Development and Validation of a Simple Procedure for the Kinetic Spectrophotometric Quantitative Determination of Ceftriaxone Using Potassium Caroate

Mykola Blazheyevskiy, Yuliia Serdiukova*, Svitlana P. Karpova

National University of Pharmacy, 53, Pushkinska str., Kharkiv, 61002, Ukraine

tamadiw@gmail.com

Keywords: *Ceftriaxone, Potassium Caroate, spectrophotometry, kinetics.*

A simple procedure for the quantitative determination of the Ceftriaxone pure substance by the spectrophotometric method in its kinetic modification using Caro's acid has been developed and validated. The scheme of the chemical transformation of Ceftriaxone with the reaction of potassium caroate has been proposed. The appearance of a new wave gives the possibility of developing a new procedure for the quantitative determination of Ceftriaxone. The obtained results of accuracy and precision are as follows: RSD = 1.63-2.25 %, δ = 0.33-0.96 %. LOD = 0.1 μg/mL, LOQ = 0.33 μg/mL.

Introduction

The quantitative determination of drugs becomes more and more important. The control of the quality and quantity is one of the obligatory steps for manufacturing medicines. The number of medicines produced increases from year to year and the quality of the drugs have to be controlled. Therefore, the development of new procedures that are easy to perform and cost-effective is of great interest. The procedures proposed should be unified, selective, sensitive, and precise, and they should be validated by the monograph "Validation of analytical methods" of the State Pharmacopeia of Ukraine (SPhU).

Antibiotics are extremely important in medicine. Cephalosporins belong to the most commonly used types of antibiotics.

Ceftriaxone is a third-generation cephalosporin having 2-(2-amino-1,3-thiazol-4-yl)-2-(methoxyimino)-acetylamino and [(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)-sulfanyl]-methyl side groups. It is an antibacterial drug, an EC 3.5.2.6 (beta-lactamase) inhibitor, and a drug allergen. This cephalosporin contains in its structure a 1,2,4-triazine, a 1,3-thiazole, and an oxime O-ether (**Figure 1**).

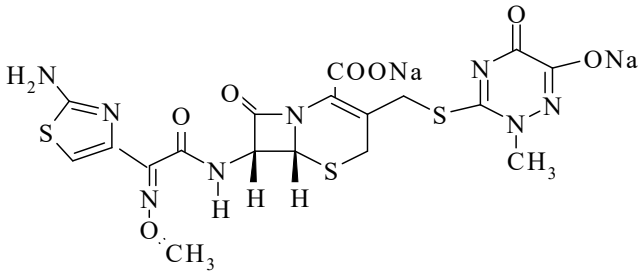

Figure 1. The chemical structure of Ceftriaxone.

The SPhU and BP describe HPLC for the cephalosporin determination; this is by far the best method, but it requires lengthy preparation, is expensive, and is difficult to perform [1-6]. The classical iodometric method is provided for the assay of most Pharmacopeial β-lactams, for which iodometric titration is particularly adapted [7]. The iodometric method is not applicable to antibiotics, the initial substances of their production as well as their degradation products being oxidized by iodine. It is therefore not suitable for controlling the purity of antibiotics of this group [8]. Usually, titration is a rapid and easy procedure, but compared to it, iodometric titration of cephalosporins is a long-lasting procedure (approximately 40 min) [7].

However, the development of new methods for titrimetric determination is relevant due to its simplicity, reliability, speed, and economic benefits. One of such procedures is described in the work of Nabi et al. [9]. The iodometric determination of some drugs of the cephalosporin series using Caro's acid was proposed by Blazheevsky M.Ye. and Serdiukova Yu.Yu. [10- 14].

Chromatographic methods for the quantitative determination of substances are the most accurate and sensitive. These are modern techniques that are very promising, and some procedures are described in the literature for the quantitative determination of Ceftriaxone, [15-23].

Comparing the currently existing polarographic methods for the determination of cephalosporins with the classical microbiological and iodometric methods regarding their accuracy, correctness, and selectivity, the advantages of the polarographic method in all three aspects were shown. [24-29].

The possibility of the selective determination of β-lactam preparations without the preliminary stage of hydrolytic cleavage in the presence of related substances was demonstrated in several spectrophotometric methods. Some methods of β-lactam determination have been developed by IR spectrophotometry using chemical transformations [30, 31]. Most spectrophotometric procedures for the β-lactam determination were developed in the visible and near-ultraviolet range. Other authors also quantitatively analyzed Ceftriaxone by spectrophotometry. [32-39]. The methods listed above are long-lasting, require heating and toxic reagents, thus justifying the development of quick and easy procedures using "Green chemistry" reagents.

