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Journal of Pharmaceutical and Biomedical Analysis
32 (2003) 175–180
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Short communication

Polymeric matrix membrane sensors for sensitive potentiometric determination of some β-blockers in pharmaceutical preparations

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Received 12 November 2002; received in revised form 24 December 2002; accepted 25 December 2002

Abstract

Five poly(vinyl chloride) matrix membrane sensors responsive to some β-blockers (atenolol, bisoprolol, metoprolol, propranolol and timolol) are described and characterized. The sensors are based on the use of the ion-association complexes of the β-blocker cations with tungstophosphate anion as electroactive materials. The performance characteristics of these sensors, evaluated according to IUPAC recommendations, reveal fast, stable and near-Nernstian response for 10^{-2}–2×10^{-7} mol l^{-1} of different β-blockers over the pH range 2–9. Many inorganic and organic cations as well as drug excipients and diluents normally used in drug formulations do not interfere. The sensors are used for direct potentiometry of β-blockers in some pharmaceutical preparations. Validation of the method according to the quality assurance standards shows suitability of the proposed sensors for use in the quality control assessment of these drugs. Results with an average recovery of 99.1% and a mean standard deviation of ±1.3% of the nominal are obtained which compare fairly well with data obtained using the British Pharmacopoeia method.

Keywords: β-Blocker sensors; Tungstophosphate; Potentiometry; Pharmaceutical analysis

1. Introduction

β-Blockers are clinically important drugs used in the treatment of disorders such as hypertension, angina pectoris and arrhythmia [1]. They are also abused in sports because of their blood pressure regulatory and tremor decreasing effects [2]. The United States [3] and British [4] Pharmacopoeias described titrimetric, spectrophotometric and chromatographic methods of assay. Other methods in common use for determining β-blockers involved spectrophotometry [5–8], fluorimetry [9–11], colorimetry [12,13], high performance liquid chromatography [14–17], gas chromatography [18–20] and polarography [21–24]. Little work, however, has been described for the use of ion

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0731-7085/03/$ - see front matter
doi:10.1016/S0731-7085(03)00015-3

selective membrane sensors for determining this group of drugs. Propronolol β-blocker has been assayed by a kinetic procedure through its reaction as a secondary amine with 1-fluoro-2,4-dinitrobenzene and following the release of fluoride ion with a fluoride ion selective electrode [25]. The method suffered from lack of selectivity as almost all amino compounds react similarly. Polymeric membrane electrodes for some β-adrenergic blocker agents have been suggested based on the use of their ion-pair complexes with dinonylnaphthalene sulfate, tetraphenylborate and tetrakis-(2-chlorophenyl-borate) [26–29] as ion exchangers.

In the present work, potentiometric sensors for atenolol, bisoprolol, metoprolol, propranolol and timolol β-blockers are described. These sensors incorporate β-blockers–tungstophosphate ion-association complexes embedded in PVC matrix membranes plasticized with suitable solvent mediators. Performance characteristics of these sensors reveal low detection limit, high sensitivity, good selectivity, fast response, long life span and applicability for accurate determination of β-blockers in dosage forms.

2. Experimental

2.1. Apparatus

All potentiometric measurements were made at 25 ± 1 °C with an Orion (Model 720) pH/mV meter. An Orion single junction Ag/AgCl reference electrode (Model 90-01) filled with 10% (w/v) KCl or a double junction Ag/AgCl Orion reference electrode (Model 90-92) with 10% (w/v) KNO_3 in the outer compartment was used in conjunction with the drug sensor. A HORIBA pH combined electrode Model F-22E was used for pH measurements.

2.2. Reagents

All chemicals were of analytical reagent grade and double distilled water was used throughout unless specified otherwise. Dioctylphthalate (DOP), tetrahydrofuran (THF), and tungstophosphoric acid (TPA) were obtained from Sigma (St. Louis, MO). Stock 10^{-1} mol l^{-1} β-blockers (atenolol, bisoprolol, metoprolol, propranolol and timolol) solutions were prepared by dissolving 0.266, 0.325, 0.684, 0.295 and 0.432 g, respectively, in 100 ml doubly distilled water.

