Synthesis and Potentiometric Study of Atenolol Selective Electrodes and Their Use in Determining Some Drugs

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Abstract

Atenolol ion selective electrodes were constructed. This construction was based on drug complex formation with phosphomolybdic acid as ionophor and plasticizer, Di-butylphthalate (DBPH), Tri-butylphosphate (TBP), O-nitrophenyloctylether (ONPOE) and Di-octyl phthalate (DOP) in PVC matrix membrane.

The matrix membrane was formed by mixing an appropriate plasticizer and drug complex with poly(vinyl chloride) PVC. The properties of following electrodes were studied, concentration range, slope, detection limit, response time, life time, pH effect and selectivity. The results showed that membranes (At-PMA+DBPH) and (At-PMA+ONPOE) gave a linear range from 1×10^{-5} to 1×10^{-1} and 5×10^{-6} to 1×10^{-2} respectively, with slopes of (55.6 and 40.5) mV/decade, correlation coefficients are 0.9996 and 0.9984, the detection limit was (8.5×10^{-6} and 3.5×10^{-5}) M, and the response time for 10^{-3} M were (15 and 25) second respectively.

The proposed electrodes were successfully applied to the determination of atenolol in a pharmaceutical preparation and gave a good accuracy.

Introduction

The ion-selective method are widely used for pharmaceutical analysis with advantages of determining sample directly, rapidly and simply. Liquid membrane ion-selective electrodes (ISE) in particular have much importance for the analysis of pharmaceutical products. The relatively low cost, high simplicity, selectivity and low analysis time are advantages of using ISE compared with tedious procedures suggested in the pharmacopeias [1].

Atenolol (Fig.(1)) (RS)-4-(2-hydroxy-3-isopropylaminopropoxy) phenylacetamide, $C_{14}H_{22}N_2O_3$, is a cardio selective β-blocker. It is reported to lack intrinsic sympathomimetic activity and membrane-stabilising properties. It may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin and β-methyldopa [2].

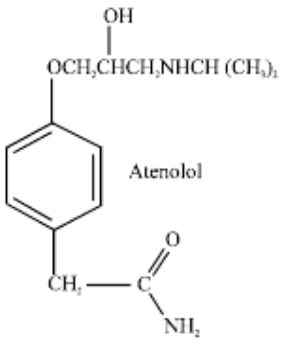


Fig.(1) Structure of Atenolol –(RS)-4-(2-hydroxy-3- isopropylaminopropoxy) phenyl acetamide.

Several analytical methods have been reported for the determination of atenolol in pharmaceutical formulations. The United States Pharmacopeia (2003) describes a method that uses high performance liquid chromatography (HPLC) with UV detection for assay of atenolol tablets [3].

The method recommended by British Pharmacopoeia (2001) involves UV spectrophotometry [4]. In Brazilian Pharmacopeia, however, a method for assay of atenolol was not found. Other methods reported in the literature for the determination of atenolol in pharmaceutical formulations include visible spectrophotometry [5], UV derivative spectrophotometry [6], HPLC [7],

high performed thin layer chromatography [8], potentiometry [9], capillary electrophoresis [10], and voltametry [11].

Ion-selective electrodes play an important role in pharmaceutical analysis [12] due to their simplicity, rapidity and accuracy. Ion selective electrodes for amines and amiloride were prepared using phosphomolybdic acid ionophore and various plasticizers: (DBPH), (TBP), (NPOE) and (DOPP). The response characteristics of these electrodes, including slope of the calibration plot, the corresponding concentration range, detection limit, response time, lifetime, pH effect, and the selectivity were studied [13]. Determination of a Novel Phenylpiperazine Antidepressant and Nefazodone [14]. Promethazine-selective PVC membrane electrodes based on ion pair compound (complex) of PMH-PT and (DBP,TBP,ONPOE,DBPH) as plasticizers were constructed and used as a method for potentiometric determination [15]. Amoxicillin trihydrate and cephalexin monohydrate ion selective electrodes were constructed [16]. Several indium ion selective electrodes were constructed based on 15-crown-5 (15C5), dicyclohexano-18-crown-6 ($DCH_{18}C_6$) and dibenzo-24-crown-8 ($DB_{24}C_8$) as sensors and di-octyl phenyl phosphonate (DOPP), di-butyl phthalate (DBPH), tri-butyl phosphate (DBP), tri-n-amyl phosphate (TAP) and bis (2-ethyl hexyl) phosphate (BEHP) as plasticizers in a PVC matrix membrane. Electrode parameters, pH effect and interferences were also studied [17]. In the present study, we constructed and characterized several electrodes for the potentiometric determination of atenolol. The membranes consisted of atenolol-phosphomolybdic acid as an active material with different plasticizers. The electrode parameters were investigated via potentiometric measurements including direct, standard addition and titration methods.

