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Ion Selective Membrane Electrodes for Determination of Cetrimide in Pure form and in Pharmaceutical Formulations

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Abstract- This paper presents a comparative study between five ion selective electrode sensors which were constructed and validated to determine Cetrimide (CET) by direct potentiometry in pure drug and its mouthwash without sample pre-treatment. Precipitation based technique was used for sensors fabrication. The CET complexes with different types of polyvinylchloride matrix and different cationic exchangers, CET- carboxylated polyvinylchloride (sensor 1), CET- tetrakis (sensor 2), CET- phosphotungestate (sensor 3), CET-tetraphenylborate (sensor 4) and CET- carboxylated polyvinylchloride / tetrakis (sensor 5) were obtained in situ by soaking the PVC membranes in 1×10^{-4} M CET solution. Nitrophenyl octyl ether (NOPE) was used as plasticizer. Proposed sensors showed fast, stable Nernstian responses across a relatively wide CET concentration range of 7.81×10^{-6} M to 1×10^{-3} M (for sensor 1, 2 & 5) and 3.13×10^{-5} M to 1×10^{-3} M (for sensor 3 & 4) in the pH range of 1-10 (for sensors 1, 2 & 5) and 5-7 (for sensors 3 & 4). Suggested sensors were found to be stable for several weeks without any measurable change in sensitivity. Validation of the method according to IUPAC recommendations showed suitability and selectivity of the proposed electrodes for the use in quality control assessment of CET in presence of different interferents. Proposed sensors were successfully applied for CET determination in pure form and in its mouthwash where good responses were obtained regarding accuracy and precision.

Keywords- Cetrimide, Carboxylated polyvinylchloride, Tetraphenylborate, Phosphotungestate, Tetrakis

1. INTRODUCTION

Cetrimide (CET) (Figure 1) is a quaternary ammonium compound; it is chemically designated as trimethyltetradecylammonium bromide [1,2]. It is used as an antiseptic with detergent properties. It acts as a cationic surfactant with bactericidal activity and frequently used in different pharmaceutical preparations. It is used in many mouthwashes to relief gum sores and for dental care. It is also used as wound disinfectant in its combination with Chlorohexidine. It acts as an important pharmaceutical ingredient in medical shampoos for treating psoriasis and seborrhea [1].

Different analytical techniques were described for quantitative determination of Cetrimide as: gas chromatography [3], capillary electrophoresis with indirect UV detection [4] due to CET low UV absorptivity and TLC-densitometry by colorimetric detection [5]. All these methods require a derivatization step due to the absence of a chromophoric group in CET. For determination of number of quaternary ammonium compounds including CET, colorimetric spectrophotometric method was developed [6]. For the improvement of the official iodometric titration assay of CET [2], determination with 1,3-dibromo-5,5-dimethylhydantoin can be recommended[7]. First derivative UV spectrophotometric method was developed for simultaneous determination of CET and Chlorohexidine gluconate [8].

Only one potentiometric detection method based on ion selective electrode (ISE) was described for determination of CET by utilizing two ionic exchangers which were incorporated in the electrode matrix during preparation for electrodes fabrication, CET-tetraphenyl borate and phosphotungstate ion pair [9].

Remote sensing and direct measurements of untreated samples are the greenest methodologies as there will be no need for neither hazardous reagents nor organic solvents. Ion selective electrodes (ISEs) based on material transport across a specific membrane are now widely used in the determination of drugs in pure and pharmaceutical dosage forms. The high selectivity of these electrodes imparts a great advantage over other techniques, as analytes in colored, turbid and viscous samples can be determined accurately without separation [10,11]. Furthermore, they show rapid response to changes in concentration and are tolerant to small changes in pH. They are also simple and cheap to develop setup and run [12]. A special advantage in case of determination of CET by direct potentiometry is that no derivatization will be required. Various reports have been published which highlight the important contribution of ion selective sensors for quantification of drugs [13,14].

The aim of this work was to develop new, eco-friendly, economic and portable ion selective electrodes which can be used in routine quality control for the determination of CET in its drug substance and in its available pharmaceutical mouthwash without the need of preliminary derivatization, extraction or separation steps.

