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Direct Determination of Captopril Using Electrogenerated Halogens for Pharmaceuticals Quality Control

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Abstract

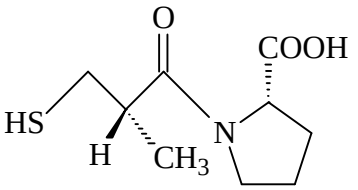
Simple, rapid, accurate and inexpensive coulometric method for captopril determination using electrochemically generated halogens as titrants is proposed. The stoichiometric coefficients of the reactions are 1:3, 1:3 and 1:1, for chlorine, bromine and iodine, respectively. Procedure for direct determination of captopril in pharmaceuticals has been developed with an RSD of 0.01-0.04. The data were compared with the results obtained by anodic adsorptive stripping voltammetry. Good agreement of the data obtained allows to propose coulometric determination for pharmaceuticals quality control.

Keywords: *Coulometric titration; Electrogenerated halogens; Pharmaceutical analysis; Captopril.*

1. Introduction

Captopril is a specific inhibitor of the angiotensin-converting enzyme. Captopril is used therapeutically as an antihypertensive agent. It blocks an enzyme system which causes artery walls to relax reducing blood pressure. In addition, it is applied in the management of heart failure following myocardial infarction and in diabetic nephropathy [1].

Captopril is 1-(3-mercapto-2-methyl-1-oxopropyl)-L-proline.



It is the only antihypertensive pharmaceutical with thoil-group in structure. Therefore, it has the ability to act as a scavenger of free radicals in living systems. So, captopril shows antioxidant properties [2-4].

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Like other thiols, captopril undergoes rapid oxidation to disulfide metabolites both *in vitro* and *in vivo.* Intracellularly, disulfide metabolites are reduced to the free thiol and so they act as storage of free captopril. Only the free captopril is pharmacologically active. However, the formation of the inactive disulfides is reversible, so a longer duration of action than predicted by the blood concentration of free captopril takes place [2].

Therefore, the determination of captopril is important from a physiological point of view as well as for the purposes of quality control. Various instrumental techniques have been developed for determination of captopril including chromatography [5-8], optical [9-12] and electrochemical [13-15] methods.

A number of flow injection methods have been proposed for captopril determination. An automated flow injection manifold based on the indirect biamperometric detection of the captopril by using Fe(III)/Fe(II) as an indicating redox system and a Z-shaped flow-cell configuration was developed. The calibration curve is linear over the range 0.03 – 3.6 μg mL^{-1} of captopril [16].

A novel chemiluminescence flow system for captopril is described. It is based on the direct chemiluminescent reaction between captopril and Ag (II) in acidic medium. The unstable Ag (II) is on-line electrogenerated via a Pt anode from $AgNO_3$ in HNO_3 medium by constant-current electrolysis. The chemiluminescence emission intensity was linear with captopril concentration in the range 0.02÷10 μg mL^{-1}; the detection limit was 6×10^{-9} g mL^{-1} (3σ) [17].

A highly sensitive kinetic spectrophotometric method [18] was performed for the determination of captopril in pharmaceutical preparations and biological fluids. The method is based on a catalytic acceleration of the reaction between sodium azide and iodine in an aqueous solution. Concentration range of 0.1–1.5 μg mL^{-1} was determined by measuring the decrease in the absorbance of iodine at 348 nm by a fixed time method. The decrease in absorbance after 5 min was markedly correlated to the concentration. The detection limit of captopril was 20 ng mL^{-1} (S/N = 3).

Most of the mentioned methods are applied to the determination of captopril in pharmaceuticals. A specific hyphenated high performance liquid chromatography–mass spectrometric assay was developed for the determination of captopril in plasma. The drug was extracted from plasma using liquid–liquid extraction with a mixture of diethylether:dichloromethane. After the addition of the internal standard, samples were applied to a prepacked C_8 Waters Symmetry column. The ion trap mass spectrometric detector was equipped with electrospray ionization source operating in the positive ion mode. Drug determination was accomplished monitoring captopril at molecular ion *m*/*z* 218 and mass spectrometric (daughter) at *m*/*z* 171.6. The method was applied to captopril determination in

human plasma after the administration of captopril 50 mg tablets to healthy volunteers, who have participated in a pharmacokinetic study [19].

