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Ion Selective Membrane Electrodes for the Determination of Mixture of Analgin and Camylofin Dihydrochloride in their Pure Form and Combined Dosage Form

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Abstract- In the present work two selective and sensitive polyvinyl chloride matrix membrane electrodes were developed for the determination of analgin and camylofin dihydrochloride. Sensor I was developed using tetraheptylammonium bromide as an anion exchanger with 2-nitrophenyl octyl ether as a plasticizer for the determination of the anionic drug analgin. Sensor II was developed using potassium tetrakis 4-chlorophenyl borate as a cationic exchanger and dioctyl phthalate as a plasticizer for the determination of the cationic drug camylofin. Selective molecular recognition component 4-tert-butylcalix [8]arene was used as ionophore to improve the selectivity of sensor II. The linearity range of the proposed sensors was (1.56×10^{-4}-1.00×10^{-2}) and (1.00×10^{-6}-1.00×10^{-2}) mol L^{-1} with Nernstian slopes of (-53.45±2.93) and (30.20±1.66) for the sensors I and II, respectively. The Nernstian slopes were also estimated over the pH ranges of 4.5-10.5 and 4.5-7.5 for both sensors. The proposed sensors showed useful analytical features for the determination of both drugs in bulk powder, in laboratory prepared mixtures and in their combined solid dosage form. The method was validated according to ICH guidelines.

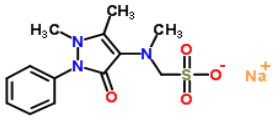
Keywords- Ionophore, Ion selective electrodes, Camylofin, Analgin, PVC

1. INTRODUCTION

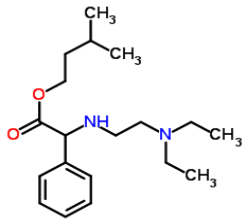
Quantitative analysis of pharmaceuticals is important throughout the various stages of drug development and manufacture, thus it is considered essential to explore accurate and rapid methodology with low cost and possess no need for sample pretreatment, hazardous solvents or extraction steps. From this perspective we exploit the chance of having two active constituents of different ionic characteristics in our binary mixture under study.

Analgin (AG) (Figure 1.a) is also known as metamizole sodium or dipyrone. It is [(2, 3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1*H*-pyrazol-4-yl)methylamino] methanesulfonate monohydrate [1]. AG is an analgesic, antispasmodic and antipyretic agent which is most commonly given orally or parenterally to prevent and treat pain related to surgery or for the treatment of acute pain. Pharmacological actions are similar to aspirin which is able to inhibit the cyclooxygenase pathway [2].

Camylofin dihydrochloride (CAM) (Figure 1.b) is 3–methyl butyl 2–(2–diethyl aminoethyl amino)–2–phenyl acetate hydrochloride [3]. It belongs to the group of spasmolytic, anticholinergic and gastrointestinal sedatives. CAM is an antispasmodic used for the treatment of functional bowel disorders [3]. Therefore both AG and CAM are co-formulated together in an antispasmodic tablet known as Spasmopyralgin tablet which provide a powerful antispasmodic, analgesic and antipyretic effects.



(a)



(b)

Fig. 1. Chemical structures of (a) Analgin (AG); (b) Camylofin dihydrochloride (CAM)

The literature survey revealed that there are no published methods for the simultaneous determination of both compounds, but there are some publications for the determination of each compound in combination with other drugs [4-15].

AG was determined separately or in a combination with other drugs by several methods including spectrophotometric methods [4,5], chromatographic method [6], flow injection analysis method , voltammetric method [7] and titrimetric method [8].Several methods have been employed for the determination of CAM in a combination with other drugs including HPLC methods [9-12], HPTLC method [13] and GC methods [14,15].

