Bull. Pharm. Sci., Assiut University, Vol. 35, Part 2, 2012, pp. 199-214

Bulletin of Pharmaceutical Sciences
Assiut University

BATCH AND FLOW INJECTION POTENTIOMETRIC MONITORING OF CEFTRIAXONE SODIUM IN PHARMACEUTICAL PREPARATIONS USING TWO NOVEL MEMBRANE SENSORS

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Two novel potentiometric sensors are prepared, characterized and successfully used for static and continuous determination of ceftriaxone sodium (CRXN). Both sensors are based on the use of plasticized PVC matrix membranes incorporating tetradodecylmethyl ammonium bromide (TDMAB), ortridodecylmethyl ammonium chloride (TDMAC) ion-exchangers and used for quantitative determination of CRXN at concentration level down to 29 µM using both sensors with a good accuracy. Both sensors offer the advantages of fast response, reasonable selectivity, elimination of drug pre-treatment or separation steps, low cost and possible interfacings with computerized and automated systems. The use of plasticized membrane electrodes were used for continuous monitoring of CRXN offers the advantages of simple design, ease of construction and possible applications to small volumes of drug solutions with little manipulation and without pre-treatment. Both detectors display a wide dynamic measurement range of the drug under continuous mode of operation with a flow rate of 2.0 ml.min^{-1} and used for quantitative determination of CRXN. The developed sensors were utilized in static continuous modes successfully for the determination of CRXN in pure powders and in dosage forms. It is worth noting that the developed membrane electrodes exhibited good selectivity toward CRXN over other cephalosporins such as; cefradine, ceftazidime, cefadroxil, cefaclor and cefoperazone, as well as other additives found in the pharmaceutical preparations such as; glucose, fructose and maltose.

INTRODUCTION

Cephalosporins are the second major group of β-lactam class of antibiotics, isolated from Cephalosporium species or prepared semi-synthetically. They are antibiotics with broad spectrum on antimicrobial properties. They have an added advantage over the first known group of this class of antibiotics, penicillin, that penicillin allergic patients can be treated with these antibiotics; cephalosporins. Their antibacterial and pharmacokinetic properties have wide therapeutic use[1]. The broad spectrum of activity and favourable safety profile make the cephalosporins one of the most widely prescribed class of antimicrobials. The earlier generation cephalosporins are commonly used for community-acquired infections, while the later generation agents, with their better spectrum of activity against Gram-negative bacteria make them useful for hospital-acquired infections or complicated community-acquired infections[2]. CRXN (Fig. 1) is a parenteral third generation cephalosporins (M.W. 661.6). It displays a broad spectrum of activity against Gram-negative and Gram-positive pathogens[2].

Due to the extensive use of cephalosporins in our market and the great importance of them, many reports have been suggested for quantification and stability assessment of them. These methods include spectrophotometry[3-11]

Received in 15/10/2012 & Accepted in 17/12/2012

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spectrofluorimetry[12-15], TLC[16&17], HPTLC[18-20] and HPLC[21-26]. Most of these methods, however, utilize expensive instrumentation, suffer from lack of selectivity, involve careful control of the reaction conditions or derivatization reactions, and require time-consuming pre-treatment steps which affect their usefulness for routine analysis.

In view of the above factors, a potentiometric method was considered, being cheaper, faster and sometimes more efficient than HPLC. Very little work was found in the literature for the electrochemical determination of the investigated drug[27&28].

Application of potentiometric sensors in the field of pharmaceutical and biomedical analysis has been advocated. The approach provides simple, fast, and selective technique for determination of various drugs[29-34]. However, as far as the available literature is concerned, very little records were known about the use of this technique for the analysis of one member of the cephalosporins namely; cefuroxime[35&36].

The objective of the present study is to construct potentiometric membrane sensors for static and hydrodynamic, flow injection analysis (FIA) of CRXN in pure powder and its pharmaceutical preparations. The developed sensors incorporate ion-exchangers; TDMAC or TDMAB embedded in plasticized PVC matrix membranes. Performance characteristics of both sensors reveal low detection limit, good sensitivity and selectivity, fast response, long life span and application for accurate determination of CRXN in pharmaceutical preparations under static and hydrodynamic (FIA) modes of operation.

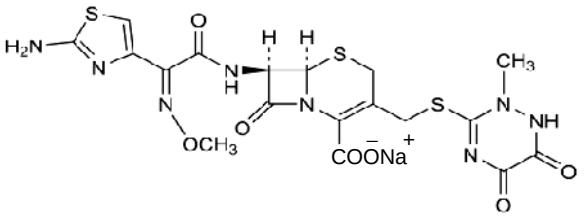

Fig. 1: Chemical structure of ceftriaxone sodium (CRXN).

EXPERIMENTAL

Apparatus

All membrane potential measurements were made at 25±1°C using data acquisition system, eight-channel electrode-computer interface (Nico-2000 Ltd., London, UK) controlled by Nico-2000 software. An Orion Ross pH electrode (Model 80-02) was used for pH adjustment. A double-junction Ag/AgCl electrode (Orion Model 90-02-00) with an Orion (90-02-02) internal filling solution was used as the reference electrode. The outer compartment of the reference electrode was filled with 1.0 M lithium acetate. The components of the FIA system were similar to those used previously[37]. The flow injection analysis (FIA) system manifold (Fig. 2) consisted of a two channel Ismatech MS-REGLO model, peristaltic pump polyethylene tubing (0.71 i.d.) and an Omni fit injection valve (Omni fit, Cambridge UK) sample loop of 150 µl volume, the potential signals were recorded using a high impedance data acquisition 8-channel box connected to a PC through the interface Nico-2000 (Nico-2000 Ltd) and Nico-2000 software. Spectronic™, Genesys™, ultraviolet-visible spectrophotometer (Milton Roy Co., USA) with matched 1 cm quartz cells connected to an IBM computer loaded with the Winspec™ application software.

