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Research Article

POTENTIOMETRIC DETERMINATION OF CLORAZEPATE DIPOTASSIUM IN HUMAN PLASMA AND IN PHARMACEUTICAL PREPARATION

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ABSTRACT

Three developed techniques for the selective determination of clorazepate dipotassium were described. The three techniques were investigated with dioctyl phthalate (DOP) as a plasticizer in a polymeric matrix of polyvinyl chloride(PVC). These sensors for clorazepate cation were based on the use of the ion-association complexes of this cation with tetraphenyl borate, phosphotungestic acid and ammonium reineckate counter anions as ions exchange sites in a plasticized PVC matrix, either as ion selective membranes (sensor1, 1`and 1``), microcoated wire (sensor 2, 2` and 2``) or as microsized graphite sensor (sensor 3, 3`and3``). All these sensors were prepared and fully characterized in terms of composition, life span, usable pH range, response time and temperature. These sensors showed near Nernstian responses with slopes in the range of 56.7-59.4 mv decade^{-1} in a pH range of 4-7 over the concentration ranges of 1.0 x 10^{-3} - 1.0 x 10^{-7} M and 1.0 x 10^{-3} - 1.0 x 10^{-6} M for tetraphenyl borate sensors (1, 2and3) and the rest of the studied sensors; respectively. The electrodes exhibit good selectivity for clorazepate with respect to a large number of inorganic cations, sugars and many other exepients. The proposed sensors displayed useful analytical characteristics for the potentiometric determination of clorazepate in pure form, pharmaceutical preparation and in human plasma. The proposed electrodes offer the advantages of simplicity, accuracy and direct applicability to turbid and colored samples without any interference.

Keywords: Clorazepate dipotassium, Sodium tetraphenyl borate (NaTPB), Phosphotungestic acid (PTA), Ammonium reineckate (ARNC), Potentiometry and Plasma.

INTRODUCTION

Since the introduction of the first 1, 4–benzodiazepine, chlordiazepoxide [1], in 1960, they have become the drugs of choice for the treatment of anxiety, sleep disorders, status epilepsy and other convulsive disorders. In addition they are also used as muscle relaxants, for the alleviation of pain and as induction agents in anesthesiology [2]. Since benzodiazepines are widely seen in clinical forensic cases, their measurement in formulations and specimens is widely practiced [3, 4]. Clorazepate dipotassium is representative example of minor tranquillizer drugs which is used to relieve anxiety, nervousness and tension associated with anxiety disorders [5].

Clorazepate is 7-chloro, 1, 3 dihydro, 2, oxo-5(2) phenyl 1-H, 1, 4 benzodiazepine, 3 Carboxylic acid [6].

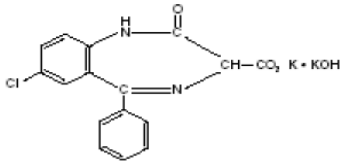

Fig. 1: Structural formula of Clorazepate dipotassium.

The USP (2005) adopts a non-aqueous titration method for the analysis of clorazepate [7]. Several methods have been reported for the quantitative determination of clorazepate dipotassium and other benzodiazepines including spectrophotometric [8-14], spectrofluorimetric [15, 16], colorimetric [17-18], polarographic [19-21], densitometric [22], capillary electrophoresis [23], gas chromatographic [24-30], high pressure liquid chromatographic [31-40],, micellarelectrokinetic chromatographic [41-43], and potentiometric methods[44].

MATRIALS AND METHODS

Instrument

-Jenway digital ion analyser model 3330 (UK) with Ag/AgCldouble junctionreference electrode no 924017-LO-Q11Ccontaining 10% (W/V) KNO_3 solution in the outer compartment.

- Bandelin sonorox, Rx 510 S, magnetic stirrer (Hungarian).

- pH glass electrode Jenway (UK), No. 924005-BO3-Q11C.

- Thermostatic shaker Schutzart DIN 40050-IP 20, 1 Nenn temp: 100 º C,

Type: WB 14.

Elemental analysis is carried out in Micro Analytical Center, Faculty of Science, Cairo University.

Reagent and Materials

Reference samples

Clorazepate dipotassium reference sample, kindly provided by the Global Napi pharmaceuticals, 6th October city, Egypt. Its purity was found to be 99.39±0.47 according to the reported HPLC method[31].