However, most of these methods involve the use of complicated procedures, long analysis time, high instrumental cost and extraction operations that are sensitive to various

interferences as well as being not applicable to colored and turbid solutions. On the other hand particularly, Ion-selective electrodes (ISEs) in pharmaceutical analysis have acquired increasing prominence due to several advantages such as using instrumental simplicity, moderate cost, portability [16], low energy consumption, limited sample pretreatment, rapidity, being non-destructive and adaptability to small sample volumes and on-line monitoring [17-21].However; no previous methods were reported for the determination of both drugs in their mixture form. So our scientific aim for the development of a simple, accurate, reproducible and rapid method that can simultaneously determine each drug in the presence of the other is considered important for analysis of their combined dosage form.

Efforts to improve ion-selective electrodes characteristics have been proposed through the use of species capable of molecular recognition [22-26]. For this reason, different types of ionophores such as 4-tert-butylcalix [8] arene (tBC8) have been implemented in the present work.

Calixarenes; are macrocycle or cyclic oligomers based on a hydroxyl alkylation product of phenols and aldehydes having hydrophobic cavities that can hold smaller molecules or ions. Calixarenes of varying cavity size can form a variety of host-guest type of inclusion complexes similar to cyclodextrins [27]. The larger internal cavity size of calix [8] arene in sensor II, the higher the stability and the best Nernstian slope. In the present work, simple potentiometric electrodes have been developed and optimized for rapid, reproducible, selective, sensitive, accurate, and low-cost estimation of the anionic and the cationic drugs, AG and CAM respectively without prior separation from their combined formulation matrix. The suggested method was validated according to ICH guidelines [28].

2. EXPERIMENTAL

2.1. Apparatus

Jenway digital ion analyzer model 3330 (Essex, UK) with Ag/AgCl double junction reference electrode no. Z113107-1EAPW (Aldrich Chemical Co. Steinheim, Germany) and a pH glass electrode (Jenway, Essex, UK) no. 924005-BO3-Q11C. Magnetic stirrer, Bandelin Sonoro, R×510S (Budapest, Hungary) was used during potential measurements.

2.2. Materials

2.2.1. Reference samples and pharmaceutical formulation

Standards of AG and CAM were obtained from El Kahira Pharmaceuticals and Chemical Industries Company, Shoubra, Cairo, Egypt. Their purity percentages were certified to be 100.40% and 98.99% respectively.

All chemicals and solvents used were of analytical grade and the used water was bi-distilled. Polyvinyl chloride (PVC), tetraheptylammonium bromide (THB), 2-nitrophenyl

octyl ether (2-NPOE), dioctyl phthalate (DOP), potassium tetrakis (4-chlorophenyl) borate (KTCPB), 4-tert-butylcalix[8]arene (tBC8) and tetrahydrofuran (THF), (Aldrich, Germany). Potassium chloride, sodium hydroxide, hydrochloric acid, was obtained from (El-Nasr pharmaceutical chemical company, Cairo, Egypt).

Spasmopyralgin tablets manufactured by El Kahira Pharmaceuticals and Chemical Industries Company; BN.: (1410400) were purchased from local market. Each tablet claimed to contain 255 mg AG and 25 mg CAM as active ingredients.

2.2.2. AG stock and working standard solutions

AG stock solution **(**1.00×10^{-2} mol L^{-1}**)** was prepared by transferring 0.0833 g of AG into a 25-mL volumetric flask, dissolving in a minimum amount of bi-distilled water then the volume was made up to the mark with the same solvent. AG working solutions (1.56×10^{-4}–5.00×10^{-3} mol L^{-1}) were prepared by suitable dilutions from its stock solution using bi-distilled water as a solvent.

2.2.3. CAM stock and working standard solutions

CAM stock solution (1.00×10^{-2} mol L^{-1}) was prepared by transferring 0.0801 g of CAM into a 25-mL volumetric flask, dissolved in a minimum amount of bi-distilled water then the volume was made up to the mark with the same solvent. CAM working solutions (1.00×10^{-6}–1.00×10^{-3} mol L^{-1}) were prepared by suitable dilutions from its stock solution using bi-distilled water as a solvent.