Materials and reagents

- All solvents used were of analytical-reagent grade.
- High molecular weight polyvinyl chloride (PVC) was obtained from Poly sciences (Warrington, PA). Dichloro-tin(IV)-tetraphenylporphorin (Sn TPP-Cl_2), copper-octaethylporphorin (Cu OEP), zinc-octa-ethylporphorin (Zn OEP), tridodecylmethyl ammonium chloride (TDMAC), tetra-dodecylmethyl ammonium bromide (TDMAB), bis(2-ethylhexyl) sebacate (DOS), benzyltributyl ammonium bromide (BTBAB), o-nitropheynloctylether (o-NPOE), ethylenebis-triphenylphosphine bromide (EBTPPB) and 2-fluorophenyl-2-nitrophenylether (FPNPE) were obtained from Fluka (Ronkonkoma NY). Tetrahydrofuran (THF) was purchased from Fisher (Fairlawn, NJ). Tris-(hydroxymethyl)-aminomethane (TRIS) was obtained from Sigma (St. Louis, MO). Dichloro-bis(triphenyl-phosphine)palladium(II) (Pd TPP-Cl_2) was obtained from Aldrich (Milwaukee, WI). The sodium salts of thiocyanate and sulfate were obtained from

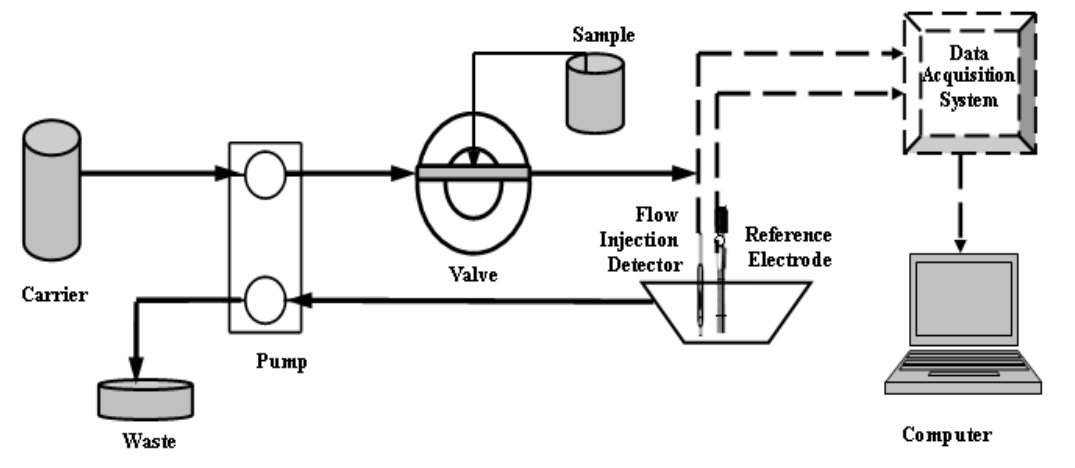

Fig. 2: Manifold for the FIA set up used for the determination of CRXN.

Matheson (Cincinnati, OH). Sodium salts of iodide and nitrate were purchased from J.T. Baker (Philipsburg, NJ). Sodium salt of acetate was obtained from Sigma (St. Louis, MO). Sodium chloride was obtained from Fisher Scientific (Cincinnati, OH). Ceftriaxone sodium and ceftazidime-pentahydrate (T3A Pharma Group, Assiut, Egypt). Cefaclor monohydrate and cefradine anhydrous (Sigma Chemical Co., St. Louis, USA), cefadroxil monohydrate (Amoun Pharmaceutical Industries Co., APIC, Cairo, Egypt) and cefoperazone sodium (Pfizer Co., Egypt) were obtained as gifts and were used as supplied. Pharmaceutical formulations containing the studied drugs were purchased from the local market.

- Acetate buffer was prepared by titrating 50 mM solution of the acid form with concentrated sodium hydroxide to a pH-value of 5.5±0.01. Phosphate buffer was prepared by titrating 50 mM solution of the acid form with concentrated sodium hydroxide to a pH-value of 7.0±0.01 and Tris buffer was prepared by titrating 50 mM of the base form with concentrated hydrochloric acid to a pH-value of 7.4±0.01. All standard solutions and buffers were prepared with doubly distilled water.

Preparation of standard solutions

A stock solution (10^{-2} M) of CRXN at pH 5.5 was prepared by dissolving 66.2 mg of CRXN in 10 ml acetate buffer pH 5.5. Dilute solutions of CRXN were freshly prepared by diluting the stock solution with acetate buffer (pH 5.5). All experiments were performed using doubly distilled water. The stock and working standard solutions were freshly prepared.

Sensors construction

Table 1 shows the composition of membranes used in this study and formulated with different ion-exchangers, different ionophores and solvent mediators. Different compositions were prepared aiming for the selection of the best sensing system that would provide the bestperformance characteristics.

A 2.0 mg portion of TDMAC or TDMAB ion-exchanger (corresponding to 1.0 wt%) was thoroughly mixed with 132.0 mg of *o*-NPOE (corresponding to 66.0 wt%), 66.0 mg of PVC (corresponding to 33.0 wt%) and 2.0 ml THF in a glass ring placed on a glass plate covered with filter paper and left to stand overnight to allow slow evaporation of THF at room temperature[38]. The master membrane was sectioned with a cork borer (7 mm diameter) and glued to a PVC tubing (~3 cm length, ~8 mmi.d.) using THF. A solution of 1 mM NaCl plus 1 mM CRXN in 50 mM acetate buffer, pH 5.5, was used as the internal filling solution. Ag/AgCl internal reference electrode (1.0 mm diameter) was immersed in the internal reference solution. Prior to use, membrane electrodes were conditioned for ~24 hrs in a solution having the same composition as the internal filling solution and were stored in the 1 mM NaCl solution when not in use. All potentiometric measurements were made at ambient temperature.

Table 1: Composition and response characteristics of metallo-porphyrins and ion-exchangers based membrane electrodes for CRXN determination.

