ENANTIOSELECTIVE DOT SENSOR BASED ON CARBON PASTE AND 5,10,15,20-TETRAPHENYL-21H,23H-PORPHINE FOR S-CAPTOPRIL ANALYSIS

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S-Captoprilul este un inhibitor al enzimei convertoare de angiotensină (ACE) utilizat la scală largă pentru tratarea hipertensiunii şi a altor afecţiuni cardiace. R-Captoprilul nu prezintă, însă, proprietăţi inhibitoare. De aceea, este necesară dezvoltarea unor metode fiabile pentru enantioanaliza S-Captoprilului – atât din materialul brut cât şi din produsele sale farmaceutice. 5,10,15,20-Tetrafenil-21H,23H-porfirina a fost aleasă ca şi modificator al matricei de carbon în construcţia senzorului potenţiometric enantioselectiv. Domeniul linear de concentraţie s-a situat în intervalul 10^{-8} - 10^{-6} mol/L, prezentând o pantă de 55.79mV/decada de concentraţie şi o limită de detecţie de $1x10^{-9}$ mol/L. Recuperarea din comprimate a fost de 97.32% ±0,15.

S-Captopril is an angiotensin-converting enzyme (ACE) inhibitor, which is extensively used for treatment of hypertension and congestive heart failure. R-Captopril possesses non-ACE inhibiting activity. Therefore, it necessary to develop reliable methods for the enantioanalysis of S-captopril – raw material and in its pharmaceutical formulations. 5, 10, 15, 20-Tetraphenyl-21H, 23H-porphine was used as modifier for the design of a carbon paste based enantioselective potentiometric electrode. The linear concentration range was between 10-8 and 10-6 mol/L with a slope of 55.79mV/decade of concentration and a detection limit of 1x10-9mol/L. The recovery of S-captopril in pharmaceutical formulations was 97.32% ±0,15.

Keywords: S-Captopril, enantioanalysis, potentiometry

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1. Introduction

S-Captopril, namely 1-(3-mercapto-2-methyl-1-oxopropyl)-l-proline, is an angiotensin-converting enzyme (ACE) inhibitor. It reacts by blocking an enzymatic system, to produce the relaxation of the artery walls and accordingly, the blood pressure is reduced [1, 2]. The compound contains two asymmetric centers. One of the stereoisomers, namely, R-captopril, that has no ACE activity, is being formed in the synthesis of S-captopril as a by-product. Therefore, is important to be able to determinate only the S-enantiomer from pharmaceutical formulations in order to establish the required purity.

For the detection of captopril a large number of different analytical procedures were employed, the main aim of the studies were the quantitative determination of captopril in pharmaceutical formulations but also in biological fluids. Many spectrophotometric methods based on different oxidation reactions [3] or on complex formation [4, 5, 6, 7, 8] were studied. Other methods like, HPLC [9, 10], electrochemistry [11-15], GC-MS [16, 17], chemiluminescence [18], and capillary electrophoresis [19] showed a good reliability. LC/MS is also an important tool used in the identification, structure characterization and quantitative analysis of captopril, despite the expensive costs involved and tedious time of work [20].

Potentiometric methods which use ion-selective membranes electrodes (ISE) are able to provide reliable results in the detection of captopril from pharmaceutical formulations because they are based on the direct determination of the ions activity in solution, and they are also the cheapest alternative. Another advantage of using ISE is the simplicity of the procedure and the speed of the determination. Many experiments were based on the reactivity of the thiol group for captopril determination in pharmaceutical formulations [21, 22].

Carbon paste based electrodes were successfully used as potentiometric sensors for the analysis of pharmaceutical compounds and other compounds of clinical importance [23, 24]. A very important role is played by the modifier of the carbon paste, this one enhancing the electrochemical response. Porphyrins are recognized for their electrocatalytic activity towards oxidation of organic compounds of biological importance [25].

The aim of this paper is to present a new enantioselective potentiometric sensor based on 5,10,15,20-tetraphenyl-21H,23H-porphine (TPP) and carbon paste enantioselective dot sensor that can be reliably used for the detection of S-Captopril from its pharmaceutical formulations.

2. Experimental

Reagents and materials

S-captopril (SCpt) (SQ-014534) and R-captopril (RCpt) (SQ-034459) were supplied by Bristol–Myers Squibb. Pharmaceutical Research Institute

(Princeton, NJ, USA). The 5,10,15,20-tetraphenyl-21H,23H-porphine, L-hydroxyproline and graphite powder (1-2 μm, synthetic), were supplied by Aldrich. Paraffin oil was supplied by Fluka (Buchs, Switzerland). All the solutions were prepared with deionised water obtained from a Direct-Q® 3Water Purification system (Millipore Corporation, Molsheim Cedex, France) and were buffered with phosphate buffer solution pH 3.6 supplied by Merck.

Instrumentation

Potentiometric measurements were recorded using a PGSTAT 302N potentiostat/galvanostat connected to a two-electrode cell, linked to a computer via an Eco Chemie (Utretch, The Netherlands) software version 4.9. An Ag/AgCl (0.1 mol/L KCl) electrode served as reference electrode.

