Journal of Applied Pharmaceutical Science Vol. 4 (07), pp. 032-037, July, 2014
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2014.40705
ISSN 2231-3354

Comparative Study of Calix-6-arene, 2-Hydroxy Propyl Beta Cyclodextrin and 18-Crown-6 as Ionophores in Potentiometric Ion-Selective Electrodes for Determination of Trigonelline in *Trigonella foenum-graecum* Seeds Extract and Plasma

Maha. F. Abdel Ghany[a], Lobna. A. Hussein[a], Hend. Z. Yamani[a]*

[a] Pharmaceutical Analytical Chemistry Department, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt.

ARTICLE INFO

Article history:
Received on: 22/01/2014
Revised on: 13/02/2014
Accepted on: 25/02/2014
Available online: 28/07/2014

Key words:
Ion selective electrodes; ionophores; trigonelline; *Trigonella foenum-graecum*; plasma.

ABSTRACT

The present work evaluates the influence of Calix-6-arene, 2-hydroxy propyl β-cyclodextrin and 18-crown-6 as ionophores on the fabrication of trigonelline selective electrodes 1, 2 and 3, respectively. The three proposed sensors showed Nernstian slopes of 59, 60 and 55.75 mV/concentration decades over pH range 4-9 for sensors 1, 2 and 3, respectively. Both sensors 1 and 2 covered the concentration range $10^{-3} – 10^{-5}$ M, while sensor 3 showed linear response over the range $10^{-2} – 10^{-4}$ M. The proposed sensors offer the advantages of fast response and moderate stability time. The selectivity coefficients of the developed sensors indicated excellent selectivity for trigonelline. The proposed electrodes were successfully applied for direct determination of trigonelline in pure form, *Trigonella foenum-graecum* seeds extract and plasma without prior separation or pretreatment steps. The proposed sensors can be used in quality control labs and in clinical trails for routine analysis of trigonelline in *Trigonella foenum-graecum* seeds extract and plasma.

INTRODUCTION

Trigonelline (Fig. 1) is a major phytoconstituent in *Trigonella foenum-graecum* which can be used as a bioactive marker for determination of the quality of crude drugs and its formulations (Sunita *et al.*, 2011). Several reports focused on therapeutic activities of trigonelline as a potent hypoglycemic (Mishkinsky *et al.*, 1967; Hamza *et al.*, 2012), hypo-cholesterolemic, neuroprotective, antimigraine, sedative, memory-improving, antibacterial, antiviral, and anti-tumor (Ghule *et al.*, 2012). Different Methods were reported in literature for determination of trigonelline in *Trigonella foenum-graecum* seeds or in plasma or in presence of its degradates using HPLC (Zhao *et al.,* 2002), HPTLC (Chopra *et al.,* 2006; Chopra *et al.,* 2007) and LC/Ms (Lang *et al.,* 2008). Although the numerous advantages of ion selective electrodes (ISE), it was not used for determination of trigonelline before. Potentiometric methods using ISE have found wide applications, due to their numerous advantages. The high selectivity of these electrodes imparts a great advantage over other techniques. No sample pretreatment needed before the analysis. Analytes in colored, turbid and viscous samples can be determined accurately. They show rapid response to changes in the concentration. Furthermore, they may be used for measurement over a wide concentration range. ISE are generally tolerant to small changes in pH. A further advantage is that they are relatively simple and cheep to develop and run. Moreover, the chemical design of the electrodes has been developed to give superior selectivity and response (El-Kosasy *et al.,* 2005). ISE based on polymeric membranes containing neutral or charged carriers (ionophores) are one of the most successful electrochemical sensors in routine use today (González-Bellavista *et al.,* 2007).

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* *Corresponding Author*
Hend Zaki Yamani, Postal address: Pharmaceutical Analytical Chemistry Department, Faculty of Pharmacy, Ain Shams University, Abbassia, 11566 Cairo, Egypt. Telephone: +201281031901, : +226875797,
Email: hend.z.yamani@gmail.com

The ISE dynamic response is generated by selective complexation of the target ion by ionophores dispersed in a poly (vinylchloride) (PVC) matrix (Chandra and Lang, 2006).