Pharmaceutical preparations

Tranxene capsules manufactured by Global Napi pharmaceuticals under license of Sanofi Winthrop, France. Each capsule is claimed to contain 10mg of clorazepate dipotassium, batch No, 22101.

Reagents

All chemicals were of analytical-reagent grade unless otherwise stated and bidistilled deionized water was used throughout. stock solution of Clorazepate dipotassium (1.0 x 10^{-2}M, M.wt. 408.93) was prepared in 0.1 N HCl. Clorazepate solutions (1.0 x 10^{-2}M - 1.0 x 10^{-7}M) were freshly prepared by serial dilution of a 1.0 x 10^{-2}M stock solution.Graphite rod, dibutyl phthalate (DBP), dioctyl phthalate (DOP), dioctylsebacate (DOS) and tricresyl phosphate (TCP) were used as received from Aldrich. Frozen human plasma was obtained from VACCERA.

For preparation of ion exchangers, aqueous solutions of sodium tetraphenyl borate (NaTPB), phosphotungestic acid and ammonium reineckateNH_4 $[Cr(NH3)_2(SCN)_4]$ in concentration of 1.0 x 10^{-2}M were prepared from material of analytical grade purity. Poly vinyl chloride (PVC), high molecular weight ~10, 000 (BDH), tetrahydrofuran (THF) solvent with a purity of 99% (BDH), 0.1 N HCl and 0.1 N NaOH were used for pH adjustment.

Procedures

1. Sensors preparation and calibration

1.1. Preparation of ion-Exchangers and membrane formation for the proposed sensors:

A 50 ml aliquot of 1.0 x 10^{-2}M aqueous Clorazepate dipotassium solution was mixed with 50 ml of aqueous 1.0 x 10^{-2}M aqueous

NaTPB, aqueous PTA and aqueous ARNC, respectively and continuously stirred. Each ion extchanger complex was precipitated, filtered off through a G4 sintered glass crucible, washed thoroughly with bi-distilled water, dried at room temperature and ground to a fine powder. A 10 mg of Clorazepate ion extchanger was mixed with 350 mg of DOP plasticizer and 190 mg of PVC powder and dissolved in 5 ml of THF. The solution was poured into Petri dishes (5 cm diameter) and then the following procedure was followed:

1.1.A. Fabrication and calibration of sensors 1, 1` and 1``:

The solvent in the previously prepared solutions was left to evaporate slowly at room temperature. The membrane formed was used for sensor construction as described in Moody et al procedure [45]·A master membrane of 0.1mm thickness was obtained. From the master membrane, a disk (about 8 mm diameter) was cut using a cork borer and pasted using THF to an interchangeable PVC tip that was clipped into the end of the electrode glass body. A solution containing equal volume of 1.0 x 10^{-2}M potassium chloride and 1.0 x 10^{-2}M Clorazepate dipotassium was 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 sensors was preconditioned by soaking overnight in a 1.0 x10^{-2}M Clorazepate dipotassium solution before use and stored in distilled water between measurements. The electrochemical cell for potential measurements was: Ag / AgCl(internal reference electrode)/ 1.0 x 10^{-2}M Clorazepate dipotassium, 1.0 x 10^{-2}M KCl (internal reference solution) // PVC membrane // test solution (pH 4-7) //Ag /AgCl double junction reference electrode. The membrane sensors were calibrated by immersion in 1.0 x 10^{-2} -1 x 10^{-7}M Clorazepate solution and allowed to equilibrate with constant stirring in conjunction with a reference electrode. The sensors were stored in bidistilled deionized water between measurements. The electrode potential was recorded as a function of Clorazepate concentration. The calibration plot obtained was used for subsequent measurements of unknown Clorazepate concentrations.

1.1.B Procedure for Preparation of electroactive coating membranes.

The Petri dishes prepared under ***1.1.A***.were covered with filter paper and left to stand for one hour to allow slow evaporation of the solvent, producing the master thick PVC solution.

1.1.B.1.Procedure for Preparation of microcoated wire sensors(sensor2, 2`, 2``).