Carbon paste based dot sensor design

100 mg of paste obtained by mixing paraffin oil and graphite powder in a ratio of 1 :4 (w/w) was modified by the addition of 100μL chiral selector, 5,10,15,20-tetraphenyl-21H,23H-porphine solution (10^{-3} mol/L), prepared in THF. The resulted paste was pressed into a plastic tube with an active diameter of 300 μm. Electrical contact was done using an Ag/AgCl wire inserted into the carbon paste. The surface of the electrode can be renewed by polishing with alumina paper (polishing strips 30144-001, Orion). The electrode can be used for a long period, between measurement being stored in a dry state, covered or away from day light, at room temperature.

Potentiometric measurements

Direct potentiometric measurements were performed at room temperature. The potentials for a series of standard solutions in the range of 10^{-12} to 10^{-2} mol/L for S-captopril (S-cpt) and R-captopril (R-cpt) were recorded. The electrodes were placed in each standard solution, the potentiometric response being plotted on graphs E (mV) vs. pS-Cpt (pS-Cpt = - log[S-Cpt]) for each compound. The concentrations of the unknown samples were calculated from the obtained calibration graph by extrapolation.

Uniformity test of Captopril tablets

10 tablets of Captopril were used, each one of them being placed into a 100 ml volumetric flask. They were dissolved in a 1:1 buffer solution (pH 3.60): deionised water mixture. The concentration of each tablet was determined using the calibration graph obtained in direct potentiometric measurements.

3. Results and discussion

Response characteristics of the enantioselective dot sensor

Dot sensors response characteristics were investigated using direct potentiometry.

The calibration plot of the dot enantioselective sensor showed nearly linear Nernstian responses for S-captopril for a concentration range between 10^{-8} and 10^{-6} mol/L, with a correlation coefficients of 0.9998. No response was obtained for R-Cpt. The slope of the electrode was 55.79±0.40 mV/decade of concentration. The standard potential was E^0=485.18 mV and the detection limit was 2.01×10^{-9} mol/L. The response time was less than 1 min. The proposed electrode was stable for more than a month test period (RSD < 0.5%).

Effect of the pH on the electrode response

The influence of the pH on the potentiometric response of the dot sensor was recorded by using standard solutions of 2×10^{-6} mol/L S-captopril at pH values ranging from 1 to 12. The pH of these solutions was adjusted by the addition of small amounts of HCl or NaOH (0.1 mol/L) to each sample. The potential of the dot sensor does not depend on pH between 4 and 11 (Fig.1).

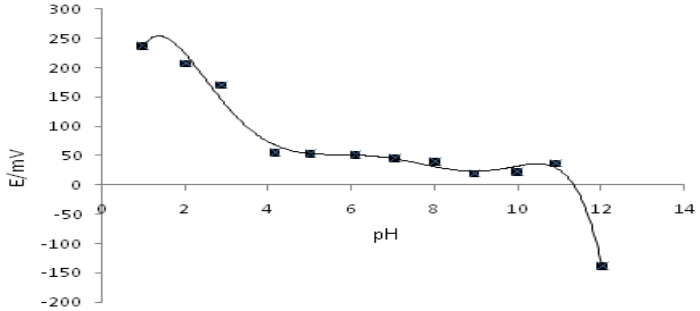

Fig.1. The pH influence of on the potential of the dot sensor based on TPP for a 2×10^{-5} mol/L S-captopril solution

Electrode selectivity

R-captopril and L-hydroxyproline were tested as possible interferents. The choice of these substances was due to the fact that they can be by-products in the synthesis of S-captopril. The mixed solutions method was chosen for the selectivity investigation. The ratio between the possible interferent and the analite was 10: 1.

Potentiometric selectivity coefficients, K_{sel}^{pot}, were determined. The values for pK_{sel}^{pot} ($pK_{sel}^{pot} = -\log K_{sel}^{pot}$) are 3.20 and 3.66 for R-Cpt and L-hydroxy proline, respectively, showing that the proposed electrode is selective and enantioselective.

Analytical Applications

To assess the described method feasibility, a uniformity contents test was performed, by using a commercial pharmaceutical formulation, namely Captopril tablets (Terapia-Ranbaxy Romania). S-captopril can be reliably assayed in the tablets, with an average recovery of 97.32±0.15%.

4. Conclusions

This study presented the application of a dot enantioselective sensor, using the 5,10,15,20-tetraphenyl-21H,23H-porphine as chiral selector. The electrode exhibited high sensitivity, good selectivity over L-hydroxyproline and enantioselectivity over R-captopril, and low detection limits. S-captopril can be reliable determined from pharmaceutical formulations. The sensor has a simple design, and can be reliably built. Other advantages in the use of this method are the high precision, short response time, and stability. The dot sensor can be reused after storing a longer period in a dry and dark place by simply renewing the active surface with alumina paper.

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