Asian Journal of Chemistry Vol. 20, No. 5 (2008), 3817-3827

Polymeric Membrane Electrode for Potentiometric Determination of Atenolol in Tablets and Biological Fluids

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A PVC membrane electrode of atenolol and phosphomolybdic acid association complex was constructed. The basic electrode's performance characteristics were evaluated. The prepared electrode exhibits a Nernstain response (30.8 ± 0.1 mV/decade) over the concentration range of atenolol 1×10^{-2}–1×10^{-6} M of solutions of pH 3-8. Common organic and inorganic cations showed negligible interference. Direct potentiometric determination of 10×10^{-2}–1×10^{-6} M aqueous atenolol using this membrane electrode system showed an average recovery of 99.03 with mean standard deviation ± 0.7. The electrode gave a good stability, reproducibility and fast response. These characteristics of the electrode enable it to be used successfully for the determination of atenolol in pure form, pharmaceutical preparations and in biological fluids.

Key Words: Ion-selective electrode, Atenolol, Potentiometry.

INTRODUCTION

Atenolol, chemically known as 2-[4-(2-hydroxy-3-isopropyl amino propoxy)phenyl]acetamide, is a class of drugs called β-blockers which affect the heart and circulatory system. It is used to lower blood pressure, lower heart rate, reduce chest pain (angina) and to reduce the risk of recurrent heart attacks. Atenolol is a cardioselective β-blocker that is used for the treatment of hypertension and for the management of angina pectoris[1]. The chemical structure of atenolol is given in (Fig. 1).

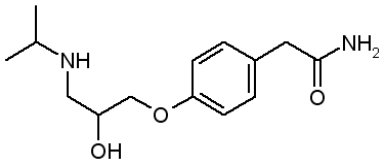

Fig. 1: Chemical structure of atenolol

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The misuse of β-blockers in sports was referred to that these drugs are used to lower blood pressure and slow the heart rate. Although they reduce the ability to perform physical exercise and are therefore not the subject of drug testing in endurance events. They help allay anxiety and steady the nerves and therefore may help competitors in archery, darts, shooting, bowls and snooker. Side-effects include cold extremities, fatigue and in extreme cases, heart failure.

Several methods have been reported for the determination of atenolol including spectrophotometry[2-9], high performance liquid chromatography[10-20], thin layer chromatography[21], capillary zone electrophoresis[22-26], electrochemical methods[27,28], colorimetric methods[29], potentiometric methods[30]. Although potentiometric methods of analysis using ion-selective electrodes are simple, economical and applicable for the samples, the present work describes a new selective membrane electrode of plasticized PVC type, for the determination of atenolol in pure solutions, pharmaceutical preparations and in biological fluids. The electrode is based on the incorporation of an ion-pair complex of the phosphomolybdate anion with atenolol cation in a poly (vinyl chloride) matrix.

EXPERIMENTAL

All chemicals used of analytical or pharmacopoeial grade. Double distilled water was used throughout the experiments. Atenolol was provided by Kahira Pharmaceutical Co. Egypt. Poly (vinyl chloride) (PVC) was from Aldrich, Germany. Di-butyl sebacate was from Fluka, Switzerland. Phosphomolybdic acid, tetrahyrofuran and methanol were from Memphis-Delagrange, France. Tenormine® Ateno®, Atelol® tablets were from Local drug stores. Stock solution of atenolol 10^{-1} M was prepared in methanol. Different standard solutions (1×10^{-2}–1×10^{-6} M) were prepared by serial dilution of the stock solution with deionized water. All atenolol solutions were kept in dark at 4 ºC in airtight containers.

Jenway 3010 pH/mV meter (U.K.) with an atenolol-PVC membrane electrode in conjunction with double junction Ag/AgCl electrode (Orion 90-02) (Taiwan, R.O.C.) containing 10 % w/v potassium nitrate in outer compartment. An Orion 91-02 glass-calomel combination electrode, (Taiwan, R.O.C.) was used for pH adjustment. All potentiometric measurements were carried out at 25 ± 1 ºC with constant magnetic stirring.

Recommended procedures

Preparation of atenolol-phosphomolybdate ion-pair: The ion-pair was prepared by mixing 50 mL aliquots of 1×10^{-2} M atenolol and phosphomolybdic acid. The resulting yellow precipitate was filtered through G_4 sintered glass crucible and washed thoroughly with deionized water, then dried at room temperature for 24 h. Membrane composition, electrode construction and

electrode calibration have been discussed before in the part of general recommended procedures.