2.3. Procedures

2.3.1. Fabrication of PVC master membrane sensors

Fabrication of sensor I**:** In a glass petri dish (5-cm diameter), 0.4 mL of 2-NPOE was thoroughly mixed with 190 mg PVC and 10 mg THB. The mixture was dissolved in 10 mL THF. The petri dish was then covered with a Whatman No. 3 filter paper and left to stand overnight to allow solvent evaporation at room temperature. A master membrane with a thickness of 0.1 mm was obtained.

Fabrication of sensor II**:** In a glass petri dish (5-cm diameter), 0.4 mL DOP was mixed with 190 mg PVC, 50 mg KTCPB, and 50 mg tBC8. The mixture was dissolved in 15 mL THF and then the procedure was completed as previously mentioned under *fabrication of sensor I.*

The sensors were assembled using a disk of an appropriate diameter (about 8 mm) was cut using cork borer from the previously prepared master membranes and cemented to the flat end of PVC tubing with THF.

For sensors I and II respectively; equal volumes of 1.00×10^{-2} mol L^{-1} AG or CAM and 1.00×10^{-2} mol L^{-1} potassium chloride (prepared in bi-distilled water) were mixed and used as an internal reference solution. Ag/AgCl wire (1 mm diameter) was immersed in the internal reference solution as an internal reference electrode. The sensor was conditioned by soaking in a 1.00×10^{-2} mol L^{-1} AG stock standard solution for 24 h and storing in the same solutions when not in use. Each sensor separately was conjugated with double junction Ag/AgCl reference electrode, calibrated by being immersed into 25 mL aliquots transferred into a series of 50 mL beakers of its respective drug solutions (1.56×10^{-4} –1.00×10^{-2} mol L^{-1}) and (1.00×10^{-6}–1.00×10^{-2}) for sensor I and sensor II respectively, and allowed to equilibrate while stirring until constant reading of the potentiometer. Then the electromotive forces (e.m.f) were recorded within ±3 mV. Calibration graphs were plotted relating the recorded electrode potentials obtained by the two proposed sensors versus log molar concentrations of the corresponding drugs and the regression equations were computed. The Sensors I and II were washed with bi-distilled water before and after each run till reaching a constant potential.

2.3.2. Direct potentiometric determination of laboratory prepared mixtures containing different ratios of AG & CAM

Into a series of 25-mL volumetric flasks, different volumes of AG stock standard solution (1.00×10^{-2} mol L^{-1}) and CAM stock standard solution (1.00×10^{-2} mol L^{-1}) were accurately measured and transferred. The volumes were completed to the mark using bi-distilled water. The prepared solutions were determined using the specified sensors for each drug. In conjunction with the double junction Ag/AgCl reference electrode. The membrane sensor was washed between measurements with bi-distilled water. The e.m.f. produced by the two proposed electrodes was recorded for each drug and the concentration of AG and CAM was calculated from the corresponding regression equations.

2.3.3. Direct potentiometric determination of AG and CAM in Spasmopyralgin tablets

Ten tablets were accurately weighed, their average weight was calculated and then the content of the tablets then finely powdered. An amount equivalent to 33.33 mg of AG and 32.05 mg of CAM were accurately weighed and transferred to a 100-mL volumetric flask and diluted to the mark with bi-distilled water. The concentration of both solutions is claimed to be 1.00×10^{-3} mol L^{-1} for AG and CAM. The prepared electrodes (sensors I and II) in conjunction with the double junction Ag/AgCl reference electrode were immersed in the prepared solution and the resulting potential was recorded and the respective concentration was calculated from the corresponding regression equations. Alternatively, the standard addition (spiking) technique was used by measuring the potential displayed by the drug test solution (20 mL) before and after addition of 0.2 mL of 1.00×10^{-3} and 1.00×10^{-2} standard AG and CAM solution. The change in electrode potential (ΔE) was recorded and used for

calculation of the concentration of the drug.

