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ENALAPRIL AND RAMIPRIL SELECTIVE MEMBRANES*

Key words: Enalapril-selective membrane sensor, ramipril sensor, drug analysis, standard addition method

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ABSTRACT

The construction and general performance characteristics of potentiometric plastic-membrane sensors for enalapril and ramipril drug-anions, are described. The electroactive materials are based on ion pair complexes between enalapril and ramipril anions, respectively, with Aliquot 336S cation. Both electrodes show near Nernstian response over the range 1×10^{-2} - 10^{-5} mol/L, with a detection limit of

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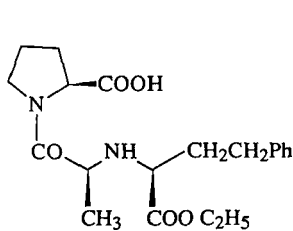
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about 2.4×10^{-6} mol/L for enalapril and 6×10^{-6} mol/L for ramipril. The selectivity of the electrodes to a number of organic and inorganic anions is reported. The electrodes proved useful in the determination of the active ingredient in their respective pharmaceutical preparations. The method is simple, rapid and does not require prior sample pre-treatment.

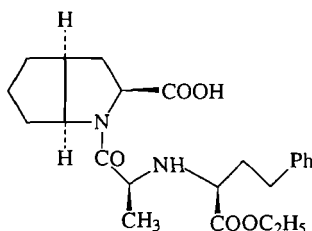
INTRODUCTION

Developments in pharmaceutical analysis with ion-selective membrane electrodes¹⁻³ have enabled the direct and selective measurement of the activity of various organic cations or anions of pharmaceutical interest, in most instances without prior separation of the active substance from the formulation matrix. It is possible to develop methods for drug substances determination in pharmaceutical preparations that would need only a pre-dilution step (e.g. injection preparations) or dissolution of tablets in the measuring solvent.

Enalapril maleate (I) and ramipril (II) belong to a new class of antihypertensive agents which act through inhibition of angiotensin converting enzyme (ACE)⁴.



Enalapril (I)



Ramipril (II)

The official standard methods for enalapril maleate are based on HPLC⁵⁻⁷, TLC⁷ and flow injection spectrophotometry⁸, while those for ramipril are based on HPLC⁹⁻¹⁰ methods.

This paper describes the preparation and characterization of two ion-selective membrane electrodes, one sensitive for ramipril and the other for enalapril. The electrodes exhibit useful analytical characteristics for the determination of the active ingredients in their respective pharmaceutical tablet formulations without any prior separation with good reproducibility.

EXPERIMENTAL

Apparatus

A Praticonic digital pH/mV meter, Model 870 MV (± 0.01 mV precision) was used for all the direct potentiometric measurements. The electrodes were used in conjunction with an ORION 91-01 double junction reference electrode with saturated $\text{Na}_2\text{B}_4\text{O}_7$ solution in the outer compartment. pH measurements were performed with a Radiometer electrode. The sensor response characteristics were evaluated with the SERECHAR computer program on a 80386 DX (IBM Compatible PC).

Reagents and materials

Enalapril maleate substance (Lot # L 154, 739-001DO70) and three tablets formulations Renitic[®] (5, 10 and 20 mg) were supplied by Merck Sharpe & Dohme (West Point, PA, USA) while ramipril substance and one tablet formulation Delix[®] (5 mg) were supplied by Hoechst (Frankfurt, Germany). The other materials such as dinonylphthalate (DNP), polyvinylchloride (PVC) of relative high molecular mass, tetrahydrofuran (THF) and tricaprilmethyl ammonium chloride (Aliquot 336S) were of analytical reagent grade. Solutions were prepared by dilution while keeping the pH at a constant value (phosphate buffer pH 6.8).

Electroactive material

Five grams of Aliquot 336S were mixed with 50 g of n-dodecanol and then equilibrated with ten separate 10-15 mL aliquots of 10-2 mol/L enalapril maleate

or ramipril solutions. The organic phases were washed with distilled water until the reaction of chloride ion was negative and then centrifugated until a clear solution was obtained.

Membrane material

The quaternary ammonium cation, tricaprylmethylammonium is a well-known ion-pairing extracting agent and was used to obtain the ion-pair association complex with enalapril and ramipril anions, respectively. The ion-pair complexes were embedded in a PVC matrix containing DNP as plasticizer. The membrane composition was 4.0% (w/w) electroactive material, 64.0% (w/w) DNP and 32.0% (w/w) PVC.