The possibility of kinetic-spectrophotometric determination of some cephalosporins was shown by Blazheyevskiy M.Ye. [40-42].

The extensive literature review revealed kinetic-spectrophotometric procedures as the most prospective and the best alternative procedures to be developed for the Ceftriaxone

quantitative determination. This can be achieved using a proper oxidation analytical reagent, which must meet all the claims of analytical reagents.

Potassium Caroate ($KHSO_5$) belongs to these reagents. It is a commercially available powder giving stable solutions that can used in the experiments. This research is thus devoted to the development and validation of a novel procedure for the Ceftriaxone quantitative determination using Potassium Caroate as an analytical reagent in the kinetic-spectrophotometric modification.

This work aims at studying a new reaction of Ceftriaxone with Potassium Caroate and validation of the kinetic-spectrophotometric procedure of Ceftriaxone S-oxidation and the per hydrolysis product in bulk.

Experimental part

All the chemicals were of analytical reagent grade, and the solutions were prepared with double-distilled water.

The triple potassium salt of Caro's acid was used as an oxidizing agent, $2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$ (the commercial name "Oxon®" produced by DuPont). The active substance was potassium hydrogenperoxomonosulfate, $KHSO_5$. The choice of the reagent was determined by its rather high oxidative activity, $E_0 = 1.84$ V, availability, and satisfactory solubility in water.

Preparation of 0.02 mol·L^{-1} solution of potassium caroate. 0.615 g of $2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$, was dissolved in a 100 mL volumetric flask in double-distilled water. The concentration of potassium caroate was controlled by iodometric titration.

0.51 mol·L^{-1} of sodium hydroxide solution was prepared by dissolving 2 g sodium hydroxide in a 100 mL volumetric flask.

The Ceftriaxone pure substance was used in this work (the content of the main substance = 99%, w = 8.85).

The titrant volume was measured using a 10 mL micro burette with an accuracy of ±0.01 mL.

Preparation of Ceftriaxone solution, $1 \cdot 10^{-2}$ mol·L^{-1}. 0.6620 g of Ceftriaxone sodium was diluted in double-distilled water in a 100 mL flask at 20 ° C.

The procedure for the S-oxidation reaction kinetics study. 10.0 mL of 0.02 mol·L^{-1} potassium caroate solution was transferred into a 100 mL volumetric flask using a pipette, 5.0 mL of 0.01 mol·L^{-1} Ceftriaxone solution was added, and a stopwatch was switched on. The solution was diluted to the volume and mixed. At certain intervals, 10 mL of the mixture obtained was transferred into a titration flask using a pipette, 1 mL of 0.1 mol·L^{-1} sulfuric acid solution, and 1 mL of 5 % potassium iodide solution were added. The isolated iodine was titrated with a 0.02 mol·L^{-1} titrated solution of sodium thiosulfate in the presence of starch.

It was determined that the oxido-reduction reaction between Cetriaxone and

potassium caroate was quantitative and stoichiometric: 1 mol of the drug was per 4 mol of $KHSO_5$.

Electronic spectra were registered using a "SPECORD M-40" spectrophotometer, UV VIS ("Zeiss", Jena, Germany). A SF-46 (LOMO) spectrophotometer with 1 cm match quartz cells were used for spectral measurement. L = 1 cm quartz cell was used to measure the optical density; solutions were thermostated before mixing in a UTU-2 thermostat (Zeamit, Horizont Krakow-Poland), the time was measured using a stopwatch.

The pH values of solutions were measured with an EGL-43-07 glass electrode using an "Ionomer laboratory I-160M" ionometer together with an EAL-1M3.1 saturated silver-silver chloride reference electrode.

Preparation of model working solutions. Seven solutions with accurate weights were prepared in the following concentrations: 60%, 80%, 100%, 120%, 140%, 160%. The accurate weight (0.3333; 0.4444; 0.5546; 0.6665; 0.7776; 0.8887, respectively) of pure substance was dissolved in a 100.0 mL volumetric flask. 10 mL of the solution obtained was introduced into a 100 mL volumetric flask containing 4 of 0.02 $mol{\cdot}L^{-1}$ $KHSO_5$ solution and 1 of 0.5168 $mol{\cdot}L^{-1}$ NaOH solution. The content was shaken and finally diluted to the volume with double distilled water. After the NaOH solution was added, the stopwatch was switched on. The resulting solution was transferred to a 1 cm cell to measure the absorbance at the wavelength of 295 nm in 20 min against water. A kinetic dependence curve of absorbance A versus time (min) was obtained.

