PAPAVERINE PVC MEMBRANE ION-SELECTIVE ELECTRODES BASED ON ITS ION-EXCHANGERS WITH TETRAPHENYLBORATE AND TETRATHIOCYANATE ANIONS

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Summary - The construction and general performance of novel potentiometric membrane ion selective electrodes for determination of papaverine hydrochloride has been described. They are based on the formation of the ion association complexes of papaverine (PA) with tetraphenylborate (TPB)(I) or tetrathiocyanate (TTC)(II) counter anions as electro-active material dispersed in a PVC matrix. The electrodes show fast, stable, near Nernstian response for 1×10^{-2} to 6×10^{-5} M and 1×10^{-2} to 1×10^{-5} M for PA-TPB and PA-TTC respectively at 25°C over the pH range of 3-5.0 with a cationic slope of ~ 56.5 ± 0.5 mV/decade for both sensors respectively. The lower detection limit is 4×10^{-5} and 8×10^{-6} M for PA- I and PA-II respectively with fast response time ranging from 20-45 sec. Selectivity coefficients for PA relative to a number of interfering substances were investigated. There is a negligible interference from the studied cations, anions, and pharmaceutical excipients. The determination of 4.0- 3000.0 μg/ml of PA in aqueous solutions shows an average recovery of 99.1 % and a mean relative standard deviation of 1.4 at 100μg/ml. The direct determination of PA in some formulations (Vasorin injection) gave results that compare favorably with those obtained using the British Pharmacopoeia method. Potentiometric titration of PA with sodium tetraphenylborate and potassium thiocyanate as titrants utilizing the papaverine electrode as an end point indicator electrode has been carried out.

INTRODUCTION

Papaverine hydrochloride is 6,7-dimethyl-1-(3,4-dimethyl benzyl) isoquinoline hydrochloride[1]. It relaxes the various smooth muscles, including the smooth musculature of the larger blood vessels, especially coronary, systemic peripheral and pulmonary arteries and it increases cerebral blood flow. It has been suggested that vasodilatation is related to its ability to inhibit cyclic nucleotide phosphodiesterase[2].

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Papaverine was reported to be present in considerable amount (580 mg per 100 gm fresh leaf) of Sauropus androgynus leaf. As the nutritive value of these leaves was observed to be superior to other commonly consumed leafy vegetables in India, an attempt has been carried out to popularize this vegetable for human consumption. However, excessive consumption of the leaf reportedly caused dizziness [3], drowsiness, constipation, and etc.

Various methods have been reported for the determination of papaverine, including spectrophotometry[4], atomic absorption spectrometry[5,6], fluorometry[7], TLC[8], capillary electrophoresis,[9] HPLC,[10-12] and potentiometry.[13,14] The British Pharmacopoeia method involves the potentiometric titration of the drug with perchloric acid[1] using calomel or Ag/AgCl as reference electrode and glass or platinum or silver as indicator electrode.

In recent years, the potentiometric membrane sensors have been widely used in pharmaceutical analysis.[15-19] This is mainly due to simple design, low cost, adequate selectivity, low detection limit, high accuracy, wide concentration range and applicability of the selective electrodes to colored and turbid solutions. Papaverine selective electrode comprising a liquid membrane containing PA-TPB ion-pair soluble in chlorobenzene has been reported.[13] Another plastic membrane ion-selective electrode constructed using tricresyl phosphate dispersed in a PVC matrix and loaded on a PTFE film[14] has been described for the determination of some basic drugs including papaverine. The present work describes the construction, potentiometric characterization, and pharmaceutical application of a new papaverine PVC electrode based on the use of PA-I and PA-II ion pairs as electro-active material and dioctylphathalte as a plasticizer.

EXPERIMENTAL

Apparatus

All potentiometric measurements were made at 25 ± 1°C unless otherwise stated using an Orion pH/mV meter (model 330) and a combined Ross glass pH electrode (Orion 81-02) was used for pH measurements. An Orion double junction Ag/AgCl reference electrode (model 90-02) containing 10% (w/v) potassium nitrate in the outer compartment was used.