The covers were removed for a length of about one cm at both ends of an insulated platinum wire. One end of the wire was immersed in the previously prepared PVC solution (***1.1.B***)and was left to stand for 10 min. to allow complete air drying, forming a thin membrane around the wire end.

Immersing and air drying of the wire were repeated until a globular membrane of about 3 mm diameter around the wire end was formed. The resultant dry coated wire membrane sensors had to be conditioned by soaking in 1.0 x 10^{-2}M drug solution for 3 hours and had to be stored in the same solution when not in use. The electrochemical cell for potential measurements was: Platinium wire // PVC membrane // test solution (pH 4-7) //Ag /AgCl double junction reference electrode.

The potential readings of stirred 1.0x10^{-2}-1.0x10^{-7}M Clorazepate solutions were measured at 25±1^{0}C and recorded after stabilization to ±0.2 mv. A calibration graphs were constructed and used for subsequent measurements of unknown Clorazepate test solutions.

1.1.C Procedure for Preparation of microsized graphite sensors (sensor 3, 3`and 3``)

A graphite rod (5 mm in diameter and 15 mm long) was inserted in a polyethylene tube, such that its tip is exposed (5 mm diameter & 0.3 mm length) from the other end of the protruded rod served as a measuring surface. This end of the rod was washed with acetone, dried in air for 3 hours, and dipped rapidly into the previously prepared master thick PVC solution(***1.1.B***). The solvent was allowed to evaporate in air after each dipping, and the dipping process was repeated 4-6 times to produce a uniform membrane on the surface of the graphite rod. Drops of mercury were added in the polyethylene tube to ensure electrical contact with the connection cable. The coated graphite rod was conditioned by soaking in a 10^{-2} M Clorazepate solution for 2 hours, the sensors stored in the same solution when not in use. The electrochemical cell for potential measurements was: Metallic mercury // graphite rod // PVC membrane // test solution (pH 4-7) Ag /AgCl double junction reference electrode.

2. Direct determination of Clorazepate in its pure powdered sample:

The prepared electrodes in conjunction with the double junction Ag/AgCl reference electrode were immersed in 50 ml aliquots of solutions of Clorazepate covering the concentration range of (1× 10^{-7} - 1× 10^{-2} M) into a series of 100 ml beakers. They were allowed to equilibrate while stirring using a magnetic stirrer and the emfs were recorded within ± 1 mV. The membrane sensors were washed with double distilled water between measurements. Calibration graphs were plotted relating the recorded potentials vs. –log drug concentrations. These calibration graphs or the computed regression equations were used for subsequent measurements of unknown concentrations of Clorazepate.

2.1. Identification of the slope, response time and operative life of the studied electrodes

The electrochemical performance of the nine proposed sensors was evaluated according to the IUPAC recommendations data[46, 47].

The dynamic response times for the electrodes in the discussion to reach values ± 1 mV of the final equilibrium potential after increasing the drug concentration 10 folds were measured.

2.2. Effect of pH

The effect of pH on the potential values of the proposed electrodes was studied over pH range of 1 to 10 by adding drops of 1 N HCl and 1 N NaOH to the previously mentioned solutions, the potentials obtained at each value were recorded.

2.3. Effect of temperature

The effect of the temperature was studied, the potential response displayed by the investigated electrodes as a function of temperature in the range of 20°- 40°C at 5°C interval was monitored. The potentials obtained at each temperature were recorded.

2.4. Effect of interfering compounds on the electrode selectivity

The potential response of the nine studied sensors in the presence of the drug and a number of related substances was studied, and the potentiometric selectivity coefficient, -log ($K^{Pot}_{Primary\ ion,\ interferernt}$) was used to evaluate the extent to which a foreign ion would interfere with the response of the electrodes to its primary ion. The selectivity coefficients were calculated by the separate solutions method (SSM) [46], where potentials were measured for 10^{-3} M drug solution and then for 10^{-3}M interferent solution, separately, The selectivity coefficientcalcus were calculated from the following equation

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

Where E_1 is the potential measured in 10^{-3} M solution of drug solution, E_2 the potential measured in 10^{-3} M solution of interferent and S is the slop of the calibration curve.

