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Full Paper

Novel Poly (vinyl chloride) Matrix Membrane Sensors for Determination of Cilostazol in Presence of Its Degradation Product and in Plasma

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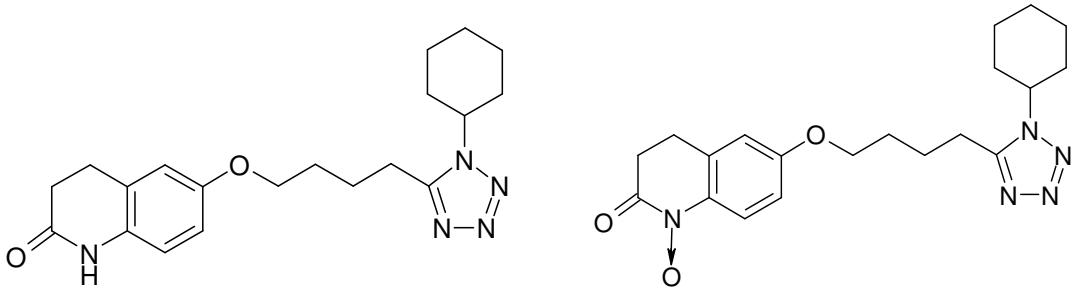
Abstract- Three novel techniques for selective determination of Cilostazol in presence of its oxidative degradation product were described. The three techniques involve the construction and studying of electrochemical response characteristics of novel poly (vinyl chloride) [PVC] matrix membrane sensors for cilostazolcation by using the ion-association complexes of this cation with sodium tetraphenyl borate (NaTPB), phosphotungestic acid (PTA) and ammonium reineckate (amm.RNC) counter anions as ion exchange sites in a plasticized PVC matrix, either as ion selective membranes, microcoated wire or as micro sized graphite selective sensors. The preparation and full characterization of these sensors, including composition, life span, usable pH range, response time and temperature were described. The electrodes were used for potentiometric determination of cilostazol in pure form, pharmaceutical products, plasma and in presence of its oxidative degradation product. These sensors showed near-Nernstian slopes of 56.14, 58.82, 56.23, 56.7, 59.14, 56.84, 58.72, 59.44 and 58.37mV over the concentration ranges of 1.0×10^{-7}-1.0×10^{-2} M for NaTPB and PTA sensors and 1.0×10^{-6}-1.0×10^{-2} M for amm.RNC sensors. The electrodes show good selectivity for cilostazol relative to a large number of inorganic cations, organic cations, sugars and amino acids. The behavior of the three sensors in presence of human plasma was also studied and reasonable results were obtained. The methods were successfully applied for

determination of the intact drug in bulk powder and in presence of its oxidative degradation product; therefore it can be used as stability indicating methods.

Keywords- Cilostazol, Sodium tetraphenyl borate (NaTPB), Phosphotungestic Acid (PTA), Ammonium reineckate (amm.RNC), PVC sensors, Plasma

1. INTRODUCTION

Cilostazol (CILO) 6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxyl]-3,4-dihyro-2(1*H*)-quinolinone; Fig.1, is a phosphodiestrase inhibitor with an antiplatelet and vasodilating activity used in the management of peripheral vascular diseases [1]. The drug is metabolized to at least 11 metabolites [2]. It was determined in presence of some of its metabolites in liver microsomal solutions [3], and in human plasma using HPLC with gradient elution and either UV [4,5] or MS [6] detection. Also, HPLC methods were reported for its determination in pharmaceutical formulation [7] and human plasma [8]. To the best of our knowledge, there is no work in the literature reported about the potentiometric method for the analysis of CILO either in biological fluids, in pharmaceutical formulations or in plasma. Hence the authors have made an attempt to develop precise and sensitive sensors for the estimation of CILO in pure drug, in pharmaceutical formulations and in plasma without previous treatment. The high selectivity of the investigated sensors imparts a great advantage over other techniques [9]. Analytes in turbid, colored, and viscous samples can be determined with good accuracy. The developed sensors show rapid response to concentration changes. In addition, they can be used for determinations over wide concentration range. Ion-selective electrodes tolerate small changes in pH. Also, the developed sensors are relatively simple and not expensive to develop, set up and run. Moreover, the chemical design of the electrodes has been developed to give superior selectivity and response [10].