Electroanalytical techniques (such as voltammetry, amperometry and etc.) are characterized by simplicity, sensitivity, cost-efficiency, precision, accuracy and speed and have been used for captopril determination.

A simple, precise, rapid and low-cost potentiometric method for captopril determination in pure form and in pharmaceuticals has been proposed. Captopril was potentiometrically titrated in aqueous solution with NaOH using a glass pH electrode coupled to an autotitrator. No interferences were observed in the presence of common components of the tablets as lactose, microcrystalline cellulose, croscarmellose sodium, starch and magnesium stearate [20].

Chemically modified electrodes are described for determination of captopril [21, 22]. They have shown the high selectivity and electrocatalytic activity toward the oxidation of captopril. The electrodes were used for the voltammetric determination of captopril in pharmaceuticals and human serum samples.

The determination of captopril was studied by square wave cathodic adsorptive stripping voltammetry on a hanging mercury drop electrode [23]. The calibration curve was linear from 0.5 to 180 mg L^{-1} of captopril (depending on the preconcentration time), the limit of detection at a S/N ratio of 3 was 0.5 mg L^{-1} with 300 s of preconcentration and the relative standard deviation was 3.2 % at the 20 mg L^{-1} level (with 120 s of preconcentration, n=8). The method was applied for the determination of captopril in two pharmaceutical formulations.

Adsorptive stripping voltammetry was used for determination of trace levels of captopril in phosphoric acid media (pH 2.3). The adsorptive peak was observed at −0.49 V vs. Ag/AgCl. Method was applied to determination of captopril in pharmaceutical formulations, urine and blood-serum. The limit of detection was 0.019 ng mL^{-1} [24].

The main disadvantage of the last two methods is necessity to remove oxygen from electrochemical cell by inert gas.

The aim of present work is to propose new method for the direct determination of captopril in pharmaceuticals using electrogenerated halogens as titrants in constant-current coulometry. This method has been successfully used for organic analysis of various compounds [25].

2. Experimental

2.1. Coulometric determination

Electrochemical generation of halogens were carried out using a P-5827 M potentiostat at a current density 5 mA cm^{-2} in aqueous solutions 0.2 M KBr and 0.2 M KCl in 0.1 M H_2SO_4 and 0.1M KI in tartrate buffer solution (pH 3.56). The titration end-point was measured amperometrically with two polarized platinum electrodes (ΔE = 300 mV). A smooth platinum plate with a surface area of 1 cm^2 served as the working electrode, and platinum coil separated from the anodic compartment with a semipermeable diaphragm - as the auxiliary electrode.

Coulometric titration was carried out in a 50.0 mL cell. The supporting electrolyte (20.0 mL) and an aliquot portion of captopril (50-500 μL) solution were inserted into the cell, the electrodes were dipped and the generating circuit and timer were switched on simultaneously. Alteration of indicative current in time was marked. Titration curve had the next view ____/ .

The titration end-point was determined by bend on indicative curves and the mass of captopril was calculated using formulae:

$$m = I \times t \times M / n \times F ,$$

where is I – current strength, A; t – time of achievement of the titration end-point, s; M – molecular weight of compound, g mol^{-1}; n – number of electrons participating in reaction; F-Faraday constant 96500 Cl mol^{-1}.

2.2. Voltammetric determination

Voltammetric measurements were performed using voltammetric analyzer "Ecotest-VA" (Russia). The electrochemical cell (V=50 mL) consisted of working platinum microelectrode, a silver-silver chloride reference electrode and a counter electrode (platinum wire). 0.1 mol L^{-1} HNO_3 was chosen as supporting electrolyte. After adding 20.0 mL of supporting electrolyte and aliquot portion of captopril test solution, voltammograms with linear sweep of potential were recorded at following conditions: preconcentration during 20 s under stirring at 1.2 V, potential scan rate is 50 mV s^{-1}, potential range from 0.8 to 0 V. The voltammetric determination of captopril was based on preconcentration of oxidation product in disulfide form. Then, cathodic voltammogram of the adsorpted disulfide was recorded [26].

All experiments were carried out at room temperature.