Effect of pH: The effect of pH on the potential of the electrode was studied using two pH/mV meters. The combined glass calomel electrode was connected to one instrument and the PVC atenolol membrane with the double junction Ag/AgCl reference electrode was connected to the second instrument.

30 mL aliquots of 1×10^{-5} M, 1×10^{-4} M and 1×10^{-3} M drug solutions were transferred to a 100 mL beaker, where the three electrodes were immersed; the potential readings corresponding to different pH values were recorded.

The pH was gradually increased or decreased by the addition of small aliquots of dilute solutions of (0.1 or 1.0 M) sodium hydroxide or 0.1 N hydrochloric acid respectively and the pH-mV was plotted.

Selectivity of the electrode: Selectivity coefficients were determined by the separate solution method[31], in which the following equation was applied.

$$\log K^{Pot}_{AN,J^{z+}} = (E_2 - E_1)/S + \log[AN] - \log[J^{z+}]^{1/z}$$

where, E_1 is the electrode potential in 1×10^{-3} M atenolol solution. E_2 is the potential of the electrode in 1×10^{-3} M solution of the interferent ion J^{z+} and the S is the slope of the calibration plot. The selectivity of the electrode towards sugars, amino acids, certain cations was studied.

Analytical applications

Determination of atenolol in dosage forms

Application to tablets: Powder and mix 10 tablets and calculate the average weight of 1 tablet. Transfer a quantity of the powder to prepare a 1×10^{-2} M solution in 25 mL beaker, using appreciate amount of methanol about 5 mL and complete with distilled water, then adjust the pH of the solution to 5 using 0.1 N hydrochloric acid. The solution was transferred into 50 mL beaker. Serial dilutions ranging from (1×10^{-3}–5×10^{-6} M) were prepared. The PVC atenolol membrane electrode was immersed in the solution. The electrode system was allowed to equilibrate with stirring and the e.m.f. recorded and compared with the calibration graph. The standard addition (spiking technique) was also applied.

Content uniformity assay of atenolol tablets: 10 Individual tablets of 50 mg atenolol were placed in separate 100 mL beaker and dissolved in 90-100 mL of distilled water. The electrode was directly immersed into 10 mL of each sample for five times and should be washed with deionized water to reach steady potential between the individual measurements. The mean potential was used to evaluate the content uniformity from the calibration graph.

Dissolution test: Place 900 mL of distilled water into the dissolution vessel and equilibrate to 37 ± 0.5 ºC, place one tablet in the dissolution vessel and immediately operate the apparatus (pharmatest dissolution apparatus, Germany) at 2:50 rpm after the stated time, withdrawn 20 mL of the dissolution medium. For the potentiometric determination, after an appropriate time interval (0.5-5 min), the potential values were recorded and the amount of the atenolol was calculated from the calibration graph[32].

Determination of atenolol in biological fluids

Application to serum and urine[33]: Adjust urine pH to 5 (using 0.1 N hydrochloric acid) and pH of serum to 7 (use phosphate buffer). Add hydrochloric acid to urine and phosphate buffer to serum dropwise until the suitable pH obtained. Transfer 5 mL previously adjusted urine or serum into small separatory funnels and then separately add 5 mL of 10^{-2}, 10^{-3}, 10^{-4} and 10^{-5} M standard drug solution, followed by the addition of 20 mL of toluene for urine or 20 mL of diethyl ether for serum. Shake each funnel for 5 min and transfer aqueous layer to centrifuge tube. Centrifuge for 2 min at 1500 rpm, transfer each solution to a 50 mL volumetric flask and dilute to volume with deionized water. Apply above procedure as described under electrode calibration.

RESULTS AND DISCUSSION

The field of potentiometry with ISEs has been established and enormous exploratory efforts in the theory and methodology of ISEs and their possible application to chemical problems have been developed. Recently, ISEs were used to solve some analytical problems such as the direct determination of drugs in the presence of their degradation products and biological fluids. Fabricated membrane, which is a type of plastic membrane, is used. The technique of fabricating electrodes was pioneered by Moody and Thomas[34].

The aim of the present study was to develop a rapid, simple and sensitive method for the determination of atenolol, a widely used β-blocker drug, to facilitate its routine determination and quality control.