(A) **(B)**

Fig. 1. Structural formula of **(A)** Cilostazol and **(B)** its oxidative degradation product

The scientific novelty of the present work is that the method used is rapid, simple, accurate, selective, and less expensive and less time consuming compared to other reported TLC and HPLC methods.

The aim of the present study is to develop, optimize and validate potentiometric method for determination of CILO in pure form, in presence of its oxidative degradation product, in its tablets dosage form and in plasma.

2. EXPERIMENTAL

Potentiometric measurements at 25±1°C were done using Jenway digital ion analyser model 3330 (UK) with Ag/AgCl double junction reference electrode No. 924017-LO-Q11C containing 10% (W/V) KNO_3 solution in the outer compartment. Adjustment of pH was made with pH glass electrode Jenway (UK), No. 924005-BO3-Q11C using magnetic stirrer (Hungarian) Bandelinsonorox, Rx 510 S and thermostatic Shaker Schutzart DIN 40050-IP 20, 1 Nenn temp: 100 ºC was used.

2.1. Reagent and Materials

2.1.1. Pure samples

CILO was kindly provided by (Glenmark Pharmaceuticals Ltd., India) certified to have a purity of 99.98%.

2.2.2. Pharmaceutical preparations

Pletaal® tablets (100 and 50 mg, Batch no.: 2E91PA, 2C95PB; respectively) was manufactured by Egypt OTSUKA Pharmaceutical Co., S.A.E. under license of OTSUKA Pharmaceutical Co. Ltd., Japan, and labeled to contain 100 and 50 mg CILO per tablet.

2.2.3. Reagents

All chemicals were of analytical-reagent grade unless otherwise stated. Double distilled deionized water was used throughout. Cilostazol (MW: 369.46 g/mol) was dissolved in 20 mL 1N acetic acid and then diluted to the mark with deionized water to freshly prepare 1.0×10^{-2} -1.0×10^{-7}M. Graphite rod, dibutyl phthalate (DBP), dioctyl phthalate (DOP), dioctylsebacate (DOS) and tricresyl phosphate (TCP) were used as received from Aldrich, 6% H_2O_2 and frozen human plasma was obtained from (VACSERA).

For preparation of ion exchangers, aqueous solutions of sodium tetraphenyl borate (NaTPB), phosphotungestic acid (PTA) and ammonium reineckate $NH_4[Cr(NH_3)_2(SCN)_4]$ in concentration of 1.0×10^{-2} M were prepared from material of analytical grade purity. Poly vinyl chloride (PVC), high molecular weight ~10,000 (BDH) and tetrahydrofuran (THF) solvent with a purity of 99% were used.

2.4. Procedures

2.4.1. Sensors preparation and calibration

2.4.1.1. Preparation of ion-Exchangers for membrane formation and for microcoated wire sensors

A 50 mL aliquot of 1.0×10^{-2} M aqueous CILO solution was mixed with 50 mL of aqueous 1.0×10^{-2} M aqueous sodium tetraphenyl borate (NaTPB), phosphotungestic acid (PTA), and ammonium reineckate (amm.RNC); respectively and continuously stirred. Each ion pair 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 portion of CILO ion pair was mixed with 350 mg of TCP 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:

2.4.1.2. 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 [10]; a master membrane of 0.1 mm 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 1.0×10^{-2} M potassium chloride and 1.0×10^{-2} M CILO 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 1.0×10^{-2} M CILO solution before use and stored in distilled water between measurements. The electrochemical cell for potential measurements was: Ag / AgCl (internal reference electrode) / 1.0×10^{-2} M CILO, 1.0×10^{-2} M KCl (internal reference solution) // PVC membrane // test solution (pH 5-7) //Ag /AgCl double junction reference electrode. The membrane sensors were calibrated by immersion in 1.0×10^{-2} -1×10^{-7}M CILO solution and allowed to equilibrate with constant stirring in conjunction with a reference electrode. The sensors were stored in bi-distilled deionized water between measurements. The electrode potential was recorded as a function of CILO concentration. The calibration plot obtained was used for subsequent measurements of unknown CILO concentrations.

