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Green Potentiometric Method for Determination of Triprolidine Hydrochloride and Pseudoephedrine Hydrochloride in their Different Pharmaceutical Matrices using Liquid and Solid Contact Gold Electrodes

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Abstract- Factors affecting the performance of polyvinyl chloride based ion selective electrode such as using different cationic exchangers and ionophores as well as sensor fabrication procedures were recently the scope of study by several researchers. This work presents an environment friendly electro-analytical method for the determination of Triprolidine HCl (TRI) and Pseudoephedrine HCl (PSE). A comparative study was held between five suggested sensors for each drug to reach optimum response. They were developed using several exchangers as tetraphenylborate (TPB), phosphotungestate (PT) and tetrakis with different ionophores as β-cyclodextrin (β-CD) and calixarene using nitrophenyl octyl ether (NPOE) as a plasticizer. Also different strategies were applied for their membrane fabrication. Conventional sensors (3a and 3b) and solid contact gold sensors (a and b) showed the best sensitivity as well as the fastest response for determination of TRI and PSE, respectively .The two conventional sensors were composed of (PVC/TPB/β-CD/NPOE) and (PVC/PT/calixarene/NPOE) in addition to the solid contact gold sensors were composed of (TPB/β-CD/NPOE) and (PT/calixarene/NPOE). Moreover those sensors succeeded to determine TRI and PSE in their different pharmaceutical formulations. Method validation was assessed according to IUPAC recommendations. The method is considered to be a green eco-friendly technique that neither requires sample pre-treatment nor derivatization.

Keywords- Triprolidine HCl; Pseudoephedrine HCl; Ion selective electrode; Solid contact gold electrode; Ionophore

1. INTRODUCTION

Triprolidine Hydrochloride (TRI) is an alkylamine derivative, which is chemically known as (E)-2-[3-(1-Pyrrolidinyl)-1-*p*-tolylpropenyl] pyridine hydrochloride, *trans*-2-[3-(1-Pyrrolidinyl)-1-*p*-tolylpropenyl] pyridine hydrochloride [1] (Figure 1A). It has antihistaminic with antimuscarinic and mild sedative effect. It is used for the symptomatic relief of allergic conditions including urticaria, rhinitis and pruritic skin disorders. Its combination with PSE is often used for the treatment of rhinitis and common cold [2].

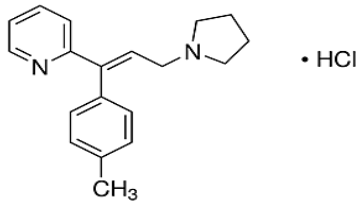
Pseudoephedrine Hydrochloride (PSE) is chemically known as Benzenemethanol, [1-(methylamino) ethyl]-, [S-(R,R)]-, hydrochloride [1] (Figure 1B). It is a direct and indirect acting sympathomimetic and a stereoisomer of ephedrine with similar action and less CNS effects. It acts as an effective upper respiratory decongestant and it is commonly combined with other active ingredients in preparations intended for the relief of cough and cold symptoms [2].

Several analytical techniques have been reported for quantitative determination of TRI and PSE, including different HPLC methods to analyze TRI and PSE either alone or in combination with other drugs in their pharmaceutical dosage forms [3-10]. The two compounds were determined using capillary electrophoresis technique in presence of paracetamol [11]. TRI and PSE were simultaneously analyzed by using spectrophotometric technique [12-15]. Also ion selective electrodes for TRI [16, 17] and PSE [18, 19] have been constructed for their separate determination.

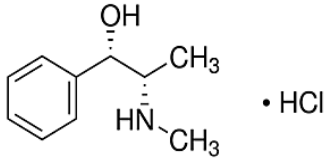
Nowadays, electrochemical techniques are considered one of the greenest methodologies that applied in the pharmaceutical research field, as either hazardous reagents or organic solvents will not be required. Ion selective electrodes (ISEs) based on material transport across a specific membrane are now 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 [20, 21]. 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 [22]. Various reports have been published which highlight the important contribution of ion selective sensors for quantification of drugs [23, 24].

The main aim of this work was to evaluate the influence of several factors including different cationic exchangers and ionophores on the performance of polyvinyl chloride (PVC) based membrane sensors. Also to assess the competitive performance of conventional and solid contact fabrication techniques. These factors have not yet been investigated in any previous work concerning potentiometric determination of TRI and PSE. In addition to developing economic, green and inline ion selective electrodes, they can be applied for routine quality control assessments of TRI and PSE different pharmaceutical matrices without any sample extraction, pre-treatment or derivatization steps and without the need of

sample withdrawal at time intervals.



(A)



(B)

Figure 1. (A): Chemical structure of TRI; (B): Chemical structure of PSE

2. EXPERIMENTAL

2.1. Instrument

A Jenway digital ion analyzer model 3330 (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. The determination of the samples was occurred using Magnetic stirrer, Bandelin Sonorox, Rx510S (Budapest, Hungaria).

2.2. Materials and reagents

2.2.1. Pure standard

Triprolidine HCl and Pseudoephedrine HCl working standards were kindly supplied by GlaxoSmithKline Beecham Cairo, Egypt. Their purity was certified and assessed to be 100.00% according to their official pharmacopeial method [1].