PVC Membrane sensor	Plasticizer	Electroactive species	Additive	Slope	Linear range (M)
E_1	*o*-NPOE	TDMAB	-	-28.84	$2.9x10^{-5} – 1x10^{-2}$
E_2	DOS	TDMAB	-	-28.63	$2.9x10^{-5} – 1x10^{-2}$
E_3	FPNPE	TDMAB	-	-	-
E_4	*o*-NPOE	TDMAC	-	-25.71	$2.9x10^{-5} – 1x10^{-2}$
E_5	DOS	TDMAC	-	-22.39	$2.9x10^{-5} – 1x10^{-2}$
E_6	FPNPE	TDMAC	-	-	-
E_7	*o*-NPOE	BTBAB	-	-	-
E_8	*o*-NPOE	EBTPPB	-	-	-
E_9	*o*-NPOE	Pd TPP-Cl_2	-	-10.65	$1x10^{-4} – 1x10^{-2}$
E_{10}	*o*-NPOE	Sn TPP-Cl_2	-	-16.21	$1x10^{-4} – 1x10^{-2}$
E_{11}	*o*-NPOE	Cu OEP	TDMAB (50 mol %)	-22.15	$1x10^{-4} – 1x10^{-2}$
E_{12}	*o*-NPOE	Zn OEP	TDMAB (50 mol %)	-23.27	$1x10^{-4} – 1x10^{-2}$

The sensors were calibrated under static mode of operation by transferring different aliquots of $1x10^{-2} – 1x10^{-3}$ M aqueous solution of CRXN to 10 ml beaker containing 10.0 ml of acetate buffer, pH 5.5. The sensors were immersed in the solution in conjunction with a double junction Ag/AgCl reference electrode. The potential readings were recorded after stabilization to ±0.2 mV and the EMF was plotted as a function of logarithm CRXN concentration.

To investigate the influence of dielectric constants of plasticizerson the performance of the developed sensors, different plasticizers were used (*o*-NPOE ε = 24; FPNPE ε = 50; and DOS ε = 3.88) and used in membrane preparation to select the solvent mediator which exhibits the best working characteristics[39] (ε is the dielectric constant of the plasticizer).

Different buffers were tested in the analysis using the proposed electrodes such as acetate buffer (pH 5.5), phosphate buffer (pH 7.0) and Tris buffer (pH 7.4) to select the buffer system that exhibits the best performance characteristics.

Tubular detector construction

Tubular sensors were constructed as described previously[37]. Coating solutions were prepared by mixing 2.0 mg portion of TDMAC or TDMAB ion-exchanger, 132.0 mg of *o*-NPOE, 66.0 mg of PVC and 2.0 ml THF. This solution was deposited 3-4 times using a dropper directly into a hole sectioned in the tube. The tubular sensor was inserted into the flow injection system as schematically shown in figure 2. A 50 mM acetate buffer (pH 5.5) was used as a carrier solution at a flow rate of 2 $ml.min^{-1}$.

The detector was calibrated at 25°C under hydrodynamic mode of operation by injection of CRXN samples through a valve loop of 150 µl in the carrier stream. After a steady-state, the baseline was reached; the potential signals were recorded using a high-impedance data acquisition 8-channel box connected to a PC as mentioned above. An Orion Ag/AgCl double junction reference electrode was placed in a Petri-dish downstream from the indicator sensor just before the solution went to waste.

Determination of CRXN in pharmaceutical preparations

CRXN is found in the market in the form of vials only. The available pharmaceutical preparations of this drug were analysed such as; Cefotrix® 0.25 gm, Cefotrix® 0.5 gm, Cefotrix® 1 gm, Cefaxone® 0.25 gm, Cefaxone® 0.5 gm, Cefaxone® 1 gm and Ceftriaxone® 1 gm; for intravenous and intramuscular injections. An accurately weighed amount of powder equivalent to 66.2 mg of CRXN was transferred into a 10-mL volumetric flask, dissolved in about 5 mL of 50 mM acetate buffer, pH 5.5, diluted to the mark with the same buffer, mixed well and filtered through a double filter paper; the first portion of the filtrate was rejected. Further dilutions with the same buffer were made and then the general procedure was followed.

For CRXN measurement under static mode of operation, a 10-ml aliquot of the drug solution was potentiometrically measured. The drug sensor and reference electrode were immersed in the solution, and the potential readings were recorded after reaching the equilibrium response. The concentration of CRXN was calculated using a calibration graph.

For continuous measurements (FIA), a flow stream of 50 mM acetate buffer of pH 5.5 carrier solution was allowed to pass through the tubular electrode at a flow rate 2.0 $ml.min^{-1}$. Successive 150 µl aliquots of the standard CRXN and unknown test sample solutions were injected into the flowing stream. The corresponding potential change was measured and recorded vs. time. A typical calibration plot was made and used to determine the concentration of the unknown samples.

RESULTS AND DISCUSSION

Response characteristics of the developed sensors

Plasticized PVC membrane electrodes formulated with different electro-active species (ion exchangers or metal ion complexes) were prepared and evaluated. Membranes were formulated using a casting solution of the composition 1:33:66 wt% of electro-active species, PVC and plasticizer, respectively. Such polymer-membrane electrodes based on either ion-exchangers (TDMAB, TDMAC, BTBAB and EBTPPB) or metal-ion complexes (PdTPP-Cl_2, SnTPP-Cl_2, CuOEP and Zn OEP) were prepared.

As shown in figure 3, TDMAB and TDMAC based membrane sensors exhibited near-Nernstian responses (-28.84 and -25.71 $mV.decade^{-1}$) over the concentration ranges of $2.9x10^{-5}$ – $1x10^{-2}$M. However, sensors incorporating BTBAB or EBTPPB as cationic exchangers did not exhibit any detectable responses. Cu, Zn, Pd, and Sn based ion-carriers were selected as ionophores based on the well-known drug interactions with such metal ions[40-42]. However, due to the high hydrophilicity of the drug[2] (see the selectivity order based on ion-exchange mechanism below) and its weak binding ability to such metal ion complexes, were found to be not suitable carriers for such drug type. For instance, sensors incorporating Cu OEP and Zn OEP based membrane sensors exhibited near-Nernstian responses (-22.15 and -23.27 $mV.decade^{-1}$) over the concentration ranges of $1x10^{-4}$ – $1x10^{-2}$ M. Unfortunately, the obtained responses were found to be of the Hofmeister type and due to the presence of 50% TDMAB as an additive in the membrane construction, as indicated by the selectivity order. On the other hand, membrane electrodes based on Pd TPP-Cl_2 and Sn TPP-Cl_2 exhibited sub-Nernstian responses (-10.65 and -16.21 $mV.decade^{-1}$, respectively) over the concentration ranges of $1x10^{-4}$ – $1x10^{-2}$ M. Therefore, membrane electrodes based on TDMAB and TDMAC were selected for further investigations.