2.3.4. Estimation of the slope, response time and operative life of the proposed sensors

The electrochemical performance of the two proposed sensors was evaluated according to the IUPAC recommendations data [29].

2.3.5. Effect of PH and interfering substances on the electrode selectivity

The effect of pH on the potential values of the two sensors was studied over the pH ranges of (4.5–10.5) and (4.5–7.5) for the sensors I and II; respectively. This was manipulated by adding diluted aliquots of 0.1 mol L^{-1} hydrochloric acid and 0.1 mol L^{-1} sodium hydroxide solutions on the 1.00×10^{-3} mol L^{-1} solution of both drugs. The potential obtained at each pH value was recorded. The potential response of the two proposed sensors in the presence of a number of related substances was studied and the potentiometric selectivity coefficient [-log ($K^{Pot}_{\text{Primary ion, interferent}}$)] was calculated to estimate the degree to which a foreign substance would interfere with the response of the electrodes to their primary ion (AG in case of sensor I and CAM in case of sensor II). The selectivity coefficients were calculated by the separate solutions method (SSM) [30], using the following equation:

$$- \log (K^{pot}_{\text{primary ion interferent}}) = E_1\text{-}E_2 / S$$

Where E_1 is the potential measured in 10^{-3} mol L^{-1} of 1^{ry} ion solution, E_2 the potential measured in 10^{-3} mol L^{-1} of interfering solution and S is the slope of the investigated sensor.

3. RESULTS AND DISCUSSION

Selective membranes in ion-selective electrodes (ISEs) have shown both ion exchange and perm-selectivity of the sensor ions [31]. It is well known that the sensitivity and selectivity depend significantly on the membrane composition and the properties of the solvent mediator employed as well as the plasticizer/PVC ratio used [32]. It is rewarding to get newly fabricated electrodes with competitive properties for determination of pharmaceutical active constituents so utilizing the properties of the composite materials as efficiently as possible to achieve this goal is crucial. Taking these points in contemplation, we have extensively worked in the design and optimization of the proposed electrodes.

3.1. Sensors fabrication

3.1.1. PVC matrix

It has been reported that PVC matrix is a regular support and reproducible trap for ion association complexes in ISEs. Nevertheless, its use creates a need for plasticization and places a constraint on the choice of mediator [31].

3.1.2. Plasticizers

The solvent mediator, in particular, has a dual function: it acts as a liquefying agent, making the membrane material workable, that enables homogenous solubilization and modifies the distribution constant of the ion-exchanger used and sustains these characteristics on continued use. The proportion of solvent mediator must be optimized in order to minimize the electrical asymmetry of the membrane in order to keep the sensor as clean as possible and to stop leaching to the aqueous phase [33].

In the present investigation, different plasticizers were tried. The optimum available mediator for fabrication of sensor I was found to be 2-NPOE, while DOP was the optimum mediator for sensor II. They act by plasticizing and adjusting the membrane permittivity to provide the highest possible selectivity and sensitivity.

3.1.3. Ionophores

The molecular recognition and inclusion complexation are of current interest in host–guest and supramolecular chemistry and offer a promising approach to chemical sensing. The response of ionophore -based potentiometric sensors is usually governed by the molecular recognition ability of the analyte (guest) and the host molecule [32].

Calixarenes are well-known as selective ligands for various ions through dipole–dipole interactions. They can complex with a large variety of cation substrates to form stable host–guest inclusion complexes. This property of calixarenes has been largely exploited for the development of a number of cation selective electrodes [34].

The present work evaluates the possibility of using 4-tert butylcalix[8]arene (tBC8) as sensor ionophores in the preparation of CAM-selective electrode II.

3.1.4. Ion exchangers

It is well known that lipophilic ionic sites promote the interfacial ion-exchange kinetics and decrease the bulk resistance by providing mobile ionic sites in the electrode matrix [35].

