Original Article

Membrane electrodes for determination of two antihypertensive drugs in pharmaceutical formulations of either single or binary mixtures and in biological fluids

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ABSTRACT: Membrane-selective electrodes were used to determine benazepril hydrochloride (BZ) and trandolapril (TR) in their binary mixtures with hydrochlorothiazide (HZ) and verapamil (VR), respectively. This method involves construction of four water insoluble ion-association complexes: benazepril-tetraphenyl borate (BZ-TPB), benazepril-reineckate (BZ-R), trandolapril-tetraphenyl borate (TR-TPB), and trandolapril-reineckate (TR-R). These complexes were used as electroactive materials in polyvinyl chloride (PVC) matrix membrane sensors in order to determine the two aforementioned drugs in their pharmaceutical formulations and in plasma. The performance characteristics of these sensors, evaluated according to IUPAC recommendations, revealed a fast, stable, and linear response for BZ and TR. The suggested procedures were checked using laboratory-prepared mixtures and were successfully used to analyze their pharmaceutical preparations. The results obtained using the proposed method were statistically analyzed and compared with those obtained using previously reported methods.

Keywords: Benazepril hydrochloride, trandolapril, ion selective electrodes, PVC membranes, ammonium reineckate, sodium tetraphenyl borate

1. Introduction

Benazepril hydrochloride (BZ) is 3(S)-3-[[(1S)-1-ethoxy-carbonyl)-3-phenylpropyl] amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid, while trandolapril (TR) is 1-[2-[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxypropyl[octahydro-1H-indol-2-carboxylic acid (*1*). They belong to the class of angiotensin-converting enzyme inhibitors used as antihypertensive drugs either alone or in combination with hydrochlorothiazide (HZ) or verapamil (VR), respectively (*2*).

Several analytical methods, including spectrophotometry, have been described for simultaneous determination of BZ/HZ in their binary mixture; these methods include the derivative technique (*3,4*), the chemometric method (*4,5*), Vierordt's technique (*6,7*), the absorbance ratio method (*4,6*), and isosbestic point measurement (*8*). Other methods involve HPLC (*7,9,10*) and TLC techniques (*10*). BZ has been determined alone using potentiometric coated wire electrodes (*11*).

A review of the literature revealed that there are few methods of determining TR, including HPLC (*12-14*) and enantioselective biosensors (*15,16*). TR and verapamil have been simultaneously determined using HPLC (*17*) and HPTLC densitometric methods (*18*).

The current work describes simple potentiometric sensors based on the use of the ion association complexes of both BZ and TR cations with tetraphenyl borate and reineckate anions as ion exchangers in a plasticized PVC matrix. These sensors were found to be suitable for the selective determination of BZ in a binary mixture with hydrochlorothiazide and for the determination of TR in a binary mixture with verapamil; neither determination required preliminary separation or extraction. These sensors also allow the potentiometric determination of both drugs BZ and TR in plasma without preliminary extraction and separation steps. The advantages of the suggested potentiometric sensors are their simplicity, low cost, fast response, wide working pH range, wide response range, and use with turbid and colored solutions.

2. Materials and Methods

2.1. *Apparatus*

Potentiometric measurements were made at 25 ± 1°C with a Hanna (Model 211) pH/mV meter. A single-junction calomel reference electrode (Model HI 5412) was used in conjunction with the drug sensor. A WPA pH

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combined glass electrode (Model CD 740) was used for pH measurements.

2.2. *Reagents*

All chemicals were of analytical reagent grade unless otherwise stated and doubly distilled deionized water was used.

The working standard for BZ was graciously supplied by Novartis Pharma Co., Cairo, Egypt. Its purity was certified to be 99.79 ± 0.80% according to a previously reported method (*8*). The working standard for TR was graciously supplied by Abbott Laboratory, USA. The purity of the sample was found to be 99.94 ± 1.69% according to a previously reported method (*17*).

Aqueous $1.00 \times 10^{-3} - 1.00 \times 10^{-6}$ M BZ and TR solutions were prepared by serial dilution of 1.00×10^{-2} M stock solutions. All pharmaceutical samples of BZ and TR were obtained from local drug stores.