2.4.1.3. Procedure for Preparation of electroactive coating membranes

The Petri dishes prepared under 2.4.1.1.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.

2.4.1.4. Procedure for Preparation of microcoated wire sensors (sensor 2, 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 and 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 1.0×10^{-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: Platinum wire // PVC membrane // test solution (pH 6) //Ag /AgCl double junction reference electrode.

The potential readings of stirred 1.0×10^{-2}-1.0×10^{-7} M Cilostazol 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 Cilostazol test solutions.

2.4.1.5. Procedure for Preparation of micro sized 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 (2.4.1.1). 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 Cilostazol 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 6) Ag /AgCl double junction reference electrode.

2.5. Application to pharmaceutical formulations

The content of 10 tablets was powdered and an accurately weighed portion equivalent to 36.95mg were transferred to a 100 mL volumetric flask, 20 mL 1N acetic acid were added and filled to the mark with bidistilled deionized water to prepare a 10^{-3} M aqueous solution of Cilostazol. The potential were measured using the proposed sensors and the concentration was determined using their corresponding calibration plots.

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

Nine mL of human plasma were placed into three stoppered shaking tubes (10 mL); 1 mL of 10^{-2}, 10^{-3} and 10^{-4} M CILO was added separately and shaken. 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.

2.7. Stability study

Degraded samples of 10^{-3} M CILO solution was prepared by adding 10 mLof 6% hydrogen peroxide to 50 mL of 10^{-3} M drug solution and then the solution was refluxed for 2 h. at 100 ◦C, followed by cooling. The produced solution was tested for the degradation process using TLC using the mobile phase ethyl acetate: methanol (8:2 v/v). Standard drug solution of 10^{-3} M was mixed with its degraded sample in different ratios. The e.m.f of these laboratories prepared mixtures was recorded. Results were compared with the calibration plots.