Reagents and materials

All chemicals used were of analytical reagent grade unless otherwise stated and doubly distilled water was used throughout. Polyvinyl chloride powder (PVC) high molecular weight, dioctylphathalte (DOP), o-nitrophenyloctyl ether (NOPE), tetrahydrofurane (THF) of purity > 99 % were obtained from Aldrich Chemical Company. Papaverine hydrochloride, sodium tetraphenylborate, potassium thiocyanate, zinc nitrate were obtained from BDH. Vasorine injection (60mg/2 ml) was obtained from Memphis Company for pharmaceutical industries, Egypt. Phosphate buffer of pH 5.0 and universal buffer of pH 4.0 were prepared.

Preparation of the papaverine-PVC membrane electrodes

The white precipitate was formed upon the addition of 25 or 50 ml of 1×10^{-2} M of papaverine hydrochloride solution to 25 ml of 1×10^{-2} M sodium tetraphenylborate or zinc thiocyanate, filtered off on a Whatman filter paper No.42 , washed with water then dried at room temperature for 24h and ground to fine powder. Four portions of 10 mg (two of PA-I and two of the PA-II) of ion associate complex, were thoroughly mixed with 190 mg PVC powder, 350 mg of DOP or NOPE plasticizer and 5 ml THF in four glass Petri dishes (5cm diameter) were added. After the constituents being well mixed, the solvent has been allowed to evaporate overnight while the sensing membranes have been formed. Each of PVC master membrane was sectioned with a cork

borer (10 mm diameter) and glued to a polyethylene tube (3 cm length, 8 mm I.D.) using THF.[20, 21] Laboratory made electrode bodies were used, which consisted of a glass tube, to which a polyethylene tube is attached at one end and filled with internal reference solution (equal volumes of 1×10^{-2} M aqueous solution of each of papaverine hydrochloride and KCl). Ag/AgCl internal reference electrode (1.0 mm diameters) was used. The indicator electrode was conditioned by soaking in a 1×10^{-2} M aqueous papaverine hydrochloride solution for 1 h and stored in the same solution when not in use.

Calibration of the papaverine electrodes

The PA-I or PA.-II PVC membrane electrodes were calibrated by immersion in conjunction with the Ag/AgCl reference electrode in a 50-ml beaker containing 9.0 ml of phosphate buffer solution of pH 5 or universal buffer of pH 4. Then 1.0 ml aliquot of papaverine solution of concentration ranging from 1×10^{-1} to 1×10^{-5} M was added with continuous stirring and the potential was recorded after stabilization to ± 0.2 mV. Calibration graphs were then constructed by plotting the recorded potentials as a function of -log[papaverine]. The resulting graphs were used for subsequent determination of unknown papaverine concentration.

Determination of papaverine in Vasorin injection ampoules

Papaverine was determined in Vasorin injection solution (60mg/2ml ampoules), by transferring the contents of 5 ampoules to a 25-ml measuring flask, making up to volume with water and shaking well. A suitable aliquot of solution was transferred to the measuring cell containing 9.0 ml of phosphate buffer of pH 5 or universal buffer of pH 4.0, and the e.m.f. of the electrode systems was measured. The concentration of papaverine is calculated from the pre-constructed calibration graphs.

RESULTS AND DISCUSSION

TPB and TTC were used as ion-pairing agents for the preparation of electro-active ion association complexes for papaverine. Sparingly soluble complexes of PA- I and PA-II have been instantaneously formed upon the addition of papaverine hydrochloride solution to TPB or tetrathiocyanate solutions. The dry powders of the formed ion pairs were used for the construction of new papaverine ion selective electrodes. The elemental analysis showed that the compositions of PA: I and PA: II complexes are 1:1 and 2:1 respectively. Plastic membranes were prepared by using casting solutions of the composition 2:28:70% (w/w) ion pair, PVC, and DOP or NPOE plasticizer, respectively. The advantage of the proposed method is wider working concentration range; lower limit; applications (both direct potentiometric and titration) and handling are offered by the proposed method compared with liquid membrane sensor.[13] The proposed method has been developed for papaverine compared with the published method[14] for basic drugs including papaverine.