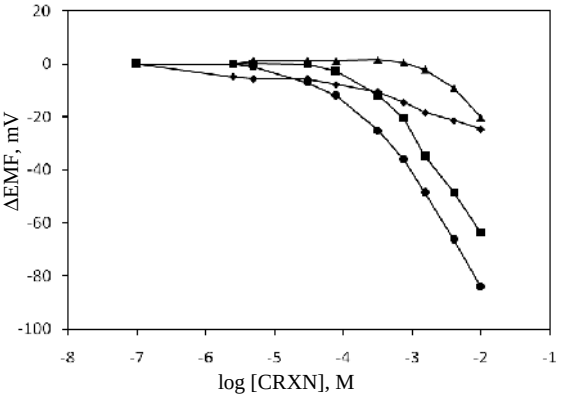

Fig. 3: Potentiometric response of various PVC membrane electrodes towards CRXN measured in 50 mMacetate buffer, pH 5.5. The ion-exchangers tested were (●) TDMAB, (■) TDMAC, (▲) EBTPPB and (♦) BTBAB.

Potentiometric response characteristics of CRXN selective membrane electrodes were studied in order to probe the effect of different buffers on the potentiometric responses. Tris buffer (pH 7.4), acetate buffer (pH 5.5) and phosphate buffer (pH 7.0) were tested to select the buffer system which gives the best performance characteristics. It was found that no responses were obtained upon using Tris buffer and phosphate buffer; however acetate buffer gave near-Nernstian response, so it was selected for all subsequent work. This may be attributed to that upon using acetate buffer, pH 5.5, about 99.9% of CRXN was ionized in the anionic form [$CRXN^{-2}$] so maximum response was obtained at this pH [pKa of CRXN; 2.37 (COOH), 3.03 (aminothiazole) and 4.21 (hydroxytriazinone)][43].

The dielectric constants of solvent mediators much influence the sensor characteristics and response. The performance characteristics of the proposed membrane sensors are greatly affected by the used plasticizer. Sensors were constructed using three different plasticizers; *o*-NPOE, DOS and FPNPE then the performance characteristics were investigated (Table 1). It was found that *o*-NPOE was the best plasticizer which exhibited the best performance characteristics proved by giving nearer-Nernstian slopes -28.84 and -25.71 mV.decade^{-1} for TDMAB and TDMAC based membrane sensors, respectively (Table 1 and Figs. 4&5).

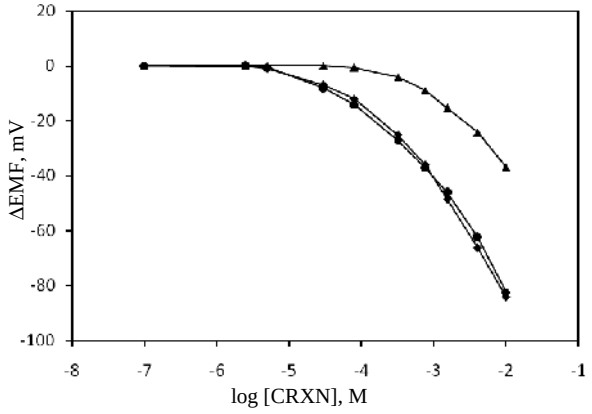

Fig. 4: Potentiometric response of TDMAB based membrane electrodes formulated with different solvents mediators; (♦) *o*-NPOE, (●) DOS and (▲) FPNPE.

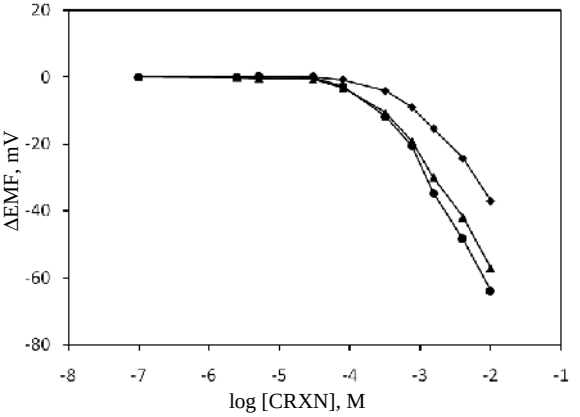

Fig. 5: Potentiometric response of TDMAC based membrane electrodes formulated with different solvent mediators; (●) *o*-NPOE, (▲) DOS and (♦) FPNPE.

Results from three replicate studies using TDMAB and TDMAC based membrane sensors exhibited near-Nernstian slopes of -28.84 and -25.71 mV.decade^{-1} over the concentration ranges of $2.9x10^{-5}$ – $1x10^{-2}$ M, with detection limits of $1.17x10^{-5}$ and $1.25x10^{-5}$ M (7.74 and 8.77 µg.ml^{-1}) for TDMAB and TDMAC based membrane sensors, respectively (Table 2). The response characteristics (e.g., selectivity, response time, linear range.....etc.) of different types of CRXN selective membrane electrodes (TDMAB, TDMAC) are summarized in (Table 2). TDMAB and TDMAC based membrane sensors are successfully formulated for determination of CRXN and remained suitable for use for about 8 weeks (Table 2).

The developed sensor responses are greatly affected by the pH of the medium. The potentiometric responses of TDMAB and TDMAC based membrane sensors were examined at different pH values over a pH range of 2.9-12.4. This was performed in presence of 10^{-3} and 10^{-2} M CRXN. In each concentration level, the pH of CRXN solution was adjusted using either hydrochloric acid or sodium hydroxide solutions. The potential was then recorded after the pH was stabilized. The variation in the pH range 4-7 has no significant effect on the potentiometric responses for both TDMAB and TDMAC based membrane sensors. It was found that the potentials of the prepared membrane sensor considerably declined with negative drift at pH values higher than ~7 then remain constant above pH ~8 (Fig. 6). This may be due to due to progressive

Table 2: Summary of response characteristics of TDMAB and TDMAC based membrane sensors under static mode of operation for determination of CRXN.

Parameter	TDMAB *	TDMAC *
Slope, (mV per decade)	-28.84	-25.71
Working range, M	$2.9 \times 10^{-5} - 1.0 \times 10^{-2}$	$2.9 \times 10^{-5} - 1.0 \times 10^{-2}$
Lower limit of linear range, (M)	2.9×10^{-5}	2.9×10^{-5}
Response time ($t_{95\%}$) For conc. < 10^{-3} (sec.) For conc. ≥ 10^{-3} (sec.)	 <30 <10	 <30 <10
Working range, (pH)	4-7	4-7
Detection limit, (M)	1.2×10^{-5}	1.25×10^{-5}
Life span, (week)	8	8
Standard deviation, (%)	1.17	1.42

*Average of five measurements.