Experimental Part

Equipment

An expandable ion analyzer (WTW model, Germany), a pH meter (WTW model pH 720, Germany), and a saturated calomel electrode (Gallenkamp, USA) were used in this work.

Reagents and Solutions

Atenolo standard was a gift from the State Company of Drug Industries and Medical Appliances (Samara IRAQ-SDI). Novaten tablet, 100 mg atenolol (Ajanta Pharma, India) was obtained from local pharmacies.

Di-n-butyl phosphate 98.9% (DBP), tri-n-butyl phosphate 97% (TBP), o-nitrio phenyloctyl ether 98% (ONPOE), and di-n-butyl phthalate 99% (DBPH) were obtained from Fluka AG, Switzerland. Stock solutions of 0.1 M for each of LiCl, KCl, $CaCl_2$, $MgCl_2$, $FeCl_3$ and $AlCl_3$ were prepared. More diluted solutions were prepared by subsequent dilution of the stock solutions. A Standard solution of 0.1 M atenolol was prepared by dissolving 1.3315 g of standard atenolol in a small amount of ethanol and the volume was made up to 50 mL with deionized water.

Preparation of ion-pair compound

A-PMA ion-pair was prepared by mixing 50 mL of 0.01 M atenolo with 50 mL of 0.01 M phosphomolybdic acid with stirring. The resultant precipitate was filtered, washed with water, and dried at 60 ◦C.

Casting the membrane

Atenolol matrix was immobilized into the PVC matrix membrane as described by Moody et al. [18]. A 0.040 g (A-PMA) matrix was mixed with 0.36 g of plasticizer and 0.17g of PVC powder, after that 7.0 mL of THF was added with stirring until the formation of viscous solution. The above solution poured into a glass casting ring (30 mm length and 35 mm in diameter) resting on a glass plate, and a pad of filter was placed on top of the glass. The solvent was then allowed to evaporate at room temperature over about 2 days.

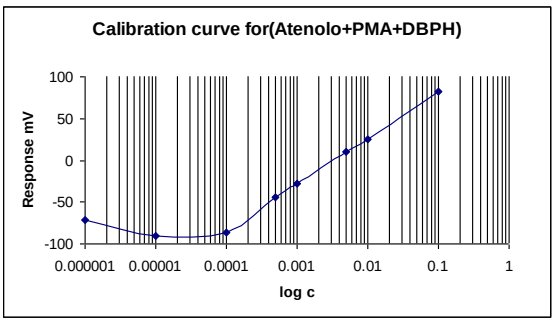
Results and Discussion

Respnse characteristics of prepared atenolol are summarized in Table (1). performances of electrodes prepared using an ion-pair complex as an electractive material and different plasticizers were compared experimentally.

Table (1)
Respnse characteristics of AT – PMA selective electrodes using different plasticizers.

Membrane Composition	*AT-PMA +DOPH*	*AT-PMA +TBP*	*AT-PMA +ONPOE*	*AT-PMA +DBPH*
Slope mV/decade	60.8	47.5	40.5	55.6
Linearity Range/M	1×10^{-1}- 5×10^{-4}	1×10^{-4} –1×10^{-1}	5×10^{-6}-1×10^{-2}	1×10^{-5} –1×10^{-1}
Correlation coefficient	0.9994	0.9997	0.9984	0.9996
Detection Limit/M	4×10^{-4}	$7.5\text{x}10^{-5}$	3.5×10^{-5}	8.5×10^{-6}
Life time/day	90	14	29	45