Results and discussion

The method proposed was based on the determination of Ceftriaxone in a pure substance and a powder for injections by the product of two conjugate reactions of peroxoacidic oxidation and perhydrolysis in basic medium using Caro's acid as an analytical reagent ($KHSO_5$). It was developed for the first time, and a reaction mechanism was proposed from the literature background and our experimental study as shown in **Figure 2.**

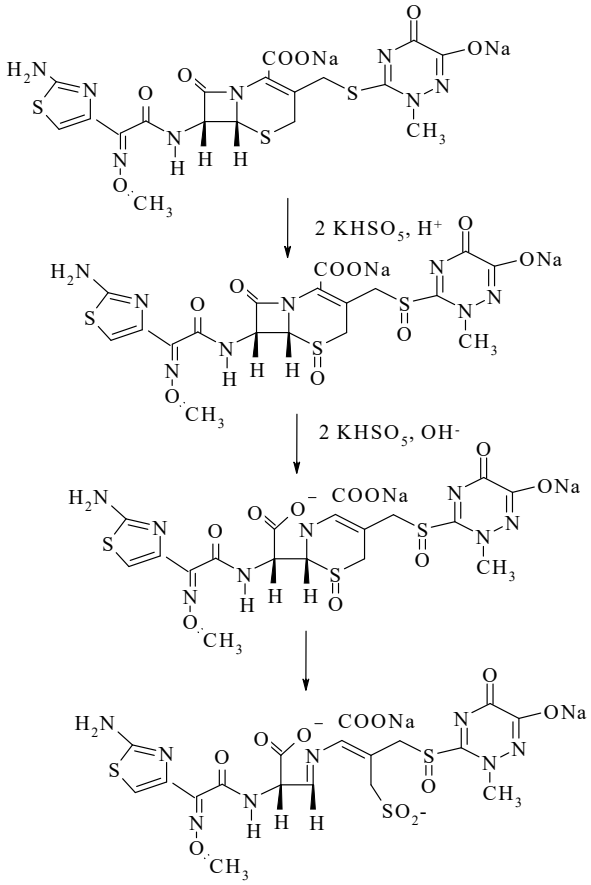

Figure 2. Chemical transformations of Ceftriaxone using Caro's acid.

The redox interaction between Ceftriaxone and potassium caroate in acidic medium (pH = 3-5) was stoichiometric and fast: 1 mol of Ceftriaxone per 2 mol of $KHSO_5$ (the observation time was 30 min) was determined by the iodometric method.

In basic medium, Ceftriaxone S,S'-dioxide underwent hydrolytic cleavage. **Figure 3** shows the electronic spectra of Ceftriaxone and the reaction product. The appearance of a new band of absorbance at λ_{max} = 295 nm demonstrates its formation during the alkaline hydrolysis of Ceftriaxone S,S'-dioxide in the presence of potassium caroate (the perhydrolysis reaction).

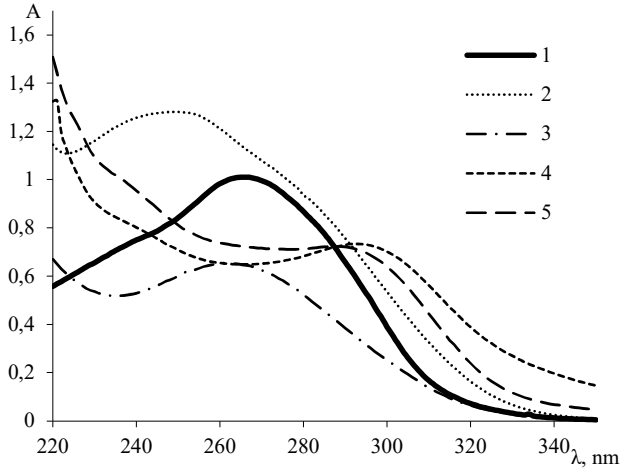

Figure 3. Electronic spectra of Ceftriaxone (CFT) absorption (1) and products of conjugated reactions of S-oxidation and perhydrolysis with Caro's acid

(1) c(CFT) = $4 \cdot 10^{-5}$ mol·L^{-1},

(2) c(CFT) = $4 \cdot 10^{-5}$ mol·L^{-1} and c(NaOH) = 0.02 mol·L^{-1},

(3) c(CFT) = $4 \cdot 10^{-5}$ mol·L^{-1} and c($KHSO_5$) = $8 \cdot 10^{-4}$ mol·L^{-1} (the volume was diluted with HCl 0.1 mol·L^{-1}),