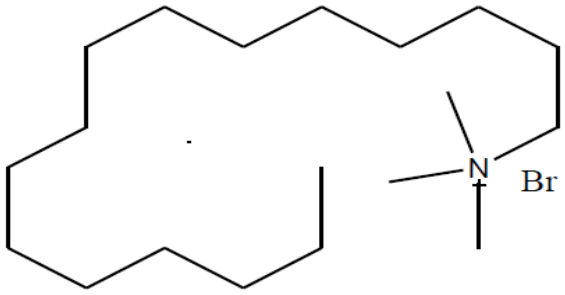


Fig. 1. chemical structre of cetrimide

2. EXPERIMANTAL

2.1. Instrument

A Jenway digital ion analyzer model 3510 (UK) with Ag/AgCl double junction reference electrode No. Z113107-1EAPW (Aldrich Chemical Co.) was used. The influence of pH on the response of the electrodes was studied using pH glass electrode Jenway (Jenway, UK) No. 924005-BO3-Q11C. A magnetic stirrer, Bandelin Sonorox, R×510S (Budapest, Hungaria) was used during potential measurements.

2.2. Materials and reagents

2.2.1. Pure standard

Cetrimide, working standard, was kindly supplied by Chemical Industries Development "Cid", Giza, Egypt. Its purity was certified to be 100%.

2.2.2. *Pharmaceutical formulation*

Citrolin- F® mouthwash and gargle used as mouth and throat disinfectant, manufactured by Pharco pharmaceuticals, Alexandria, Egypt. Batch No. 267, each 100 mL of the mouthwash was labeled to contain 25 mg of Cetrimide, 3 mg of Lidocaine HCl, 50 mg Sodium fluoride and 20 mg Chlorohexidine gluconate.

2.2.3. Chemicals and reagents

All chemicals and solvents used were of analytical grade and water used was double distilled.

Nitrophenyl octyl ether (NPOE) and dioctyl phthalate (DOP) were obtained from Sigma (St. Louis, USA). Polyvinylchloride (PVC) and Polyvinylchloride carboxylated (PVC-COOH) were purchased from Fluka Chemie (GmbH Germany). Sodium tetraphenyl borate

(TPB), sodium phosphotungestate tribasic hydrate (PT) and tetrahydrofuran (THF) were obtained from BDH (Poole, England). Tetrakis (4-chlorophenyl) borate (TpClPB) was purchased from Aldrich (Steinheim, Germany). Sodium hydroxide, 2 M aqueous solution, Hydrochloric acid, 2 M aqueous solution and potassium chloride solution were prepared and obtained from Prolabo (VWR International, West Chester, Pennsylvania, USA).

2.3. Standard solutions

(**a**) Cetrimide stock solution (1×10^{-2} M)

The solution was freshly prepared daily by transferring 0.336 g of CET, accurately into100-mL volumetric flask then dissolving in 90-mL double-distilled water and the volume was completed with water. The stability of the prepared solution was studied, and it was found to be stable with no apparent degradation at least 24 h at 25°C.

(**b**) Cetrimide working solutions

Working solutions with concentrations 1×10^{-3}, 5×10^{-4}, 2.5×10^{-4}, 1.25×10^{-4}, 6.25×10^{-5}, 3.13×10^{-5} (for sensors 3&4) 1.56×10^{-5}, 7.81×10^{-6} M for sensors (1,2&5).The concentration (1×10^{-3} M) of CET was prepared by transferring 10 mL from stock solution into 100 mL volumetric flask and the volume was completed with water. Other different concentrations of CET were determined by a stepwise dilution of 1×10^{-3} M solution with deionized water and continuous EMF measurements instead of serial dilutions in order to minimize the variations due to experimental conditions.

2.4. Procedures

2.4.1. Preparation of the membrane sensors

A portion of 10 mg of TpClPB for sensors (2), PT for sensor (3) and TPB for sensor (4) was thoroughly mixed with 0.19 g PVC. For sensors (1) only a portion of 0.19 g PVC-COOH was used. For sensor (5) a portion of 0.19 g PVC-COOH and 10 mg of TpClPB were mixed. For all sensors 0.35 mL NOPE were added in a 5 cm glass petri dish then all membrane components were dissolved in 5 mL THF. The petri dishes were covered with filter paper and left to stand overnight to allow solvent evaporation at room temperature. Master membranes with thickness of 0.1 mm were obtained and used for the construction of the electrodes.