2.3. β-Blockers ion exchangers

Tungstophosphate–drug ion pair complexes were prepared by slow addition of 20 ml of 10^{-2} mol l^{-1} tungstophosphate solution to 10 ml aliquots of 10^{-2} mol l^{-1} aqueous solutions of the β-blockers. The mixtures were stirred for 10 min, the precipitate filtered off on G4 sintered glass crucible, washed with distilled water, dried and ground to fine powder. Elemental analysis revealed the formation of 1:2 tungstophosphate–bisoprolol, metoprolol, propranolol and timolol complexes and 1: 1 tungstophosphate–atenolol complex.

2.4. β-Blockers sensors

A portion of β-blockers ion pair complex (10 mg) was thoroughly mixed with 0.19 g of PVC, 0.35 g of DOP and 5 ml THF in a glass petridish (5 cm diameter) covered with filter paper and left to stand overnight to allow slow evaporation of the solvent at room temperature. A master PVC membrane (ca. 0.1 mm thick) was obtained and used for construction of the sensors as previously described [30–32]. The internal reference solution consisted of equal volumes of 1×10^{-2} mol l^{-1} β-blocker aqueous solution and 1×10^{-2} mol l^{-1} sodium chloride solution. An Ag/AgCl internal reference wire electrode (1 mm diameter) was immersed in the internal solutions. The sensors were conditioned by soaking in 1×10^{-2} mol l^{-1} β-blockers aqueous solution for 1 day and were stored in the same solution when not in use. Atenolol sensor was soaked and stored in dry air.

The sensors were calibrated by transferring 1.0 ml aliquots of $0.1–1 \times 10^{-6}$ mol l^{-1} aqueous solutions of β-blockers to 50 ml beakers containing 9.0 ml of de-ionized double distilled water or 0.01 mol l^{-1} NaCl solution followed by insertion of the corresponding β-blocker-PVC membrane

sensor in conjunction with either a single or a double junction Ag/AgCl reference electrode. The potential readings were recorded after stabilization to ± 0.2 mV and emf was plotted as a function of logarithm β-blocker concentration. The calibration graphs were used for subsequent determination of unknown β-blockers concentration.

2.5. Determination of β-blockers in pharmaceutical preparations

Five tablets of the drug formulations were weighted and finely powdered in a small dish. An accurately weighted portion of the powder, equivalent to one tablet, was dissolved in the minimum volume of double distilled de-ionized water and few drops of 0.1 mol l^{-1} HCl. The solution was filtered into a 50 ml calibrated flask, diluted to the mark with 0.01 mol l^{-1} NaCl solution and shaken well. A 10 ml aliquot of the drug solution was potentiometrically measured as described above and the potential reading was compared with the calibration plot. Alternatively, the standard additions (spiking) technique was used by measuring the potentials displayed by the drug test solution before and after addition of 0.1 ml aliquot of 1×10^{-2} mol l^{-1} standard β-blocker solution. The change in the electrode potential (ΔE) was recorded and used for calculation of the concentration of the drug [31].

3. Results and discussion

3.1. Sensors characteristics and calibration data

Atenolol (At), bisoprolol (Bi), metoprolol (Mt), propanolol (Pr) and timolol (Ti) β-blockers react with tungstophosphate (TP) to form water insoluble 1:1 (At TP) ion association complex in case of atenolol and 2:1 $(drug)_2$ TP ion association complexes in case of bisoprolol, metoprolol, propranolol and timolol drugs as confirmed by elemental analysis. This indicates that all drugs behave as monovalent species due to the presence of one amino group in each molecule except atenolol which behave as a divalent species due to the presence of two amino groups in each molecule. The complexes were prepared, characterized, and incorporated with a suitable solvent mediator in poly(vinyl chloride) matrix membranes. Plastic membranes prepared by using a casting solution of the composition 2:34:64% (w/w) ion pair complex, PVC and DOP plasticizer, respectively, were used for constructing the sensors.

The electrochemical performance characteristics of the sensors were systematically evaluated according to IUPAC recommendations [33]. The performance characteristics of the sensors, based on data collected over a period of 20 weeks for five sensor assemblies for each drug under static conditions are given in Table 1. Calibrations were done at constant ionic strength (0.01 mol l^{-1} NaCl) and in water background. Results from six replicate studies gave sub-Nernstian slopes of 48–54 mV per decade for all monovalent drug ions (Bi, Mt, Pr and TP) and super-Nernstian slope of 34 mV per decade for the divalent atenolol ion. The results also showed that potentiometric response with 0.01 mol l^{-1} NaCl background offers stable potential and better calibration slope than those obtained in pure aqueous media. Instability of the response in pure aqueous solution may be due to the Ag colloidal contaminants at the liquid junction.

