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Standardization Method of Quantitative Determination of Iodide Ions in Substances and Tablets Containing Iodine Adducts.

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ABSTRACT

This article is devoted to development of methods of iodide anions quantitative determination in substance solutions containing iodine adducts and their tablets by capillary electrophoresis.
Keywords: substance, tablets, iodine adducts, pharmacopoeia, validation, capillary electrophoresis.

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INTRODUCTION

In accordance with the requirements of the State Pharmacopoeia of the Republic of Kazakhstan, the methods of quantitative determination of medicines, including the analytical normative documentation (AND), methods for assessing the quality of drugs must be validated. Capillary electrophoresis is a relatively new and developing method of separation of complex mixtures, which allows analyzing ionic and neutral compounds of different nature, including drugs with high efficiency and rapidity, the software of the analysis and calculation of data [1, 2].

The principle of operation is the migration and separation of components of the liquid mixture in an electric field. Separation occurs in quartz capillary cavity in a buffer solution for a few minutes. The method allows to simultaneously identify and quantify the multiple components of the mixture. Integrated detector with diode array greatly increases the sensitivity of the system.

Wide dynamic linear range of the instrument (1×10^4) in combination with low noise on the baseline (<50 μAU) can detect trace level of up to 0.05% of the main peak. Capillary electrophoresis method in analytical chemistry is widely used to solve a variety of tasks, including, for the study of natural and biological systems [3]. The versatility of the method is used in areas ranging from drug development to quality control.

MATERIALS AND METHODS

Validation of the method performed according to a standard method [4] and the recommendations of the European Pharmacopoeia [5] on the capillary electrophoresis instrument Agilent 1600 (Germany). The purpose of this validation was to determine the metrological characteristics of methodical procedure "Analysis of the content of iodide ions in solution by capillary electrophoresis" in SCAID after changing the parameters of the method and provide documentary evidence of compliance techniques to their intended use.

We use the 3D-CE ChemStation Rev. A.10.02 Agilent Technologies software. The device characteristics: wavelength range from 190 nm to 600 nm, the mean square deviation (MSD) output signal at 1% of the migration time and 4% peak area. We used a capillary with an inner diameter - 50 mm and a length - 56 cm. As the standard sample iodide ions used the state standard sample (SSS) 9426-2009 (St. Petersburg).

The methodical procedure has been validated according to standard operating procedure "Validation of analytical techniques" developed at the SCAID. As a criterion for validation of analytical methods used requirements outlined in ICH guidelines Q2 (R1) (CPMP/ICH/381/95) [6]. The following validation parameters and the corresponding eligibility criteria were selected: accuracy (systematic error), repeatability, limit of quantification (LOQ) and the operating range.

The electropherograms of iodide ions (200 ppm) SSS solution were recorded in six replicates, as mobile phase used Agilent borate buffer solution pH 9.3. Data processing included determining noise levels for SSS solution, conducting statistical processing of the parameters obtained peaks and concentrations, as well as measurement of signal/noise ratio. Also it was determined the optimum operating range of iodide ion concentrations for a given procedure.

The "accuracy" of methodical procedures determined by comparing SSS with the known analyte content according quality certificate. The iodide ion concentration of SSS with 200 ppm (200 mg/l) was determinated in six replicates. Iodide ion concentration was calculated from peak area by formula 1.

$$Cx = \frac{100 \times S_x}{S_o} \quad (1)$$

where:

C_x – sample solution concentration, mg/l

S_x - The peak area of the sample solutionS_o - Peak area of a standard solution with a concentration of iodide, 100 mg/l

The "repeatability" was defined in a similar way using the same SSS dilution. Mean square deviation is calculated according to the formula 2.

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$$MSD = \sqrt{\sum_{i=1}^{n} \frac{(x_i - \bar{x})^2}{(n-1)}} \quad (2)$$

where: x_i – separate measurement;
$\bar{x}$ – Mean;
n – amount of sampling.