2.4.2. Preparation of the electrodes assemblies

From the prepared master membranes, a disk (≈5 mm diameter) was cut using a cork borer and pasted using THF to an interchangeable PVC tip that was clipped into the end of the glassy electrode body. Equal volumes of 10^{-4} M CET and 10^{-4} M KCl were mixed and this solution was used as internal solution for electrodes. Ag/AgCl wire (1 mm diameter) was immersed in the internal reference solution as an internal reference electrode. The electrodes

were conditioned by soaking in 1×10^{-4} M CET solution for one day and were stored dry when not in use.

2.4.3. Sensors calibration

The conditioned sensors were calibrated by separately transferring 20 mL of 1×10^{-3} M CET solution in 50 mL beakers. Different concentrations of CET were determined by a stepwise dilution of 1×10^{-3} M solution with deionized water and continuous EMF measurements instead of serial dilutions in order to minimize the variations due to experimental conditions. The electrode system was immersed in each solution in conjunction with an Ag/AgCl reference electrode. The emf within ±1 mV readings were recorded after equilibrate while stirring. Linear correlation was obtained in the range of 7.81×10^{-6} M to 1×10^{-3} M (for sensor 1, 2 & 5) and 3.13×10^{-5} M to 1×10^{-3} M (for sensor 3 & 4). The membrane sensors were stored in deionized bidistilled water. The electrode potential was plotted versus negative logarithmic concentration of drug. The obtained calibration plot was used for subsequent measurements of unknown concentration of CET samples.

2.4.4. Effect of pH

The effect of pH on the response of the investigated electrodes was studied using 1×10^{-4} M solutions of CET with pH ranging from 1 to 10. The pH was adjusted with 2 M hydrochloric acid and sodium hydroxide solutions.

2.4.5. Determination of Cetrimide in its pharmaceutical mouthwash

A volume of 3.36 mL of Citroline mouth wash was accurately transferred to a 25 mL volumetric flask, in order to prepare 10^{-4} M CET. The volume was completed to the mark with distilled water. The potentiometric measurements were performed using the proposed sensors in conjunction with the Ag/AgCl reference electrode, and the potential readings were compared to that of the same concentration of standard CET or from the corresponding regression equation.

3. RESULTS AND DISCUSSION

Selective membranes in ion selective electrodes have shown both ion exchange and perm-selectivity for the sensor ion. In this study, five ion selective membrane sensors were proposed for determination of CET either in its pure powder form or in its pharmaceutical dosage form.

3.1. Membrane compositions

Preparation of the proposed sensors originates from the fact that CET behaves as a cation, due to the presence of tertiary amine functional group. This fact suggests the use of cationic exchangers. The type of the ion exchanger affects the response of the sensor, therefore, different cationic exchangers were used in order to study there effect on the drug sensors. Four cationic exchangers, namely PVC-COOH, TpClPB, PT and TPB were used for the preparation of the membrane sensors as they form insoluble ion association complexes with suitable grain size with CET. The ratio of CET to the ion exchangers in the formed complexes was found to be 1:1 as proven by the obtained Nernstian slopes (about 60 mV/decade) so CET acts as amino ionic species. The cationic exchangers were incorporated with a suitable solvent mediator in polyvinylchloride matrix to produce plastic membranes which were used for constructing the electrodes. The complexes were formed in situ by soaking the prepared membranes in 1×10^{-4} M CET solution, while the reported sensors were prepared by ion pair association complex technique then incorporated it in PVC membrane [9]. The latter were used to analyze CET in single pharmaceutical dosage form not in combination with other drugs as this study.