Performance characteristics of the developed electrodes

The potentiometric response characteristics of the developed papaverine electrodes based on the use of PA- I and PA- II ion pair complexes with DOP or ONPOE as a plasticizers in PVC matrix were evaluated according to IUPAC recommendations.[22] The response characteristics of papaverine sensors based on these complexes are summarized in Table 1. It can be seen that the PA-I (DOP, NPOE), and II sensors show a good performance in terms of detection limit, calibration slope and

response time. Both sensors display a slope of 56.5 ± 0.5, 55 ± 0.5, and 56.0 ± 0.5mV per ten fold change in concentration and a linear response over the concentration range 1×10^{-2} - 1×10^{-5} M for PA-I (DOP; NPOE) and PA- II with limit of detection are 4×10^{-5}, 8×10^{-6} and 8×10^{-6} M respectively. The calibration slop of papaverine sensors over the linear response range is stable within ± 0.5 mV log [papaverine].

TABLE 1. - Response characteristics of different papaverine-PVC matrix membrane electrodes.

Parameter	Value		
	PA-I		PA-II
	DOP	ONPOE	DOP
Slope, mV/ decade	56.5 ± 0.5	55.0 ± 0.5	56.0 ± 0.5
Linear range, M	1×10^{-2}-6×10^{-5}	1×10^{-2}-1×10^{-5}	1×10^{-2} - 1×10^{-5}
Intercept, mV	275± 0.6	274± 0.6	274± 0.6
Correlation Coefficient, (r)	0.998	0.997	0.998
Lower detection limit, M	4×10^{-5}	8×10^{-6}	8×10^{-6}
Response time, s 1×10^{-3} M	20 ± 0.5	25 ± 0.5	20 ± 0.5
Working pH range	3-5.0	3-5.5	3 – 5.0
Precision	0.4	0.382	0.357
Accuracy	2.5%	2.5%	2.5%

Effect of pH on the different papaverine membranes

The electrode response for different papaverine concentrations was tested at different pH values, the pH being adjusted using hydrochloric acid or sodium hydroxide. The papaverine electrodes were dipped into papaverine solution of 1×10^{-2}, 1×10^{-3}, and 1×10^{-4} M, and the potential of the electrodes were recorded and plotted against the pH of solution (Fig.1). The figures show that the slope per concentration decade is constant at ~ 56 mV in the pH range 3.0 - 5.0 for the three membranes. At pH values higher than 6, the potential decreases to negative values, this is due to the dissociation of papaverine (dissociation constant pK 6.4.[23]). Upon testing different buffer solutions in the optimum pH range of the electrodes, phosphate buffer of pH 5.0 was found suitable for the PA-I membrane plasticized with DOP. While the electrode plasticized with NPOE, showed Nernestian response for the drug in aqueous solution. PA-II-DOP membrane was found to possess a Nernestian response in a universal buffer of pH 4.0.

Effect of plasticizer type on the characteristic performance of the sensors

The effect of plasticizer composition was studied in case of PA-I using DOP and NPOE plasticizer. Plasticizer play an important role in response characteristic of the sensor e.g. calibration range and lower limit of detection, 1×10^{-2} -6×10^{-5} M in case of NPOE compared by DOP 1×10^{-2} – 4×10^{-5} M with lower limit of detection 8×10^{-6} M compared with 4×10^{-5} M. Moreover, the effect of plasticizer in case of PA- II was studied and no difference match was observed with two plasticizer (DOP and NPOE).