RESULTS

According to the requirements of the verification methodology [7] and ICH Q2 (R1) (CPMP/ICH/381/95) the criteria for the adoption of the accuracy by concentration is ± 3% of the true value for iodide ions SSS (200 ppm (mg/l)) concentration. Acceptance criteria are characterized by repeatability of MSD value and shall not exceed ± 4% for peak area and ± 3% for the value of iodide ions concentration. The results of determining the parameters of "accuracy" and "repeatability" are shown in Table 1.

Table 1 - Results of the evaluation parameter "accuracy" of capillary electrophoresis method

Repetitive measurements (parallel)	Accuracy		Repeatability	
	S, мUA·sec.	C, mg/l	S, мUA·sec.	C, mg/l
1	690.96	196.83	690.96	196.83
2	696.44	198.39	696.44	198.39
3	700.49	199.54	700.49	199.54
4	703.86	200.50	703.86	200.50
5	704.53	200.69	704.53	200.69
6	708.41	201.80	708.41	201.80
Mean	700.78	199.63	700.78	199.63
True value	—	200.00	—	200.00
Accuracy	—	0.37 (0.19%)	—	—
MSD	—	—	6.28 (0.90%)	1.79 (0.89%)
Note: S – area peak, C – iodide ion concentration				

The data showed that the parameter "accuracy" (systematic error) of the method is 0.37 ppm (mg/l) or 0.19%. This value is within the limits set by the validation plan "Analysis of the content of iodide ions in solution by capillary electrophoresis" in SCAID. Furthermore it is shown that the MSD for the iodide ion concentration is 0.89% to 0.90% by peak area. These completely meet the acceptance criteria of validation plan.

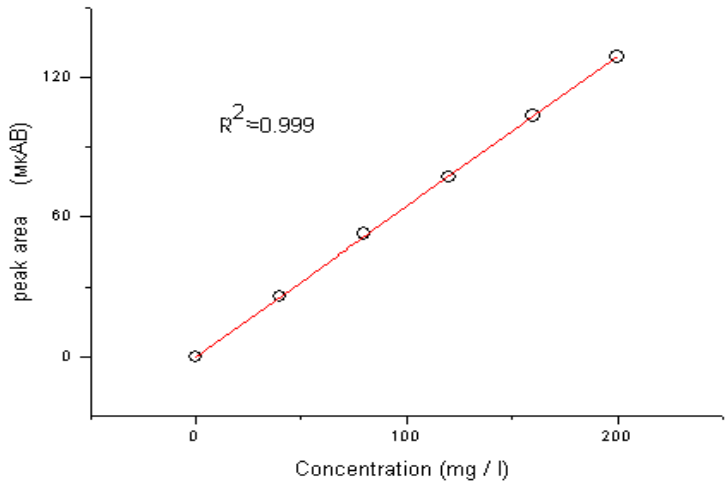

Figure 1. Calibration line of iodide ions working concentration solutions

The limit of quantification was determined by comparing the noise and signal using Agilent Chemstation software. The acceptance criteria of this parameter can be considered a signal/noise ratio of at least 10:1 [7]. This validation signal in accordance with the instrument reports, was 77 ((mAU) miles units absorption), and the noise is less than 0.1 (mAU). According to the established acceptance criteria the minimum concentration (LOQ) should be greater than 10 times the noise, ie, be equal to or greater than 1 (mAU). Signal 77 (mAU) corresponding to 200.0 ppm, respectively 1 (mAU) is 2.6 ppm, which is the lower limit of concentration.

The optimum working range of the method is selected experimentally. Concentration range was chosen in which the observed linear dependence of the peak areas of iodide ion concentrations of calibration solutions (Figure 1).

DISCUSSION

According to the results of experimental determination of the optimal working range we have established that the most effective working range of concentrations for this method is the concentration of iodide ions from 2.6 ppm to 240 ppm. The upper limit of the operating range is 120% of the maximum iodide concentration determined experimentally within the linear dependence.
Table 2 shows the validation parameters and their characteristics.