AG ion selective electrode membrane must exhibit anion exchange capacity. This was achieved by using a newly introduced lipophilic anionic exchanger; tetraheptylammonium bromide (THB) and the results obtained by the proposed tetraheptylammonium bromide (THB) sensor (sensor I) showed great accuracy, higher reproducibility, and selectivity for AG determination.

On the other hand, the fact that CAM behaves as cation suggests the use of ion-exchanger of cationic type; potassium tetrakis 4-chlorophenyl borate (KTCPB) was the chosen cationic exchanger in the fabrication of sensor II. Preliminary trials were done based on the use of precipitation based technique using the ion-association complexes of CAM with the counter anion (ammonium reineckate) in a plasticized PVC matrix, but the formed

membranes showed non-reproducible drifting signal. This may be attributed to the leaching of the ion-association complex out of the membrane.

3.2. Sensors calibration and response time

Table (1) shows the results obtained over a period of three weeks for the sensor I, and two weeks for the sensor II. Typical calibration plots are shown in Figures (2, 3); the slope was computed from the linear part of the calibration graph. The slopes were found to be -53.45±2.93, 30.20±1.66 mV/concentration decades for the sensors I and II, respectively. The sensors displayed constant potential readings within ±3 mV from day to day. The required time for the sensors to reach values within ±3 mV of the final equilibrium potential after increasing drug concentration was found to be 10-20 seconds for AG and CAM electrodes (sensor I and II).

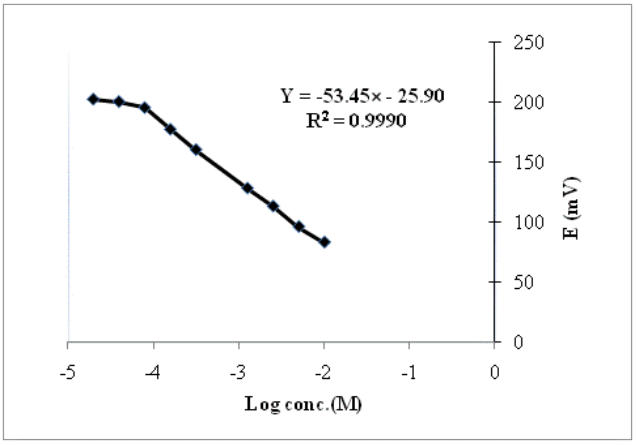


Fig. 2. Potentiometric profile of AG sensor

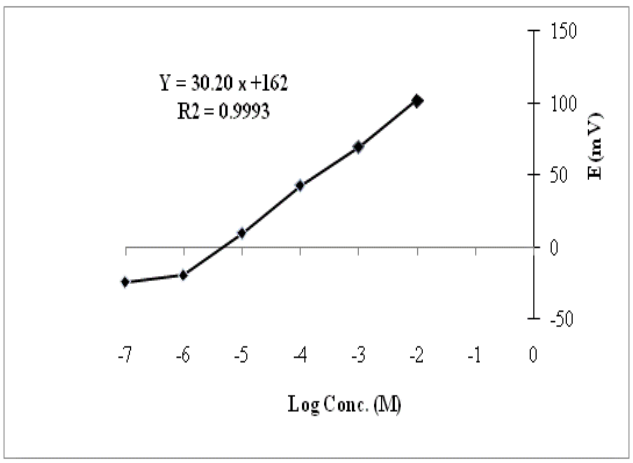


Fig. 3. Potentiometric profile of CAM sensor

Table 1. Response characteristics of the investigated electrodes

Parameters	**Sensor I**	**Sensor II**
slope mV/decade	-53.45	30.20
Intercept (mV)	25.90	162
correlation coefficient	0.9990	0.9993
Response time (seconds)	10-20 sec.	10-20 sec.
Working pH range	4.5-10.5	4.5-7.5
Concentration range (M)	1.56×10^{-4} –1.00×10^{-2}	1.00×10^{-6}-1.00×10^{-2}
Life span (weeks)	4-6 weeks	4-6 weeks
Precision (Recovery%±SD)		
Repeatability[1]	99.24±2.12	100.80±0.32
Reproducibility[1]	100.12±1.90	100.44±1.91
Average recoveries %[1]	100.04	99.98
Robustness[2]	2.19	1.67