Construction of the electrodes

The basic principle of the electrodes construction was described elsewhere^{12,13}. The electroactive material (50 mg) was well mixed with 800 mg plasticizer and later with 400 mg PVC powder dissolved in 10 mL THF. The clear liquids were poured into a 28 mm glass ring on a glass plate. A pad of filter paper placed on the top of the ring was kept in plane by a heavy metallic weight and each assembly was left for 72 h to allow slow evaporation of the solvent. A disc (9 mm diameter) was cut out from the membrane and fixed to the end of a 10 mm Tygon tube using PVC-THF solution as adhesive. The other end of the Tygon tube was filled into a glass tube to form the electrode body. A silver/silver chloride wire was inserted and the electrode bodies were filled with 10^{-3} mol/L enalapril or ramipril solution. The electrodes were pre-conditioned for 24 h by soaking into a 10^{-2} mol/L corresponding solution and stored between the measurements into a 10^{-3} mol/L solution.

Recommended procedures

Standard addition method: For analate addition (sample addition to a standard), the tablets were analysed by finely powdering five tablets from the same

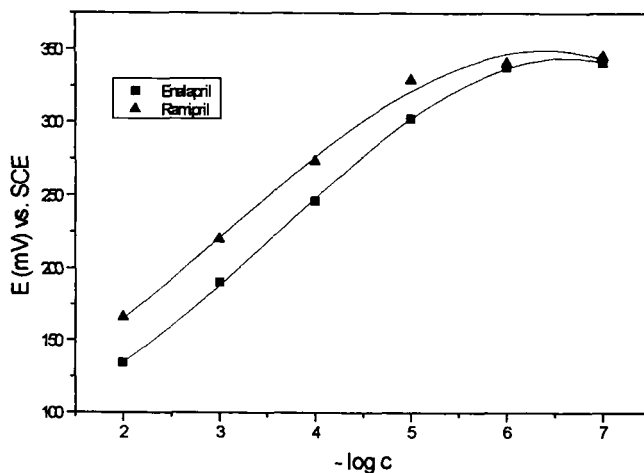


Figure 1. Calibration graph for enalapril and ramipril membrane

Table 1
Response characteristics

Parameter	Results	
	Enalapril-sensor	Ramipril-sensor
Slope (mV per decay) ^a	55.8 ± 0.3	53.8 ± 0.7
Intercept, E (mV) ^b	22.5 ± 0.8	65 ± 1.2
Linear range (mol/L)	10 ⁻² - 5.2 × 10 ⁻⁵	10 ⁻² - 10 ⁻⁵
Detection limit (mol/L)	2.4 × 10 ⁻⁶	6 × 10 ⁻⁶

^a Standard deviation of average slope for multiple calibrations

^b Standard deviation of values recorded over a period of two months

batch for Delix 5 and Renitic 5, a portion of powder equivalent to about 5 mg of active substances were transferred into a 25 mL volumetric flask. Fifteen mL phosphate buffer (pH 6.8) was added and then the solutions were made up to volume with distilled water (solution A). For Renitic 10 and Renitic 20, a portion of powder equivalent to about 10 mg and 20 mg enalapril maleate, respectively,

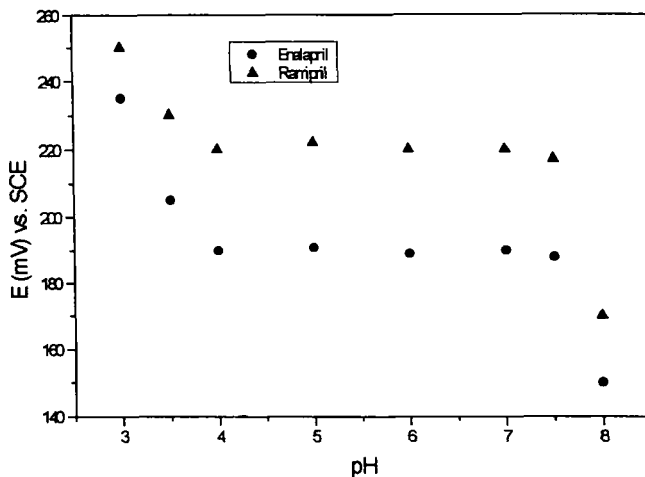


Figure 2. Effect of pH on the response of enalapril (●) and ramipril (▲) electrodes.