Atenolol-phosphomolybdate is a stable ion-pair complex which is water insoluble but readily soluble in an organic solvent such as tetrahydrofuran (THF). The obtained complex was incorporated into a PVC membrane with the following plasticizers: di-octyl phthalate (membrane I), tri-n-butyl phosphate (membrane II), o-nitro phenyl octyl ether (membrane III), and di-n-butyl phthalate (membrane IV).The low slope value obtained for membrane(II)may be attributed to the plasticizers used (TBP) which contained long alkyl group connected to phosphate groups, this may decreased the ion-exchange process between the electro-active compound (AT-PMA) and the external solution of atenolol, or may be attributed to the steric factor of the plasticizers (TBP) which decreased the bond strength with the electro-active compound. The non-Nernstian slope behaviors for membrane (III) could be attributed to the low viscosity of ONPOE (11.44 cST) and lead to leaching of the complex from the membrane to the external pair complex (AT-PMA) in membrane and the external solution of atenolol. Near Nernstian slopes were obtained for the electrodes based on DOPH and DBPH (membranes I and IV). A typical calibration plot for electrodes I and IV are shown in Fig.(2).



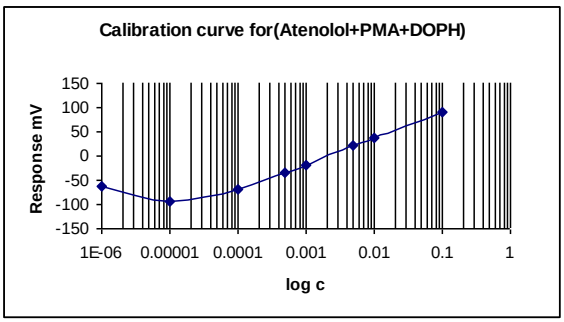


Fig.(2) Calibration curves of Atenolol selective electrodes. DBPH, DOPH.

Electrode parameters for DOPH as a plasticizer gave a good response that may be due to attributed to the compatibility of the plasticizer used to the electro-active compound from both structure and composition. Also Electrode parameters for DBPH as a plasticizer gave a good response that may be attributed to the compatibility of the plasticizer which was used to the electro active compound from both structure and coosition, also may be due to high viscosity ≈ 82CST, The electrode had good stability and was used for the quantitative determination of pharmaceutical drugs.

Effect of pH:

The effect of pH on the electrode potentials for Atenolol selective membrane electrodes was examined by measuring the e.m.f. of the cell in Atenolol solutions at three different concentration (10^{-4}, 10^{-3}, 10^{-2}) M in which the pH measured from 1.0-11.5. The pH was adjusted by introducing few drops of ammonia and hydrochloric acid solution and the results are listed in Table (2).

Table (2)
Working pH ranges for atenolol selective electrodes.

Number	Membrane Composition	pH range		
		1×10^{-2}	1×10^{-3}	1×10^{-4}
I	AT- PMA + DOPH	2.1 – 7.4	2.3 – 7.4	3.2 – 9.7
II	AT - PMA + TBP	2.1– 8.9	2.0 – 9.6	2.1 – 9.3
III	AT - PMA + ONPOE	2.6 – 9.0	2.1 – 8.9	2.1 – 9.6
IV	AT - PMA+ DBPH	2.2 – 9.8	2.1 – 9.7	2.5 – 10.5

A typical plot for the pH effect on atenolol electrodes based on DBPH plasticizer is shown in Fig.(3).

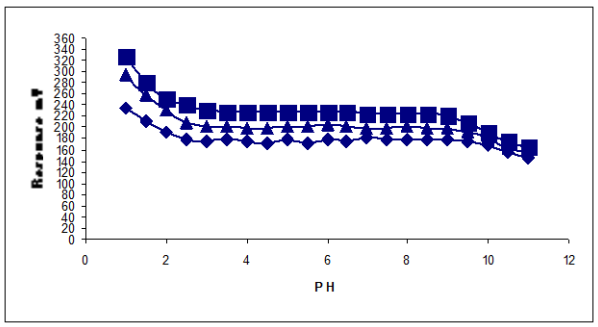


Fig.(3) Effect of pH on the potential of the Atenolol electrodes at concentrations (■ 10^{-2}, ▲ 10^{-3} and ♦ 10^{-4}) M.