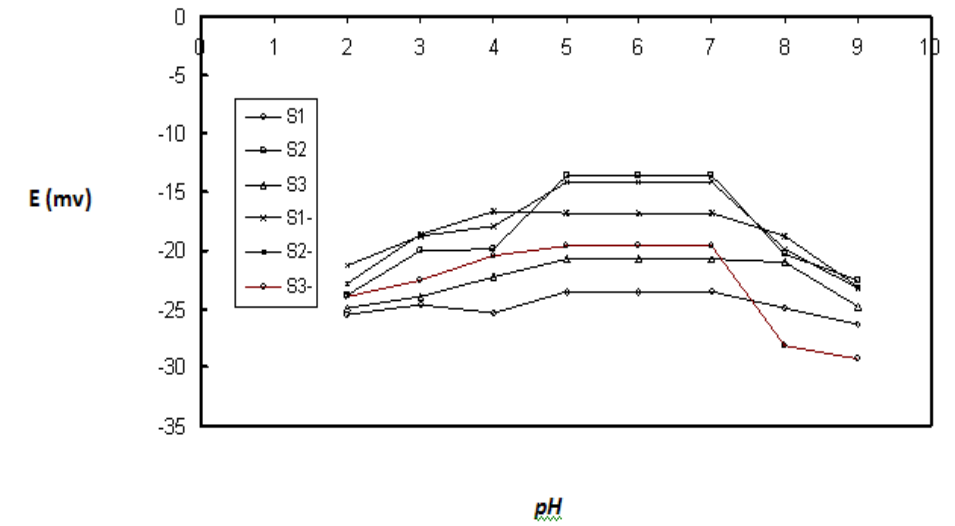
3. RESULTS AND DISCUSSION

The present study originates from the fact that CILO behaves as cationic in acidic medium. This fact suggests the use of anionic type of ion exchangers, sodium tetraphenyl borate, phosphotungestic acid and ammonium reineckate with their low solubility products and suitable grain size. The PVC was used as a polymer matrix in fabrication of the nine sensors. CILO was found to form 1:1 ion association complexes with NaTPB, PTA and amm.RNC as provided 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 [11]. The influence of the plasticizer type and concentration on the characteristics of the CILO sensors were investigated by using four different plasticizers with different polarities including: DBP, DOS, TCP and DOP, the use of TCP 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 TCP as a plasticizer for micro sized sensors (1`, 1``, 2`, 2``, 3` and3``) were optimized.

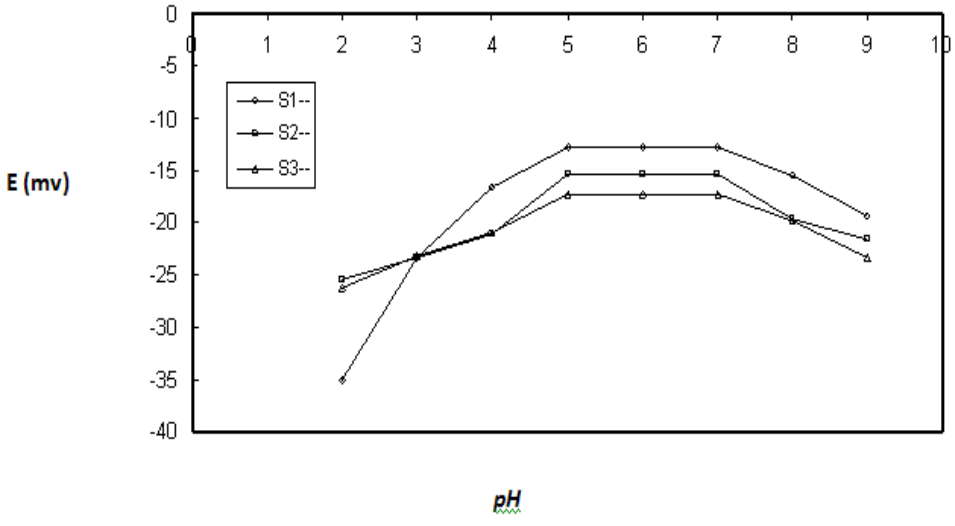
Microelectrodes have been the subject of much research in recent years [12]. The advantages they offer over conventional electrodes are well known, their small physical size allows exploration of microscopic domains, such as biological systems, their fast response time, due to the reduced diffusion layer, allows rapid scan rates to be used [13]. Metallic and graphite- based conductors of many geometric shapes have been suggested, such as wire, disc and cylinders [14,15]. These electrodes behave as two interface devices, membrane/ electrolyte interface and membrane / metal interface [16]. Thus, the membrane potential in the cell regards the potential difference between the two interfaces.

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.

The electrochemical performance characteristics of the proposed sensors were systematically evaluated according to IUPAC standards [17,18].



A



B

Fig. 2. (A) Effect of pH on the response of the studied sensors upon using 10^{-4} M Cilostazol sensors (S_1, $S_{1`}$, $S_2$,$S_{2`}$, S_3, and $S_{3`}$). **(B)** Effect of pH on the response of the studied sensors upon using 10^{-4} M Cilostazol sensors ($S_{1``}$, $S_{2``}$, and $S_{3``}$)

