PHARMACEUTICAL SCIENCES | ФАРМАЦЕВТИЧЕСКИЕ НАУКИ

DIPEROXYAZELAIC ACID AS REDOX TITRANT. PART II. POTENTIOMETRIC DETERMINATION OF N-ACETYCISTEINE IN ACC-100 PHARMACEUTICAL PREPARATION

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ABSTRACT

A new redox method for the quantitative determination of micro-quantities of N-acetylcysteine (ACC) in the presence of ascorbic acid (AA), which is based on stoichiometrical and quantitative oxidation processes of analyzed analyte to the different products depending on pH medium generating by diperoxyazelaic acid in a situ iodine (triiodide) by the method of potentiometric titration was developed. A method is characterized by high sensitivity and sufficient accuracy and precision and also easy to perform. RSD was ≤1.62% (δ=0… 0.3%) for 1.63-3.26 mg ACC in the presence 1.76-3.52 mg AA in model solution. A method for determination of ACC in commercial samples (sachets) of famous pharmaceutical preparation ACC®100, that contain as antioxidant preservative of 12.5 mg ascorbic acid was proposed. The RSD was 1.02-1.61% (trueness, δ +0.33%... 0.44%).

Keywords: N-Acetylcysteine, Ascorbic acid, Potentiometric titration, Diperoxyazelaic acid.

INTRODUCTION

N-acetyl-L-cysteine (ACC) - (2R)-2-acetylamino-3-sulfanylpropanoic acid - a chemical structure is a derivative of cysteine with an acetyl group attached to the amino group of cysteine. In medical practice the using combined preparations in which ascorbic acid acts part stabilizator, its content considerably less than such ACC. So, in the famous preparation of ACC®100 of production of enterprise of «Salutas Pharma GMBH» of company «Hexal AG»(Germany) content of ascorbic acid makes 12.5 mg against 100 mg of ACC. There are also saccharin, saccharose, orange flavour entered to this composition also as excipient to 3.0 g of one included to package [1].

For the quantitative determination of ACC in the presence AA in samples with complex multi foundation should be applied some chromatographic separation [3] and / or selective physicochemical methods [3-5]. So, a method of capillary area electrophoreses is an addictive and at the same time alternative of method of liquid chromatography, characterized high efficiency, small expense in relation to cheap reagents and simplicity of exploitation, capillaries are easily regenerated. However, as well as any instrumental, the method of CZE provides some financial expenses on acquisition of device, although such equipment is universal. To determine the ACC and AA, which are contained in preparations in a relatively big quantities appropriate are cheaper to use and available at the same time titrimetric method.

Previously one of us have been shown the possibility of separate determination of AA and ACC in mixtures by redox potentiometric titration using as titrant organic [6] or inorganic [7] peroxy acids. The disadvantages of the recommended methods in State Pharmacopoeia of Ukraine (SPhU) of the iodimetric determination of ACC in individual preparations include inconvenience is the need of deep cooling solution sample before titration (+10 ºC) and relatively low sensitivity and accuracy , due to the use of a relatively high concentration of titrant (0.05 mol/L) [8].

The our aim was to work out unified methods for determining small amounts of ACC in the presence of AA using dyperoxyazelaic acid as titrant by redox potentiometric titration with iodine generated in situ:

It was found that ACC by iodine and / or thriiodide in terms of titration (excess ACC regarding titrant) at room temperature is S-oxidized to different products, depending on the pH, namely at pH 1.1 (0.1 mol/L HCl) oxidized of ACC is likely to thiosulfinate ester ACC interacting with iodine in molar ratios of 1:1 (ACC 0.01mmol consumed 0.005 mmol DPAA), while at pH 4.7 (0.1 mol/L KH2PO4) ACC by iodine is S-oxidized more deeply probably to N-acetylsulfate acid and / or the corresponding tiosulfonate interacting with iodine in a molar ratio of 2:1 (0.01 mmol ACC spent 0.01 mmol DPAA). AA under these conditions always form dehydroascorbic acid interacting with iodine in a molar ratio of 1:1 and / or own DPAA - in a molar ratio of 2:1. Titration mixture of ACC and AA generated iodine gives only one potential jump at the point which corresponds to their total content [See of Part 1].

EXPERIMENTAL PART

Ascorbic acid, a substance production by Northeast Pharmaceutical Group Co, Ltd (China), a series DY0261520104 (26.01.2015). N-acetylcysteine substance, manufacturer Moehs Catalana S.L., Spain, 091 108 series.

The analyzed drug ACC®100 (Manufacturer, Salutas Pharma GmbH, Barleben, Germany: 100 mg ± 5% ACC, 12.5 mg ascorbic acid, the other auxiliaries to 3.0 g ± 5% powder for oral solution in pathos (certificate 2D1628 series as of 08.10.2012).