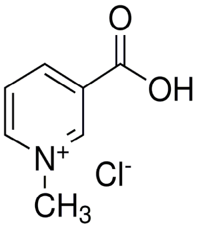

Fig. 1: Chemical structure of trigonelline hydrochloride.

Calixarenes, cyclic oligomers of phenol-formaldehyde condensates, have drawn much attention as a fascinating class of cyclophanes possessing ionic and molecular-binding properties. Derivatives containing a wide range of functional groups have been synthesized and shown to exhibit different degrees of receptor ionophoric activity (Lu *et al.,* 2002).

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Their ability to complex cations, anions, and neutral molecules has made them a standard among supramolecular host molecules. Their configuration includes a number of selective factors, such as cavity-size, conformation and substituents, which leads to the formation of typical host–guest complexes with numerous compounds and allow for a variety of applications in ion-selective membranes and electrodes (Duncan and Cockayne, 2001; Kivlehan *et al.,* 2007; Vaze & Srivastava, 2008; Kumar and Shim, 2009). The structure of calixarenes is shown in (Fig. 2A).

Cyclodextrins are optically active oligosaccharides that form inclusion complex with organic molecules; because their chemical structure provides well-defined inclusion cavities with a specific receptor function (Bender and Kamiyama, 1978). The structure of cyclodextrins is shown in (Fig. 2B). Crown ethers are heterocycles that, in their simplest form, are cyclic oligomers of dioxane. The essential repeating unit of any simple crown ether is ethyleneoxy. Their selective receptor properties in conjunction with the relative ease of synthesis and structural modification make crown ethers attractive targets as ionophores (George *et al.,* 2004). Crown ethers have different types that show binding selectivity toward a wide range of metal ions, nonmetal ions, and neutral molecules.Because of their remarkable binding properties, the study of crown ethers has largely contributed to the development of host-guest chemistry and the emergence of supramolecular chemistry (Gokel, 1999). The structure of 18-crown-6 is presented in (Fig. 2C). The present work describes the use of calix-6-arene, 2-hydroxy propyl β-cyclodextrin and 18-crown-6 as ionophores for the development of novel sensors for the determination of trigonelline in pure form, *Trigonella foenum-graecum* seeds extract and plasma.

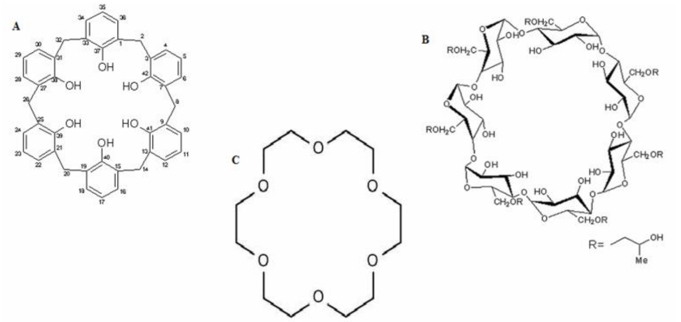

Fig. 2: Chemical structure of: A: calix-6-arene molecule; B: 2-hydroxy propyl β-cyclodextrin molecule; C: 18-crown-6 molecule.

EXPERIMENTAL

Apparatus

A Jenway digital ion analyzer; model 3330 (Essex, UK) with Aldrich Ag/AgCl double junction reference electrode no. 113107 (Munich, Germany) was used for potential measurements. A Jenway pH glass electrode no. 924005-BO3-Q11C (Essex, UK) was used for pH adjustments. Solution stirring was done using Bandelin Sonorex magnetic stirrer; model Rx 510 S (Budapest, Hungary).

Samples

Pure Sample

Trigonelline hydrochloride (purity 100%) was purchased from Sigma Aldrich (St. Louis, MO, USA).