Table 1. Response characteristics for Cilostazol by the proposed sensors

Parameter	*Sensor 1*	*Sensor 1`*	*Sensor 1``*	*Sensor2*	*Sensor 2`*	*Sensor 2``*	*Sensor 3*	*Sensor 3`*	*Sensor 3``*
Validation of the regression equations									
Slope(mV per decade)	56.14	56.70	58.72	58.82	59.14	59.44	56.23	56.84	58.37
Intercept (mV)	202.98	212.86	222.04	221.70	219.76	222.43	204.45	207.74	216.39
Correlation coefficient (r)	0.9999	1	1	1	1	1	0.9999	1	1
Validation of the responses									
Response time (min.)	2	2	1	2	2	1	2	2	1
Working pH range	6	6	6	6	6	6	6	6	6
Conc. range (M)	1×10^{-7}-1×10^{-3}	1×10^{-7}-1×10^{-3}	1×10^{-6}-1×10^{-3}	1×10^{-7}-1×10^{-3}	1×10^{-7}-1×10^{-3}	1×10^{-6}-1×10^{-3}	1×10^{-7}-1×10^{-3}	1×10^{-7}-1×10^{-3}	1×10^{-6}-1×10^{-3}
LOD (M)[a]	4.50×10^{-8}	4.50×10^{-8}	3.50×10^{-7}	5.50×10^{-8}	3.50×10^{-8}	3.50×10^{-7}	2.50×10^{-8}	3.50×10^{-8}	4.50×10^{-7}
Life time (weeks)	4	4	6	4	4	6	4	4	6
Average recovery (%)	99.61	99.09	98.46	98.33	99.12	99.84	99.49	99.07	98.99
R.S.D[b]	0.7	0.8	0.8	0.9	0.7	0.8	0.8	0.9	0.8
Precision									
Repeatability %[c]	99.56 ± 0.62	99.09 ± 0.32	100.09 ± 0.23	99.07 ± 0.77	100.40 ± 0.19	100.21 ± 0.93	100.39 ± 0.13	99.55 ± 0.48	99.71 ± 0.90
Intermediate precision %[d]	100.09 ± 0.56	99.34 ± 0.28	99.08 ± 0.33	99.69 ± 0.59	99.13 ± 0.88	98.79 ± 0.79	99.95± 0.62	99.11 ± 0.17	98.95 ± 0.50

[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 = 3×3(1×10^{-2}, 1×10^{-3}, 1×10^{-4} M)

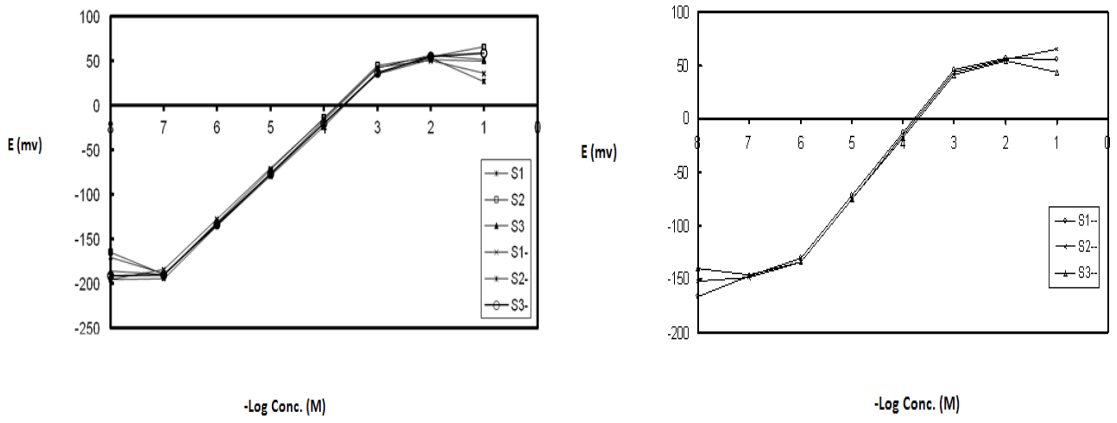
[d]n = 3×3(1×10^{-2}, 1×10^{-3}, 1×10^{-4} M)

Table 2. Determination of Cilostazol in its pharmaceutical preparation and in spiked plasma by the proposed sensors