2.2.2. Pharmaceutical formulations

- Actifed® tablet manufactured by GlaxoSmithKline Beecham Cairo, Egypt (Batch No. A522124) each tablet is labeled to contain 2.5 mg TRI and 60 mg PSE.
- Actifed® syrup manufactured by GlaxoSmithKline Beecham Cairo, Egypt (Batch No. A522919) each 5 mL is labeled to contain 1.25 mg TRI and 30 mg PSE.
- Actifed® expectorant manufactured by GlaxoSmithKline Beecham Cairo, Egypt (Batch No. A519333) each 5 mL is labeled to contain 1.25 mg TRI, 30 mg PSE and 100 mg Guaifenesin.
- All the pharmaceutical formulations were purchased from the local market.

2.2.3. Chemicals and reagents

All chemicals and solvents used throughout this work were of pure analytical grade and

water used was bi-distilled. Sodium phosphotungestate tribasic hydrate (Na-PT), potassium tetrakis (4-chlorophenyl) borate (TpClPB), beta-cyclodextrin (β-CD) and calix[8]arene were purchased from Sigma-Aldrich (Germany). Nitrophenyl octyl ether (NPOE) and gold wire of purity 99.99% with 2.00 mm diameter and 10 mm length were obtained from Sigma (St. Louis, USA). Sodium tetraphenylborate (Na-TPB), tetrahydrofuran (THF) and polyvinyl chloride (PVC) of high molecular weight were purchased from BDH (Poole, England). Sodium hydroxide (NaOH), hydrochloric acid (HCl) (37.00% w/v) and potassium chloride (KCl) were prepared and obtained from Prolabo (Pennsylvanina, USA).

2.3. Standard stock solutions (1×10^{-2} M)

They were prepared by accurately transferring 0.31 g of TRI and 0.20 g of PSE into separate 100 mL volumetric flasks, then dissolving the compounds in 90 mL bi-distilled water and completing to volume with the same solvent.

2.4. Procedures

2.4.1. Membrane sensors construction

In separate petri dishes, 10.00 mg of ion exchangers Na-TPB (for sensor 1a, 3a, &1b), Na-PT (for sensor 2a, 4a, 2b & 3b) and K-TpClPB (for sensor 4b) were thoroughly mixed with 0.19 g PVC and 0.35 mL NPOE in a 5 cm glass petri dish. β-CD (10.00 mg) was added to sensors 3a, 4a, 1b and 2b, while calixarene (10.00 mg) was added to sensors 3b and 4b. 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 0.10 mm were obtained and used for the construction of the conventional electrodes.

Solid contact sensors (a & b) were prepared by mixing 0.19 g PVC, 0.35 mL NPOE and 10.00 mg Na-TPB and β-CD (for solid contact sensor a) and 10.00 mg Na-PT and calixarene (for solid contact sensor b). All membrane components were then dissolved in 5 mL THF, then two gold wires solid contact were coated with the prepared paste while manually rotated and left to dry till acquiring uniform layer of the sensing membrane.

2.4.2. Preparation of the electrodes assemblies

For conventional electrodes, a disk (≈ 5 mm diameter) was cut from the prepared master membranes 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 1×10^{-3} M drug (TRI or PSE) and 1×10^{-3} M KCl was mixed and this equimolar mixture 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.

For solid contact electrodes, the gold wire was firmly inserted into rubber support held in polyethylene body; the exposed surface of the wire (0.5 cm) was coated with sensing paste while the other side was connected to copper wire for potentiometric measurements. The electrodes were conditioned by soaking in 1×10^{-3} M drug solution (TRI or PSE) for one day and were stored dry when not in use.

2.4.3. Sensors calibration

The conditioned sensors were calibrated by transferring 25 mL of 1×10^{-2} M Tri and PSE solutions into 50 mL beakers, separately. Different concentrations of Tri and PSE were determined by a stepwise dilution of 1×10^{-2} M solutions with deionized water and continuous electromotive force (EMF) measurements. The electrode system was immersed in Tri and PSE standard solutions in conjunction with an Ag/AgCl reference electrode. The emf readings of equilibrium state were recorded within ±1mV. The membrane sensors were stored in deionized bi-distilled water. The electrode potential was plotted versus logarithmic concentration of each drug. The obtained calibration plots were used for subsequent measurements of unknown concentration of Tri and PSE samples using the corresponding electrode.

2.4.4. Effect of pH

The effect of pH on the response of the proposed electrodes was investigated using 1×10^{-4} M solutions of TRI and PSE with pH ranging from 1 to 12. The pH was adjusted using 2 M hydrochloric acid and 2 M sodium hydroxide solutions.

2.4.5. Sensors selectivity

The potentiometric selectivity coefficients (K_{AB}^{Pot}) of the proposed sensors towards different substances were evaluated according to IUPAC guidelines using separate solution method [25].

2.4.6. Determination of TRI and PSE in different pharmaceutical matrices

Accurate portions equivalent to 1.57 mg TRI and 1.01 mg PSE of Actifed® different pharmaceutical formulations were accurately transferred into separate 50 mL volumetric flasks to prepare 1×10^{-4} M TRI and PSE. The volume was completed to the mark with bi-distilled water.

Five tablets of Actifed® tablet were weighed and finely powdered in a small dish, then accurately weighed portions of the powder (140 mg and 3.72 mg) were transferred into separate 50 mL volumetric flasks for determination of TRI and PSE, respectively.

Accurate volumes of 6.30 mL and 0.17 mL of Actifed® syrup and expectorant were accurately transferred into separate 50 mL volumetric flasks for determination of TRI and PSE, respectively.

The potentiometric measurements were performed using 3a, 3b and solid contact sensors in conjunction with the Ag/AgCl reference electrode and the recovery % was obtained either by comparing the potential readings with those of the same concentrations of standard TRI and PSE or from the corresponding regression equations. Standard addition technique has been carried out to assess the validity of the developed method.