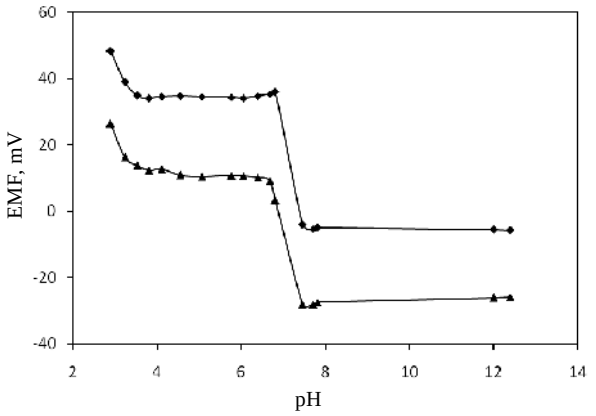

Fig. 6: Influence of pH on the potentiometric response of TDMAB based membrane sensorin presence of: (▲) 10 mM and (♦) 1 mM CRXN.

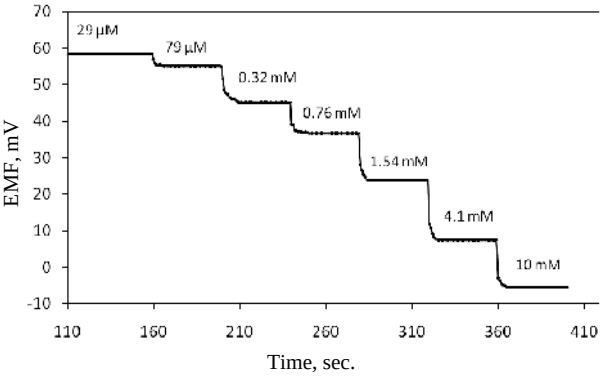

Fig. 7: Response time of TDMAB based membrane sensor towards CRXN measured in acetate buffer pH 5.5.

degradation of CRXN at higher pH values and the hydroxide anion interference. However, at lower pH values, the sensors responses were severely influenced by H_3O^+ and the decrease of the ionized/non ionized ratio of CRXN. Based on this, the working pH range for the developed sensors is from pH 4 to 7.

The dynamic response times of the TDMAB and TDMAC based membrane sensors were examined by recording the potential readings at time intervals of 5 seconds. The relation between potential reading and response time was plotted for 29 µM to 10 mM CRXN. The time required to attain 95% of the equilibrium by both sensors was less than 10 s for drug concentration $\geq 10^{-3}$ M. These results indicated that both sensors are amenable for use with automated systems (Fig. 7).

Selectivity coefficients ($K^{pot}_{CRXN,\beta}$), of TDMAB and TDMAC based membrane sensors towards some interfering ions were determined by the separate solutions method (SSM)[44]. In this method, the selectivity coefficients of CRXN sensors were evaluated at a concentration of (1 M) measured in 50 mM acetate buffer pH 5.5 (Figs. 8&9). The selectivity coefficients ($\log K^{pot}_{CRXN,\beta}$) were determined with the rearranged Nicolsky equation[44]:

$$\log K^{pot}_{CRXN,\beta} = \left(\frac{E_1 - E_2}{S}\right) + \left(1 + \frac{Z_1}{Z_2}\right)\log(a) \qquad (1)$$

where, E_1 is the potential measured in 1M CRXN, E_2 the potential measured in 1 M of the interfering ion, Z_1 and Z_2 are the charges of the CRXN and interfering species β, respectively and S is slope of the calibration plot.

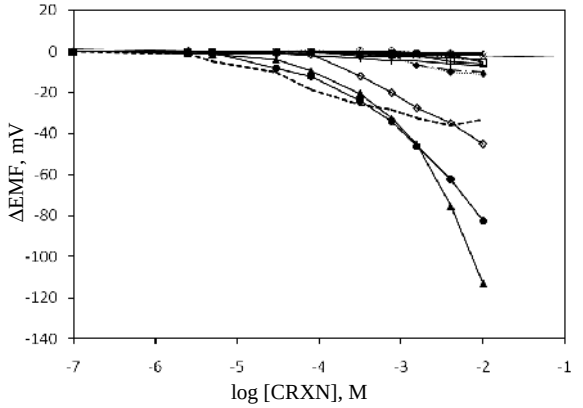

Fig. 8: Potentiometric responses of CRXN selective electrodes using TDMAB based membrane electrodes, measured in 50 mM acetate buffer pH 5.5, of towards various anions, additives and some cephalosporins: (●) CRXN, (---) Cefadroxil, (◊) Cefoperazone, (….) Cl^-, (Δ) SO_4^{-2}, (▲) NO_3^-, (○) CH_3COO^-, (*) Cefradine, (—|—) Cefaclor, (-.-.-.) Ceftazidime, (…♦…) glucose, (□) fructose and (—) maltose.

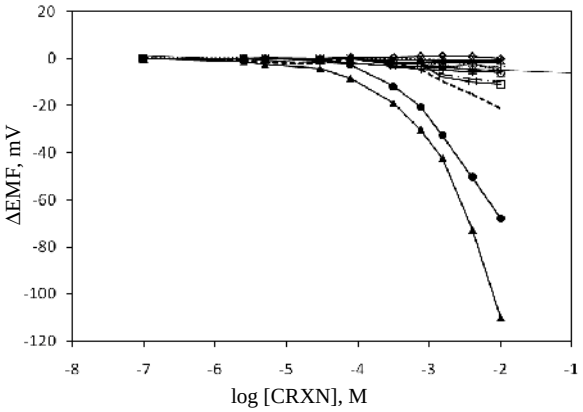

Fig. 9: Potentiometric responses of CRXN selective electrode using TDMAC based membrane electrode, measured in 50 mM acetate buffer pH 5.5, towards various anions, additives and some cephalosporins: (●) CRXN, (---) Cefadroxil, (◊) Cefoperazone, (….) Cl^-, (Δ) SO_4^{-2}, (▲) NO_3^-, (○) CH_3COO^-, (*) Cefradine, (—|—) Cefaclor, (-.-.-.) Ceftazidime, (□) glucose, (Δ) fructose and (—) maltose.