2.5. Application to pharmaceutical formulations

The content of 10 tablets were powdered and an accurately weighed, portion equivalent to 0.4089 g were transferred to a 100 ml volumetric flask and filled to the mark with bi-distilled deionized water to prepare a 10^{-2}M aqueous solution of clorazepate. The potential were measured using the three different sensors and the concentration was determined using their corresponding calibration plots.

2.6. Direct potentiometric determination of clorazepate in spiked human plasma sample

Nine ml of human plasma were placed into three stoppered shaking tubes (10mL), and then 1 ml of 10^{-2}, $10^{-3}$and 10^{-4}M clorazepate was added separately and shaked. The membrane sensors were

immersed in conjunction with the Ag/AgCl reference electrode in these solutions. The membrane sensors were washed with water between measurements. The potentials readings produced by immersing the prepared electrodes in conjunction with the double junction Ag/AgCl reference electrode in the prepared solutions were recorded and compared with the calibration plots.

RESULTS AND DISCUSSION

The present study originates from the fact that Clorazepate behaves as cationic in acidic medium. This fact suggests the use of anionic type of ion exchangers, sodium tetraphenyl borate, phosphotungestic acid and ammonioum renickate with their low solubility products and suitable grain size. The PVC was used as a polymer matrix in fabrication of the nine sensors. Clorazepate was found to form 1:1 ion association complexes with NaTPB, PTA and ARNC, as proved by IR data and elemental analysis. PVC act as regular support matrices for the membrane and reproducible traps for the ions sensed, but its use creates a need for a plasticizer [48]. The influence of the plasticizer type and concentration on the characteristics of the Clorazepate sensors were investigated by using four different plasticizers with different polarities including: DBP, DOS, TCP and DOP, the use of DOP results in a Nernstian linear plot over a wide concentration range. Also it was found to be the optimum available mediator for the PVC membrane sensors. It plasticizes the membrane, dissolves the ion-association complexes and adjusts both of the membranes permittivity and ion-exchanger sites mobility to give the highest possible selectivity and sensitivity. The concentration of DOP as a plasticizer for all the proposed sensors was optimized. In recent years, molecular recognition at the surface of solid materials has attracted the interest of researchers who are trying to realize functional materials for chemical sensors. Although, the investigated coated wire sensors consists of membrane of PVC / sensing system / mediator in ratios 34:2:64 without an internal reference system, there is a confident view that the coated wire sensors have an inbuilt reference system which is attributed to the permeability of PVC to both water and oxygen and, thus, setting up an oxygen electrode at the wire membrane interface to function as an internal reference system [45].

Table (1) shows the slopes of lines, response times, detection limits and intervals of linearity over a period of one month for the three different assemblies of each sensor at optimal pH using the recommendations of IUPAC [46, 47].The sensors displayed constant potential readings within 1 mv from day-to-day and the calibration slopes did not change by more than 1 mv per decade over a period of one month for the nine sensors. In measurements with the investigated sensors, the experimental conditions were studied to reach the optimum.

The potential response displayed by each investigated electrode was monitored as a function of the temperature and the drug concentration in the range of 20-40^{0}C. The suggested electrodes exhibited slight increase in their potentials as the temperature increased, however the calibration graphs obtained at different temperature were parallel.The limit of detection, slop and response time did not significantly vary with variation of temperature, indicating reasonable thermal stability up to 40^{0}C. A pH value within the range of 4-7 was found optimum from the point of view of sensor function. Fig. 2 shows the potential-pH profiles for 10^{-4}M drug solutions using sensors 1- 9, respectively. Its apparent that the sensor responses were fairly constant at pH 4-7. Above pH 8, drug precipitation occurs, while in highly acidic solutions, less than pH 3.7 less Nernestian responses were displayed by sensors.

Typical calibration plots of the nine sensors were shown in fig. (3a, b&c) which declare linear responses of clorazepate dipotassium over the concentration ranges of 1.0 x 10^{-3} - 1.0 x 10^{-7} M and 1.0 x 10^{-3} - 1.0 x 10^{-6} M for tetraphenyl borate sensors (1, 2and3)and the rest of the studied sensors; respectively. The reliability of the proposed sensors for quantification of clorazepate dipotassium was assessed by determining 10^{-2}–10^{-7} M of the pure powder of the drug on the investigated sensors using both the calibration graph and the computed regession equation. The good agreement between the results obtained for the determination of the capsules by both the proposed poteniometric procedures and the reported HPLC method[31], suggests the successful application of the proposed method for the pharmaceutical formulation.