Electrochemical performance characteristics of the electrode

Nature and response characteristics of the electrode: Atenolol reacts with phosphomolybdic acid to form a stable atenolol-phosphomolybdate ion-pair complex which is water insoluble but readily soluble in an organic solvent such as tetrahydrofuran. The complex was prepared and tested as active material with di-butyl sebacate as a solvent mediator in a poly(vinyl chloride) membrane response for atenolol. The critical response characteristics of atenolol-PVC membrane electrode were determined and results are summarized in Table-1. The electrode exhibits a Nernstain response over the concentration range from 1×10^{-2}–1×10^{-6} M atenolol with a cationic slope

of 30.8 ± 0.1 mV/decade change in concentration (Fig. 2). The choice of membrane solvent to achieve the required selectivity is based on its electric permittivity and its immiscibility with aqueous phase, high viscosity, low solubility of the matrix in the membrane and ability to dissolve ion-pair complex. The response time of the electrode was tested for 1×10^{-2}–1×10^{-6} M atenolol solutions. The sequence of measurements was from low to high concentrations. This electrode exhibits a fast dynamic response of 40 s. The electrode used for a period of 30 d without significant change in the electrode parameters.

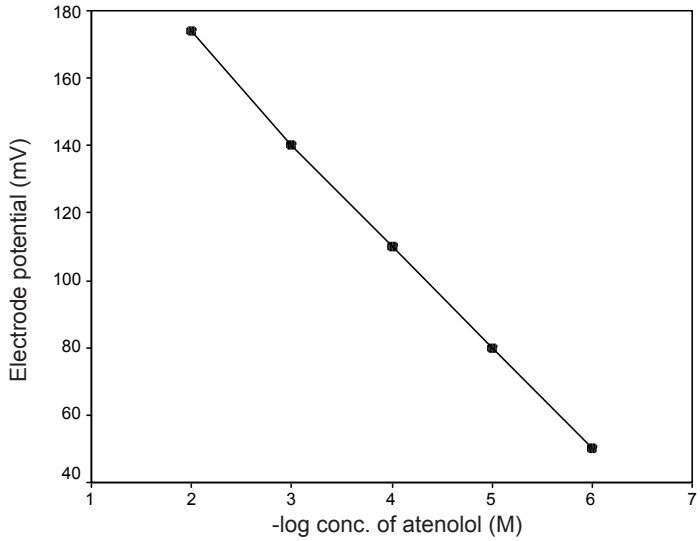

Fig. 2. Typical calibration graph of atenolol-phosphomolybdate-PVC membrane electrode

TABLE-1
CRITICAL RESPONSE CHARACTRISTICS OF ATENOLOL-PHOSPHOMOLYBDATE-PVC MEMBRANE ELECTRODE

Parameter	Value
Slope/mV decade	30.8 ± 0.1
Intercept/mV	234
Correlation coefficient (r)	0.9996
Linear range/M	1×10^{-2}–1×10^{-6}
Working pH range	3-8
Response time for 10^{-3}M atenolol/s	40
Life time/d	30

Effect of pH: The effect of pH of the different atenolol solutions (10^{-5}, 10^{-4}, 10^{-3} M atenolol) on the electrode potential was investigated. The solutions were acidified by the addition of small volumes of hydrochloric acid 0.1 N then the pH value was increased gradually using sodium hydroxide (0.1 or 1.0 M) for each pH value. The potential was recorded and thus the potential-pH curves for three atenolol concentrations were constructed (Fig. 3). As is obvious, within the pH range 3-8, the electrode potential is practically independent of pH and in this range the electrode can be safely used for atenolol determination. The potential decrease gradually and this can be related to the interference of the hydronium ion. The decrease occurring at higher pH values is most probably attributed to the formation of the ionization of the hydroxyl group, leading to a decrease in the concentration of the atenolol.

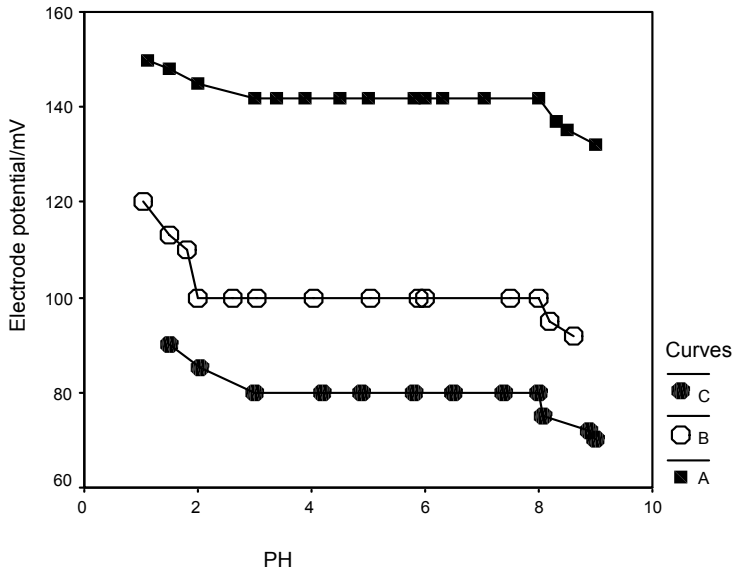

Fig. 3. The effect of pH on potential/mV of atenolol-phosphomolybdate-PVC membrane electrode, 1×10^{-3} M (A), 1×10^{-4} M (B), 1×10^{-5} M (C)