Market Sample

Trigonella foenum-graecum seeds were obtained from a local market and authenticated by Phytochemistry Department, Faculty of Pharmacy, Ain Shams University (Cairo, Egypt).

Chemicals and Reagents

All chemicals and reagents used were of analytical grade, and water was bi-distilled. Calix-6-arene, 2- hydroxy propyl β-cyclodextrin and 18-crown-6 were purchased from Alfa Aesar (Ward Hill, Massachusetts, USA). Polyvinyl chloride (PVC) was obtained from Fluka (Steinheim, Germany). 2-Nitrophenyl octyl ether (NPOE) and tetrahydrofuran (THF) were purchased from Sigma Aldrich (Steinheim, Germany). Potassium chloride (KCl), sodium hydroxide (NaOH) and hydrochloric acid (HCl) were obtained from Prolabo (Pennsylvania, USA). Methanol and iso-propanol were purchachrd from Scharlu (Barcelona, Spain). Frozen human plasma was obtained from VACSERA (Giza, Egypt).

Standard Solutions

Trigonelline Hydrochloride Standard Stock Solution (1 x 10^{-1} M)

It was freshly prepared by dissolving 1.736 g of pure trigonelline hydrocholride in 100 ml of bi-distilled water.

Trigonelline Hydrochloride Standard Working Solutions (1 x 10^{-2} to 1 x 10^{-6} M)

They were prepared by suitable dilution from stock solution using bi-distilled water.

Procedures

Fabrication of Membrane Sensors

In a glass Petri dish (5 cm diameter), 0.19 g of PVC and 0.4 g of NPOE were mixed with 0.04 g calix-6-arene, 2-hydroxy propyl β-cyclodextrin or 18-crown-6 for preparation of electrodes 1, 2 and 3, respectively. The mixture was then dissolved in 6 ml THF. The Petri dish was covered by a filter paper and left to stand for 24 h to allow solvent evaporation at room temperature. A master membrane of 0.1 mm thickness was obtained.

From the master membrane, a disk (8 mm diameter) was cut using cork borer and pasted using THF to interchangeable PVC tip that was previously clipped into the end of the electrode glass body. Equal volumes of 10^{-2} M trigonelline hydrochloride and 10^{-2} M KCl were mixed and used as an internal reference solution. Ag/AgCl wire (1 mm diameter) was immersed in the internal reference solution as internal reference electrode. The electrodes were preconditioned by immersing in 10^{-2} M trigonelline hydrochloride solution for 24 h and stored in the same solution when not in use.

Sensors Calibration

The conditioned electrodes were calibrated by separately transferring 50 ml aliquots of trigonelline hydrochloride solutions covering the concentration range of (1 x 10^{-2} to 10^{-6} M) into a series of 100 ml beakers. The sensors and the reference electrode were immersed in each solution with constant stirring using a magnetic stirrer. The potential recordings within ± 1 mV were recorded. The electrodes were washed with bi-distilled water between measurements. The electrode potential was plotted versus the negative logarithmic concentration of trigonelline hydrochloride. The regression equation for linear part of the curve was computed.

Study of Experimental Conditions

Identification of Slope, Response Time and Operative Life of the Studied Sensor

The electrochemical performance of the studied electrodes was evaluated according to IUPAC recommendation data (IUPAC, Analytical Chemistry Division, Commission on Analytical Nomenclature, 2000).

The dynamic response time of the electrodes were tested for concentrations of the drug solution from 1 x 10^{-6} M to 1 x 10^{-2} M; the sequence of measurement was from low to high concentrations.

The required time for the electrodes to reach values within ±1 mV of the final equilibrium potential after increasing the drug concentration 10-folds was measured. The long-term reproducibility and stability of the potentials were evaluated by determining replicate calibration graphs over a period of 5 weeks. The electrodes were stored in 1 x 10^{-2} M trigonelline standard solution when not in use and washed thoroughly with bi-distilled water between measurements.