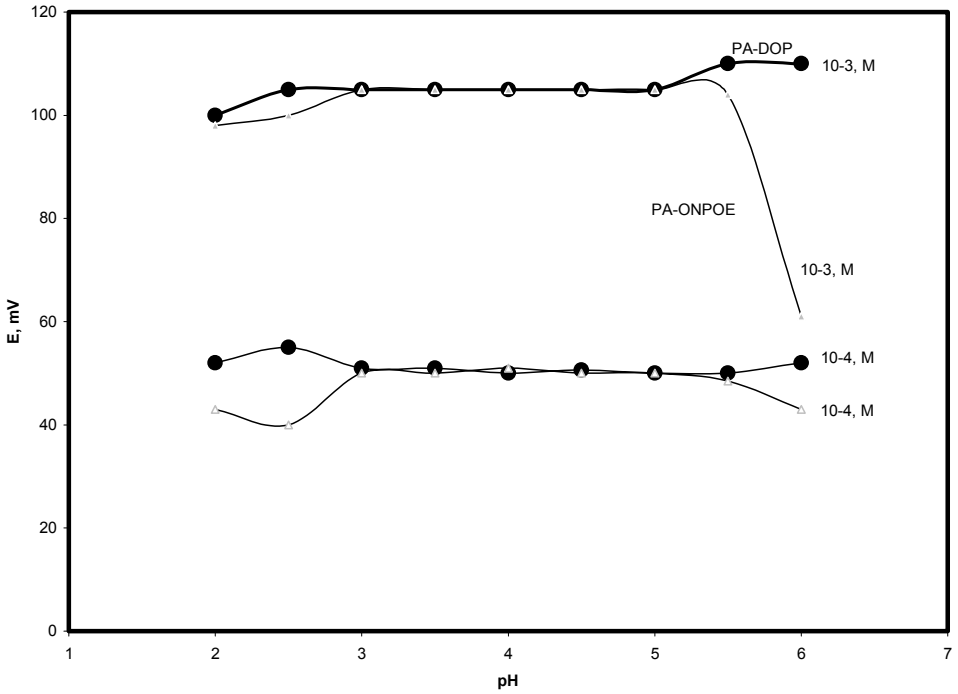

FIGURE 1.a. - Effect of pH on the response of PA-I PVC (DOP and ONPOE plasticizer) electrode using two series of papaverine solution 1×10^{-4}, and 1×10^{-3} M.

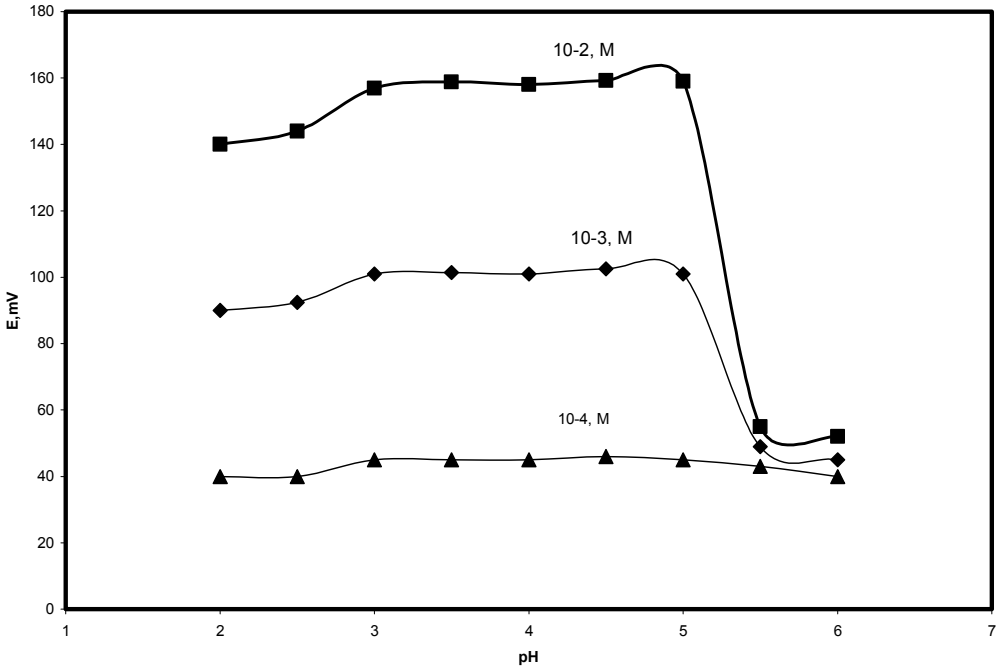

FIGURE 1.b. - Effect of pH on the response of PA-II PVC (ONPOE plasticizer) electrode using three series of papaverine solution 1×10^{-2}, 1×10^{-3}, and 1×10^{-4} M.

Response time

The average response time is defined[22] as the time required for the electrode to reach a stable potential within ±1 mV of the final equilibrium value, after successive immersion of the electrodes in different papaverine solutions each having a 10-fold difference in concentration. This time was found to be 20 s for papaverine concentration 1×10^{-3} M and 45 s for concentration $\leq1\times10^{-4}$ M for the three different membranes. Day-to-day reproducibility of the electrodes was found to be within ± 0.5 mV for the same solution and the useful lifetime of these electrodes ranged to 4 weeks, during which the potential slope was reproducible to within ±1 mV/ a concentration decade. Also after more than two months a new section from any of the three master membranes was found to function properly.