It is worth noting that the two membrane electrodes prepared exhibited good selectivity toward CRXN over other cephalosporins such as; cefradine, ceftazidime, cefadroxil, cefaclor and cefoperazone and other additives found in the pharmaceutical preparations such as; glucose, fructose and maltose. This enables us to use such sensors for determination of CRXN successfully without interference from other cephalosporins and the encountered additives. Moreover, the selectivity of the proposed electrodes toward other inorganic anions showed that the exhibited anionic responses follow the classical Hofmeister pattern for anions that is based on anions lipophilicity, in which the more lipophilic species are the preferred ones[45]. As shown in (Table 3), the selectivity pattern for TDMAB based membrane sensor was SCN^- > I^- >NO_3^- > CRXN > cefoperazone > cefadroxil > ceftazidime > cefradine > Cl^- > acetate > SO_4^{-2} > cefaclor. While that for TDMAC based membrane sensor was SCN^- > I^- > NO_3^- > CRXN > cefadroxil > ceftazidime > acetate > Cl^- > cefaclor > cefradine > SO_4^{-2} > cefoperazone.

Table 3: Potentiometric selectivity coefficients of *o*-NPOE plasticized TDMAC and TDMAB based PVC membrane sensors.

Interfering ion, B	$\log K^{pot}_{CRXN,\beta}$	
	TDMAB	TDMAC
Cl-	≤-5.51	≤-5.24
SO4--	≤-5.75	≤-5.41
NO3-	0.34	0.68
I-	2.74	2.74
SCN-	4.45	4.79
CH3COO-	≤-5.55	≤-5.14
Glucose	≤-5.14	≤-4.89
Fructose	≤-5.34	≤-5.41
Maltose	≤-5.62	≤-5.24
Cefradine®	≤-5.47	≤-5.38
Cefadroxil®	≤-4.10	≤-4.11
Cefaclor®	≤-5.79	≤-5.27
Ceftazidime®	≤-5.34	≤-5.01
Cefoperazone®	≤-2.88	≤-5.48

[a]maximal selectivity limit (≤) was used for ions that exhibited minimal response towards interferent ions[44].

Batch monitoring of CRXN in pharmaceutical preparations

The available pharmaceutical dosage forms of CRXN were analysed by the two proposed potentiometric sensors, as well as by reported method[4]. The two proposed potentiometric sensors were applied successfully for determination of the CRXN in its pharmaceutical dosage forms under static mode of operation. This finding indicated good

accuracy and precision in the determination of the cited drug in its pharmaceutical dosage forms. The results obtained (Table 4) were satisfactory compared to those obtained from the reported method[4]. No significant difference was found by applying *t*- and *F*-tests at 95% confidence level indicating good accuracy and precision. *F*-test revealed that there was no significant difference between the means and variances of the two sets of results.

Recovery studies were also carried out by standard addition method under static mode of operation. Recovery experiments were made to evaluate the accuracy of the proposed potentiometric methods on both the pure authentic and the dosage forms. Different concentrations of the authentic drug being determined were added to the sample preparation which was then analysed for the total amount of the drug present. The difference between the analytical results of the samples with and without the added drug gave the recovery of the amount added drug, (Table 5). The results clearly proved the accuracy of the proposed method for selective determination of the investigated drug without interference from common excipients.

Table 4: Determination of CRXN in its pharmaceutical formulations by the two proposed potentiometric sensors under static mode of operation in comparison with the reported method[4].

Pharmaceutical product	Recovery % ± SD[a,b]		
	TDMAB based membrane sensor	TDMAC based membrane sensor	Reported method[c]
Cefotrix®vials[d] 250 mg of ceftriaxone sodium/vial (IV, IM)	100.17 ± 1.07 *t* = 0.68 *F* = 1.38	99.79 ± 1.06 *t* = 0.07 *F* = 1.42	99.72 ± 1.26
Cefotrix®vials[d] 500 mg of ceftriaxone sodium/vial (IV, IM)	99.88 ± 1.64 *t* = 0.46 *F* = 1.77	99.3 ± 1.38 *t* = 0.27 *F* = 1.23	99.51 ± 1.23
Cefotrix®vials[d] 1000 mg of ceftriaxone sodium/vial (IV, IM)	98.83 ± 1.40 *t* = 1.11 *F* = 1.54	98.68 ± 1.46 *t* = 1.26 *F* =1.39	99.83 ± 1.72
Cefaxone®vials[e] 250 mg of ceftriaxone sodium/vial (IM)	98.82 ± 1.15 *t* = 0.43 *F* = 1.38	99.27 ± 1.45 *t* = 0.25 *F* = 2.23	99.08 ± 0.98
Cefaxone ®vials[e] 500 mg of ceftriaxone sodium/vial (IV, IM)	99.43 ± 1.09 *t* = 0.64 *F* = 1.11	99.25 ± 1.18 *t* = 0.41 *F* = 1.06	98.25 ± 1.15
Cefaxone ®vials[e] 1000 mg of ceftriaxone sodium/vial (IV, IM)	100.27 ± 1.33 *t* = 1.70 *F* = 2.35	100.34 ± 1.54 *t* = 1.63 *F* = 3.17	99.17 ± 0.86
Ceftriaxone®vials[f] 1000 mg of ceftriaxone sodium/vial (IV, IM)	100.16 ± 1.23 *t* = 1.91 *F* = 1.17	99.63 ± 0.86 *t* = 1.31 *F* = 1.73	98.87 ± 1.12

[a]Each value is the mean of five determinations.
[b]The tabulated values at 95% confidence limits are t = 2.78 and F = 6.39, respectively.
[c]Reference 4.
[d] T3A Pharma Group, Assiut, Egypt.
[e]Pharco Pharmaceuticals, Alexandria, Egypt.
[f]Kahira Pharm. & Chem. Ind. Co. under licence from Novartis Pharma S.A.E., Cairo, Egypt.

Table 5: Standard addition method for the assay of CRXN in its pharmaceutical dosage forms using TDMAB and TDMAC based membrane sensors under static mode of operation.