Effect of pH

The electrodes response was tested at different pH values over a pH range 2-11. The pH was adjusted using HCl and NaOH solutions. The concentrations used were 1 x 10^{-3} M and 1 x 10^{-4} M. The electrode potential was plotted versus pH.

Effect of Temperature

The response of the electrodes was monitored as a function of temperature. The potential of sensor using 1 x 10^{-3} M drug solution was recorded in the range 25 – 45°C at 5°C interval. The electrode potential was plotted versus temperature.

Sensors Selectivity

The response of the electrodes was examined in presence of a number of possible interfering substances. The potentiometric selectivity coefficient ($K^{Pot.}_{Primary\ ion,\ interferent}$) was used to evaluate the extent to which a foreign ion would interfere with the response of the electrode to its primary ion.

Selectivity coefficient were calculated by separate solution method where potentials were measured for 1 x 10^{-3} M drug solution and 1 x 10^{-3} M aqueous interferents solutions, separately. The potentiometric selectivity coefficients were then calculated using the rearranged Nicolsky-Eisenman equation (IUPAC, Analytical Chemistry Division, Commission on Analytical Nomenclature, 2000).

$$\text{Log } K^{Pot}_{A,B} = [(E_B - E_A) / (2.303\ RT / Z_AF)] + [1 - (Z_A / Z_B)] \log [A]$$

Where E_A is the potential measured in 10^{-3} M drug solution, E_B is the potential measured in 10^{-3} M interferent solution, Z_A and Z_B are the charges of drug and interferent; respectively, and 2.303 RT / Z_AF represents the slope of the calibration curve (mV / concentration decade).

Direct Potentiometric Determination of Trigonelline Hydrochloride in Trigonella foenum-graecum Seeds Extract

Trigonella foenum-graecum seeds samples were cleaned manually to remove all foreign materials then milled, passed through a stainless steel sieve (20-40 mesh) and stored at 4 °C until use.

An accurately weighed sample (1 g) of the seeds powder was extracted at 80 °C for 3 h under reflux with 100 ml of 50% methanol in a round-bottom flask heated in a water bath (optimum conditions for extraction was studied before).

In a 25 ml volumetric flask, 2.5 ml of the extract was transferred and diluted to the mark with bi-distilled water. The membrane sensors were immersed in conjunction with the reference electrode in the extract. The emf produced was measured by the proposed sensors, and the concentration of trigonelline was determined from the corresponding regression equation.

Direct Potentiometric Determination of Trigonelline Hydrochloride in Plasma

Into three stoppered tubes, 4.5 ml of human plasma were placed, then 0.5 ml of 1 x 10^{-2} to 1 x 10^{-4} M trigonelline hydrochloride solutions was added separately and mixed to prepare 1 x 10^{-3} to 1 x 10^{-5} M trigonelline hydrochloride solutions in plasma. The membrane sensors were immersed in conjunction with the reference electrode in these solutions. The emf produced was measured, and the concentration of trigonelline was determined from the corresponding regression equation.

RESULTS AND DISCUSSION

Sensors Fabrication

The molecular recognition and inclusion complexation are of current interest in host–guest and supramolecular chemistry and offer a promising approach to chemical sensing (Mittal *et al.*, 2007; Zanganeh and Amini, 2008). The use of selective inclusion complexation and complementary ionic or hydrogen bonding are two main strategies for preparing synthetic host molecules, which recognize the structure of guest molecules (Górski *et al.*, 2010). Plasticizer has a great influence on the dielectric constant of the membrane phase, the mobility of the ionophore molecules, and the state of ligands. Plasticizer facilateites the inclusion of organic molecules and ensures stable potentials with long lifetime (Gholivand *et al.*, 2009).

Sensors Performance Characteristics

The electrochemical performance characteristics of the investigated electrodes were summarized in (Table 1).