Table 1: **Response characteristics for clorazepate dipotassium by the proposed sensors**

Parameter	Sensor1	Sensor1`	Sensor1``	Sensor2	Sensor2`	Sensor2``	Sensor3	Sensor3`	Sensor3``
Validation of the regression equations									
Slope(mV per decade)	58.7	56.7	58	59	59.4	57.9	59.1	58.2	57
Intercept (mV)	162.4	154.4	162.5	168.5	176.8	152.3	176.2	165.9	159
Correlation coefficient (r)	1	0.9999	0.9988	0.9999	0.9999	0.9997	0.9997	0.9997	0.9996
Validation of the responses									
Response time (Sec.)	30	30	30	30	30	30	30	30	30
Working pH range	4-7	4-7	4-7	4-7	4-7	4-7	4-7	4-7	4-7
Conc. range (M)	1x10^{-7}-1x10^{-3}	1x10^{-6}-1x10^{-3}	1x10^{-6}-1x10^{-3}	1x10^{-7}-1x10^{-3}	1x10^{-6}-1x10^{-3}	1x10^{-6}-1x10^{-3}	1x10^{-7}-1x10^{-3}	1x10^{-6}-1x10^{-3}	1x10^{-6}-1x10^{-3}
LOD (M)[a]	6.50 × 10^{-8}	5.50 × 10^{-7}	5.50 × 10^{-7}	6.50 × 10^{-8}	7.50 × 10^{-7}	7.50 × 10^{-7}	5.50 × 10^{-8}	5.50 × 10^{-7}	5.50 × 10^{-7}
Life time (weeks)	6	6	6	6	6	6	6	6	6
Average recovery (%)	98.34	99.15	98.55	98.88	99.36	99.20	98.40	98.52	98.62
R.S.D[b]	0.9	0.9	0.8	0.8	0.9	0.9	0.9	0.8	0.9
Precision									
Repeatability % [c]	101.22 ± 0.21	98.90 ± 0.51	99.57 ± 0.33	100.90 ± 0.31	99.40 ± 0.73	100.91 ± 0.11	99.39 ± 0.93	98.99 ± 0.62	100.71 ± 0.38
Intermediate precision %[d]	98.99 ± 0.41	99.76 ± 0.17	99.99 ± 0.29	98.99 ± 0.50	98.83 ± 0.58	99.79 ± 0.09	101.05± 0.12	101.11 ± 0.48	99.95 ± 0.22

[a] Limit of Detection (LOD) defined as drug concentration obtained at the intersection of the extrapolated high concentration (linear segment) with the low concentration (zero slope segment) of the calibration plot. [b]*Results of five determinations.* [c] n = 3x3(1x10^{-2}, 1x10^{-3}, 1x10^{-4} M).dn = 3x3(1x10^{-2}, 1x10^{-3}, 1x10^{-4} M).