Tetrahydrofuran (THF) 99% (Lab Scan), high molecular weight (10,000) polyvinyl chloride (PVC) powder, dibutyl sebacate (DBS) plasticizer, sodium tetraphenyl borate (TPB), and ammonium reineckate (AR) were obtained from Sigma-Aldrich. A phosphate buffer, pH 4, was prepared.

Laboratory-prepared mixtures of BZ/HZ were prepared as follows: aliquoted portions of 2.5, 5, 2.5, 1.25, and 2.5 mL of BZ from a stock solution of 1.00×10^{-2} M were accurately transferred to a series of 25-mL measuring flasks. Aliquoted portions from a 1.00×10^{-2} M HZ solution were added to prepare mixtures containing 1:1, 2:1, 1:2, 0.5:1, and 1:0.5 of BZ and HZ, respectively.

Laboratory-prepared mixtures of TR/VR were prepared as follows. Aliquot portions 2.5, 10, 2.5, 2.5 and 2.5 mL of TR from its stock solution 1.00×10^{-2} M was transferred accurately to a series of 25-mL measuring flasks. Aliquot portions from 1.00×10^{-2} M VR solution were added to prepare mixtures containing 1:1, 4:1, 1:2, 1:4 and 1:6 of TR and VR, respectively.

2.3. *Preparation of BZ and TR ion exchangers*

Benazepril-tetraphenyl borate (BZ-TPB), benazepril-reineckate (BZ-R), trandolapril-tetraphenyl borate (TR-TPB), and trandolapril-reineckate (TR-R) ion pair complexes were prepared by slow addition of 20.00 mL of 1.00×10^{-2} M BZ and TR aqueous solutions to 10.00 mL aliquots of TPB and AR, separately. The mixtures were stirred for 10 min; the precipitates were filtered off, washed with doubly distilled water, dried at room temperature, and ground to a fine powder. Elemental analyses confirmed the formation of 1:2 complexes.

2.4. *BZ and TR-PVC membrane sensors*

In a glass Petri dish (5.00 cm diameter), 10.00 mg of BZ ion exchanger or TR ion exchanger were thoroughly mixed with 350.00 mg of DBS and 190.00 mg of PVC powder. The mixture was dissolved in 5.00 mL of THF. The Petri dish was covered with filter paper and allowed to stand overnight to allow solvent evaporation at room temperature. A master membrane with a thickness of 0.10 mm was obtained.

2.5. *Sensor assembly*

A disk of an appropriate diameter (about 8.00 mm) was cut from the previously prepared master membranes and glued onto the flat end of PVC tubing with THF. A mixed solution consisting of equal volumes of 1.00×10^{-2} M BZ or TR and 1.00×10^{-2} M sodium chloride was used as an internal reference solution. Ag/AgCl coated wire (3.00 mm diameter) served as an internal reference electrode. The sensors were conditioned by soaking overnight in a solution of 1.00×10^{-2} M of either of the two drugs and storage in the same solution when not in use.

2.6. *Sensor calibration*

Along with the single-junction calomel reference electrode, the prepared electrodes were immersed in aqueous solutions of BZ and TR in a range of $1.00 \times 10^{-6} - 1.00 \times 10^{-2}$ M. The membrane sensors were washed with water between measurements.

A calibration graph was constructed by plotting the potential change with respect to the logarithm of the BZ and TR concentrations. The regression equations for the linear portion of the curves were computed and used to subsequently determine unknown concentrations of BZ and TR.

2.7. *Selectivity measurements*

Potentiometry selectivity coefficients ($K^{pot}_{BZ \text{ or } TR, I}$) were evaluated according to IUPAC guidelines using the separate solutions method (*19,20*).