The dynamic response times of the β-blocker sensors were tested for 10^{-2}–10^{-6} mol l^{-1} test solutions. The sequence of measurements was from low to high concentrations. The time required for the sensors to reach values within ± 1.5 mV of the final equilibrium potential after increasing the β-blockers concentration 10-fold was measured. The response time of the sensors for 10^{-3} mol l^{-1} β-blockers was 10–40 s. Potential stabilities of the sensors over various pH ranges were also examined for 10^{-2} and 10^{-3} mol l^{-1} β-blockers. The results revealed a stable potential over the pH 4–8 (10^{-2} mol l^{-1} acetate buffer). Long term potential stability of the sensors was fairly good as it practically unchanged over a period of 6–8 weeks.

The performances of the β-blockers sensors in the presence of some nitrogenous compounds such as amines, amino acids and some inorganic cations were assessed by measuring and comparing the

Table 1
Response characteristics of some β-blocker tungstophosphate PVC membrane based sensors

Parameter	Sensor				
	At-TP	Bi-TP	Mt-TP	Pr-TP	Ti-TP
Slope (mV per decade)	34.0±0.1	51.5±0.1	54.4±0.1	48.1±0.1	48.3±0.1
Intercept (mV)	58.7	167.3	158.6	191.1	155.7
Correlation coefficient (r)	0.9838	0.9951	0.9925	0.9830	0.9921
Lower limit of linear range (mol l^{-1})	9×10^{-7}	8×10^{-7}	4.5×10^{-7}	8×10^{-7}	6×10^{-7}
Lower LOD (mol l^{-1})	8×10^{-7}	5×10^{-7}	3.2×10^{-7}	3.5×10^{-7}	4×10^{-7}
Response time for 10^{-3} mol l^{-1} (s)	40	40	10	40	10
Recovery time (s)	50	50	50	50	50
Working range (pH)	3–7	2–8	4–9	3–8	2–8
Life span (week)	6–8	6–8	6–8	6–8	6–8
Accuracy (%)	98.1	98.8	98.7	98.1	98.4
Repeatability (CV_w (%))	0.8	0.6	0.5	0.7	0.6
Between day-variability (CV_b (%))	1.1	0.9	0.8	0.8	0.9
Standard deviation (%)	1.2	1.1	1.1	0.9	1.2
Working range, (mol l^{-1})	10^{-2}–3×10^{-7}	10^{-2}–3×10^{-7}	10^{-2}–2×10^{-7}	10^{-2}–1×10^{-7}	10^{-2}–2×10^{-7}

*, Average of six measurements.

selectivity coefficient values ($K^{pot}_{D,I}$). The separate solutions method [31,33] with a fixed concentration of the interferent (1×10^{-3} mol l^{-1}) was used for evaluation of the selectivity. The results obtained by all the developed sensors (Table 2) showed reasonable selectivity for β-blockers in the presence of many nitrogenous compounds. Pharmaceutical additives, diluents and ingredients commonly used in drug formulations such as lactose, maltose, carboxymethylcellulose and magnesium stearate have no effect when present in a concentration level of up to a 10^4-fold excess over the drug (Table 2).

Potentiometric determination of β-blockers standard aqueous solutions (5–10 mg ml^{-1}) as well as drug formulations in triplicate using the standard addition method showed results with an average recovery of 99.8% and a mean standard

Table 2
Potentiometric selectivity coefficients ($K^{pot}_{D,I}$) of β-blockers tungstophosphate PVC membrane based sensors