	Drug Recovery [a] %									**Published method [8]**
	Sensor 1	**Sensor 1`**	**Sensor 1``**	**Sensor 2**	**Sensor 2`**	**Sensor 2``**	**Sensor 3**	**Sensor 3`**	**Sensor 3``**	
Pletaal® tablets **100 mg (B.N.** 2E91PA)	99.75±0.35	98.93±0.73	99.50±0.42	100.37±0.11	99.07±0.08	100.04±0.28	100.40±0.29	99.18±0.09	99.08±0.44	99.35±0.26
Pletaal® tablets **50 mg (B.N.** 2C95PB)	99.66±0.10	99.12±0.81	99.90±0.63	100.21±0.42	99.14±0.29	99.59 ±0.11	100.24±0.90	98.26±0.05	100.96±0.63	
Spiked plasma	99.42±0.33	101.09±0.29	100.09±0.11	99.15±0.48	100.20±0.11	99.09±0.82	99.92±0.24	100.02±0.11	99.09±0.71	

[a] Average of five measurements

Table (1) shows all the validation parameters of the proposed method including linearity, accuracy and precision, over a period of six weeks for three different assemblies of each sensor at optimal pH and temperature at 25±1°C using the recommendations of IUPAC [17, 18]. We noticed that NaTPB and PTA sensors having the widest concentration range (10^{-2} - 10^{-7} M) all over the investigated sensors, amm. RNC sensors (by the three techniques) having the fastest response time (1 min), long life time (six weeks) and the most ideal Nernstian response(≈ 60 mV) while the coated wire sensors (with either NaTPB, PTA or amm. RNC) having the advantages of ideal Nernestian slopes. All 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 about three to four weeks 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°C.



A **B**

Fig. 3. (A) Profile of the potential in mV to the –Log concentration of Cilostazol sensors 1, 1`, 2, 2`, 3 and 3`**(B)** Profile of the potential in mV. to the –Log concentration of Cilostazol sensors 1``, 2`` and 3``

All electrodes exhibited constant slope values and gradual increase in their potentials as the temperature increased. A pH value within the range of 5-7 was found optimum from the point of view of sensor function. Figs.2A and 2B show the potential-pH profiles for 10^{-4} M drug solutions using the developed sensors. It's apparent that the sensor responses were fairly constant in 1 N acetic acid solutions of pH 6. Above pH 7, drug precipitation occurs, while in highly acidic solutions, less than pH 5less Nernstian responses were displayed by sensors.

Typical calibration plots of the nine sensors were shown in Fig. 3A and 3B which declare linear responses of Cilostazol over concentration ranges of 10^{-2}-10^{-7} M for NaTPB and PTA sensors and 10^{-2}-10^{-6} M for amm.RNC sensors. The excellent agreement between the results

obtained for the determination of the tablets by both the proposed potentiometric procedures and the published method [8],suggests the successful application of the proposed method for the pharmaceutical formulations, Table (2).

The investigated potentiometric method can be successfully applied as stability indicating method for the determination of Cilostazol in presence of its oxidative degradation product without prior separation. Table (3) shows the results obtained upon analysis of synthetic mixtures of intact drug and it oxidative degradate using sensor 2``. It is obvious from the result in this table that the proposed sensors can be successfully used for selective determination of the intact Cilostazol in presence of it'sdegradate without any interference.

Table 3. Recoveries of Cilostazol in synthetic mixtures with its oxidative degraded samples using sensor 2``

Drug Recovery [b] **%**		
Ratio drug degraded sample [a]	***Sensor 2``***	**Published method[8]**
100:0	99.68±0.16	99.74±0.14
90:10	100.11±0.24	100.9±0.34
80:20	99.04±0.27	99.15±0.61
70:30	101.10±0.04	100.13±0.90
60:40	99.17±0.15	100.55±0.35
50:50	99.40±0.25	100.09±0.49
40:60	107.90±0.95	101.61±0.33
30:70	108.31±0.44	99.37±0.90
20:80	109.88±0.34	100.11±0.68
10:90	111.12±0.54	100.91±0.87

[a] The drug solutions were always 10^{-3} M. aqueous.; [b] It is a mean of five determinations.