3. RESULTS AND DISCUSSION

The suggested ion selective electrodes for determination of TRI and PSE offer many advantages over other reported electrochemical methods, including better sensitivity and higher concentration range [16-19]. The developed electrodes were established using several numbers of cationic exchangers, ionophores and different strategies for membrane fabrication. In this study, four conventional ion selective electrodes were studied for determination of TRI and PSE either in its pure powder form or in its different pharmaceutical matrices. According to the obtained slopes and concentration ranges, the best membrane composition was applied for the construction of the solid contact gold sensors for both drugs.

3.1. Membrane compositions

Fabrication of sensors for basic drugs is relied on the formation of ion association complexes of these species with the cationic exchanger compounds. Construction of the proposed sensors originates from the fact that TRI and PSE behave as cations, due to the presence of basic amino functional group (Figure 1A & 1B). For this reason, cationic exchangers have been used for membrane preparation. The type of the ion exchanger affects the response of the sensor [26], therefore, different cationic exchangers were investigated to choose the best one in terms of sensitivity and selectivity. Cationic exchangers as sodium tetraphenylborate (TPB), sodium phosphotungstate (PT) and potassium tetrakis (TpClPB) were used for the preparation of the membrane sensors and the results were represented by the slopes obtained for all studied sensors, as shown in Table 1. The ratio of TRI and PSE 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 TRI and PSE act as monoionic species. The cationic exchangers were incorporated with a suitable solvent mediator in PVC matrix to produce plasticized membranes which were used for the construction of the electrodes. The ion complexes were formed in situ by soaking the prepared membranes in 1×10^{-3} M TRI and PSE solutions. The extraction of TRI and PSE into the membrane sensor is a result of the ion-pair tendency to exchange with the two drugs cations. In situ formation of the complex makes

the preparation of the proposed sensors simpler, economic and less time consuming than the previously reported sensors, which were prepared by ion pair association complex technique then incorporated it in PVC membrane [16-19].

Table 1. Different cationic exchangers and ionophores effect on the slope and concentration range of TRI and PSE

Drug	Sensor	Cationic exchanger	Ionophore	Plasticizer	Slope (mV/concentration decade)	Concentration range (M)
(a) TRI	**1a**	Na-TPB	-	NPOE	41.88	6.10×10^{-7} -1×10^{-2} M
	2a	Na-PT	-	NPOE	49.44	3.91×10^{-5}-1×10^{-2} M
	3a	Na-TPB	β-CD	NPOE	58.53	9.77×10^{-6} -1×10^{-2} M
	4a	Na-PT	β-CD	NPOE	54.33	9.77×10^{-6} -1×10^{-2} M
	Solid contact a	Na-TPB	β-CD	NPOE	54.71	4.88×10^{-6} -1×10^{-2} M
(b) PSE	**1b**	Na-TPB	β-CD	NPOE	35.91	7.81×10^{-5}-1×10^{-2} M
	2b	Na-PT	β-CD	NPOE	50.54	1.56×10^{-4} - 1×10^{-2} M
	3b	Na-PT	Calixarene	NPOE	54.93	9.77×10^{-6} -1×10^{-2} M
	4b	K-TpCIPB	Calixarene	NPOE	50.01	1.95×10^{-5}-1×10^{-2} M
	Solid contact b	Na-PT	Calixarene	NPOE	57.19	4.88×10^{-6} -1×10^{-2} M

The PVC is a regular support matrix for the membrane preparation and while using it a plasticizer is needed [27]. The plasticizer represents the second factor that allows TRI and PSE ions to be extracted from an aqueous solution into the membrane, as an organic phase. NPOE was the solvent mediator of choice for TRI and PSE. It plasticizes the membrane and adjusts both the membrane permittivity and ion-exchanger sites mobility to give highest possible selectivity and sensitivity [28].

Cyclodextrins are known to accommodate a wide variety of guest molecules to form stable host–guest inclusion complexes; they are viewed as molecular receptors [29]. Calixarenes are cavity-shaped cyclic oligomers that act as selective ligands for various ions through dipole–dipole interactions, which lead to the formation of typical host–guest complexes with numerous compounds [30]. For these characteristics, cyclodextrins and calixarenes were used as ionophores to enhance the interaction properties between host and guest molecules also they were applied for preparing electrochemical sensors for many organic pharmaceutical cations. According to the obtained results, the membrane selectivity and sensitivity are improved by the addition of an ionophore to the membrane composition. Incorporation of β-CD and calixarene in the construction of sensors 3a, 3b and the two solid contact sensors increases the sensors Nernstian slope and drug concentration rang (Table 1).

3.2. Response characteristics and validation parameters of sensors

The electrochemical performance characteristics of the designed sensors were evaluated according to IUPAC guidelines [25]. The response time of all electrodes was tested for various concentration ranges of the intended drugs, as presented in Table 2.