Pharmaceutical formulation	Authentic drug added ($mol.L^{-1}$)	TDMAB		TDMAC	
		Authentic drug found ($mol.L^{-1}$)	Recovery (%) ± SD[a]	Authentic drug found ($mol.L^{-1}$)	Recovery (%) ± SD[a]
Cefotrix® vials250	1.0×10^{-5}	0.95×10^{-5}	95.0±1.4	0.93×10^{-5}	93.0±1.5
	5.0×10^{-5}	4.81×10^{-5}	96.2±0.9	4.74×10^{-5}	94.8±0.6
	7.0×10^{-5}	6.73×10^{-5}	96.1±1.1	6.77×10^{-5}	96.7±0.9
Cefotrix® vials500	1.0×10^{-5}	0.98×10^{-5}	98.0±0.5	0.91×10^{-5}	91.0±1.2
	5.0×10^{-5}	4.86×10^{-5}	97.2±0.9	4.91×10^{-5}	98.2±0.7
	7.0×10^{-5}	6.57×10^{-5}	93.8±0.8	6.72×10^{-5}	96.0±0.9
Cefotrix® vials1000	1.0×10^{-5}	1.03×10^{-5}	103.0±1.5	0.96×10^{-5}	96.0±1.4
	5.0×10^{-5}	4.94×10^{-5}	98.8±0.7	4.94×10^{-5}	98.8±0.6
	7.0×10^{-5}	6.68×10^{-5}	95.4±0.9	6.78×10^{-5}	96.8±0.8
Cefaxone® vials250	1.0×10^{-5}	0.95×10^{-5}	95.0±0.7	0.90×10^{-5}	90.0±1.2
	5.0×10^{-5}	4.88×10^{-5}	97.6±0.6	4.98×10^{-5}	99.6±0.6
	7.0×10^{-5}	6.88×10^{-5}	98.2±1.2	6.89×10^{-5}	98.4±0.7
Cefaxone® vials500	1.0×10^{-5}	0.96×10^{-5}	96.0±1.4	0.97×10^{-5}	97.0±0.6
	5.0×10^{-5}	5.17×10^{-5}	103.4±0.7	4.82×10^{-5}	96.4±0.5
	7.0×10^{-5}	6.90×10^{-5}	98.5±0.9	6.70×10^{-5}	95.7±0.9
Cefaxone® vials1000	1.0×10^{-5}	0.89×10^{-5}	89.0±1.6	0.96×10^{-5}	96.0±1.1
	5.0×10^{-5}	4.99×10^{-5}	99.8±0.6	4.82×10^{-5}	96.4±0.7
	7.0×10^{-5}	6.93×10^{-5}	99.0±1.1	6.77×10^{-5}	96.7±0.8
Ceftriaxone® vials1000	1.0×10^{-5}	0.87×10^{-5}	87.0±1.4	0.95×10^{-5}	95.0±0.8
	5.0×10^{-5}	5.03×10^{-5}	100.6±0.8	4.93×10^{-5}	98.6±0.5
	7.0×10^{-5}	7.32×10^{-5}	104.6±0.9	6.80×10^{-5}	97.1±0.5

[a]Average of six determination.

Flow injection monitoring (FIA) of CRXN in pharmaceutical preparations

A tubular-type detector incorporating TDMAB and TDMAC based membrane sensors were prepared and used under hydrodynamic mode of operation for continuous CRXN quantification. The general intrinsic response characteristics of the detector revealed that the dependency of the peak height, peak width, and time to recover the base line depend on the flow rate of the carrier buffer solution. Successive injection of CRXN standard solutions through a valve loop of 150 µl in the carrier stream with different carrier flow rates (i.e. 1.0-4.0 $ml.min^{-1}$) revealed that as the flow rate increased the response peaks width decreased with a decrease in the peak height. Consequently, the recommended optimal flow rate was chosen to be 2.0 $ml.min^{-1}$. With a flow rates of 1 $ml.min^{-1}$, the tubular sensor required longer washing time to recover the base line leading to a decrease in the number of sample outputs. At flow rates higher than 3.0 $ml.min^{-1}$, the peak height declined.

A linear relationship between CRXN concentrations and FIA signals was obtained over the range 1-10 mM (Fig. 10). The slope of the calibration plot was near-Nernstian (-23.07±0.32 $mV.decade^{-1}$) for TDMAB based PVC membrane sensor. Table 6 shows the general response characteristics of the tubular TDMAB and TDMAC based membrane sensors under FIA mode of operation. The results obtained for determining CRXN in drug formulations using FIA are shown in table 7.

Validation of the proposed potentiometric methods for determining CRXN was made by measuring the range (R), lower limit of detection (LOD), accuracy (recovery), linearity (correlation coefficient) and sensitivity (slope). Results obtained support the application of the proposed potentiometric methods for quality control assessment of drug formulations.

Table 6: Response characteristics of tubular TDMAB and TDMAC based membrane sensors under hydrodynamic (FIA) mode of operation.

Parameter	TDMAB	TDMAC*
Slope, (mV per decade)	-23.07	-21.07
Correlation coefficient, (r)	0.996	0.994
Working range, mM	1 – 10	1 – 10
Intercept, (mV)	2.5	18.5
Lower limit of detection (mM)	0.5	0.6
Optimum flow rate, (ml min^{-1})	2	2
Carrier 50 mM acetate buffer, (pH)	5.5	5.5

* Based on three measurements.

Table 7: Determination of CRXN in its pharmaceutical formulations by the two proposed potentiometric methods under FIA mode of operation and the reported method[4].