Response Time

Response time is define as the time needed for the electrode to reach stable potential within ±1 mV of the final equilibrium value [19]. The measured response time for the atenolol electrode based on DOPH for 1 x10^{-3} M atenolol solution was 15and 18 s for 1.00 x 10^{-4} M atenolol solution, while for the electrode based on ONPOE plasticizer the response time was 25 and 29 s for 1.00 x 10^{-3} and 1.00 x 10^{-4} M atenolol solutions, respectively.

Selectivity

Potentiometric selectivity coefficients were performed by separate method using concentrations 10^{-1}-10^{-5}M for Atenolol and different interfering cations Li^{+}, K^{+}, Mg^{+2}, Ca^{+2}, Al^{+3}, Fe^{+3} and the potentiometric selectivity coefficients was calculate according to the equation: [20]

$$\log K^{pot}_{ate.} = [(EB - EA) / (2.303\ RT/zAF)] + (1 - zA/\ zB) \log aA$$

E*A* and E*B*, z*A* and z*B*, a*A* and a*B* are the potentials, charge numbers and activities for the primary and interfering ions, respectively, at a*A* = a*B*.

The values of the selectivity coefficient for the electrode based on DBPH and TBP plasticizers for some inorganic cations are listed in Table (3) and (4).

Table (3)
Selectivity coefficients for electrodes at different concentration of Atenolol for DBPH electrode.

Interfering Ion	Concentration 10^{-1}M		Concentration 10^{-2}M		Concentration10^{-3}M		Concentration10^{-4}M		Concentration10^{-5}M	
	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$
Li+	-154	1.32×10^{-3}	-176	5.092×10^{-3}	-184	0.042	-180	0.417	-184	0.5736
K+	-156	1.22×10^{-3}	-171	6.21×10^{-3}	-183	0.0434	-190	0.281	-181	0.64616
Ca^{2+}	-193	4.398×10^{-4}	-166	3.51×10^{-4}	-172	6.723×10^{-4}	-202	3.744×10^{-4}	-240	2.8714×10^{-5}
Mg^{2+}	-130	1.082×10^{-3}	-167	7.278×10^{-4}	-171	2.212×10^{-3}	-184	3.562×10^{-3}	-185	1.7433×10^{-3}
Fe^{3+}	-127	8.302×10^{-4}	-162	4.114×10^{-4}	-167	8.199×10^{-4}	-195	4.944×10^{-4}	-193	1.855×10^{-4}
AL^{3+}	-150	8.515×10^{-5}	-172	8.046×10^{-5}	-190	8.590×10^{-5}	-200	4.446×10^{-5}	-220	6.1659×10^{-6}

Table (4)
Selectivity coefficients for electrodes at different concentration of Atenolol for TBP electrode.

Interfering Ion	Concentration $10^{-1}M$		Concentration $10^{-2}M$		Concentration$10^{-3}M$		Concentration$10^{-4}M$		Concentration$10^{-5}M$	
	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$	E_B (mV)	$K_{A,B}$
Li+	-48	5.534×10^{-3}	-104	0.0263	-115	0.1722	-121	0.486	-119	0.7559
K+	-119	1.365×10^{-3}	-135	7.62×10^{-3}	-141	0.061	-139	0.237	-140	0.3265
Ca^{2+}	-146	0.158	-186	9.92×10^{-5}	-298	1.973×10^{-4}	-217	1.049×10^{-4}	-219	4.3880×10^{-5}
Mg^{2+}	-160	$8.387*10^{-5}$	-192	7.804×10^{-5}	-200	1.821×10^{-4}	-220	2.942×10^{-5}	-225	3.4529×10^{-5}
Fe^{3+}	-140	1.27×10^{-4}	-164	1.107×10^{-4}	-180	1.281×10^{-4}	-215	2.441×10^{-5}	-200	1.3715×10^{-5}
AL^{3+}	-150	8.515×10^{-5}	-172	8.046×10^{-5}	-190	8.590×10^{-5}	-200	4.446×10^{-5}	-220	6.1659×10^{-6}

The results in Tables (3) and (4) showed that the selectivity coefficients for monovalent interfering ions is in the order mono> di> trivalent. This may be attributed to the difference in ionic size, mobility and permeability.

A typical plot is shown in Fig.(4) for the interference of Al^{+3} on the DBPH electrode.