Selectivity of the electrode: Potentiometric selectivity coefficients were evaluated by the separate solution method. Table-2, showed that the proposed atenolol-phosphomolybdate-PVC membrane is highly selective toward atenolol ion. The electrode showed no response to a number of potentially interfering ionic excipients usually used in the manufacturing of the pharmaceutical preparations, such as starch and lactose. In the case of amino acids the high selectivity is mainly attributed to the difference in polarity and lipophilic character of their molecules relative to atenolol.

TABLE-2
SELECTIVITY COEFFICIENTS FOR SOME COMMON CATIONS WITH AMINOPHYLLINE-TUNGSTOPHOSPHATE-PVC MEMBRANE ELECTRODE

Interferent	$K^{pot}_{At.}+Cl^-$	Interferent	$K^{pot}_{At.}+Cl^-$
Starch	6.40×10^{-3}	Magnesium sulphate	3.90×10^{-4}
Glucose	4.30×10^{-3}	Zinc sulphate	1.10×10^{-2}
Lactose	4.10×10^{-3}	L-valine	1.03×10^{-3}
Ammonium chloride	2.30×10^{-2}	Tryptophan	1.20×10^{-3}
Calcium chloride	8.20×10^{-4}	Atropine sulphate	3.10×10^{-4}
Potassium chloride	3.70×10^{-3}	Propranolol hydrochloride	5.70×10^{-2}
Sodium chloride	1.70×10^{-3}	Urea	2.50×10^{-3}
Barium chloride	5.60×10^{-4}	Caffiene	3.60×10^{-3}
Nickel chloride	3.50×10^{-2}	Ephedrine hydrochloride	3.20×10^{-2}
Sodium citrate	4.60×10^{-3}		

Quantification, accuracy and precision: Direct potentiometric determination of atenolol using the atenolol-phosphomolybdate-PVC membrane electrode was performed and calculated from the calibration curve. The statistical data of the analytical results obtained by the proposed method (direct and standard addition techniques) for the drug in pure form were compared with the official method (non-aqueous potentiometric determination of atenolol[35]) and listed in Table-3. Furthermore, the results obtained were encouraging so the proposed method was applied for the determination of atenolol in some of its pharmaceutical preparations, the results are compared with official method and listed in Table-4 and biological fluids, as in Tables 5 and 6.

TABLE-3
DETERMINATION OF ATENOLOL IN PURE FORM USING ATENOLOL-PHOSPHOMOLYBDATE-PVC MEMBRANE ELECTRODE IN COMPARISON WITH REFERENCE METHOD [Ref. 35]

Statistical parameters	Official method[35]	Direct potentiometry	
		Calibration graphs	Standard addition method
Mean % recovery	99.62	98.99	99.03
N	6	9	7
Variance	0.230	0.578	0.490
SD	0.480	0.760	0.700
SE	0.196	0.253	0.265
RSD	0.482	0.768	0.707
t		(1.969) (2.160)*	(1.790) (2.201)*
F		(2.510) (3.690)*	(2.130) (4.390)*

*Theoretical values of t and F at p = 0.05.

TABLE-4
COMPARATIVE ANALYTICAL RESULTS OF THE PROPOSED AND OFFICIAL METHOD FOR THE TESTED DRUG IN SOME PHARMACEUTICAL PREPARATIONS[35]

Sample and source	Statistical parameters	Direct potentiometry		Official method[35]
		Calibration graph	Standard addition	
Tenormine® tablets (Kahira, Egypt) 100 mg/tablet	Mean % recovery	98.65	98.67	99.32
	N	6	6	5
	Variance	0.137	0.159	0.309
	SD	0.370	0.399	0.556
	SE	0.151	0.163	0.249
	RSD	0.375	0.404	0.560
	t	(2.301)(2.262)*	(2.184)(2.262)*	
	F	(2.26)(5.19)*	(1.94)(5.19)*	
Ateno® tablets (Eipico, Egypt) 100 mg/tablet	Mean % recovery	99.15	98.99	99.72
	N	6	7	5
	Variance	0.153	0.335	0.289
	SD	0.391	0.579	0.538
	SE	0.160	0.219	0.241
	RSD	0.394	0.585	0.540
	t	(1.97)(2.262)*	(2.241)(2.228)*	
	F	(1.89)(5.19)*	(1.16)(4.53)*	
Atelol® tablets (Pharco, Egypt) 50 mg/tablet	Mean % recovery	97.80	98.01	98.68
	N	7	7	5
	Variance	0.817	0.293	0.369
	SD	0.904	0.541	0.608
	SE	0.342	0.204	0.272
	RSD	0.924	0.552	0.616
	t	(2.013)(2.228)*	(1.971)(2.228)*	
	F	(2.21)(4.53)*	(1.26)(4.53)*	

*Theoretical values of t and F at p = 0.05.