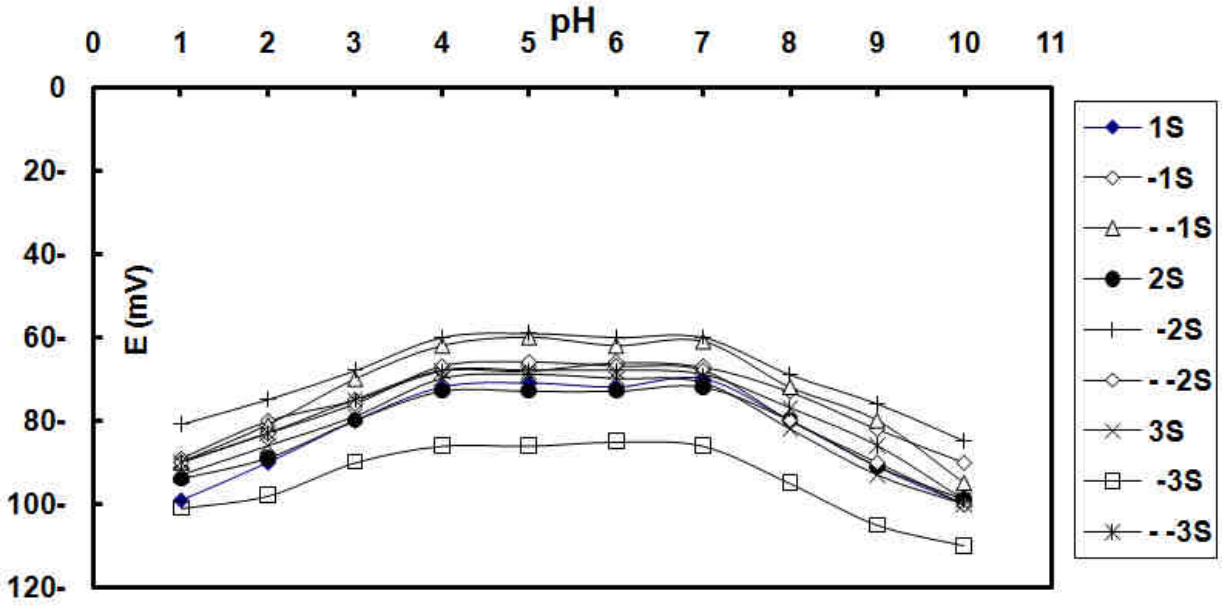

Fig. 2: Effect of pH on the response of the studied sensors upon using 10^{-4}M Clorazepate dipotassium.

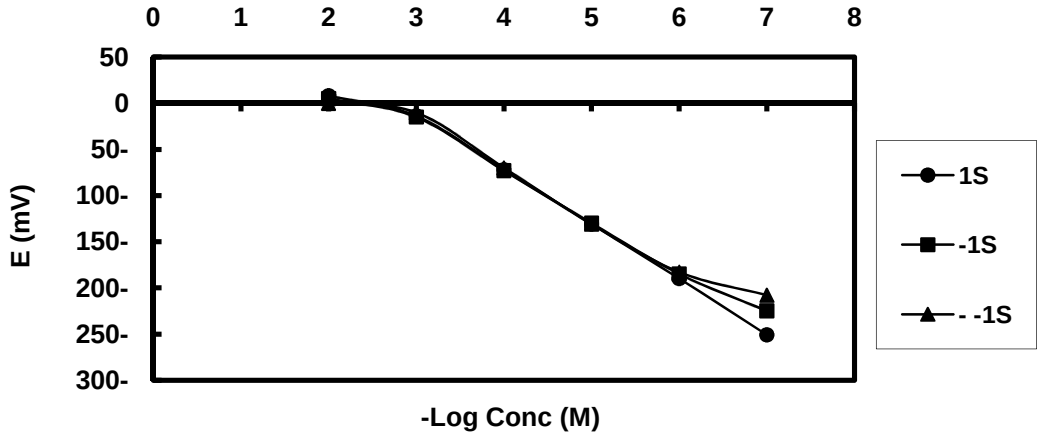

Fig. 3a: Profile of the potential in mV. to the –Log concentration of Clorazepate dipotassium in sensors 1, 1`and 1``

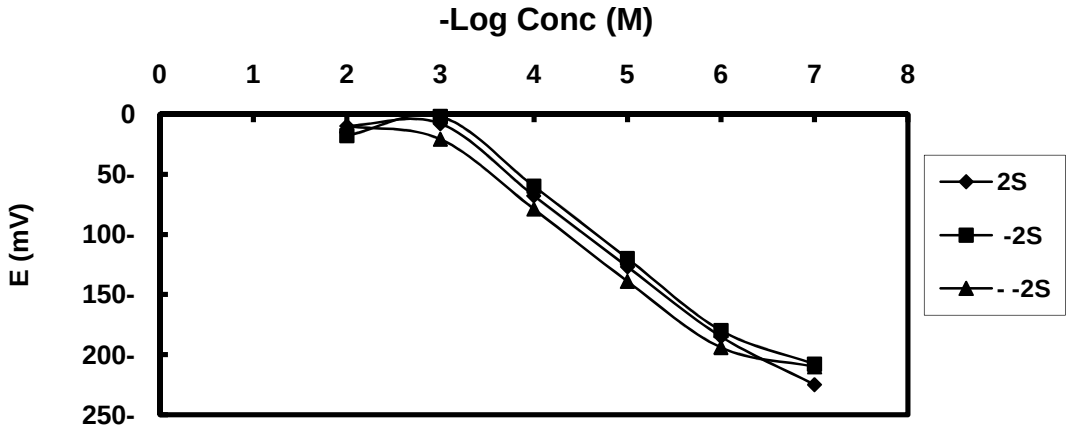

Fig. 3b: Profile of the potential in mV. to the –Log concentration of clorazepate dipotassium in sensors 2, 2`and 2``.