(4) c(CFT) = $4 \cdot 10^{-5}$ mol·L^{-1}, c($KHSO_5$) = $8 \cdot 10^{-4}$ mol·L^{-1} and c(NaOH) = 0.02 mol·L^{-1},

(5) c(CFT) = $4 \cdot 10^{-5}$ mol·L^{-1}, c(NaOH) = 0.02 mol·L^{-1} and c($KHSO_5$) = $8 \cdot 10^{-4}$ mol·L^{-1}.

The appearance of a new band gave the possibility for developing a new procedure of the Ceftriaxone quantitative determination. To solve this question, optimal conditions should be developed.

The effect of Caro's acid

1 mL of $1 \cdot 10^{-2}$ mol·L^{-1} solution of Ceftriaxone was pipetted into 100 mL volumetric flasks containing 1 mL, 2 mL, 3 mL, 4 mL and 5 mL of 0.02 mol·L^{-1} $KHSO_5$ solution and 1 mL of 0.5168 mol·L^{-1} NaOH solution. The content of the mixture of each flask was mixed well, and the increase in absorbance at 295 nm was recorded for 30 min against the reagent blank as a function of time. It showed the dependence of absorption at 295 nm of Ceftriaxone alkaline solutions against time as a function of the acid concentration. A linear dependence was observed for the first 30 min.

The absorbance changed significantly with an increase in the concentration of Caro's acid (**Figure 4**).

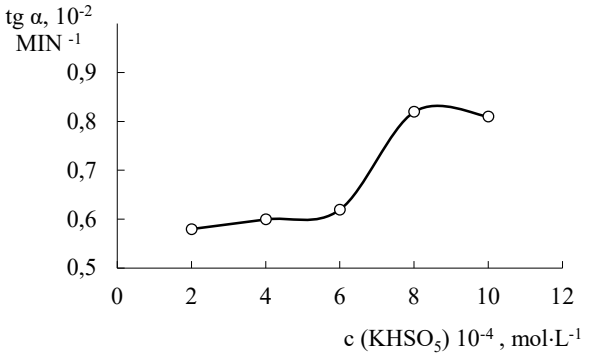

Figure 4. The effect of 0.02 M Caro's acid on the slope in the reaction between Ceftriaxone ($1 \cdot 10^{-3}$ mol·L^{-1}) and Caro's acid.

The maximum slope was obtained when 4.0 mL of 0.02 M Caro's acid was used. The

concentration of potassium caroate of $8 \cdot 10^{-4}$ mol·L^{-1} was chosen as the optimal one.

The effect of the Sodium Hydroxide concentration

1 mL of $1 \cdot 10^{-2}$ mol·L^{-1} solution of Ceftriaxone was pipetted into 100 mL volumetric flasks containing 0.5 mL, 1 mL, 2 mL, and 4 mL of 0.5168 mol·L^{-1} NaOH solution and 4 mL of 0.02 mol·L^{-1} $KHSO_5$ solution. The content of the mixture of each flask was mixed well, and the increase in absorbance at 295 nm was recorded for 30 min against the reagent blank as a function of time (**Figure 5**). It showed the dependence of the absorption at 295 nm of Ceftriaxone alkaline solutions against time as a function of the acid concentration. A linear dependence was observed for the first 10-15 min.

The maximum slope was obtained when 1 mL of 0.5168 mol·L^{-1} NaOH was used. No changes in absorption could be detected above this volume. Thus, 1 mL of 0.5168 mol·L^{-1} NaOH was chosen as the optimal value.

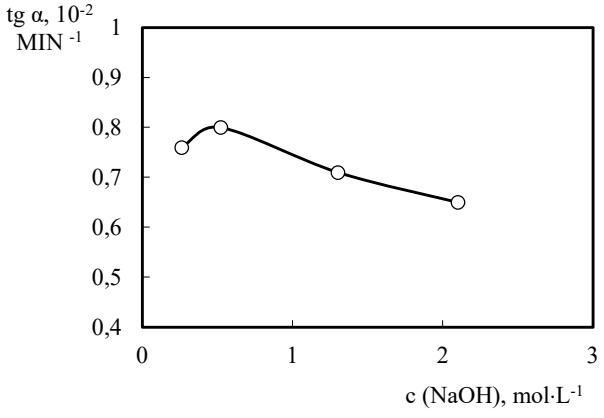

Figure 5. The effect of the sodium hydroxide concentration on the slope in the reaction between Ceftriaxone ($1 \cdot 10^{-3}$ mol·L^{-1}) and alkaline Caro's acid.