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 ($K^{Pot}_{Primary\ ion,\ Interferent}$) 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) [18], where potentials were measured for 10^{-3} M drug solution and then for 10^{-3} M Interferent solution, separately, then potentiometric selectivity coefficient was calculated as follows:

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

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.

The results revealed that the proposed sensors have reasonable selectivity, (Table 4).

Table (2) shows the results obtained for the determination of Cilostazol 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.

Table 4. Potentiometric selectivity coefficients of the proposed sensors using separatesolution method

Interferent[a]	***Sensor 1***	***Sensor 1`***	***Sensor 1``***	***Sensor2***	***Sensor2`***	***Sensor 2``***	***Sensor3***	***Sensor3`***	***Sensor 3``***
Glucose	3.5×10^{-4}	4.1×10^{-3}	3.5×10^{-3}	6.5×10^{-3}	1.6×10^{-3}	3.5×10^{-3}	2.5×10^{-4}	4.1×10^{-3}	4.4×10^{-4}
Lactose	5.1×10^{-3}	4.5×10^{-3}	3.7×10^{-3}	3.1×10^{-4}	5.9×10^{-3}	3.6×10^{-3}	3.1×10^{-3}	4.0×10^{-3}	4.0×10^{-3}
Mannitol	6.0×10^{-3}	5.1×10^{-3}	5.0×10^{-4}	3.3×10^{-3}	4.4×10^{-4}	4.2×10^{-3}	5.0×10^{-3}	4.6×0^{-4}	4.8×10^{-4}
Sodium chloride	6.1×10^{-3}	3.9×10^{-4}	4.1×10^{-3}	4.6×10^{-3}	1.1×10^{-3}	4.0×10^{-3}	4.1×10^{-3}	3.6×10^{-3}	3.8×10^{-3}
Potassium chloride	4.3×10^{-3}	3.5×10^{-3}	3.3×10^{-3}	3.7×10^{-3}	2.9×10^{-4}	3.0×10^{-3}	3.3×10^{-3}	2.8×10^{-4}	2.9×10^{-3}
Ammonium chloride	4.8×10^{-3}	4.1×10^{-3}	3.8×10^{-3}	2.6×10^{-3}	3.7×10^{-3}	3.7×10^{-3}	3.8×10^{-3}	3.2×10^{-3}	6.3×10^{-3}
Methylparaben	3.5×10^{-3}	3.0×10^{-3}	2.7×10^{-3}	3.9×10^{-3}	1.9×10^{-4}	2.1×10^{-3}	2.5×10^{-4}	2.0×10^{-3}	2.4×10^{-3}
Polyethylene glycol	3.2×10^{-3}	2.1×10^{-3}	2.4×10^{-3}	4.7×10^{-3}	2.7×10^{-3}	2.6×10^{-3}	2.2×10^{-3}	2.6×10^{-3}	2.3×10^{-4}
Hydroxypropyl cellulose	2.9×10^{-4}	2.5×10^{-4}	2.6×10^{-3}	3.1×10^{-3}	2.4×10^{-3}	2.3×10^{-3}	2.6×10^{-3}	2.4×10^{-3}	2.6×10^{-3}
Cilostazol Oxidative Product	4.8×10^{-2}	3.0×10^{-2}	2.3×10^{-2}	3.9×10^{-2}	1.4×10^{-2}	2.7×10^{-2}	4.8×10^{-2}	3.1×10^{-2}	3.3×10^{-2}

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

4. CONCLUSION

The described sensors are sufficiently simple and selective for the quantitative determination of Cilostazol in pure form, plasma, oxidative degradation product and pharmaceutical formulations. Among the types of ion exchangers used, it was evident that ammonium reineckate sensors have the most near Nernstian response in addition to fastest response time (only 1 min.) among other sensors. Among the proposed techniques, coated wire sensors represent the simplest, fastest and cleanest of all proposed techniques. In addition, coated wire sensors have the most near Nernstian response and the widest concentration range 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 Cilostazol in quality control laboratories.

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