were transferred into a 50 mL volumetric flask; 25 mL phosphate buffer (pH 6.8) was added and the solutions were made up to volume with distilled water (solution B and C). The e.m.f. is measured in an electrochemical cell containing 25 mL of standard at 5×10^{-3} mol/L solution. A volume of 2 mL of solution A, 2 mL solution B or 1 mL of solution C is added and the new e.m.f. is measured. The changes in e.m.f. recorded are used to calculate the enalapril or ramipril content in the tablets.

RESULTS AND DISCUSSION

Electrode response

Typical calibration graphs for the enalapril (curve a) and ramipril (curve b) membrane sensors performed with solutions in the range 10^{-2} - 10^{-7} mol/L show that a linear response is observed in the range 10^{-2} - 5.2×10^5 mol/L for the enalapril sensor and 10^{-2} - 10^{-5} mol/L for ramipril sensor, in phosphate buffer (pH 6.8) as shown in Figure 1.

Table 2
Selectivity coefficients for various anions

Interfering species	Enalapril-sensor	Ramipril-sensor
Enalapril maleate	-	-
Ramipril	-	-
Acetate, citrate, iodide,	$< 10^{-4}$	$< 10^{-4}$
nitrate		
Chloride	0.75	0.99
Hydroxide	1.2×10^{-2}	7.5×10^{-2}

The critical response characteristics of the electrodes, calculated with the SERECHAR program were summarized in Table 1.

Effect of pH

The effect of pH on the potential of the two sensors was checked by recording the e.m.f. of a standard cell and varying the acidity by the addition of small volumes of nitric acid and/or ammonium solution (1.0 mol/L of each). The graphs presented in Figure 2 show the linearity in the range 4.0 - 7.5 of the potential E (mV) versus pH function. At pH values higher than 8.0 - 8.5 the potentials decreased slowly because of the interference of the hydroxide anion.

Selectivity of the electrodes

Potentiometric selectivity coefficients were evaluated by the mixed solution method¹⁴. The data presented in Table 2 show no response of the sensors to a number of potentially interfering ionic species excipients usually used during the manufacture of the pharmaceutical preparations, such as starch, gelatin, lactose, and agar.

Table 3
Quantitative determination with Enalapril SME using MOSA^a

Pharmaceutical formulation	Sample	Recovery (% of nominal) ^c	RSD (%)
Renitic 5 ^a	1	100.1	1.8
	2	99.7	1.29
	3	100.8	1.15
Renitic 10 ^b	1	98.8	1.57
	2	102.1	1.05
	3	99.3	0.9
Renitic 20 ^b	1	100.7	1.09
	2	100.5	0.85
	3	99.6	0.55

^a $V_s = 25$ mL, $V_a = 2$ mL, $c_s = 5 \times 10^{-3}$ mol/L enalapril

^b $V_s = 25$ mL, $V_a = 1$ mL, $c_s = 5 \times 10^{-3}$ mol/L enalapril

^c All values are the average of four determinations

Table 4
Quantitative determination with Ramipril SME using MOSA^a

Pharmaceutical formulation	Sample	Recovery ^b (% of nominal)	RSD (%)
Delix	1	97.3	0.7
	2	99.1	0.85
	3	102.1	1.25
	4	100.1	0.50
	5	103.5	1.62

^a $V_s = 25$ mL, $V_a = 20$ mL, $c_s = 5 \times 10^{-3}$ mol/L ramipril

^b All values are the average of four determinations

Analytical applications

The electrodes proved useful for the assay of the enalapril and ramipril content of pharmaceutical preparations by using the standard addition method. The results are given in Table 3 and 4.

As shown in the Tables 3 and 4, a high precision (RSD <2.0%) was attainable. Usually, the potentiometric determination could be performed within 15 min, in contrast to the longer times required for assay by the official standard method.

CONCLUSIONS

The electrodes exhibits useful analytical characteristics for the determination of enalapril and ramipril in pharmaceuticals. They can be used for the content uniformity assay as well as for dissolution test analysis.

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