During the experiment, it was found that the mixing order affected the kinetics and the yield of the reaction. The highest rate of the product accumulation was observed only after the preliminary addition of Caro's acid to the cephalosporin (formation of the Ceftriaxone S,S'-dioxide), and then into the base solution at optimal concentrations: $8 \cdot 10^{-3}$ mol·L^{-1} of Caro acid, 0.5168 mol L^{-1} of the alkaline solution at 298-299 K. The reaction product was not formed without an oxidizer for the first 30 min. The product formation rate was assessed by the slope (tan α, min^{-1}) of linear plots of kinetic absorption curves A against time t (in minutes). The dependence of tan α linear concentration was observed within the Ceftriaxone content in 1-10 mmol L^{-1} solution.

The effect of the Ceftriaxone concentration

1 mL, 2 mL, 4 mL, 6 mL, 8 mL, 10 mL of $1 \cdot 10^{-3}$ mol·L^{-1} solution of Ceftriaxone was pipetted into 100 mL volumetric flask containing 4 mL of 0.02 mol·L^{-1} $KHSO_5$ solution and 1 mL of 0.5168 mol·L^{-1} NaOH solution. The content of the mixture of each flask was mixed well, and the increase in absorbance at 295 nm was recorded for 30 minutes against the reagent blank as a function of time.

The initial rate of the reaction at different concentrations was obtained from the slope curves to the absorption time. The calibration graph was constructed by plotting the tangent of the initial reaction rate versus the molar

concentration of Ceftriaxone (**Figure 6**). The straight line was observed in a wide range of concentrations (1-10 mmol·L^{-1}). The regression coefficient R is 0.9989. Thus, the procedure proposed can be validated for further determination of Ceftriaxone in the kinetic fixed modification.

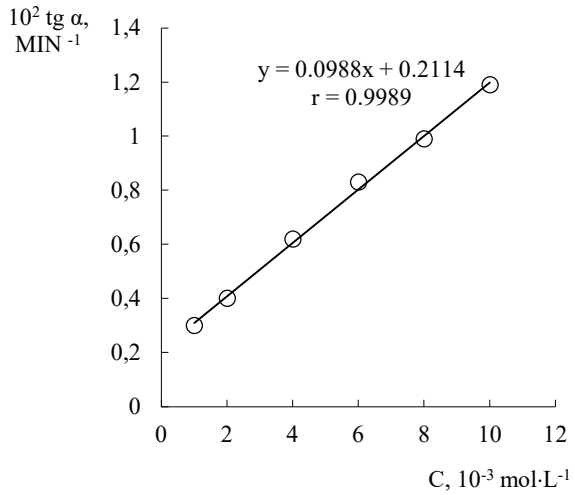

Figure 6. The calibration graph for the kinetic determination of Ceftriaxone in a pure substance by the method of peroxiacidic oxidation and perhydrolysis using potassium caroate. *c* ($KHSO_5$) =8·10^{-4} mol·L^{-1}; *c* (NaOH) =0.05 mol·L^{-1}.

Identification

The method proposed is based on the reaction of peroxiacidic oxidation and perhydrolysis. The peculiarity of the reaction is the formation of a new band, which characterizes only Ceftriaxone. Other cephalosporins after the formation of S-oxide have the maximal absorption at another wavelength, but the S,S'-dioxide of Ceftriaxone has the maximal absorption at 295 nm.

This gives an advantage as compared to other methods, and excludes the error associated with the presence of impurities.

The procedure was developed in a kinetic-spectrophotometric modification. This gives advantages when determining Ceftriaxone without any impurities since the change in absorption is measured during the experiment and the impurities do not interact during the reaction.

Linearity and Range

Linearity was studied over a wide range of drug concentration from 60-160 %. The correlation coefficient r=0.9993 obtained for the regression line showed a good relationship between the tangent of the reaction initial rate and the molar concentration of Ceftriaxone. The results are shown in **Figure 7.** The data obtained statistically are given in **Table 1**.