The three proposed sensors showed Nernstian slopes of 59.00, 60.00 and 55.75 mV/concentration decades for sensors 1, 2 and 3, respectively (Fig. 3). Both sensors 1 and 2 covered the concentration range 10^{-3} - 10^{-5} M, while sensor 3 showed Nerstian response over the range 10^{-2} - 10^{-4} M.

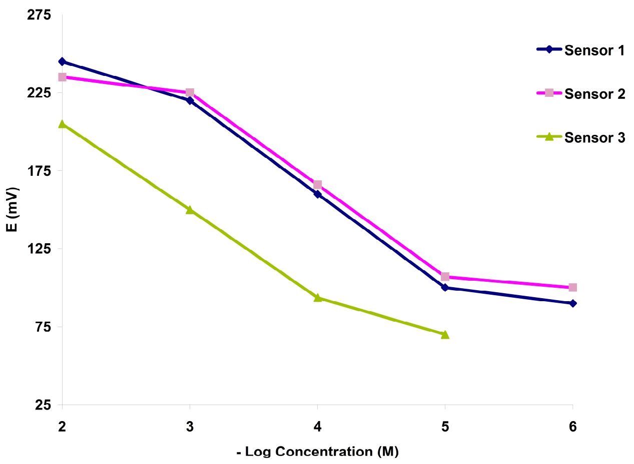

Fig. 3: Profile of the potential in mV vs. –Log concentration of trigonelline for the proposed sensors.

The Limits of detection were calculated according to IUPAC recommendations (IUPAC, Analytical Chemistry Division, Commission on Analytical Nomenclature, 2000) from the intersection of the two extrapolated linear portions of the curves and found to be 1.00 x 10^{-5} M for both sensors 1 and 2 while 9.82 x 10^{-5} M for sensors 3. Both sensors 1 and 2 showed higher sensitivity than sensor 3. The electrodes displayed constant potential readings, which did not vary by more than ± 1 mV on the same day. Linearity range from day to day and calibration slope did not change by more than ± 2 mV/concentration decades over a period of 5 weeks for sensor 1 and 2 and 4 weeks for sensor 3. This indicates the good stability of the investigated electrodes.

The required time for the electrode to reach values within ± 1 mV of the final equilibrium potential after increasing the drug concentration 10-folds ranged from 15 seconds for both sensors 1 and 2 to 25 seconds for sensor 3 which indicate the fast response time.

Table 1: Electrochemical response characteristics of the proposed trigonelline sensors and validation parameters of the assay.

Parameter	Sensor 1	Sensor 2	Sensor 3
Slope (mV/decade) [a]	60.00	59.00	55.75
Intercept	400.00	402.33	317.75
Correlation coefficient	1	0.9999	0.9999
LOD (M) [b]	1.00 x 10^{-5}	1.00 x 10^{-5}	9.82 x 10^{-5}
Response time (sec.)	15 seconds	15 seconds	25 seconds
Working pH range	4 - 9	4 - 9	4 - 9
Concentration range (M)	10^{-3} – 10^{-5}	10^{-3} – 10^{-5}	10^{-2} – 10^{-4}
Stability (weeks)	5	5	4
Average recovery (%) ± SD [a]	99.94 ± 0.33	100.16 ± 0.52	99.33 ± 0.99
Repeatability (SD_r)	0.68	0.95	0.93
Intermediate precision (SD_{int})	1.17	1.22	1.44
Ruggedness [c]	99.56 ± 0.79	100.68± 0.49	99.88 ± 0.67

[a] Average of five determinations. [b] Limit of Detection (measured by interception of the extrapolated arms of figure 3). [c] Average recovery percent of determination 10^{-3}, 10^{-4} and 10^{-5} M pure trigonelline for both sensors 1and 2, while 10^{-2}, 10^{-3} and 10^{-4} M for sensor 3 using Jenway 3510 digital ion analyzer instead of model 3330.