Effect of Diverse Ions

The potentiometric selectivity coefficient of an ISE is commonly used as a quantitative expression of the ability of the electrode to respond primarily to the analyte ion in the presence of interfering ions. The influence of some different organic, inorganic ions, sugars and amino acids on the response of papaverine electrodes was investigated. The selectivity coefficients were determined by the separate solution method (SSM)[22,24] using 1×10^{-2} M concentration of both papaverine and interfering species in phosphate buffer of pH 5.0 and universal buffer of pH 4.0 for PA-I and PA-II membranes, respectively. The selectivity coefficients were calculated using the following equation:

$$\frac{E2-E1}{S} = \log\left[a_{\text{papaverine}} + K^{pot}_{papaverine,j}\ (a_j)^{z/y}\right]$$

where E_1 and E_2 are the potential readings observed after 1 min of exposing the sensor to the same concentration of papaverine ion and interfering ions alternatively. a_{PA} and a_j are the activities or concentrations of the papaverine ion and interfering ions of z and y charges respectively, and S is the slope of calibration graph (mV/ concentration decade). Table 2 reveals that there is a negligible interference from all of the indicating species, which shows good selectivity of the proposed electrode.

TABLE 2. - Selectivity coefficients of some interfering ions, using papaverine-selective electrodes.

Interferent	$K^{pot}_{papaverine,j}$		Interferent	$K^{pot}_{papaverine,j}$	
	I	II		I	II
Na^+	1.0×10^{-2}	1.2×10^{-2}	NO_3^-	1.2×10^{-2}	1.0×10^{-2}
K^+	1.0×10^{-2}	1.0×10^{-2}	CH_3COO^-	1.0×10^{-2}	1.1×10^{-2}
Ca^{2+}	1.0×10^{-3}	1.3×10^{-3}	Citrate	2.8×10^{-3}	2.5×10^{-3}
Fe^{2+}	2.0×10^{-3}	2.0×10^{-3}	Urea	1×10^{-2}	1×10^{-2}
Cu^{2+}	2.8×10^{-3}	1.7×10^{-3}	Hydrazine	1.0×10^{-2}	1.2×10^{-2}
Zn^{2+}	3.0×10^{-3}	2.8×10^{-3}	L- Tryptophane	1×10^{-2}	1.1×10^{-2}
Mg^{2+}	2.8×10^{-3}	2.3×10^{-3}	DL-Alanine	1×10^{-2}	1.3×10^{-2}
Al^{3+}	3.3×10^{-4}	3.4×10^{-4}	Formate	1×10^{-2}	1.2×10^{-2}
CO_3^{2-}	3×10^{-3}	3×10^{-3}	Glycine	1.0×10^{-2}	1.3×10^{-2}
Cl^-	3×10^{-2}	1×10^{-2}			
PO_4^{-3}	2.8×10^{-4}	2.7×10^{-4}			

Validation of the proposed method

Limit of quantification and limit of detection

The calibration graphs constructed (Fig. 2) for PA-I -DOP, PA- I -ONPOE and PA- II -DOP were found to be linear in the range of 1×10^{-2} - 6×10^{-5}M, 1×10^{-2} to 1×10^{-5} M and 1×10^{-2} to 1×10^{-5} M respectively. The lower detection limit is 4×10^{-5}, 8×10^{-6} and 8×10^{-6} M for the three membrane electrode in the same order. The relation between potential and concentration is logarithmic X = +*S* log [PA] + y where x is equal the potential, *S* is the slope and y is the intercept and correlation coefficient.