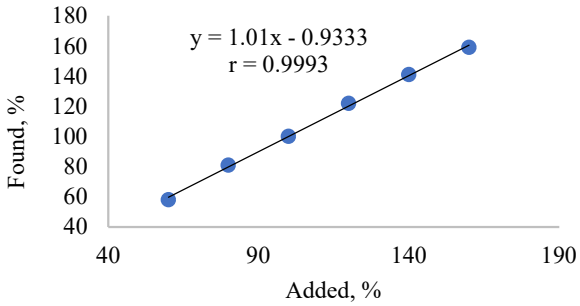

Figure 7. Linearity of the Ceftriaxone quantitative determination in normalized coordinates: *c* ($KHSO_5$) =8·10^{-4} mol·L^{-1}; *c* (NaOH) =0.05 mol·L^{-1}

LOD and LOQ were calculated based on the standard deviation of response and the slope of the calibration curve and expressed as

$$LOD=3\times S_a/b,$$

$$LOQ=10\times S_a/b,$$

where S_a is the standard deviation of response, and b is the slope of the calibration curve.

Table 1. Statistical characteristics of the straight linear dependence of the Ceftriaxone quantitative determination

Linear range, %	Intercept (*a*)	Intercept standard deviation (S_a)	Slope (*b*)	Slope standard deviation (S_b)	Correlation coefficient (*r*)	LOD, μg/mL	LOQ, μg/mL
60-160	-0.933	6.07	1.01	0.048	0.9993	0.1	0.33

The graph had a linear dependence in a wide range of concentrations: 60-160 %, the correlation coefficient (r=0.9993) was in good agreement with the required value.

Accuracy and Precision

The validity of the method proposed was studied by performing recovery studies. Precision and accuracy were considered by analyzing five replicates of sample solutions at three concentration levels. The relative standard deviations calculated were all below 2.2%, indicating excellent precision of the procedure proposed.

0.56 g (accurate weight) of Ceftriaxone were introduced in a 100 mL volumetric flask, diluted to the volume with double distilled water. Then, 1 mL of this solution was further diluted to 100 mL with double distilled water at 20° C. 10.00 mL of the solution obtained was introduced into a 100 mL volumetric flask containing 4 mL of 0.02 mol·L^{-1} $KHSO_5$ solution and 1 mL of 0.5168 mol·L^{-1} NaOH solution. The content was shaken and finally diluted to the volume with double distilled water. After the NaOH solution was added, the stopwatch was switched on. The solution obtained was transferred to a 1 cm cell to measure the absorbance at 295 nm during 20 min against water. A kinetic dependence curve of absorbance A versus time (min) was obtained.

The calculation was performed using the fixed time method by the following equation:

$$w = \frac{(A-a)\cdot M\cdot 10\cdot V_0\cdot 100}{b\cdot m_i(100-w_{H_2O})\cdot 1000\cdot V_1}100\%,$$

where A – is the optical density of the working solution at 295 nm;

a, b – are constant values: standard deviation (*a*) and slope (*b*) of the straight linear dependence (regression line) A= $b\cdot C + a$, respectively (where *C* – is the concentration of Ceftriaxone, mmol L^{-1});

Coefficients of the regression line:

a=0.2114, *b*=0.0988;

M – is the Ceftriaxone molar mass;

V_0– is the volume of the flask, mL;

V_1– is the pure substance volume taken for analysis, mL;

m_i – is the weight mass, g;

1000 – is recalculation in mg.

Five repeated estimations were performed the same way. The content of Ceftriaxone capsules was calculated, and compared with the label claim. The results are presented in **Table 2**.

Table 2. Metrological characteristics of calculation of accuracy and precision for Ceftriaxone using Caro acid

Taken	Found	Metrological characteristics P=0.95
Ceftriaxone pure substance, %		
100.00	100.12 99.15 101.08 99.15 102.01	$\bar{x} = 100.30$ $S = 1.62$ $S_{\bar{x}} = 0.53$ $\Delta\bar{x} = 1.67$ $RSD = 1.31\%$ $\varepsilon = 1.60\%$ $\delta = -0.30\%$

***** The results were compared to the HPLC standard method data (μ); δ = (x-μ)100%/μ

Three concentrations of Ceftriaxone were used to calculate accuracy and precision. 3 mL, 5 mL or 7 mL of 0.01 mol·L^{-1} Ceftriaxone solution were transferred into a 100 mL volumetric flask. Further analysis was performed as in the procedure for the quantitative determination of the Ceftriaxone pure substance. The operation was repeated 5 times. The results are shown in **Table 3**.