Table 1. Effect of different cationic exchangers and plasticizers on the slope and concentration range of CET

Cationic exchanger	**Sensor**	**Plasticizer**	**Slope (mV/ concentration decade)**	**Concentration range (M)**
PVC-COOH	Sensor **1**	NOPE	56.485±0.83	7.81×10^{-6} M – 1×10^{-3} M
TpCIPB	Sensor **2**	NOPE	48.008±2.00	7.81×10^{-6} M – 1×10^{-3} M
PT **PT**	Sensor **3**	NOPE DOP	47.328±2.00 45.757±1.36	3.13×10^{-5} M – 1×10^{-3} M 3.13×10^{-5} M – 1×10^{-3} M
TPB	Sensor **4**	NOPE	43.954±2.00	3.13×10^{-5}M – 1×10^{-3} M
PVC-COOH/ TpCIPB	Sensor **5**	NOPE	60.036±1.02	7.81×10^{-6} M – 1×10^{-3} M

The CET extraction into the membrane sensors was a result of the formed ion-pair tendency to exchange with CET cation. The results of using different ion exchangers where represented by the slopes obtained for all studied sensors, as shown in Table 1. The PVC acts as a regular support matrix for the membrane but its use creates a need for a plasticizer [15]. The plasticizer is the second factor that allows CET ions to be extracted from an aqueous solution into the membrane, as an organic phase. Two plasticizers were applied, namely nitrophenyl phenyl ether (NPOE) and dioctylphthalate (DOP), (as examples for plasticizers from diesters of dicarboxylic acids and nitroaromatic compounds respectively). After evaluation of the effect of the two plasticizers which were used in sensor 3, better results were obtained using NOPE represented in significant change in the slopes as shown in Table 1. Therefore, NOPE was found to be the optimum available plasticizer and applied for all other PVC membrane sensors in the present investigation. It plasticizes the membrane, dissolves the ion-association complexes and adjusts both of the membrane permittivity and ion-exchanger sites mobility to give highest possible selectivity and sensitivity [16].

3.2. Response characteristics and validation parameters of sensors

Electrochemical performance characteristics of the proposed sensors were systematically evaluated according to IUPAC recommendations [17].

The response time of the electrodes was tested for concentrations of the drug from 7.81×10^{-6} M to 1×10^{-3} M (for sensor 1, 2 & 5) and 3.13×10^{-5} M to 1×10^{-3} M (for sensor 3 & 4). The concentration range for all suggested sensors was developed after series of experiments and trails starting from 1×10^{-1} M. Linearity for all CET sensors was only achieved of concentration of 1×10^{-3} M. The measurements were characterized by a fast stable response within 10-30 s. The optimum equilibration time for the electrodes was 12 h, after soaking in 1×10^{-4} M CET. After this time period, the electrodes generated stable potentials in contact with the CET solution. On soaking for a longer time the slopes decreased gradually and this may be attributed to the gradual leaching of the electroactive species into the bathing solution [18]. Therefore, when not in use for a long time, the electrodes should be kept dry.

Table 2 shows the slopes of lines, response times and intervals of linearity over a period of 6 weeks for 3 different assemblies of each sensor at optimal pH and temperature at 25±1 °C. The suggested electrodes displayed constant potential readings for day to day measurements, and the calibration slopes did not change by more than ±2 mV/decade over a period of 6 weeks. The calibration plots were presented in Figure 2. The deviation of the slopes of the suggested sensors from the ideal Nernstian slope (60mV/ decade), is due to the fact that the electrodes respond to activities of the drug rather than the concentration. The detection limits of the sensors were estimated according to the IUPAC guidelines [17].

Table 2. Validation of the response characteristics of the investigated electrodes

Parameters	**Sensor 1 CET-PVC-COOH**	**Sensor 2 CET-TpCIPB**	**Sensor 3 CET-PT**	**Sensor 4 CET-TPB**	**Sensor 5 CET-PVC-COOH/ TpCIPB**
Slope (mV/decade)[a]	56.49±0.83	48.01±2.0	47.33±2.0	43.95±2.0	60.036±1.02
Intercept (mV)[a]	630.48±1.78	437.64±0.74	456.46±14.0	447.76±11.85	1029.9±4.10
Correlation coefficient (r^2)	0.9991	0.9901	0.9965	0.9904	0.9992
Concentration Range (M)	7.81×10^{-6}-1×10^{-3}	7.81×10^{-6} -1×10^{-3}	3.13×10^{-5}-1×10^{-3}	3.13×10^{-5}-1×10^{-3}	7.81×10^{-6}-1×10^{-3}
Response time (s)	10	10	24	27	15
Working pH range	1-10	1-10	5-7	5-7	1-10
Stability (weeks)	6	6	6	6	6
Average recovery [b] (%± SD)	99.47±1.07	100.80±0.79	100.41±1.31	99.89±1.55	100.42±1.64
Precision [c] (%Relative Standard deviation) Repeatability	1.08	0.78	1.30	1.55	1.63
Reproducibility	1.45	0.64	1.12	0.82	0.95
Ruggedness[d]	0.86	0.55	0.38	1.90	0.31