2.2. Sample preparation

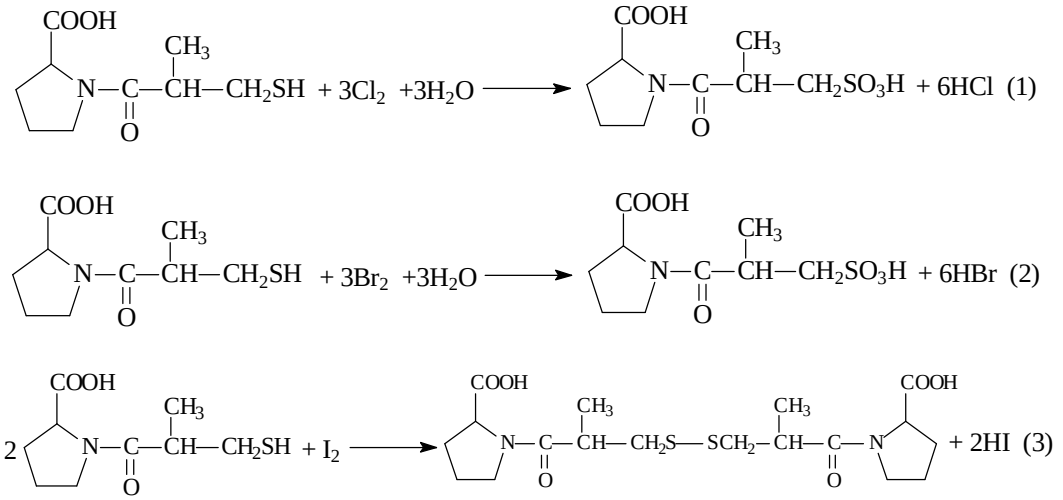
All chemicals were analytical grade. Solutions were prepared using distilled water. Captopril solutions were immediately analyzed after preparation.

For the determination of captopril in pharmaceuticals, 10 tablets were each weighed so as to obtain the mean tablet weight, mixed and powdered. A portion of the powder (approximately 100 mg) was accurately weighed and dissolved in 25.0 mL of distilled water.

3. Results and discussion

Halogens chlorine, bromine and iodine were investigated as titrants for the coulometric determination of captopril. Reaction proceeds rapidly and quantitatively with all titrants as coulometric titration of captopril standard solutions has shown. The stoichiometric coefficients of the reaction with electrochemically generated chlorine, bromine and iodine have been found and they are 1:3, 1:3 and 1:1, respectively. This fact agrees with the oxidative strength of halogens.

The following schemes of the interaction based on the results of coulometric titration of captopril can be proposed (Scheme).



Schemes of captopril reactions with electrogenerated halogens.

Coulometric determination of captopril in model solutions by oxidation with electrogenerated halogens is carried out (Table 1). The procedure was verified by the added – found method.

Table 1. Coulometric determination of captopril in model solutions (n = 5, P = 0.95).

Titrant	Added, μg	Found, μg	RSD
Cl_2	50	49±2	0.03
	150	149±3	0.01
	250	240±15	0.04
	500	486±4	0.01
Br_2	50	50±1	0.02
	150	145±2	0.01
	250	249±2	0.01
	500	496±6	0.01
J_2	50	50±1	0.02
	150	131±8	0.05
	250	233±11	0.04

On the basis of the data obtained, the procedure for the direct coulometric determination of captopril in pharmaceuticals is proposed. The technique was applied to the analysis of two brands of pharmaceutical dosage forms containing 25 mg of captopril per tablet. The coulometric data were compared with results of voltammetric determination (Table 2). As one can see from the data, the results are characterized by good agreement.

Table 2. The results of the captopril determination in pharmaceuticals (n = 5, P = 0.95).

Object	Label, mg	Titrant	Found by coulometry, mg	RSD	Found by voltammetry, mg	RSD
Captopril	25	Cl_2	25.0±0.6	0.03	24.7±0.3	0.01
		Br_2	25.0±0.2	0.01		
		I_2	24.7±0.1	0.01		
Capoten	25	Cl_2	24.8±0.2	0.01	24.8±0.2	0.01
		Br_2	24.7±0.3	0.01		
		I_2	24±1	0.04		

So, the proposed coulometric method for direct captopril determination characterized by simplicity, good reproducibility, cost-effectiveness, precision, accuracy and speed and can be recommended for pharmaceuticals quality control.

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