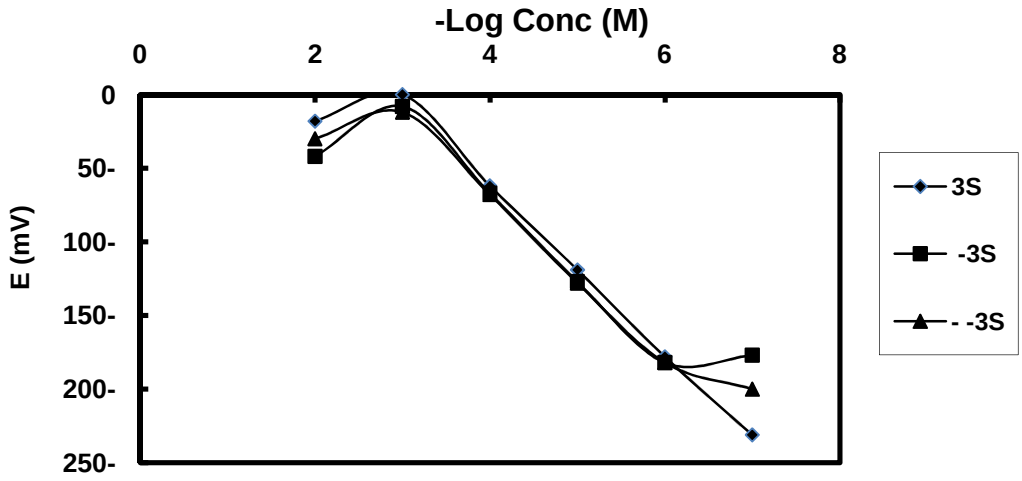

Fig. 3c: Profile of the potential in mV. to the –Log concentration of clorazepat dipotassium in sensors 3, 3`and3`.

Table (2) shows the results obtained for the determination of clorazepate in pharmaceutical formulations that proves the applicability of the method without prior treatment or extraction, using the nine sensors for the determination of clorazepate, as demonstrated by the accurate and precise percentage recovery.

To evaluate precision and accuracy, three concentrations within the linear range (10^{-5}, 10^{-4} and 10^{-3}M solutions of clorazepate) were chosen. Three solutions of each concentration were prepared and analyzed in triplicate (repeatability assay). This assay was repeated on three different days (Intermediate precision assay), Table 1.

Table 1 shows all the validation parameters of the proposed method including linearity, range, accuracy and precision.

Table (2) shows the results obtained for the determination of clorazepate in spiked human plasma. It is found that high accuracy (recovery) and precision (RSD) were given by the studied sensors.

Furthermore no adverse effect on the responses of the electrodes was observed when the drug was spiked with the human plasma samples without prior removal of the protein.

Furthermore, the potentiometric selectivity coefficients of the proposed sensors were calculated in the presence of other related organic and inorganic substances using separate solution method (SSM)[46]. The results revealed that the proposed sensors have reasonable selectivity, table 3.

CONCLUSIONS

The described sensors are sufficiently simple and selective for the quantitative determination of clorazepate in pure form, plasma and pharmaceutical formulations. The use of the proposed sensors offers advantages of fast response and elimination of drug pretreatment or separation steps. They can therefore, be used for routine analysis of clorazepate in quality control laboratories.