a. Results of three determinations
b. Average recovery % of three concentration levels, each repeated three times
c. Three concentration levels each repeated three times
d. Relative standard deviation % of the potential produced by 10^{-4} M solution using Jenway 3505 digital ion analyzer instead of 3510

Long term potential stability of the proposed sensors was fairly good as it was practically unchanged over a period of 4-6 weeks. The potentiometric response of the five studied electrodes was linear with constant slopes over a drug concentration range 7.81×10^{-6} M to 1×10^{-3} M for sensor (1,2&5) and 3.13×10^{-5} M to 1×10^{-3} M for sensor (3&4). To evaluate the accuracy and precision of the electrodes measurements, three concentrations within the linear concentration range of CET were chosen. Three solutions of each concentration were prepared and analyzed in triplicate (repeatability assay). This assay was repeated on three different days (reproducibility assay), as shown in Table 2.

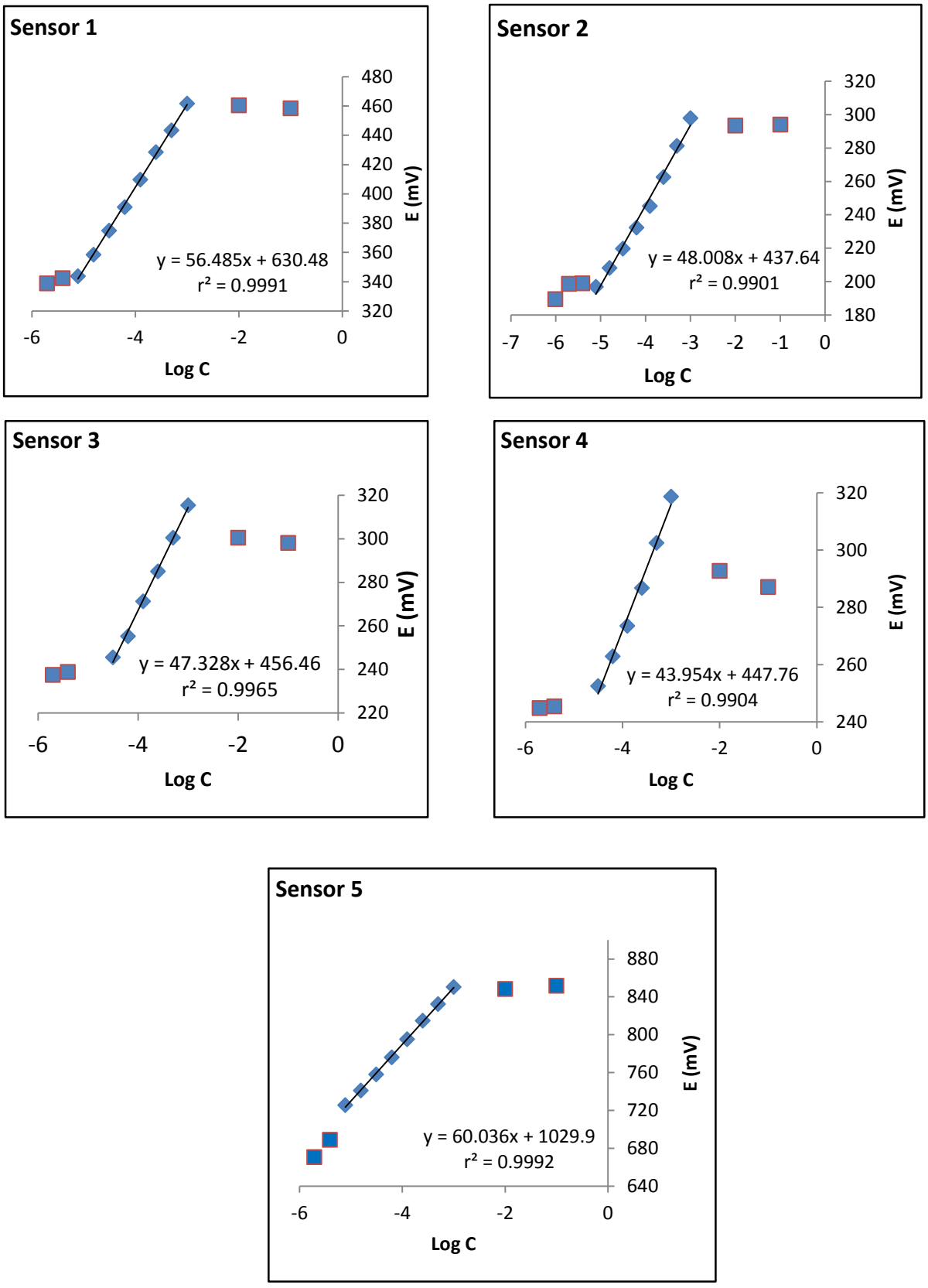
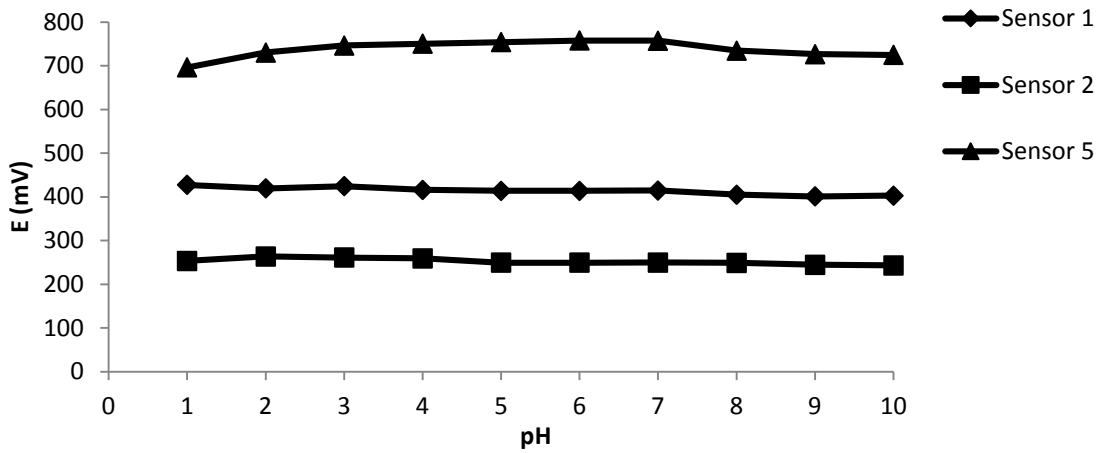
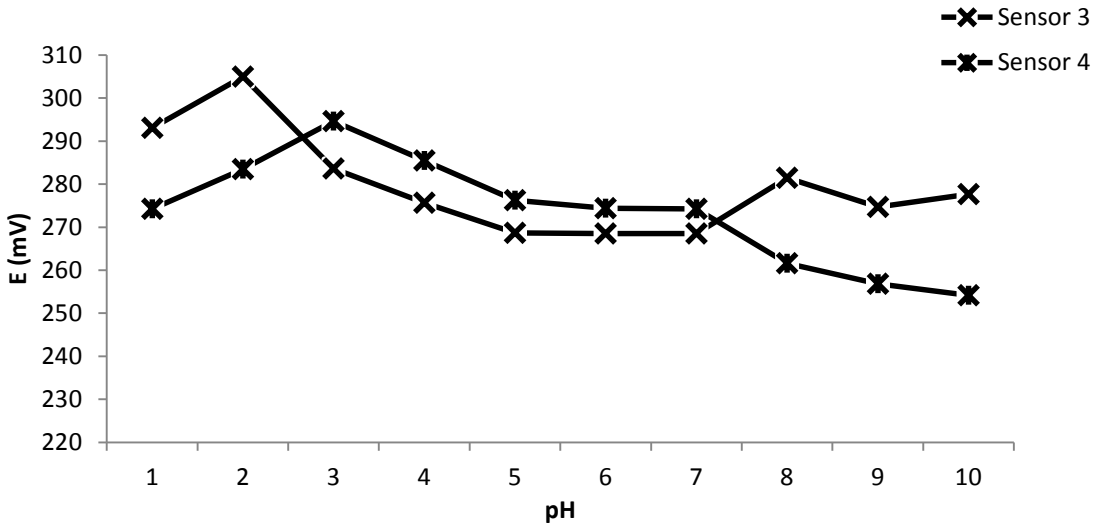