2.8. *Application to laboratory-prepared mixtures*

Along with the single-junction calomel reference electrode, the membrane sensors were immersed in corresponding laboratory-prepared mixtures. The sensors were washed with water between measurements. The electromotive force (EMF) produced for each mixture was measured with the proposed electrodes and then the concentration of BZ and TR was determined from the corresponding regression equation**.**

2.9. *Application to pharmaceutical formulations*

2.9.1. *BZ in Cibadrex tablets*

Ten tablets were weighed and powdered. A quantity

of the powdered tablets was transferred to a 50-mL volumetric flask, and then the flask was completed to the mark with phosphate buffer (pH 4) and sonicated for 15 min to prepare 1.00×10^{-3} M of BZ. The EMF produced by immersing the prepared electrodes, along with single junction calomel reference electrode, in the prepared solutions was determined and then the concentration of BZ was calculated from the regression equation of the corresponding electrode.

2.9.2. *TR in Tarka tablets*

Ten tablets were weighed and powdered. A quantity of the powdered tablets was transferred to 50-mL volumetric flask, and then the flask was completed to the mark with phosphate buffer (pH 4) and sonicated for 15 min to prepare 1.00×10^{-3} M of TR. The assay was completed as described above.

2.10. *Application to plasma samples*

Four-point five mL of plasma were placed into 4 stoppered shaking tubes, and then 0.5 mL of 1.00×10^{-2} and 1.00×10^{-3} M BZ and TR were each added separately and shaken. The membrane sensor was immersed in these solutions along with the single junction calomel reference electrode. The sensor was washed with water between measurements. The EMF produced by each solution was measured using the four proposed electrodes and then the concentration of BZ and TR was determined from the corresponding regression equations.

3. Results and Discussion

The development and use of ion-selective electrodes continue to be of interest in pharmaceutical analysis because these sensors offer the advantages of simple design, reasonable selectivity, and fast response.

The method proposed here has the advantages of being sensitive, allowing determination of BZ in the presence of HZ. The proposed electrodes have a longer life span than potentiometric coated wire electrodes for determination of BZ alone as were previously reported (*11*).

In addition, TR was formulated with VR in a medicinally recommended ratio of 1:100. Analysis of such a mixture is challenging because the amount of the major component, VR, is much greater than the amount of the minor component, TR. Therefore, the aim of this work was to develop simpler and less complicated methods for the determination of a minor component like TR in a binary mixture.

The present investigation is based on the fact that both BZ and TR behave as cations in acidic medium due to the presence of amino groups. This property suggests the use of anionic ion exchangers in the formation of ion association complexes. These are physically compatible with the matrix and serve as rapid ion exchangers for the two drugs at the membrane-sample interface.

BZ and TR reacted with sodium TPB and AR to form stable 1:2 water insoluble ion association complexes. This ratio was confirmed by elemental analysis data and by the Nernstian response of the suggested sensors. That response was about 30 mV (for both BZ and TR), the typical value for divalent drugs (*21*).

PVC acts as a standard support matrix and as a trap for the sensed ions, but its use requires the use of a plasticizer (*22*). In the present investigation, DBS was chosen from among dicarboxylic acid esters as a plasticizer. With PVC, dicarboxylic acid esters were found to be the optimum plasticizers; they dissolve the ion association complex and adjust both the membrane permittivity and ion exchange site mobility to yield the highest possible selectivity and sensitivity (*23,24*).

Electrochemical performance characteristics of the proposed sensors were evaluated according to IUPAC recommendations (*21*) (Table 1). The electrodes were found to display constant and stable potential readings within 2 mV day-to-day, and the calibration slopes for the four electrodes changed by less than 2 mV per concentration decade over a period of 1 month.

The response time of the electrodes was tested for concentrations of the two drugs from 1.00×10^{-5} – 1.00×10^{-2} M. The measurements were characterized by a fast stable response within 20-30 sec for concentrations less than 1.00×10^{-4} M and 10-20 sec for concentrations over 1.00×10^{-4} M.

The pH effect was optimized from the point of view of both sensor function and chemical form of the test substance. As shown in Figures 1 and 2, the potential-pH profiles indicated that the sensor responses were fairly steady over pH 3-5 (phosphate buffer). Within this range, drug cations are completely ionized and dissociated and therefore can be sensed. Above and below this pH range, the potentials displayed by the electrodes were noisy.