Table 2. Validation parameters of the proposed sensors for TRI and PSE

Drug	Parameters	Sensor 1a	Sensor 2a	Sensor 3a	Sensor 4a	Solid contact sensor a
TRI	**Slope (mV/decade)[a]**	41.88	49.44	58.53	54.33	54.71
	Intercept (mV)[a]	362.81	253.53	305.33	324.7	300.99
	Correlation coefficient (r)	0.9906	0.994	0.9967	0.9977	0.9983
	Concentration Range (M)	6.10×10^{-7}-1×10^{-2}	3.91×10^{-5}-1×10^{-2}	9.77×10^{-6}-1×10^{-2}	9.77×10^{-6}-1×10^{-2}	4.88×10^{-6}-1×10^{-2}
	Response time (s)	25	25	15	25	10
	Working pH range	5-7	6-7	6-8	4-7	6-8
	Stability (weeks)	6-8	6-8	6-8	6-8	6-8
	Accuracy [b] (% ± SD)	99.74 ± 1.34	99.96 ± 0.91	100.12 ± 1.45	99.73 ± 0.98	99.73 ± 1.06
	Precision [c] (%RSD) Repeatability	1.35	0.91	1.45	0.98	1.06
	Reproducibility	1.79	1.99	1.66	1.43	1.27
	Ruggedness [d]	1.04	1.36	0.81	1.10	0.98
PSE	**Parameters**	**Sensor 1b**	**Sensor 2b**	**Sensor 3b**	**Sensor 4b**	**Solid contact sensor b**
	Slope (mV/decade)[a]	35.91	50.54	54.93	50.01	57.19
	Intercept (mV)[a]	187.65	123.42	675.37	207.57	751.58
	Correlation coefficient (r)	0.989	0.9766	0.9991	0.9936	0.9953
	Concentration Range (M)	7.81×10^{-5}-1×10^{-2}	1.56×10^{-4}-1×10^{-2}	9.77×10^{-6}-1×10^{-2}	1.95×10^{-5}-1×10^{-2}	4.88×10^{-6}-1×10^{-2}
	Response time (s)	25	25	25	25	10
	Working pH range	5-7	5-7	6-7	5-7	4-7
	Stability (weeks)	6-8	6-8	6-8	6-8	6-8
	Accuracy [b] (% ± SD)	100.89 ± 0.98	100.08 ± 0.73	100.58 ± 1.01	100.42 ± 1.15	100.43 ± 1.06
	Precision [c] (%RSD) Repeatability	1.88	0.73	1.00	1.15	1.06
	Reproducibility	1.75	1.68	1.26	1.80	0.88
	Ruggedness [d]	1.84	1.36	1.01	1.75	0.62

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 1×10^{-4} M solutions for all sensors and 1×10^{-3} M for sensor 2b, using Jenway 3505 digital ion analyzer instead of 3510 in another laboratory.

High sensitivity was obtained using sensor 3a, 3b, solid contact sensor a and b, where linear correlation was obtained in the range of 9.77×10^{-6} M to 1×10^{-2} M (for sensors 3a and 3b) and 4.88×10^{-6} M to 1×10^{-2} M (for solid contact sensor a and b) A fast stable response within 10-25 seconds was observed during the measurements. The optimum equilibration time for the electrodes after soaking in 1×10^{-3} M TRI and PSE was 12 hours. After this time period, the electrodes generate stable potentials in contact with the TRI and PSE solutions. The slopes decrease gradually while soaking for a longer time due to the gradual leaching of the electroactive species into the bathing solution [31]. Therefore, the electrodes should be kept dry when not in use for a long time.

In order to measure the accuracy and precision of the electrodes, three concentrations within the linear concentration range of TRI and PSE 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.