[1] Three concentrations each repeated three times
[2]Relative standard deviation % of potential produced by 1.00×10^{-3} mol L^{-1} solution (three times) at pH 6.5 instead of pH 6 (in distilled water)

3.3. Effect of pH

For quantitative measurements with ISEs, studies were carried out to reach the optimum experimental conditions. The effect of pH on the response of the proposed sensors was studied to reach the optimum experimental conditions. Figure (4) shows the potential-pH profile for 1.00×10^{-3} AG for sensor I. Figure (5) **s**hows the potential-pH profile for 1.00×10^{-3} CAM for sensor II.

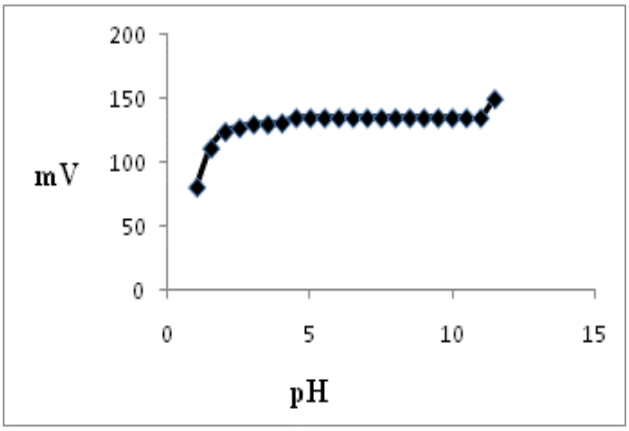


Fig. 4. Effect of pH on response of Sensor I (AG) 1.00×10^{-3} mol L^{-1}

It was apparent that the sensors responses were fairly constant in solutions of pH values 4.5-10.5 and 4.5-7.5 for the sensors I, and II; respectively, i.e. in these pH ranges the studied drugs are completely ionized, dissociated and sensed. Buffer solution such as (phosphate buffer) was tried and it was found that there is no need for addition of any buffer as buffers contain interfering substances which can avoid presence of any interfering substances found and due to wide range of pH for both sensors (I and II).

For sensor I, below pH 4.5 a slight gradual decrease in the potential with decreasing the pH without a well-defined constant region while, above pH 10.5, there is a slight increase in potential. For the sensor II, above pH 7.5, the potential showed a sharp decrease which could be due to the formation of a non-protonated tertiary amino group of CAM, while, below pH 4.5,the potentials displayed by the electrodes were noisy and unbalanced.

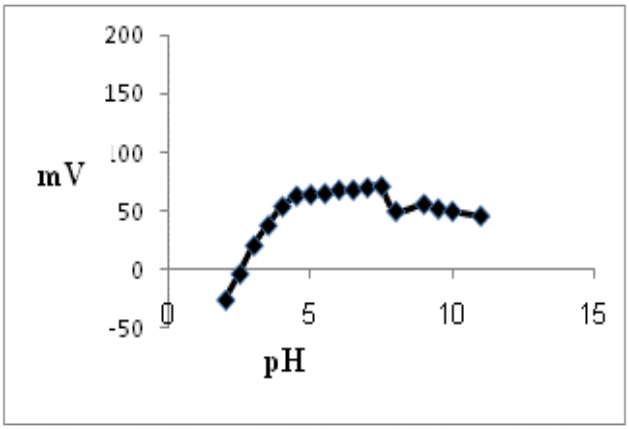


Fig. 5. Effect of pH on response of Sensor II (CAM) 1.00×10^{-3} mol L^{-1}

Table 2. Potentiometric determination of laboratory prepared mixtures containing different ratios of AG and CAM

