

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