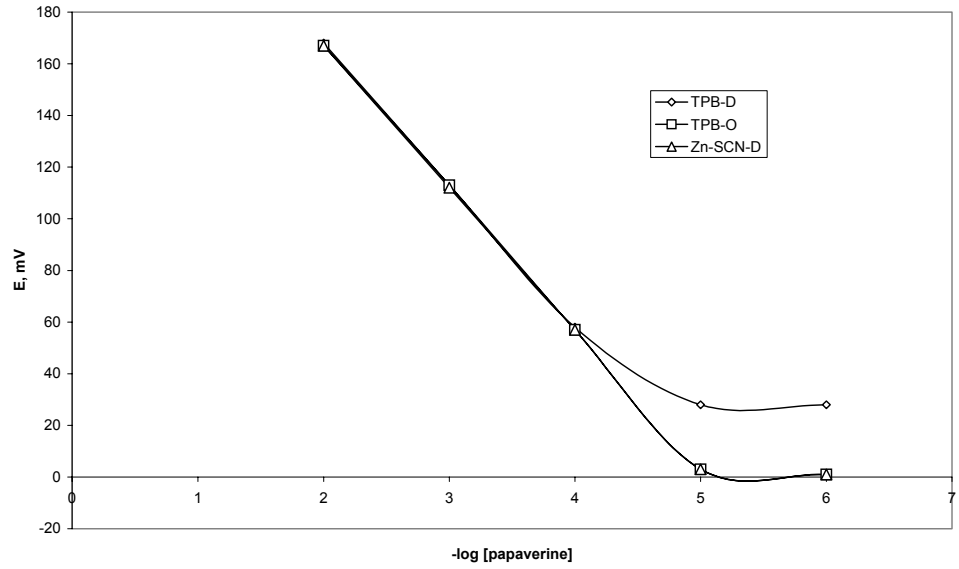

FIGURE 2. - Calibration graphs using three different membrane electrodes.

Precision and Accuracy of the method

The precision of the method was checked by the analysis of the PA five replicate of the sample that expressed as R.S.D.% at the limit of qualification LOQ range was less than 0.3 %. The accuracy was expressed in the term of %deviation of the measured concentration or relative error. Also reproducibility of the proposed method (Day to Day or intraday) was investigated. The results obtained are within the acceptance range less than 0.3% for both sensors.

Ruggedness

The ruggedness of the potentiometric method was evaluated by caring out the analysis using two different analysts (operators) and different instruments on different days. The RSD of less than 0.3 % were observed for repetitive in three different day time periods using two different instruments and operators. The results indicate that the method is capable of producing results with high precision.

Robustness

The robustness of the method was explained by the evaluation the influence of small variation of some of the most important procedure variables including pH, potential range and measuring time.

Preliminary inspection of the results under these various conditions suggested that the method is fairly robust, but the pH of the measuring solution should be in the range of pH range 3.0 – 5.0.

Determination of papaverine

For verifying the feasibility of the developed method, the determination of papaverine in water was carried out using the three developed membrane electrodes. The analysis of a papaverine solution in water was carried out using the developed electrodes; the analysis of 4-3759 μg/ml (five replicates) gave an average recovery of 98.5% and relative standard deviation of 0.24 % at 100 mg/ml, results are shown in Table 3. Applying the proposed method for the direct determination of papaverine in Vasorin injection gave good results. The average recovery for injection solution (60mg/ 2 ml ampoule) was 97.63% with a relative standard deviation (RSD) of 0.24. The results are in agreement with those obtained using the British Pharmacopoeia method[1]; the results are given in Table 4.

TABLE 3. - Determination of papaverine using PA- PVC membrane sensors.

Added (μg/ml) PA-1 (PA-II)	Found(μg/ml) PA-1(PA-II)	Recovery, %	RSD*, %
4.0	3.9 (3.9)	97.5 (97.5)	0.6 (0.6)
10.0	9.8 (9.8)	98.0 (98.0)	0.6 (0.5)
20.0	19.8 (19.7)	99.0 (98.5)	0.5 (0.5)
60.0	59.5 (59.6)	99.2 (99.3)	0.4 (0.5)
80.0	78.5 (78.5)	98.0 (98.0)	0.3 (0.3)
100.0	99.5 (99.0)	99.5 (99.0)	0.3 (0.3)
500.0	499.0 (498.0)	99.8 (99.6)	0.3 (0.3)

*Average of five determinations

TABLE 4. - Determination of papaverine in some pharmaceutical preparation using the proposed electrodes.