The potentiometric response of the four studied electrodes at the optimum pH was linear with constant

Table 1. Response characteristics of the four investigated electrodes

Parameter	BZ-TPB	BZ-R	TR-TPB	TR-R
Slope (mv/decad)	– 31.58	– 30.57	– 36.64	– 31.44
Intercept (mV)	83.28	91.02	22.39	3.24
Correlation coefficient	0.9997	0.9992	0.9997	0.9991
Detection limit (M)	2.8×10^{-6}	4.6×10^{-6}	5.2×10^{-6}	6.6×10^{-6}
Response time (sec)	20-30	20-30	20-30	20-30
Working pH range	3-5	3-5	3-5	3-5
Concentration range (M)	10^{-5}-10^{-2}	10^{-5}-10^{-2}	10^{-5}-10^{-2}	10^{-5}-10^{-2}
Life span (weeks)	4-6	4-6	4-6	4-6
Average recovery (%)	99.07	99.13	100.09	99.98
R.S.D. %*	0.75	0.91	1.26	1.43

* Results of four determinations.

slopes over a drug concentration range of 1.00×10^{-5} – 1.00×10^{-2} M for BZ and TR, respectively (Figures 3 and 4).

The accuracy of the proposed membrane sensors at quantifying blind samples of BZ and TR was assessed using the four sensors. Results indicated average recovery of 99.07 ± 0.75, 99.13 ± 0.91, 100.09 ± 1.26, and 99.98 ± 1.43 for the BZ-TPB, BZ-R, TR-TPB, and TR-R sensor, respectively.

As shown in Tables 2 and 3, the proposed method was valid and suitable for determining BZ in different laboratory-prepared mixtures with HZ or for determining TR in different laboratory-prepared mixtures with VR. Mean percentage recovery was 100.21 ± 0.86 and 99.78 ± 1.24, for BZ by BZ-TPB and BZ-R, respectively, and 100.71 ± 1.22 and 100.73 ± 0.78 for TR by TR-TPB and TR-R, respectively.

The performance of the four sensors in the presence of some nitrogenous compounds such as amines, amino acids, and some inorganic cations was assessed by measuring and comparing potentiometric selectivity coefficients ($K^{pot}_{Drug, I}$). The separate solutions method with a fixed concentration of the interferent (1.00×10^{-3} M) was used to evaluate selectivity. Results obtained

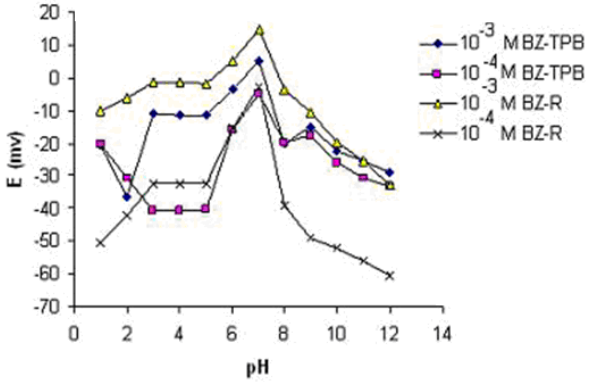

Figure 1. Effects of pH on the response of a benazepril hydrochloride-tetraphenyl borate electrode (BZ-TPB) and a benazepril hydrochloride-reineckate electrode (BZ-R).

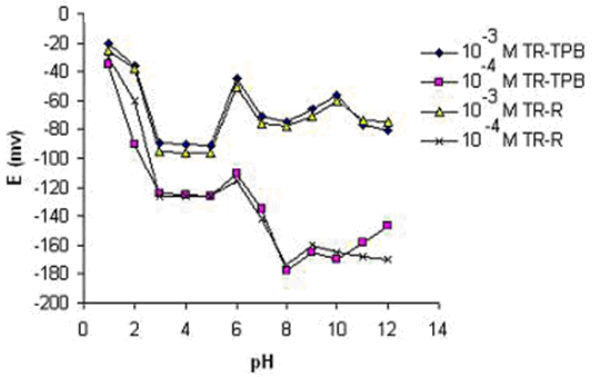

Figure 2. Effects of pH on the response of a trandolapril-tetraphenyl borate electrode (TR-TPB) and a trandolapril-reineckate electrode (TR-R).