Table 2 - Validation characteristics of determination the iodide ions by capillary electrophoresis

Parameters	Characteristics
Accuracy	0.19%
Repeatability	0.89%
Limit of quantification	2.6 mg/l
Working range	2.6 – 240.0 mg/l
Linearity	$R^2 = 0.9999$

According to the validation results was shown that the method "Analysis of the content of iodide ions in solution by capillary electrophoresis" developed in the Scientific Centre for Anti-infectious drugs (SCAID) suitable for quantitative studies, as completely corresponds to the specifications.

Testing was conducted on a validated methodology of new iodine-containing coordination compounds developed in SCAID. Objects of the study were R8 substance, which is an iodine adduct tri-(aminoethanoat)-lithium-iodide ([C2H5NO2]3[Li]+[I]-) [8] and tableted dosage forms based on it with dosages of 40 and 75 mg [9, 10].

For quantification of iodide ions was prepared 0.1% solution of substance and 2% solutions of tablets. Sample preparation was carried out in flasks in 100 ml purified water. Molecular iodine was neutralized by adding 5 ml (to solutions of substances) and 1 ml (to solutions for tablets) of 0.05 N sodium thiosulfate solution.

The prepared sample was filtered on a filter with a pore diameter of 0.45 µm, discarding the first 2 ml of filtrate. 0.5-0.7 ml of the sample solution was placed into 1 ml vials. Quantification of iodide anions conducted under the following conditions: capillary effective length is 56 cm, an inner diameter of 50 mm, capillary temperature 25 °C, voltage: -30 kV. Detection of iodide ions was performed at a wavelength of 226 nm, and the analysis time was 10 minutes. As the mobile phase used borate buffer pH 9,3 (Agilent).

Using test samples electrophoregrams on time migration peaks were identified contained iodide ions, and on the peak areas were determined their quantitative content of iodides according to Formula 3:

$$X_2 = \frac{S_1 \times V \times n}{S_0 \times m \times 10} \quad (3)$$

where:
X_2 – quantitative content of iodide;

S_0 – peak area of iodide ions standard sample;
S_1 – peak area of iodide anions sample;
V – dilution volume;
m – sample weight, g;
n – concentration of iodide ions in the standard sample solution (0.076 mg / ml);
10 – dilution of the working solution

Table 3 shows the results of quantitative determination of iodide ions in aqueous solution of R-8 substance and tablets containing one.

Table 3 - Quantitative determination of iodide ions in aqueous solution of R8 substance and tablets with R8 substance

Samples	Release time, min	Peak areas, S (mAU, sec)	Concentration, C (mg/l)	Δ, %
R8 substance				
1	6.23	389.85	83.86	0.30
2	6.21	391.97	84.31	0.23
3	6.19	391.32	84.17	0.07
Tablets R-8, 40 mg				
1	6.70	453.43	124.16	0.52
2	6.71	460.95	126.22	1.13
3	6.72	452.98	124.04	0.61
Tablets R-8, 75 mg				
1	6.53	245.58	68.58	0.00
2	6.53	254.49	68.55	0.04
3	6.54	245.70	68.61	0.04

In the result of investigations the method of quantitative determination of iodide ions in the R8 substance conatining iodine adduct by capillary electrophoresis was developed. The method allows to determine the iodide with an error (accuracy) of 1.13 (mg/l), which is 1.13%. Such an error indicates a high accuracy of the results.

CONCLUSIONS

Capillary electrophoresis was applied for the quantitative determination of iodide ions in iodine containing substance and for the quality control of the dosage forms produced from the iodine containing substance. This method showed high accuracy and reliability of the results. Thus the use of capillary electrophoresis method for the quantitative determination of the iodide ion is more reliable and quick in comparison with the method of potentiometric titration, making it more competitive.

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