Fig. 2. Potentiometric profiles of the suggested sensors

According to the obtained results, the Calibration graph slope for sensor 5 was 60.036 mV per decade of the cetrimide concentration and a standard deviation of ±1.02 mV after three replicate measurements. In order to that sensor 5 showed to be the best suggested sensor for CET determination in comparison to other suggested sensors and reported ones [9]. The reason for that is the utility of PVC-COOH and TpCIPB in combination in sensor 5, which had a significant influence on increasing both the membrane selectivity and sensitivity comparing to other suggested and reported sensors.



(a)



(b)

Fig. 3. (a) Effect of pH on the response of sensors 1,2&5 in 10^{-4} M Cetrimide. **(b)** Effect of pH on the response of sensor 3&4 in 10^{-4} M Cetrimide

3.3. PH effect on the electrodes responses

The potentiometric response of the suggested electrodes was found sensitive to pH changes. Figure 3 shows a typical pH response curve for the prepared electrodes, over a pH

range of 1–10, where the pH was adjusted with hydrochloric acid and sodium hydroxide solutions. The electrode response was hardly affected by the pH change from 1 up to 10 for sensors 1, 2 & 5 and from 5 up to 7 for sensors 3 & 4.

In this pH range CET is completely ionized, dissociated and sensed and this allowed working in water without using a buffer solution. From the obtained results, sensors 1, 2 & 5 showed that the potential approximately remained constant despite the pH change in the whole range of 1-10, which indicates the applicability of these sensors in this wide pH range. On the other hand for sensors 3 & 4, the potential remained constant only in pH range 5-7.

Below pH 1 (for sensors 1, 2 & 5) and 5 (for sensors 3 & 4), the electrodes response increased with the increase in solution acidity as the membrane may extract H^+ leading to a noisy response[19]. The decrease in potential at pH>7 (for sensors 3&4) was due to the gradual decrease in the concentration of the CET mono cation due to the formation of the non-protonated amino group.

3.4. Sensors selectivity

The selectivity of an ion-pair based membrane electrode depends on the physico-chemical characteristics of the ion-exchange process at the membrane. For example, sample solution interface, mobility of the respective ions in the membrane and on the hydrophobic interactions between the primary ion and the organic membrane [20]. Table 3 shows the potentiometric selectivity coefficients of the proposed sensors in the presence of a number of pharmaceutical active ingredients commonly used in mouthwashes and other drugs prescribed for the dental care, in order to study their effect on the assay method. The selectivity coefficients were determined by the separate solution method and calculated from the rearranged Nicolsky-Eisenman equation [17]:

$$-LogK_{AB}^{Pot} = \frac{E_1 - E_2}{2.303RT/ZAF}K + \frac{1 - Z_A}{Z_B}Loga_A$$

Where $K_{A.B}$ is the potentiometric selectivity coefficient, E_1 is the potential measured in 1×10^{-4} M CET solution, E_2 is the potential measured in 1×10^{-4} M interferent solution, 2.303RT/ZAF represents the slope of the investigated sensors, a_A is the activity of CET and Z_A and Z_B are charges on CET and interfering ion, respectively. As it was obvious from Table 3, none of the tested interfering species had a significant influence on the potentiometric responses of the electrodes towards CET.