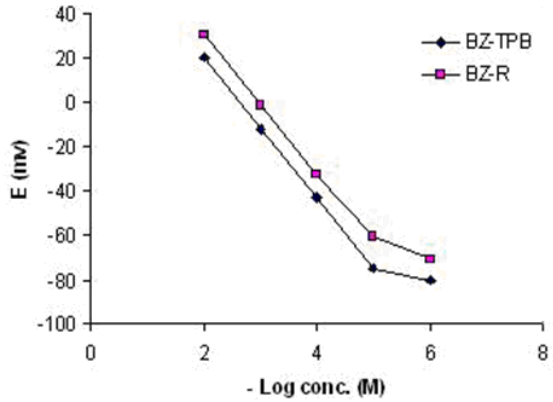

Figure 3. Profile of the potential in mV with respect to the – log concentration of benazepril hydrochloride with TPB and R.

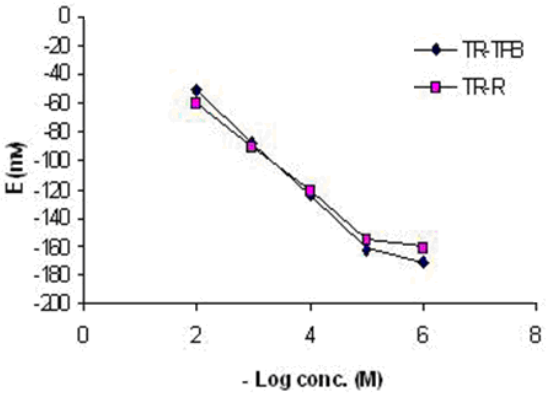

Figure 4. Profile of the potential in mV with respect to the – log concentration of trandolapril with TPB and R.

Table 2. Results of using the two electrodes to analyze benazepril hydrochloride in different laboratory-prepared mixtures with hydrochlorothiazidel

Ratio of BZ:HZ	Recovery of benazepril hydrochloride (%)*	
	BZ-TPB	BZ-R
1:1	100.58	98.41
2:1	101.24	98.92
1:2	99.51	99.47
0.5:1	100.58	100.71
1:0.5	99.15	101.37
Mean ± S.D. (%)	100.21 ± 0.86	99.78 ± 1.24

* Average of three determinations.

Table 3. Results of using the two electrodes to analyze trandolapril in different laboratory-prepared mixtures with verapamil

Ratio of TR:VR	Recovery of trandolapril (%)*	
	TR-TPB	TR-R
1:1	100.98	100.35
4:1	101.23	100.86
1:2	98.64	99.87
1:4	100.88	100.59
1:6	101.83	101.96
Mean ± S.D. (%)	100.71 ± 1.22	100.73 ± 0.78

* Average of three determinations.

with the developed sensors indicated that they had a reasonable level of selectivity (Table 4).

Pharmaceutical additives, diluents, and ingredients commonly used in drug formulations such as lactose, sucrose, magnesium sulphate, talc, and methyl cellulose did not produce interference. Thus, analysis was carried out without prior treatment or extraction. BZ-TPB and BZ-R sensors were successfully used to determine BZ in Cibadrex tablets (Table 5), and TR-TPB and TR-R sensors were used to determine TR in Tarka tablets (Table 5).

When used in biological fluids, the four electrodes were found to produce stable results as revealed by the high precision and accuracy of recovery of the spiked plasma samples. This indicated the lack of interference from plasma electrolytes (Table 6).

A statistical comparison of the results obtained using the proposed method and the previously reported procedure for BZ (*8*) or that for TR (*17*) is shown in Table 7. The values of the calculated *t* and *F* were

Table 4. Potentiometric selectivity coefficients of the four proposed electrodes according to the separate solutions method