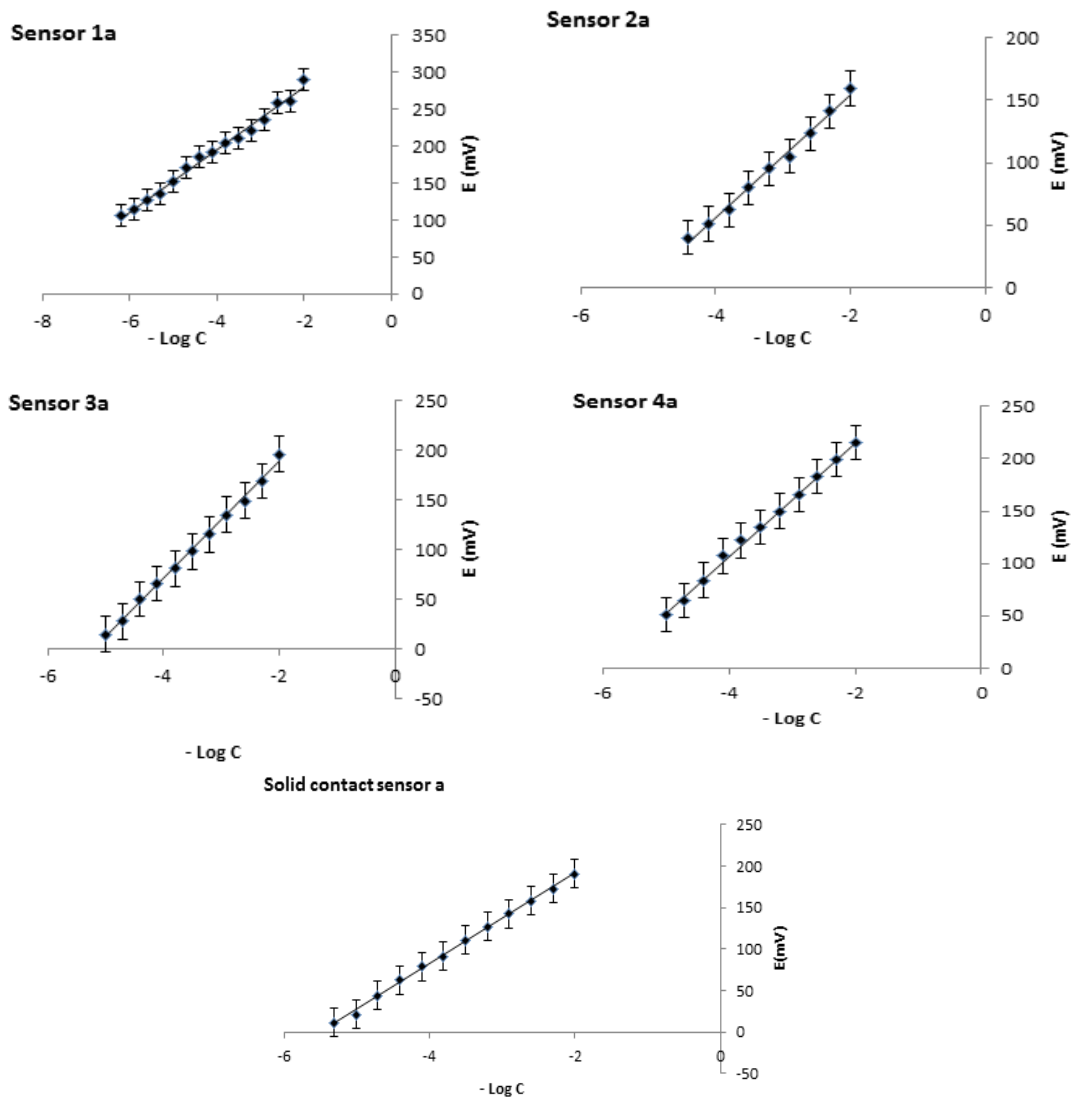


Figure 2. Potentiometric profiles of the suggested sensors for TRI

The slopes, linear ranges and validation parameters for the TRI and PSE ion-selective electrodes were displayed in Table 2. Also it represents the response times and intervals of linearity over a period of two months for 3 different assemblies of each sensor at optimal pH and temperature at 25±1°C. The calibration plots for TRI and PSE were presented in Figure (2) and Figure (3), respectively. The deviation of the slopes of the proposed sensors from the ideal Nernstian slope (60 mV/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 definition [25].

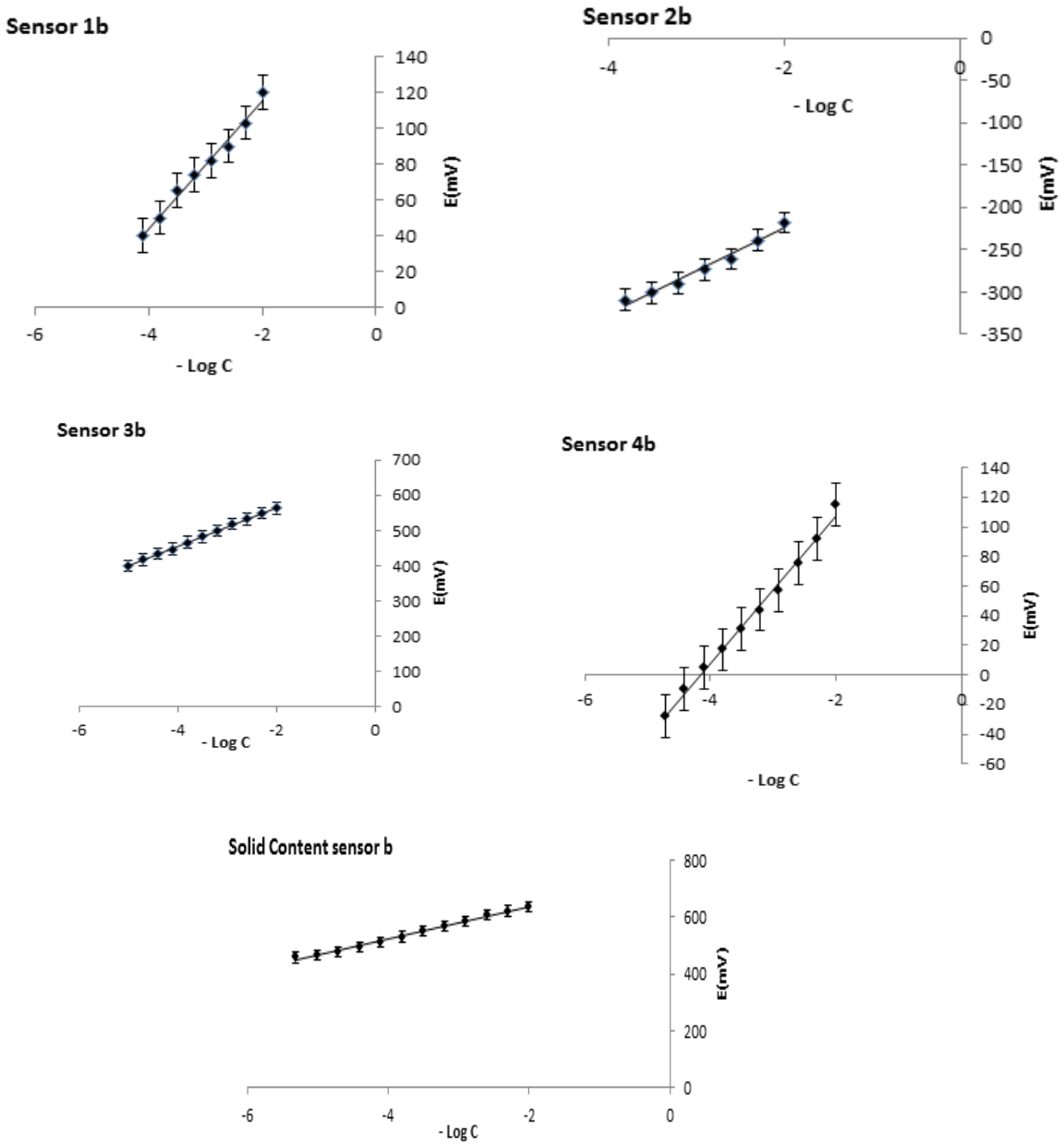
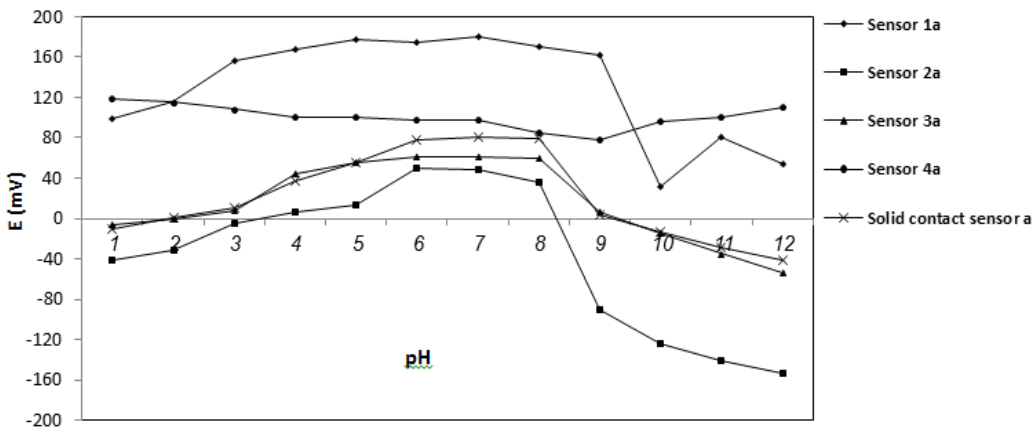