Potassium iodide, «chemical grade».

As titrant was used diperoxyazelaic acid (DPAA), which is obtained acylation of hydrogen peroxide, azelaic acid by a known method [9]. DPAA solution with a concentration of 0.01

mol/L produced by accurate sample weight-to-volume method, which is standardized by iodometric titration [10].

Titration was performed using the electrode pair of platinum indicator electrode spot «EPV-1» saturated potassium chloride reference electrode chloride type «EVL - 1M3.1» (both produced by «Factory of devices measuring» Belarus, Gomel g) and 10 mL microburette measured volume of titrant to within ± 0.01 mL. Electromotive force range without transferring ions recorded digital laboratory ionometric I-130 «Factory of devices measuring» Belarus, Gomel g) with an accuracy of ± 0.1 mV. Titration was performed at + 18-20ºC.

RESULTS AND DISCUSSION

The typical potentiometric curvers titration of ACC or ACC and AA in mixture (sum concetrations) in solutions shown in Fig. 1 or Fig. 2 and Fig. 3 respectively The results of the quantitative determination of 1.63 3.26 mg ACC in the presence 1.76 3.52 mg AA in model solutions and in the ACC®100 drug solutions listed in Table 1 and 2 respectively.

Procedure for the determinaton of ACC. Weigh accurately 0.16 g of ACC and dissolve in 100.00 mL of a freshly double distilled water. Aliquot portion (1.00 or 2.00 mL) of the test solution (0.16 g was transferred to a beaker of 50 mL, add 18-19 mL 0.1 mol/L HCl, 1.0 mL of 5 % solution of KI and titrated 0.01 mol/L solution DPAA using 10 mL microburet. Another portion of the same solution aliquots titrated similarly generated titrant using iodine in the presence of 0.1 mol/L solution KH2PO4 (pH 4.7).

The content of ACC is calculated using the formula:

X (ACC) = M(ACC) · (V2 -V1) · c (DPAA) · K · 100

Optional AA content can be calculated using the formula:

X (AA) = 2M (AA) · [V1 - (V2 -V1] · c (DPAA) · (m / m1) · K · 100

where M (ACC) the molar mass (weight) of the ACC (163.2 g/mol);

M (AA) – the molar mass (weight) of ascorbic acid (176.13 g/mol);

V1 – volume of titrant consumed in the experiment with 0.1 mol/L hydrochloric acid solution, mL;

V2 – volume of titrant consumed in the experiment with the phosphate buffer solution, mL;

c (DPAA) – molar concentration of DPAA standard solution, mol/L;

m – the average weight of a single package filling, g;

m1 – a sample of the powder granules taken to prepare the test solution, g;

K – coefficient amendments concentrations costly to 0.0100 mol/L;

100 – recalculation to 100.0 mL.

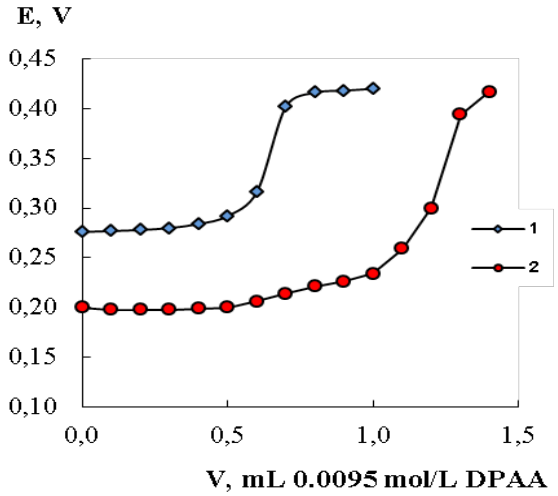

Figure 1. Potentiometric titration curvers of 0.01 mmol ACC with diperoxyazelaic acid in the presence of KI. 1 – 0.1 mol/L HCl; 2 – pH 4.7 (0.2 M KH2PO4); 0.25% KI.

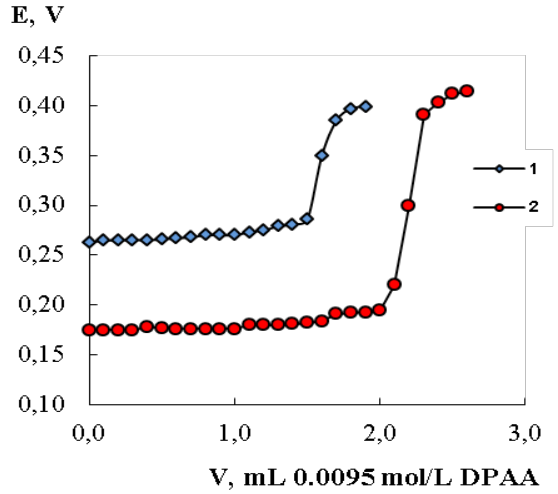

Figure 2. Potentiometric titration curvers of 0.01 mmol ACC and 0.01 mmol AA in mixtures by DPAA in the presence of KI. 1 – 0.1 mol/L HCl; 2 – pH 4.7 (0.2 mol/L KH2PO4); 0.25% KI