Interferent	Selectivity coefficient			
	BZ-TPB	BZ-R	TR-TPB	TR-R
Verapamil	–	–	3.56×10^{-4}	3.48×10^{-4}
Hydrochlorothiazide	3.51×10^{-4}	3.23×10^{-4}	–	–
Na^+	3.53×10^{-3}	2.27×10^{-3}	2.08×10^{-3}	2.78×10^{-3}
K^+	3.07×10^{-3}	2.38×10^{-3}	2.51×10^{-3}	3.35×10^{-3}
NH_4^+	2.47×10^{-3}	1.46×10^{-3}	3.70×10^{-3}	4.31×10^{-3}
Ca^{2+}	3.22×10^{-3}	2.36×10^{-3}	3.08×10^{-3}	2.84×10^{-3}
Mg^{2+}	3.43×10^{-3}	2.74×10^{-3}	2.87×10^{-3}	2.85×10^{-3}
Glucose	2.14×10^{-3}	1.89×10^{-3}	2.85×10^{-3}	2.38×10^{-3}
Lactose	3.26×10^{-3}	3.72×10^{-3}	2.86×10^{-3}	2.23×10^{-3}
Sucrose	2.66×10^{-3}	3.22×10^{-3}	2.52×10^{-3}	1.68×10^{-3}
Urea	2.56×10^{-3}	3.05×10^{-3}	2.97×10^{-3}	2.16×10^{-3}
L-Phenylalanin	2.92×10^{-3}	3.23×10^{-3}	2.70×10^{-3}	2.29×10^{-3}
Methyl cellulose	3.47×10^{-3}	2.52×10^{-3}	5.55×10^{-3}	5.71×10^{-3}
Talc	3.21×10^{-3}	1.96×10^{-3}	5.84×10^{-3}	6.31×10^{-3}

Table 5. Quantitative determination of benazepril hydrochloride in Cibadrex tablets and trandolapril in Tarka tablets using the proposed electrodes

Pharmaceutical dosage forms	Recovery ± S.D. (%)*
Benazepril hydrochloride in Cibadrex tablets (batch No. Y0002)	
BZ-TPB	99.15 ± 0.81
BZ-R	99.29 ± 1.06
Trandolapril in Tarka tablets (batch No. 551918D)	
TR-TPB	100.37 ± 0.92
TR-R	99.87 ± 1.27

* Average of three determinations.

Table 6. Determination of benazepril hydrochloride and trandolapril in spiked human plasma using the four electrodes proposed

Concentration (M)	Recovery ± S.D. of benazepril hydrochloride (%)*		Recovery ± S.D. of trandolapril (%)*	
	BZ-TPB	BZ-R	TR-TPB	TR-R
1×10^{-3}	99.41 ± 1.46	98.73 ± 1.67	100.35 ± 0.97	99.75 ± 1.26
1×10^{-4}	99.57 ± 1.32	99.03 ± 1.84	100.12 ± 1.11	99.84 ± 1.44

* Average of three determinations.

Table 7. Statistical analysis of the results obtained using the proposed method and previously reported methods to analyze benazepril hydrochloride (*8*) and trandolapril (*17*)

Values	BZ-TPB	BZ-R	Reported method (*ref. 8*)	TR-TPB	TR-R	Reported method (*ref. 17*)
Mean ± S.D.	99.07 ± 0.75	99.13 ± 0.91	99.79 ± 0.80	100.09 ± 1.26	99.98 ± 1.43	99.94 ± 1.69
n	4	4	6	4	4	5
Variance	0.563	0.828	0.640	1.588	2.045	2.856
t	1.427 (2.306)*	1.213 (2.306)*	–	0.147 (2.365)*	0.038 (2.365)*	–
F	1.14 (9.01)*	1.29 (5.41)*	–	1.80 (9.12)*	1.40 (9.12)*	–

* The values in parentheses correspond to the theoretical values of *t* and *F* at $p = 0.05$.

less than the tabulated ones, which reveals that there was no significant difference with respect to accuracy and precision between the proposed method and the previously reported procedures.

4. Conclusion

The proposed sensors for BZ and TR offer the advantages of high stability, fast response over a wide range of concentrations and pH levels, low cost, ease of fabrication, adequate selectivity in the presence of hydrochlorothiazide (for BZ) or verapamil (for TR) and related species, and direct use with turbid and colored drug solutions without any pretreatment. The proposed method can be used to determine the aforementioned drugs in pure form, in plasma, and in pharmaceutical formulations.

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