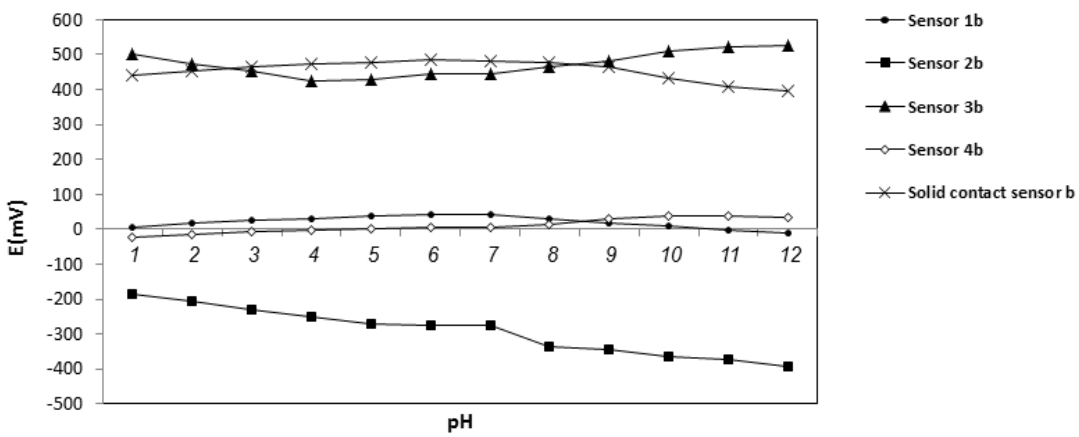
Figure 3. Potentiometric profiles of the suggested sensors for PSE

3.3. The effect of pH on the electrodes responses

The described electrodes potentiometric responses were sensitive to pH changes. Figure (4A & 4B) represents a typical pH response curve for the prepared electrodes, over a pH range of 1–12, where the pH was adjusted with hydrochloric acid and sodium hydroxide solutions. The electrode response is barely affected by the pH change from 6 up to 8 (for sensor 3a and solid contact sensor a) from 6 up to 7 (for sensor 3b) and from 4 up to 7 (for solid contact sensor b). In this pH range TRI and PSE are completely ionized, dissociated and sensed and this allowed working in water without using a buffer solution. Below pH 3, the electrodes response increases with the increase in solution acidity as the membrane may extract H^+ leading to a noisy response [32].



A



B

Figure 4. (A) Effect of pH on the response of the suggested sensors using 1×10^{-4} M TRI solution with pH ranging 1-12, the pH was adjusted with 2 M HCl and NaOH solutions; **(B)** Effect of pH on the response of the suggested sensors using 1×10^{-4} M PSE solution for all sensors and 1×10^{-3} M PSE solution for sensor 2b with pH ranging 1-12, the pH was adjusted with 2 M HCl and NaOH solutions

The decrease in potential at pH > 7.5 for all sensors (except for sensor 3a & solid contact sensor a) was due to the gradual decrease in the concentration of the TRI and PSE mono cation due to the formation of the non-protonated amino group.

3.4. Sensors selectivity

The ion-pair based membrane electrode selectivity depends on the physico-chemical characteristics of the ion-exchange process at the membrane such as the mobility of the respective ions in the membrane sample, solution interface and on the hydrophobic interactions between the primary ion and the organic membrane [33].