Pharmaceutical product	Recovery % ± SD[a,b]		
	TDMAB based membrane sensor	TDMAC based membrane sensor	Reported method[c]
Cefotrix®vials[d] 250 mg of ceftriaxone sodium/vial (IV, IM)	98.83 ± 1.43 *t* = 1.17 *F* = 1.29	100.17 ± 1.98 *t* = 0.44 *F* = 2.49	98.72 ± 1.26
Cefotrix®vials[d] 500 mg of ceftriaxone sodium/vial (IV, IM)	98.86 ± 0.77 *t* = 1.10 *F* = 2.55	100.14 ± 1.78 *t* = 0.74 *F* = 2.09	99.50 ± 1.23
Cefotrix®vials[d] 1000 mg of ceftriaxone sodium/vial (IV, IM)	100.65 ± 1.95 *t* = 1.95 *F* = 2.28	99.01 ± 1.56 *t* = 0.87 *F* = 1.22	99.82 ± 1.72
Cefaxone®vials[e] 250 mg of ceftriaxone sodium/vial (IM)	98.77 ± 1.26 *t* = 0.48 *F* = 1.75	99.14 ± 1.24 *t* = 0.17 *F* = 1.59	99.08 ± 0.98
Cefaxone®vials[e] 500 mg of ceftriaxone sodium/vial (IV, IM)	99.51 ± 1.28 *t* = 0.63 *F* = 2.27	99.61 ± 1.25 *t* = 0.72 *F* = 2.08	98.95 ± 1.15
Cefaxone®vials[e] 1000 mg of ceftriaxone sodium/vial (IV, IM)	100.28 ± 1.02 *t* = 2.05 *F* = 1.45	99.80 ± 1.29 *t* = 0.99 *F* = 2.23	99.16 ± 0.86
Ceftriaxone®vials[f] 1000 mg of ceftriaxone sodium/vial (IV, IM)	99.65 ± 1.34 *t* = 1.09 *F* = 1.40	99.62 ± 1.35 *t* = 1.03 *F* = 1.51	98.87 ± 1.12

[a]Each value is the mean of five determinations.
[b]The tabulated values at 95% confidence limits are t = 2.78 and F = 6.39, respectively.
[c]Reference 4.
[d] T3A Pharma Group, Assiut, Egypt.
[e]Pharco Pharmaceuticals, Alexandria, Egypt.
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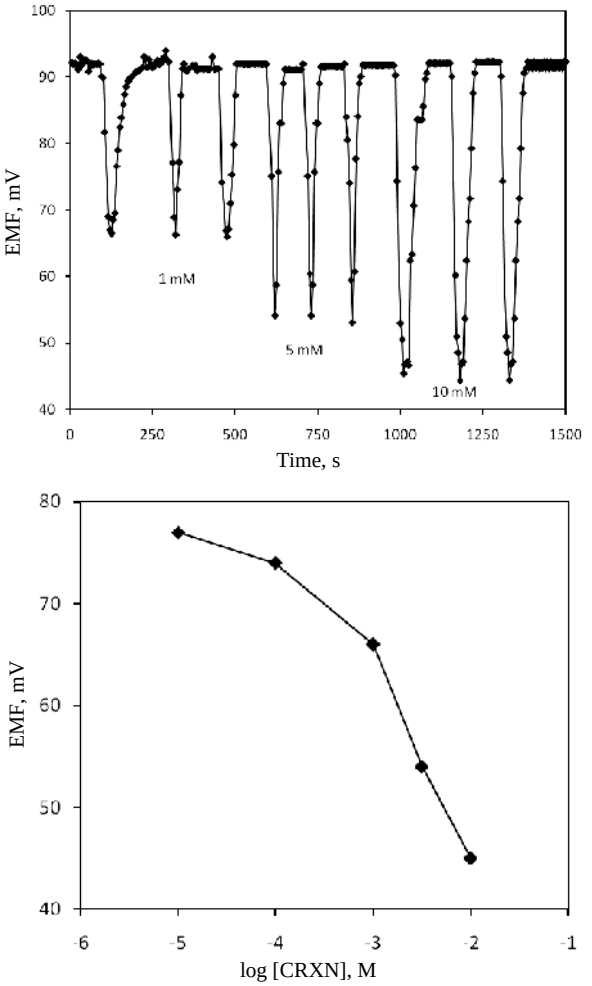

Fig. 10: Typical (FIA) peaks produced by injection of CRXN standard solutions through a valve loop of 150 µl in a stream of 50 mM acetate buffer pH 5.5 using the TDMAB based membrane sensor.

Conclusions

Two potentiometric sensors for CRXN were prepared, characterized and successfully used for static and continuous drug determination. Sensors based on the use of plasticized PVC matrix membranes incorporating TDMAB and TDMAC ion exchangers were used for quantitative determination of ceftriaxone sodium at concentration level down to 2.9×10^{-5} M with a good accuracy. The drug is determined in pure powders and in vials. The sensors offer the advantages of fast response, reasonable selectivity, elimination of drug pre-treatment or separation steps, low cost and possible interfacings with computerized and automated systems. The use of TDMAB and TDMAC based membrane sensors as two detectors for continuous monitoring of CRXN offers the advantages of simple design, ease of construction and possible applications to small volumes of drug solutions with little manipulation and without pre-treatment. The detector displays a wide dynamic measurement range of the drug under continuous mode of operation with a flow rate of 2.0 $ml.min^{-1}$.

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نشرة العلوم الصيدليـــة
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متابعة الجهد بنظامى الدفعة الواحدة وتقنية الحقن المستمر للسيفترياكسون صوديوم فى المستحضرات الصيدلية باستخدام مجسين غشائيين مبتكرين

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يختص هذا البحث بتعين السيفترياكسون صوديوم بواسطة طرق جهدية جديدة باستخدام مجسين غشائيين مبتكرين للتقدير الجهدي من نوع البولى (كلوريد الفينيل) والذى يعتمد على استخدام ربـــاعى دوديسيل ميثيل بروميد الأمونيوم أو ثلاثى دوديسيل ميثيل كلوريد الأمونيوم كمواد استبدال أيونى داخل غشاء من نوع البولى (كلوريد الفينيل) وتظهر هذه المجـــسات اســـتجابة ســـريعه وخطيـــة لتركيـــز السيفترياكسون صوديوم الى ٢٩ ميكرو مولارى بطريقة القياس الجهدى الاستاتيكى وتقنية الحقن فـــى تيار مستمر من حامض الخليك عند الأس الهيدروجينى 5,0. وقد أظهرت هذه المجسات انتقائية عالية للسيفترياكسون صوديوم على بعض السيفالوسبورينات ، الأنيونات ، ومختلف المركبات الصيدلية. ولقد أمكن تقدير السيفترياكسون صوديوم فى بعض المستحضرات الصيدلية التى تحتوى عليه. وقد ســـجلت النتائج التي تم الحصول عليها ووجد أنها تتفق اتفاقا كاملا مع الطـــرق القياســـية المـــستخدمة لتقـــدير السيفترياكسون صوديوم.