Effect of pH & Temperature

For quantitative measurements with ISEs, studies were carried out to reach the optimum experimental conditions. The influence of pH on the potential response of the electrode was studied using concentrations 10^{-3} and 10^{-4} M over the pH range 2-11. The three proposed sensors showed constant potentials over pH range 4-9 as shown in (Fig. 4).

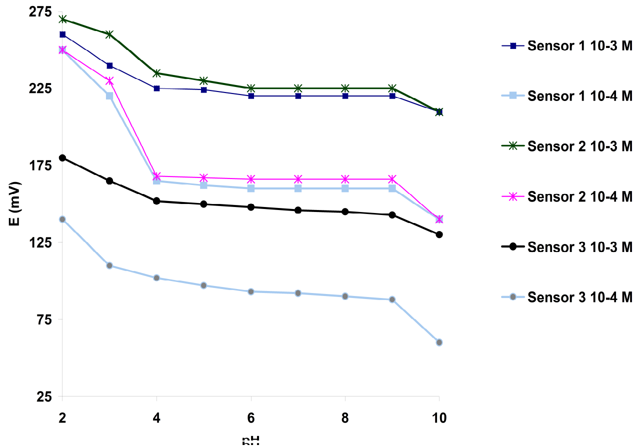

Fig. 4: Effect of pH on the response of the proposed sensors.

Therefore, pH 4-9 was assumed to be the working pH range for the proposed sensors. Upon studying the effect of temperature, the suggested electrodes exhibit slight increase in their potentials as the temperature rises in the range of 25-45º C; however, the calibration graphs obtained at different temperatures were parallel. The slope, response time and limit of detection did not significantly vary with variation of temperature up to 35º C, indicating reasonable thermal stability.

Sensors Selectivity

(Table 2) shows the potentiometric selectivity coefficients of the proposed sensors in presence of some interfering species that may present in *Trigonella foenum-graecum* seeds extract and plasma. Sensors selectivity was also determined in presence of nicotinic acid or vitamin B_3 which is one of the major thermal degradates of trigonelline via *N*-demethylation (Stadler *et al.,* 2002).

The results demonstrate an excellent selectivity of the proposed sensors. Both sensors 1 and 2 displayed higher selectivity and lower response toward interfering substances than sensor 3.

Table 2: Potentiometric selectivity coefficients (KPot.Trigonelline, interferent) of the proposed trigonelline sensors using separate solution method (SSM) (IUPAC, Analytical Chemistry Division, Commission on Analytical Nomenclature, 2000)

Interferents[a]	Selectivity coefficient[b]		
	Sensor 1	Sensor 2	Sensor 3
Isoleucine	1.6 x 10^{-3}	1.6 x 10^{-3}	2.4 x 10^{-2}
Leucine	1.5 x 10^{-3}	1.5 x 10^{-3}	2.3 x 10^{-2}
Lysine	2.4 x 10^{-3}	2.6 x 10^{-3}	1.9 x 10^{-2}
Vitamin B_2	2.8 x 10^{-3}	3.0 x 10^{-3}	2.8 x 10^{-2}
Vitamin B_3	1.8 x 10^{-3}	1.8 x 10^{-3}	1.6 x 10^{-2}
K^+	5.8 x 10^{-3}	6.0 x 10^{-3}	8.7 x 10^{-2}
Na^+	5.5 x 10^{-3}	5.2 x 10^{-3}	6.6 x 10^{-2}
Zn^{+2}	6.1 x 10^{-3}	6.3 x 10^{-3}	1.3 x 10^{-2}
Mg^{+2}	1.2 x 10^{-2}	1.1 x 10^{-2}	2.4 x 10^{-2}

[a] Aqueous Solutions of 1 x 10^{-3} M were used
[b] Average of five determinations

Potentiometric Determination of Trigonelline in *Trigonella foenum-graecum* Seeds Extract

The proposed electrodes were successfully applied for direct determination of trigonelline in *Trigonella foenum-graecum* seeds extract without prior purification or pretreatment steps for the turbid and colored samples. The concentration of trigonelline in the extract prepared under optimized heat reflux extraction conditions are summarized in (Table 3).