Table. 3. The results of calculation of accuracy and precision for the Ceftriaxone pure substance (P=0.95)

Taken, mol·L^{-1} 10^3	Found, mol·L^{-1} 10^3	Mean, mol·L^{-1} 10^3	Recovery, %	RSD, %	δ, %
3.00	2.95 2.95 2.95 3.10 3.10	3.01	100.33	2.25	0.33
5.00	5.12 4.94 4.94 5.12 5.12	5.05	100.96	1.95	0.96
7.00	6.96 6.96 6.96 7.15 7.15	7.04	100.55	1.63	0.55

*Results were compared to the HPLC standard method data (μ); δ = (x-μ)100%/μ

Conclusions

The possibility of the Ceftriaxone analytical determination by the biologically active part of the molecule (alicyclic sulfur and β-lactam ring) was shown, the proposed procedure giving reproducible and accurate results. The fixed time method can be easily applied to determine Ceftriaxone in a pure substance, providing advantages during the experiment. The procedure developed has good specificity and allows determining the content of the Ceftriaxone main component while avoiding the influence of impurities. The results of accuracy and precision are in good agreement

with the results obtained by the reference method. For a pure substance RSD = 1.63-2.25 %, δ = 0.33-0.96 %. LOD = 0.1 μg/mL, LOQ = 0.33 μg/mL. The obtained data meet the requirements of the State Pharmacopoeia of Ukraine including the accuracy, precision, LOD and LOQ as well as linearity range. The procedure of the Ceftriaxone assay developed can be included in the routine analysis of the main substance in pharmaceutical laboratories and plants.

References

[1] European Pharmacopoeia. 4 ed. (2003). Strasbourg: Council of Europe: 2975-7.

[2] European Pharmacopoeia. 6 ed. Vol. 1. (2007) Strasbourg: EDQM: 1084.

[3] British pharmacopoeia. Vol. 1. (2007) London: The stationary office: 666-7.

[4] The United States pharmacopeia. National formulary. Vol. 1. Rockville (MD) The united state pharmacopeial convention INC twin brook parkway; 2003: 498-9.

[5] Derzhavna Farmakopeya Ukrayiny. Vol. 1. (2001). Kharkiv: Derzhavne pidpryyemstvo «Naukovo-ekspertnyi farmakopeinyi tsentr», 477.

[6] Derzhavna Farmakopeya Ukrayiny. Vol. 1. (2008). Kharkiv: Derzhavne pidpryyemstvo «Naukovo-ekspertnyi farmakopeinyi tsentr», 620.

[7] Farmatsevtycheskaia khymyia: ucheb. Posobye (2004). Moscow: HEOTAR-MED, 640.

[8] Gallo ML, Campins PF, Selivano AC. Comparison of several methods used for the determination of cephalosporins. Analysis of cephalexin in pharmaceutical samples. J of pharmaceutical and biomedical analysis. 2002;29(3):405-423.

[9] Nabi SA, Abu-Nameh ESM, Helalch MIH. Titrimetric method followed by spectrophotometric determination of some selected cephalosporins. Chem anal. 1997;42(6):881-886.

[10] Blazheyesvky MYe, Labuzova YuYu. Yodometrychne vyznachennia tsefaleksynu ta tsefotaksymu za reaktsiieiu z kalii karoatom. News of Pharmacy. 2011;68(4):49-52.

[11] Blazheyesvky MYe, Labuzova YuYu. Yodometrychne vyznachennia tsefazolinu za reaktsiieiu z kaliiu hidrohenkaroatom. News of Pharmacy. 2012;71(3):48-51.

[12] Blazheyesvky MYe, Labuzova YuYu. Validatsiia yodometrychnoi metodyky kilkisnoho vyznachennia tsefaleksynu u substantsii. Problemy ekolohichnoi ta medychnoi henetyky i klinichnoi imunolohii. 2013;5(119):175-182.

[13] Serdiukova YuYu, Leonova SG. Yodometrychne vyznachennia tsefadroksylu za reaktsiieiu z kalii hidrohenkaroatom. Science Rise. 2015;15(10/4):36-41.

[14] Serdiukova YuYu, Ivashura MM, Oleksienko TO. Iodometric determination of cefuroxime by the potassium hydrogenperoxomonosulphate reaction. News of Pharmacy. 2016;86(2):6-8.

[15] Shrivastava SM, Singh R, Tariq A. A Novel High Performance Liquid Chromatographic Method for Simultaneous Determination of Ceftriaxone and Sulbactam in Sulbactomax. Int. J. Biomed. Sci. 2009;5(1):37–43.