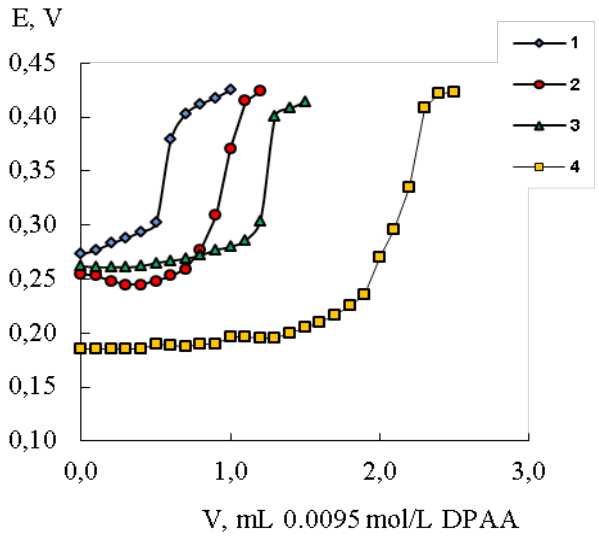

Figure 3. Potentiometric titration curvers of 1.00 mL (1, 2) and 2.00 mL (3, 4) ACC® 100 granulate solutions (3 g/100 mL) by 0.0095 mol/L solution of DPAA in the presence of KI.

1 (3) – 0.1 mol/L HCl; 2 (4) – pH 4.7 (0.2 mol/L KH2PO4); 0.25% KI, 293 K

The results are shown in Tables 1 and Table 2.

Table 1.

Results potentiometric determination of N-acetylcysteine in model solutions of mixture of ACC and AA

Ascorbic acid was taken mg	Was found, mg	Metrological characteristics
1.63	1.64 1.61 1.59 1.65 1.63 1.60 1.66	X=1.63mg S=0.026 S_k=0.010 ΔX=0.024 RSD=1.62% ε=1.35% (δ*=0%)
3.26	3.30 3.21 3.32 3.25 3.19 3.20 3.25	X=3.25mg S=0.050 S_k=0.019 ΔX=0.046 RSD=1.54% ε=1.42% (δ*=-0.3%)

Note* Was calculated using of the declared by manufacturer data

Table 2.

Results potentiometric determination of N-acetylcysteine in sachets ACC®100 (Salutas Pharma GmbH, Barleben, Germany)

Content of ACC, mg	Was found, mg	Metrological characteristcs (n=7; P=0.95)
97.7* (ser. 2D1628)	97.70 99.15 96.15 100.78 97.00 96.90 98.45	X=98.85mg S=1.58 S_k=0.60 ΔX=1.46 RSD=1.61% ε=1.61% (δ*=+0.33%)
103.6* (ser. DV2274)	101.70 102.23 103.12 104.35 104.23 103.90 102.45	X=103.14mg S=1.05 S_k=0.40 ΔX=0.97 RSD=1.02% (δ*=-0.44%)

Note. ** To calculate was used value content of ACC (μ*), indicated in the certificates of quality (data of reference HPLC method). .

A developed method is characterized by high sensitivity and sufficient accuracy and precision and also easy to perform. RSD was ≤1.62% (δ = 0... –0.3%) for 1.63 3.26 mg ACC in the presence 1.76 3.52 mg AA in model solution. A method for determination of ACC in commercial samples (sachets) of famous pharmaceutical preparation ACC®100, that contain as antioxidant preservative of 12.5 mg ascorbic acid was proposed. The RSD was 1.02 1.61% (trueness, δ +0.33%... –0.44%).

CONCLUSIONS

A new redox method for the quantitative determination of micro-quantities of N-acetylcysteine (ACC) in the presence of ascorbic acid (AA), which is based on stoichiometrical and quantitative oxidation processes of analyzed analyte to the different products depending on pH medium generating by diperoxyazelaic acid in a situ iodine (triiodide) by the method of potentiometric titration was developed. A method is characterized by high sensitivity and sufficient accuracy and precision and also easy to perform. RSD was ≤1.62% (δ=0... –0.3%) for 1.63-3.26 mg ACC in the presence 1.76-3.52 mg AA in model solution. A method for determination of ACC in commercial samples (sachets) of famous pharmaceutical preparation ACC®100, that contain as antioxidant preservative of 12.5 mg ascorbic acid was proposed. The RSD was 1.02-1.61% (trueness, δ +0.33%... –0.44%).

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