Table 3: Determination of trigonelline in ***Trigonella foenum-graecum*** seeds extract by the proposed sensors.

Trigonelline concentration (mg/g) ± SD[a]	Sensor 1	Sensor 2	Sensor 3
	7.42 ± 0.73	7.34 ± 0.82	7.32 ± 1.14

[a] Average of 3 determinations

Potentiometric Determination of Trigonelline in Presence of Plasma

The results obtained for the determination of trigonelline in spiked human plasma show that a wide concentration range of the drug can be determined by the investigated sensors with high precision and accuracy as shown in (Table 4). It is concluded that the proposed sensors can be successfully applied to in vitro studies and for clinical use.

Table 4: Determination of trigonelline in spiked human plasma by the proposed sensors.

Added (M)	Recovery% ± SD[a]		
	Sensor 1	Sensor 2	Sensor 3
10^{-2}	---------	---------	101.55 ± 0.64
10^{-3}	99.43 ± 0.75	98.87 ± 0.85	99.10 ± 1.26
10^{-4}	100.42 ± 0.90	99.58 ± 0.94	101.23 ± 0.94
10^{-5}	100.34 ± 1.15	101.02 ± 1.22	---------
Mean ± SD	**100.06 ± 0.55**	**99.82 ± 1.10**	**100.63 ± 1.33**

[a] Average of 3 determinations

Statistical Comparison

Statistical comparison showed that there is no significant difference between the results obtained from the proposed electrodes and those obtained from the reported HPTLC method (Chopra *et al.*, 2006) for determination of trigonelline as shown in (Table 5).

Table 5: Statistical comparison between the results of analysis of trigonelline by the proposed sensors and the reported HPTLC Method (Chopra et al., 2006)a.

Parameter	Sensor 1	Sensor 2	Sensor 3	Reported Method a
Mean	99.94	100.16	99.33	100.00
S.D.	0.33	0.52	0.99	0.78
N	3	3	3	5
Variance	0.11	0.27	0.97	0.61
t	(2.45)b 0.12	(2.45)b 0.32	(2.45)b 1.07	----
F	(19.25)b 5.76	(19.25)b 2.28	(6.94)b 1.59	-----

[a] HPTLC method: using n-propanol: methanol: water (8: 1:8, v/v/v) as mobile phase on TLC aluminum plates precoated with silica gel 60 F254 at 265 nm
[b] The values between parentheses are the corresponding theoretical values of t and F at 95% confidence level

CONCLUSION

The present work evaluates the influence of Calix-6-arene, 2-hydroxy propyl β-cyclodextrin and 18-crown-6 as ionophores on the response of PVC membrane based trigonelline selective electrodes including their sensitivity, selectivity, stability and accuracy.

From the obtained results, it can be clearly seen that Calix-6-arene and 2-hydroxy propyl beta cyclodextrin are considered better ionophores than 18-crown-6 in the preparation of PVC based trigonelline selective electrodes.

The use of the proposed sensors offer the advantages of fast response, moderate stability time, elimination of drug pretreatment and separation steps and high selectivity in presence of plasma and other phyto-constituents in the extract. Thus, the proposed electrodes can be considered for use in quality control labs and in clinical trials for routine analysis of trigonelline in *Trigonella foenum-graecum* seeds extract and plasma. The of use the proposed sensors may be further extended for stability indicating study on trigonelline as they showed promising selectivity in presence of one of the major thermal degradates of trigonelline.

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How to cite this article:

Maha. F. Abdel Ghany, Lobna. A. Hussein, Hend. Z. Yamani. Comparative Study of Calix-6-arene, 2-Hydroxy Propyl Beta Cyclodextrin and 18-Crown-6 as Ionophores in Potentiometric Ion-Selective Electrodes for Determination of Trigonelline in *Trigonella foenum-graecum* Seeds Extract and Plasma. J App Pharm Sci, 2014; 4 (07): 032-037.