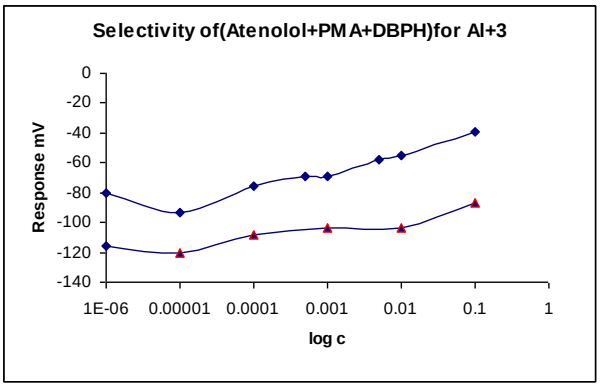


Fig.(4) Selectivity of (AT – PMA + DBPH) and the interfering cation(Al^{+3}) by separation method, ♦ Atenolol, ▲ Solution of interfering cation (Al^{+3}).

Sample Analyses:

The concentrations of a synthetic solutions of Atenolol were determined using an electrode based on DBPH plasticizer. Four potentiometric techniques were used for the determination of Atenolol namely direct, standard addition (SAM), multiple standard addition (MSA) and titration methods [21]. The relative error RE% and relative standard deviation RSD% were calculate for each method using an electrode based on DBPH and TBP electrodes. The % RSD, % RC, and % RE were calculated and are listed in Table (5).

Table (5)
Determination of Atenolol-ion samples by potentiometric techniques.

Electrode No.	*Concentrations (M)*				
	Sample	*Measurements using potentiometric methods*			
		Direct	*SAM*	*MSA*	*Titration*
AT– PMA +DBPH (IV)	1×10^{-3}	1.012×10^{-3}	1.008×10^{-3}	0.998×10^{-3}	0.95×10^{-3}
	RSD%	1.3*	0.12*	-	–
	RC%	101.2	100.8	99.8	٩٥
	RE%	1.2	0.8	0.2–	-5
	1×10^{-4}	0.994×10^{-4}	1.005×10^{-4}	1.001×10^{-4}	0.97×10^{-4}
	RSD%	2.15*	1.01*	-	–
	RC%	99.4	100.5	100.1	97
	RE%	-0.6	0.5	0.1	3
AT– PMA + TBP (II)	1×10^{-3}	0.992×10^{-3}	0.996×10^{-3}	0.998×10^{-3}	0.94×10^{-3}
	RSD%	1.29*	1.08*	-	–
	RC%	99.2	99.6	99.8	94
	RE%	-0.8	-0.4	-0.2	-4
	1×10^{-4}	1.008×10^{-4}	0.994×10^{-4}	1.006×10^{-4}	1.08×10^{-4}
	RSD%	2.11*	2.08*	-	–
	RC%	100.8	99.4	100.6	١٠٨
	RE%	0.8	-0.6	0.6	8

**** Each measurement was repeated three times.***

The plot of antilog E/S versus the volume of the five addition for 0.1 mL of 1×10^{-1} M standard Atenolol solution to the 1×10^{-4} M Atenolol is shown in Fig.(5). Gran plot paper with 10% volume correction was used.

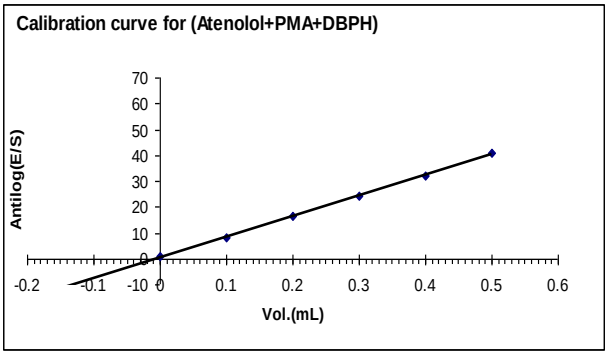


Fig.(5) Plot antilog (E/S) versus the value of the added standard for the determination of Atenolol solution (10^{-4} M) by MSA using AT-PMA +DBPH electrode.

The results in Table (1) and (5) showed that the electrodes based on DOBH and DBPH as plasticizers were the best electrodes.