The electrode response in pharmaceuticals and biological fluids: The use of atenolol drug in various fields, from clinical to abused in sports has necessitated an accurate and rapid, quantitative analysis in various matrices (dosage forms and biological fluids). This work proposed a fast, simple, easy, sensitive and straightforward potentiometric method to determine atenolol in dosage forms without the need for prior separation and preconcentration or derivatization procedures. The potential of the atenolol-phosphomolybdate-PVC membrane electrode showed no significant difference of response time between aqueous solution of pure drug and its

TABLE-5
DETERMINATION OF ATENOLOL IN PURE FORM "SPIKING TECHNIQUE" IN HUMAN URINE USING ATENOLOL-PHOSPHOMOLYBDATE-PVC MEMBRANE ELECTRODE

Calibration graph method		Standard addition method
Mean ± S.D (p = 0.05)	98.51 ± 0.619	98.29 ± 0.858
N	6	6
Variance	0.383	0.736
SD	0.619	0.858
SE	0.253	0.350
RSD	0.628	0.873

*Average of three experiments.

TABLE-6
DETERMINATION OF ATENOLOL IN PURE FORM "SPIKING TECHNIQUE" IN HUMAN SERUM USING ATENOLOL-PHOSPHOMOLYBDATE-PVC MEMBRANE ELECTRODE

Calibration graph method		Standard addition method
Mean ± SD (p = 0.05)	98.60 ± 0.837	98.31 ± 0.441
N	5	6
Variance	0.701	0.194
SD	0.837	0.441
SE	0.374	0.180
RSD	0.849	0.449

*Average of three experiments.

solutions from pharmaceutical preparations and biological fluids. The proposed method described good accuracy for the quality control tests, the content uniformity assay showed that the RSD < 1 %, with mean standard deviation ± 0.480. On the other hand Fig. 4, showed the dissolution profile of atenolol tables.

Conclusion

The described potentiometric method has simple workup procedure and require no sophisticated instrumentation. It determines only the therapeutically active, undegraded drug in the presence of its excipients without separation. The results obtained also show that the constructed electrode provides response suitable for analytical use in the determination of atenolol in drug bulk powder, dosage forms and biological fluids. A part from showing linear response within wide pH and concentration ranges with high accuracy and sensitivity also has high selectivity and reproducibility. It offers distinct

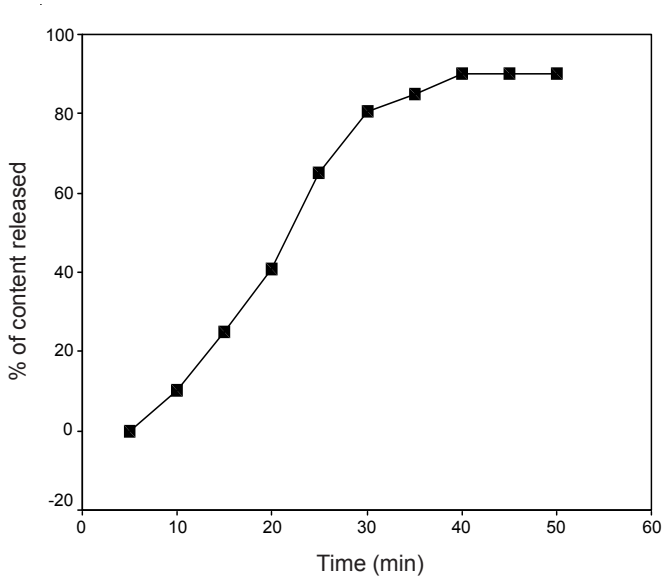

Fig. 4. Dissolution profile of atenolol 100 mg tablets

advantages in rapidity and simplicity. It is suitable for routine determination of atenolol in quality-control laboratories, for content uniformity assay or dissolution of tablets. This conclusion is justified by the results obtained from the analysis of pharmaceutical preparations, biological fluids for which precise and accurate recoveries were obtained.

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(*Received*: 26 September 2007; *Accepted*: 8 February 2008) AJC-6317