Percentage		**Recovery %**[1]	
CAM	**AG**	**Sensor I**	**Sensor II**
1	1	103.46	98.23
1	10	102.21	100.44
1	5	100.96	101.54
5	1	98.47	97.13
Mean± SD		101.27±2.13	99.33±2.02

[1] Average of three determinations

3.4. Potentiometric determination of laboratory prepared mixtures containing different ratios of AG and CAM

The results obtained upon analysis of laboratory prepared mixtures containing different ratios of AG and CAM showed that the proposed sensor I can be successfully used for selective determination of AG in presence of CAM with no need for prior separation. It was also obvious that the proposed sensor II can be successfully used for selective determination of CAM in presence of AG with no need for prior separation Table (2).

3.5. Potentiometric determination of AG and CAM in Spasmopyralgin tablets

The proposed sensors were employed for assaying of AG and CAM in the pharmaceutical formulation (*Spasmopyralgin tablets*). The results prove the applicability of the sensors as demonstrated by the accurate and precise percentage recoveries. Susceptible tablets excipients did not show any interference. Thus, the determination of AG and CAM were carried out without prior treatment or extraction using sensor I for the determination of AG and sensor II for the determination of CAM Table (3). The validity of the proposed method was further assessed by applying the standard addition (spiking) technique. The results in Table (3) demonstrate the accuracy and precision of the method.

Table 3. Quantitative determination of AG and CAM in Spasmopyralgin tablet and standard addition technique by the proposed two sensors

Pharmaceutical dosage form	***Found*±S.D of Sensor I & II***	
Dizirest B6 tablet Batch no.(1410400)	**Sensor I**	**Sensor II**
Mean±SD	98.47±0.62	99.70±1.69
Standard addition		
1.00×10^{-2}	100.93	100.99
1.00×10^{-3}	100.34	97.13
Mean±SD	100.63±0.42	99.06±2.73

*Average of three determination

3.6. Sensors selectivity

The response of the two sensors in the presence of tablet excipients, organic and inorganic related substances was assessed and the results of the calculated selectivity coefficients showed that the proposed sensors displayed high selectivity and no significant interference was observed from the susceptible interfering species as shown in Table (4).

Table 4. Potentiometric selectivity coefficients ($K^{pot}_{Primary\ ion,\ interferent}$) of AG and CAM for the proposed sensors by separate solution method [30]

Interfering sub. 1.00×10^{-3}mol.L^{-1}	**Selectivity coefficient ***	
	Sensor I	**Sensor II**
Sucrose	6.23×10^{-1}	1.39×10^{-7}
Lactose	5.97×10^{-1}	1.99×10^{-5}
Glucose	6.50×10^{-1}	1.90×10^{-7}
NaCl	5.48×10^{-1}	5.68×10^{-4}
Starch	5.71×10^{-1}	8.87×10^{-8}
K- citrate	5.24×10^{-1}	1.70×10^{-5}
$MgSo_4$	7.09×10^{-1}	2.39×10^{-7}
Na_2Co_3	5.97×10^{-1}	1.04×10^{-8}
Fructose	5.97×10^{-1}	2.69×10^{-5}

*Average of three determinations

4. CONCLUSION

The responses of the developed sensors are sufficiently precise, accurate and prove the great selectivity of the sensors for the quantitative determination of AG and CAM in pure form, in laboratory prepared mixtures and in pharmaceutical formulations. Moreover, the use of the proposed sensors compromises the great advantage of eliminating any need for drug pretreatment or separation steps. Therefore it can be used for the routine analysis of AG and CAM in quality control laboratories. In general, the ISEs proposed here offered high simplicity in design and a very low limit of detection as well as being rapid, simple, and inexpensive and could compete with the many sophisticated methods currently available.

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