Table 3. Potentiometric selectivity coefficients (K_{AB}^{pot}) of the proposed sensors for TRI and PSE by separate solution method

Drug	Interferent*	Selectivity coefficient**				
		Sensor 1a	**Sensor 2a**	**Sensor 3a**	**Sensor 4a**	**Solid contact sensor a**
TRI	**KCl**	4.51×10^{-5} M	5.14×10^{-2} M	16.37×10^{-2} M	10.58×10^{-2} M	1.43×10^{-2} M
	Urea	8.26×10^{-5} M	1.82×10^{-2} M	11.49×10^{-2} M	11.04×10^{-2} M	7.27×10^{-3} M
	Starch	5.94×10^{-5} M	2.41×10^{-2} M	8.06×10^{-2} M	14.23×10^{-2} M	7.58×10^{-3} M
	NaCl	5.32×10^{-5} M	13.15×10^{-3} M	11.05×10^{-2} M	19.97×10^{-2} M	6.41×10^{-3} M
	Glucose	4.77×10^{-5} M	1.04×10^{-2} M	3.31×10^{-2} M	30.52×10^{-2} M	8.92×10^{-3} M
	Lactose	3.24×10^{-5} M	2.00×10^{-2} M	6.37×10^{-2} M	24.69×10^{-2} M	6.14×10^{-3} M
	$CaCl_2$	1.15×10^{-4} M	7.88×10^{-3} M	5.44×10^{-2} M	6.10×10^{-2} M	5.65×10^{-3} M
	Guaifenesin	3.82×10^{-5} M	1.91×10^{-2} M	13.45×10^{-2} M	14.85×10^{-2} M	6.97×10^{-3} M
	PSE	5.04×10^{-5} M	1.44×10^{-2} M	15.74×10^{-2} M	20.84×10^{-2} M	1.02×10^{-2} M
PSE	**Interferent**	**Sensor 1b**	**Sensor 2b**	**Sensor 3b**	**Sensor 4b**	**Solid contact sensor b**
	KCl	3.02×10^{-2} M	1.00×10^{-2} M	6.27×10^{-3} M	3.98×10^{-2} M	3.18×10^{-4} M
	Urea	10.49×10^{-2} M	3.59×10^{-2} M	1.08×10^{-2} M	8.32×10^{-2} M	6.31×10^{-4} M
	Starch	6.06×10^{-2} M	2.08×10^{-2} M	1.23×10^{-2} M	7.25×10^{-2} M	3.59×10^{-4} M
	NaCl	3.39×10^{-3} M	1.44×10^{-2} M	8.06×10^{-3} M	3.63×10^{-2} M	6.84×10^{-4} M
	Glucose	1.20×10^{-3} M	1.73×10^{-2} M	7.11×10^{-3} M	10.00×10^{-2} M	8.37×10^{-4} M
	Lactose	1.01×10^{-3} M	3.14×10^{-2} M	2.30×10^{-2} M	7.95×10^{-2} M	3.31×10^{-4} M
	$CaCl_2$	1.48×10^{-3} M	3.36×10^{-2} M	3.08×10^{-2} M	9.12×10^{-2} M	2.82×10^{-4} M
	Guaifenesin	15.49×10^{-2} M	1.05×10^{-2} M	1.28×10^{-2} M	3.47×10^{-2} M	2.50×10^{-4} M
	TRI	9.09×10^{-2} M	6.23×10^{-4} M	8.09×10^{-2} M	17.38×10^{-2} M	8.37×10^{-4} M

*Interferent concentrations were 1×10^{-4} M for all sensors and 1×10^{-3} M for sensor 2b.
**Average of three determinations

The potentiometric selectivity coefficients of the proposed sensors in the presence of number of organic and inorganic related substances or industrial excipients were illustrated in Table 3, 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 [25]:

$$-\log\left(K_{A.B}^{pot}\right) = \frac{E_1 - E_2}{2.303RT/Z_A F} + \left(1 - \frac{Z_A}{Z_B}\right)\log a_A$$

where E_1 and E_2 are the potential readings recorded after exposing the electrode to the same concentration of the studied drug and the interferent, respectively. Z_A and Z_B are the charges on TRI or PSE and the interfering ion, respectively and 2.303 RT/ZAF represents the slope of the investigated sensor (mV/decade). Results obtained in Table 3 describe obviously, that none of the tested interfering species had a significant influence on the potentiometric responses of the electrodes towards TRI and PSE.

3.5. Potentiometric determination of TRI and PSE in different pharmaceutical matrices

Determination of TRI and PSE in their different pharmaceutical dosage forms without prior extraction was successfully achieved by using the new suggested sensors 3a, 3b and solid contact sensors, as none of the commonly used additives show significant interference with the drugs measurements, as shown in Table 4.

Table 4. Determination of TRI and PSE in Actifed® different dosage forms by the proposed sensors 3a, 3b and solid contact sensors and application of standard addition technique

Drug	**TRI**		**PSE**	
Pharmaceutical Dosage Form	**Recovery% (Mean ± SD)***			
	Sensor 3a	**Solid contact sensor a**	**Sensor 3b**	**Solid contact sensor b**
Actifed® Tablet (Batch No. A522124)	98.40 ± 1.85	99.48 ± 1.55	100.04 ± 0.54	99.50 ± 0.10
Actifed® Syrup (Batch No. A522919)	101.07 ± 1.60	100.00 ± 1.03	98.16 ± 0.22	100.26 ± 0.40
Actifed® Expectorant (Batch No. A519333)	100.00 ± 1.85	101.37 ± 1.57	98.01 ± 0.33	101.28 ± 0.59
Standard addition technique	**Recovery % of standard added (Mean ± SD)****			
Actifed® Tablet (Batch No. A522124)	100.42 ± 0.80	100.30 ± 1.73	100.06 ± 1.91	99.67 ± 0.83
Actifed® Syrup (Batch No. A522919)	99.61 ± 1.36	99.84 ± 1.44	99.58 ± 1.13	100.58 ± 1.60
Actifed® Expectorant (Batch No. A519333)	99.14 ± 1.29	99.36 ± 1.56	101.47 ± 1.93	99.67 ± 0.56

*Results of analysis 1×10^{-4} M 3 times.
**The concentrations of the added standards were 2×10^{-4}, 4×10^{-4} and 6×10^{-4} M.