Table3. Potentiometric selectivity coefficients (K pot CET) of CET for the proposed sensors by separate solution method

Interference 10^{-4}M	**Selectivity coefficient***				
	Sensor 1	**Sensor 2**	**Sensor 3**	**Sensor 4**	**Sensor 5**
$CaCl_2$	9.59×10^{-3}	1.59×10^{-3}	3.59×10^{-2}	2.62×10^{-2}	2.03×10^{-4}
Starch	3.39×10^{-3}	1.76×10^{-3}	1.65×10^{-2}	8.24×10^{-3}	8.41×10^{-3}
NaCl	4.70×10^{-3}	1.53×10^{-3}	1.87×10^{-2}	4.05×10^{-2}	1.95×10^{-4}
Glucose	3.71×10^{-3}	2.64×10^{-3}	1.64×10^{-2}	2.42×10^{-2}	1.12×10^{-3}
Lactose	2.61×10^{-3}	3.23×10^{-3}	1.17×10^{-2}	1.12×10^{-2}	1.73×10^{-3}
KCl	3.08×10^{-3}	1.43×10^{-3}	7.69×10^{-3}	1.21×10^{-2}	2.77×10^{-4}
Urea	2.80×10^{-3}	1.12×10^{-3}	1.04×10^{-2}	9.85×10^{-3}	1.90×10^{-4}
Lidocaine HCl	6.20×10^{-3}	3.74×10^{-2}	1.59×10^{-2}	1.33×10^{-2}	6.75×10^{-5}
Chlorohexidine	7.69×10^{-3}	1.19×10^{-2}	6.92×10^{-2}	1.57×10^{-1}	1.19×10^{-4}
NaF	3.98×10^{-3}	3.00×10^{-2}	1.87×10^{-2}	1.13×10^{-2}	2.96×10^{-6}

*Average of three determinations.

Table 4. Determination of CET in Citroline-F® mouthwash by the five proposed sensors and application of standard addition technique

Pharmaceutical formulation. Citroline-F® mouthwash (Batch No. 267)	**Sensor 1**	**Sensor 2**	**Sensor 3**	**Sensor 4**	**Sensor 5**
Recovery% (±SD)*	99.40±0.05	99.17±0.14	100.00±0.07	99.61±0.10	100.21± 0.79
Recovery of standard added %*	100.18±0.64	99.05±1.01	98.35±1.46	97.40±1.73	99.59±0.58

*Average of three determinations

The new proposed sensors were successfully applied for CET determination in its colored mouthwash without prior extraction, as none of the pharmaceutical active ingredients present in combination with CET show significant interference with the determination of CET, as shown in Table 4. Results obtained prove the applicability of the method as demonstrated by

the accurate and precise recovery percentages. The validity of the suggested methods was further assessed by applying the standard addition technique. Standard addition depends on spiking known concentration of the dosage form by known concentration of the pure standard drug substance.

According to the results described before, the utility of PVC-COOH as polymer(sensor 1) and TpCIPB (sensor 2) as cationic exchanger gives better results than PVC and other cationic exchangers (sensor 3 & 4), therefore best results obtained when they used in combination in sensor 5. They have a significant influence on increasing both membrane sensitivity and selectivity of sensor 5. Sensor 5 showed the best Nernstian slope, while sensor2, 3 & 5 had the best sensitivity. Electrode 1, 2 & 5 were faster than electrode 3 and 4, thus the response time was more or less instantaneous (up to 30 sec for electrode 4), while those of (1, 2) and 5, were 10 and 15 seconds, respectively. Described sensors 3 and 4 differed from the reported ones [9], that the sensors were prepared in situ and were able to determine CET in presence of different active ingredients combined with it in pharmaceutical dosage form.

4. CONCLUSION

The described sensors are sufficiently simple and selective for the quantitative determination of CET in pure form and in its combined pharmaceutical mouthwash. The best PVC membrane electrode performance was achieved by a membrane composition of PVC-COOH as polymer in sensor 1 and 5.The utility of PVC-COOH and TpCIPB in combination in sensor 5 has a significant influence on increasing both the membrane selectivity and sensitivity in comparison with other suggested sensors and even reported ones [9]. Therefore, sensor 5 was the best suggested sensor for CET determination according to the obtained results. Sensor 5 showed better and more stable responses for determination of CET in its combined pharmaceutical mouthwash in comparison to the reported sensors, which only determined CET in its single dosage form [9]. The described sensors also showed evidence of the ability of the Ion selective electrode technique to work in presence of different interference in CET mouthwashes not only single ones. The use of the proposed sensors offers advantages over other reported techniques of providing fast response, elimination of drug pretreatment and separation steps, lacking of expensive and sophisticated apparatus furthermore there is no need of expensive and special grade solvents. They can therefore, be used for routine analysis of CET in quality control laboratories.

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