Fig.(6) shows a typical plot for the titration curve of 0.001 M Atenolol standard solution with 0.001 M phsophomolybdic acid as a titrant using the Atenolol electrode based on membrane containing DBPH plasticizer.

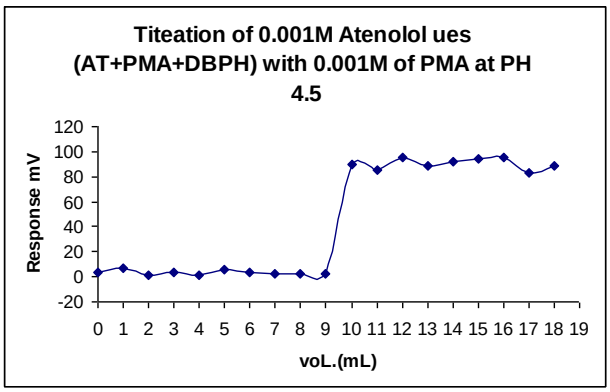


Fig.(6) Titration curve of electrode (AT-PMA +DBPH) for drug solution containing 0.001 M Atenolol with 0.001 M of PMA as titrant solution.

The direct potentiometric method was applied for the determination of atenolol in pharmaceutical tablet (Novaten) as listed in Table (6) using the electrode based on membrane (I) and (IV). The average recovery for atenolol determination in tablets was around 98.5% with a standard deviation of

about 0.1, based on an average of three measurements for each sample.

Table (6)

Atenolol tablets analyses for electrode (AT-PMA+DOPH) and electrode (AT-PMA+DBPH).

Electrode No.	*Parameter*	*Novaten*		
(AT-PMA+DOPH) (I)	Concentration(M)	1×10^{-3}	1×10^{-3}	1×10^{-3}
	Founded(M)	1.99×10^{-3}	1.004×10^{-3}	1.008×10^{-3}
	RSD%	0.889*		
	RC%	99	100.4	1.008
	RE%	-1	0.4	0.8
(AT-PMA+DBPH) (IV)	Concentration(M)	1×10^{-3}	1×10^{-3}	1×10^{-3}
	Founded(M)	1.006×10^{-3}	1.013×10^{-3}	1.002×10^{-3}
	RSD%	0.447*		
	RC%	100.6	101.3	100.2
	RE%	0.6	1.3	**0.2**

**** Each measurement was repeated three times.***

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الخلاصة

تم تحضير اقطاب بوليمرية حساسة للأتينولول معتمدة على معقد الدواء (Atenolol-phosphomolybdic acid)
كمادة فعالة مذابه في عدة مواد ملدنه هي:
Di butylphthlate (DBPH)
Di octyl phthalate (DOP)
O-nitrophenyloctylether (ONPOE)
Tri-butyl phosphate (TBP)
يمزج احد هذه الملدنات والمعقد مع PVC لتكوين الغشاء. خواص هذه الاقطاب تم دراستها من خلال تعيين مدى التركيز،ميل منحني المعايرة، ،حد التحسس،زمن الاستجابة ، عمر القطب، و تأثير الحامضية و كذلك التداخلات من دراسة الإنتقائية لبعض الأيونات الأحادية، الثنائية، الثلاثية.
وقد اظهرت النتائج ان الأقطاب المتكونة من (ONPOE , DBPH) كمواد ملدنة تمتلك المواصفات التالية:
ميل منحني معايرة mV/decade (٥٥,٦ و٥٤,٩)، مدى التراكيز التي تتحسسه هذه الاقطاب تراوحت من 1×10^{-5} M إلى 1×10^{-1} M, 5×10^{-6} M إلى 1×10^{-2} M, مع معامل ارتباط (٠,٩٩٩٦ و ٠.٩٩٩٢) بالتعاقب. وكان حد التحسس لهذه الاقطاب يساوي M ($\times10^{-}$ ٤ ^{6} ,8.5×10^{-6}) مع زمن الاستجابة بتركيز M (10^{-3}) كان بحدود (٤,٥ و ١٠) ثانية بالتعاقب.
استخدمت الاقطاب لتقدير الدواء في نماذج قياسية محضرة وكذلك في نماذج دوائية . وان الطرق التحليلية أثبتت أنها طريقة سريعة وبسيطة وتعطي نتائج جيدة.