The applicability of the method was proved as demonstrated by the obtained accurate and precise recovery percentages. The described methods validity was further verified by applying the standard addition technique. Also the statistical evaluation of the results of analysis of pure TRI and PSE by the proposed electrodes and the pharmacopeial normal phase HPLC method [1] shows no significant difference between the proposed and the official method in terms of accuracy and precision, as shown in Table 5.

Table 5. Statistical comparison of the results obtained by the proposed sensors and the official method for the determination of TRI and PSE in pure powder form

Drug	TRI			PSE		
	Sensor 3a	**Solid contact sensor a**	**Official method***	**Sensor 3b**	**Solid contact sensor b**	**Official method***
Mean	100.12	99.73	99.50	100.58	100.43	100.70
SD	1.45	1.06	0.91	1.01	1.06	0.65
RSD%	1.45	1.06	0.91	1.00	1.06	0.65
n	9.00	9.00	9.00	9.00	9.00	9.00
Variance	2.10	1.12	0.83	1.02	1.12	0.42
F-value	2.53 (3.44)	1.35 (3.44)	-	2.43 (3.44)	2.67 (3.44)	-
Student's t-test	1.09 (2.12)	0.49 (2.12)	-	0.30 (2.12)	0.65 (2.12)	-

*HPLC method [1] using a normal-phase column (ZORBAX RX-SIL, 4.6 x 150 mm, 5 µm) with a mobile phase consisting of methanol and ammonium acetate solution (17:3), a flow rate of 1.2 ml min^{-1} and UV detection at 254 nm.

- The figures between parenthesis are the corresponding theoretical values of F & t at P = 0.05.

3.6. Greenness Assessment of the Proposed Potentiometric Method versus Official HPLC Method

Potentiometric measurements are time saving, inexpensive, nondestructive and considered to be green methods with no negative influence on the environment compared with classical methods especially HPLC. The greenness of the described potentiometric methods was evaluated by the Analytical Eco-Scale approach [34], which is a comprehensive tool for semi-quantitative evaluation of analytical methodologies. This approach was used to determine the greenness of the analytical method and for comparison purposes. The evaluation relies on assigning a number of penalty points to each step of the analysis method, subtracted from a base of 100. The detailed total penalty points for our proposed potentiometric method and the official HPLC method [1] are presented in Table (6). Based on the obtained results, our potentiometric method is considered to be greener than the official HPLC one.

Table 6. Penalty points for using the proposed potentiometric method and the official HPLC method

Reagents	**Proposed method Penalty points**	**Official method* Penalty points**
Water	0	0
Methanol	0	6
Ammonium acetate	0	2
Instruments		
Digital ion analyzer	0	0
Magnetic stirrer	0	0
HPLC	0	1
Occupational hazard	0	3
Waste	3	8
Total penalty points	3	20
Analytical Eco-scale total score	97	80

*HPLC method [1] using a normal-phase column (ZORBAX RX-SIL, 4.6×150 mm, 5 µm) with a mobile phase consisting of methanol and ammonium acetate solution (17:3), a flow rate of 1.2 ml min^{-1} and UV detection at 254 nm.

According to the results presented before, the utility of TPB as a cationic exchanger and β-CD as an ionophore in the construction of sensor 3a obtains better Nernstian slope than other sensors for the determination of TRI. Therefore, the same composition was applied for the solid contact sensor a, which improved the sensor sensitivity. For PSE sensors, using PT as a cationic exchanger and calixarene as an ionophore for the construction of sensor 3b showed better results. But when they were applied for solid contact sensor b, significant effect on both membrane selectivity and sensitivity was increased as well as the sensor Nernstian slope. The optimized sensors 3a, 3b, solid contact gold sensors a and b showed potentiometric response with the slope of 58.53, 54.71, 54.93 and 57.19 mV/decade, respectively. The response time was instantaneous (up to 10 seconds for solid contact sensors), while those of the conventional sensors were 25 seconds except sensor 3a it was 15 seconds. Sensor 3a and solid contact sensor b showed the best Nernstian slope. Solid contact sensors had the best sensitivity as well as the fastest response. From applicability point of view, sensors 3a, 3b and solid contact sensors showed the most stable responses in TRI and PSE dosage forms and the standard addition technique was applied to assess the accuracy of the method. The suggested potentiometric method has the same performance characteristics of the official method, yet it is less complicated and greener for determination of the intended drugs.

4. CONCLUSION

The new described sensors are proven to be sensitive and selective for quantitative determination of cationic drugs such as TRI and PSE in their different pharmaceutical matrices. Solid contact gold electrodes provide a good alternative to other classical analytical techniques with higher sensitivity and faster response. Regarding the electro-analytical

methods, they are the greenest methods concerning with sample extraction and pretreatment, with no solvent consumption. The fabricated sensors are used by just dipping the electrode in the solution to be measured without any prior sample preparation steps, therefore they can be used for in-line monitoring of TRI and PSE containing pharmaceutical formulations. Besides, the described sensors provide many advantages over the official method, including being green, portable, and economic, highly sensitivity, fast in response and time saving. Finally, this work presents an eco-friendly alternative technique to quality control laboratories for the routine analysis of TRI and PSE.

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