Solution	*B.P	**PA-I (DOP)	(NPOE)	PA-II (DOP)
Vasorin injection (60 mg/2ml)				
R, %	98.0	97.5	98.0	97.5
S	0.15	0.11	0.11	0.13
RSD, %	0.24	0.25	0.23	0.24

* B.P (British Pharmacopoeia)

**Average of five determinations.

R (recovery), S (standard deviation), and RSD (relative standard deviation),

Determination of papaverine by potentiometric titration

The developed electrodes in conjunction with an Ag/AgCl reference electrode have been examined as end point indicator electrodes for the determination of papaverine. Titration of 1×10^{-2}M papaverine hydrochloride solution with sodium tetraphenylborate and tetrathiocyanate solution of the same concentration as titrants has been performed using (PA-II) electrode. Figure 3 shows typical potentiometric titration curves of papaverine with sodium tetraphenyl borate and tetra thiocyanate. It is clear that papaverine hydrochloride reacts with I and II with the molar ratios of 1:1 and 2:1 respectively. The inflection break at the equivalent point is ~ 200 and 175mV respectively.

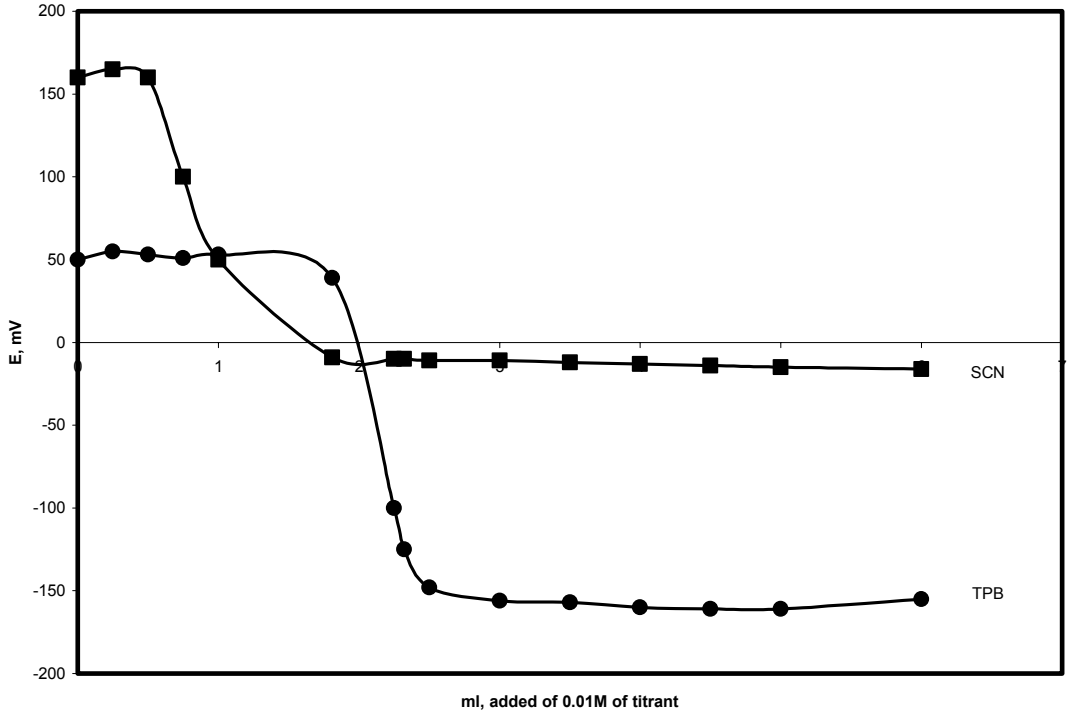

FIGURE 3. - Titration of 1.5 of 0.01 M papaverine solution with standard solution of 0.01 M potassium thiocyanate and sodium tetraphenylborate using the proposed membrane electrode(PA-II).

CONCLUSION

The developed papaverine PVC membrane electrodes described in this work offer a simple, accurate, selective, and specific tool for quantitative determination of papaverine in some pharmaceutical preparations and can be used as indicator electrodes for potentiometric titration of some anions. The results are in excellent agreement with those obtained using the British pharmacopoeia method. The electrode prepared of PA-I and PA-II ion pairs plasticized with DOP are relatively superior to the other membrane.

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