Table 2: Determination of *clorazepate dipotassium* in its pharmaceutical preparation using the proposed sensors

	Drug Recovery [a] %									HPLC([31])
	Sensor 1	1`Sensor	Sensor 1``	Sensor 2	2`Sensor	Sensor 2``	3 Sensor	3`Sensor	Sensor 3``	
Tranxene capsules	100.20±0.48	100.01±0.51	99.7±0.62	99.81±0.28	99.51±0.35	98.80±0.58	100.40±0.64	98.90±0.44	99.80±0.57	100.00±0.33
Spiked plasma	98.4±0.90	98.9±0.81	99.0±0.91	99.98±0.96	99.95±0.40	99.87±0.09	100.28±0.26	100.24±0.22	99.57±0.53	
t-value**	1.933 (2.306)	1.089 (2.306)	0.964 (2.306)	0.217 (2.306)	0.182 (2.306)	0.385 (2.306)	0.533 (2.306)	0.533 (2.306)	0.621 (2.306)	
F-value	2.12 (6.39)	2.39 (6.39)	3.53 (6.39)	1.39 (6.39)	1.12 (6.39)	3.09 (6.39)	3.76 (6.39)	1.77 (6.39)	2.98 (6.39)	

[a]Average of five measurements

**the values in parenthesis are the corresponding tabulated t and f values at p=0.05.

Table 3: Potentiometric selectivity coefficients of the proposed sensors using separate solution method

Interferent[a]	Sensor 1	Sensor1`	Sensor1``	Sensor 2	Sensor2`	Sensor 2``	Sensor 3	Sensor 3`	Sensor 3``
Lactose	$2.2x10^{-3}$	$3.1x10^{-3}$	$3.8x10^{-3}$	$2.5x10^{-3}$	$4.1x10^{-3}$	$4.4x10^{-3}$	$3.2x10^{-3}$	$2.1x10^{-3}$	$2.6x10^{-3}$
Glucose	$3.1x10^{-3}$	$4.5x10^{-3}$	$3.9x10^{-3}$	$3.6x10^{-3}$	$3.0x10^{-3}$	$4.0x10^{-3}$	$3.1x10^{-3}$	$3.5x10^{-3}$	$3.9x10^{-3}$
Mannitol	$1.9x10^{-3}$	$1.1x10^{-3}$	$1.4x10^{-3}$	$2.2x10^{-3}$	$1.6x10^{-3}$	$2.1x10^{-3}$	$2.0x10^{-3}$	$2.4x10^{-3}$	$1.4x10^{-3}$
Sodium chloride	$3.3x10^{-3}$	$3.2x10^{-3}$	$2.9x10^{-3}$	$2.0x10^{-3}$	$2.4x10^{-3}$	$2.6x10^{-3}$	$3.7x10^{-3}$	$3.5x10^{-3}$	$3.1x10^{-3}$
Potassium chloride	$3.3x10^{-3}$	$3.5x10^{-3}$	$2.9x10^{-3}$	$3.0x10^{-3}$	$2.8x10^{-3}$	$2.5x10^{-3}$	$3.3x10^{-3}$	$3.5x10^{-3}$	$2.9x10^{-3}$
Ammonium chloride	$3.8x10^{-3}$	$4.1x10^{-3}$	$3.7x10^{-3}$	$3.7x10^{-3}$	$3.2x10^{-3}$	$3.3x10^{-3}$	$3.0x10^{-3}$	$2.1x10^{-3}$	$2.7x10^{-3}$
Hydroxypropyl cellulose	$2.5x10^{-3}$	$3.0x10^{-3}$	$1.9x10^{-3}$	$2.1x10^{-3}$	$2.0x10^{-3}$	$2.4x10^{-3}$	$2.5x10^{-3}$	$3.0x10^{-3}$	$1.9x10^{-3}$
Polyethylene glycol	$2.2x10^{-3}$	$2.1x10^{-3}$	$2.7x10^{-3}$	$2.6x10^{-3}$	$2.1x10^{-3}$	$2.1x10^{-3}$	$2.2x10^{-3}$	$2.1x10^{-3}$	$2.7x10^{-3}$
Methylparaben	$2.6x10^{-2}$	$2.5x10^{-2}$	$2.4x10^{-2}$	$2.3x10^{-2}$	$2.4x10^{-2}$	$2.6x10^{-2}$	$2.8x10^{-2}$	$3.0x10^{-2}$	$2.9x10^{-2}$

[a] All interferents above were in the form of 10^{-3} M, aqueous solutions.

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