Interferent, I	$K^{pot}_{D,I}$				
	At-TP	Bi-TP	Mt-TP	Pr-TP	Ti-TP
Valine	4.0×10^{-3}	2×10^{-2}	1.4×10^{-2}	2.6×10^{-3}	1.0×10^{-2}
Ca^{2+}	3.0×10^{-3}	1.2×10^{-3}	1.7×10^{-2}	3.3×10^{-4}	0.2×10^{-2}
Urea	3.5×10^{-3}	3.3×10^{-4}	0.1×10^{-2}	3.1×10^{-4}	2.1×10^{-3}
Glycine	3.1×10^{-3}	1.4×10^{-4}	0.1×10^{-2}	2.5×10^{-4}	3.6×10^{-3}
Ba^{2+}	3.3×10^{-4}	1.4×10^{-4}	0.1×10^{-2}	3.3×10^{-4}	2.9×10^{-3}
Benzamide	3.3×10^{-3}	1.2×10^{-4}	6.3×10^{-3}	3.0×10^{-4}	2.1×10^{-3}
Cu^{2+}	2.8×10^{-3}	1.6×10^{-4}	3.8×10^{-3}	2.5×10^{-4}	2.3×10^{-3}
NH_4^+	3.5×10^{-3}	1.0×10^{-4}	5.3×10^{-3}	9.7×10^{-4}	1.8×10^{-3}
Na^+	2.6×10^{-3}	3.7×10^{-4}	5.3×10^{-4}	3.3×10^{-4}	1.2×10^{-4}
Lactose	3.9×10^{-3}	1.6×10^{-4}	9.4×10^{-3}	6.7×10^{-4}	2.6×10^{-4}
Triethanolamine	1.8×10^{-2}	1.4×10^{-4}	1.3×10^{-3}	1.3×10^{-4}	2.0×10^{-3}

Table 3
Potentiometric determination of β-blockers in some pharmaceutical preparations using β-blocker tungstophosphate PVC membrane based sensors

Sensor	Trade name and source	Nominal content (mg per tablet)	Recovery (%)*	
			Potentiometry	UV standard method BP [4]
Atenolol-tungstophosphate	Tenormin (Cairo Pharm. Company)	100	103.4±1.4	100.5±1.3
		50	103.4±1.4	100.5±1.4
	Ateno (Epico)	100	100.8±1.1	99.5±1.2
		50	100.8±1.1	99.5±1.4
	Blockum (M.U.P)	100	103.4±0.8	99.0±1.2
		50	103.4±0.9	99.3±1.4
	Atelol (Pharco.)	100	103.4±1.5	98.5±1.1
		50	103.4±1.5	98.5±1.4
Bisoprolol-tungstophosphate	Concor (Ammon/Merck)	10	101.8±1.8	100.8±1.2
		5	100.4±1.8	100.8±1.1
Metprolol-tungstophosphate	Betalock (Cid/Astra)	100	99.6±1.0	99.4±1.4
Propranolol-tungstophosphate	Inderal (Cairo Pharm. Company)	40	102.1±0.7	101.0±1.3
		10	99.8±0.7	101.0±1.4
Timolol-tungstophosphate	Timolol solution (Epico)	0.5%	99.1±3.2	98.8±1.2
		0.25%	99.1±3.2	98.8±1.2

*, Average of five measurements.

deviation of ±1.3% (Table 3). These data are in good agreement and compared fairly well with data obtained with the spectrophotometric standard method of the British Pharmacopoeia [4]. An *F*-test revealed that there was no significant difference between the means and variances of the two sets of results. Based on running duplicates, control charts (R and $\bar{X}$) were prepared for monitoring the drugs [34]. The distribution of measurements and range of determination under investigation indicated that it was under statistical control.

Validation of the proposed potentiometric methods for determining β-blockers drugs was made by measuring the range, lower limit of detection (LOD), accuracy (recovery), truness, precision (σ), repeatability (CV_w), between-day-variability (CV_b) and linearity and sensitivity (slope). Results obtained on six batches (six determination each) using the quality assurance standards [35] are depicted in Table 1. These data render the proposed potentiometric methods applicable for quality control of drug formulations.

4. Conclusions

Potentiometric sensors for atenolol, bisoprolol, metoprolol, propranolol and timolol β-blockers are prepared, characterized and used for drug determination. The sensors are based on the use of plasticized PVC matrix membrane incorporating β-blockers-tungstophosphate ion exchangers. The sensors are simple and sufficiently specific for quantitative determination of some β-blockers at a concentration level as low as 10^{-7} mol l^{-1} with an accuracy of 99.1±1.3%. The drugs are determined in pure powders and in dosage forms. The sensors offer the advantages of fast response, reasonable selectivity, elimination of drug pretreatment or separation steps, low cost and possible interfacing with computerized and automated systems. Further advantages offered by using tungstophosphate based membrane sensors are the low LOD ($3–8 \times 10^{-7}$ mol l^{-1}), long life span (8 weeks), extending working concentration range (10^{-2}–10^{-7} mol l^{-1}) and wide pH working range (pH 2–9). These are probably due to the extremely poor solubility and low leachability of tungstopho-

sphate-drug ion exchangers from the membrane of the sensors.

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