[16] Sun H, Wang H, Ge X. Simultaneous determination of the combined drugs of ceftriaxone sodium, metronidazole, and levofloxacin in human urine by high-performance liquid chromatography. J. Clin. Lab. Anal. 2012;26(6):486-492.

[17] Glaría M, Moscciati G, Ramos R. Determination of Ceftriaxone in Cerebrospinal Fluid by Ion-Pair Liquid Chromatography. Journal of AOAC Int. 2005;88(2):436-439.

[18] Gallo Martínez L, Campíns Falcó P, Sevillano Cabeza A. Comparison of several methods used for the determination of cephalosporins. Analysis of cephalexin in pharmaceutical samples. Journal of Pharmaceutical and Biomedical Analysis 2002;29(3):405-423.

[19] Baranowska I, Markowski P, Baranowski J. Simultaneous determination of 11 drugs belonging to four different groups in human urine samples by reversed-phase high-performance liquid chromatography method. Analytica Chimica Acta 2006;570(1):46-58.

[20] Hiremath B, Mruthyunjayaswamy B. Development and Validation of a High-Performance Liquid Chromatographic Determination of Ceftriaxone Sodium and Its Application to Drug Quality Control. Analytical Letters 2009;42(14):2180-2191.

[21] De Diego M, Godoy G, Mennickent S. Chemical Stability Of Ceftriaxone By A Validated Stability-Indicating Liquid Chromatographic Method. Journal of the Chilean Chemical Society 2010;55(3):335-337.

[22] Campos M, de Moura Alonso J, dos Santos Martins E, Oliveira J, Hussni C, Peccinini R. Ceftriaxone pharmacokinetics by new simple and sensitive ultra-high-performance liquid chromatography method. Diagnostic Microbiology and Infectious Disease 2017;88(1):95-99.

[23] Phattanawasin P, Sotanaphun U, Sriphong L, Kanchanaphibool I. Stability-indicating TLC-image analysis method for quantification of Ceftriaxone sodium in pharmaceutical dosage forms. Journal of Planar Chromatography – Modern TLC 2011;24(1):30-34.

[24] Guru Prasad AR, Rao VS. Polarographic determination of certain cephalosporins in pharmaceutical preparations. Res. Pharm. Sci. 2010;5(1):57-63.

[25] Ogorevc B, Hudnik V, Gomiščck S. Polarographic analysis of some cephalosporin antibiotics. Fresenius' Zeitschrift für Analytische Chemie 1988;330(1):59-64.

[26] Ogorevc B, Gomiščck S. Electrochemical analysis of cephalosporin antibiotics. Journal of Pharmaceutical and Biomedical Analysis 1991;9(3):225-236.

[27] Majdi S, Jabbari A, Heli H, Yadegari H, Moosavi-Movahedi A, Haghgoo S. Electrochemical oxidation and determination of ceftriaxone on a glassy carbon and carbon-nanotube-modified glassy carbon electrodes. Journal of Solid State Electrochemistry 2008;13(3):407-416.

[28] Altinoz S, Temizer A, Beksac S. Determination of ceftriaxone in biological material by differential-pulse adsorptive stripping voltammetry. The Analyst 1990;115(6):873.

[29] Aleksic M, Lijeskic N, Pantic J, Kapetanovic V. Electrochemical behavior and differential pulse voltammetric determination of ceftazidime, cefuroxime-axetil and ceftriaxone. Facta universitatis - series: Physics, Chemistry and Technology 2013;11(1):55-66.

[30] Patel S, Patel N, Patel M. Spectrophotometric methods for the estimation of Cephalexin in tablet dosage forms. Indian Journal of Pharmaceutical Sciences 2006;68(2):278.

[31] Talebpour Z, Tavallaie R, Ahmadi S, Abdollahpour A. Simultaneous determination of penicillin G salts by infrared spectroscopy: Evaluation of combining orthogonal signal correction with radial basis function-partial least squares regression. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 2010;76(5):452-457.

[32] Salem H, Askal H. Colourimetric and AAS determination of cephalosporins using Reineck's salt. Journal of Pharmaceutical and Biomedical Analysis 2002;29(1-2):347-354.

[33] Pérez-Bendito D, Gómez-Hens A, Silva M. Advances in drug analysis by kinetic methods. Journal of Pharmaceutical and Biomedical Analysis 1996;14(8-10):917-930.

[34] Saleh G, El-Shaboury S, Mohamed F, Rageh A. Kinetic spectrophotometric determination of certain cephalosporins using oxidized quercetin reagent. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 2009;73(5):946-954.

[35] Omar MA, Abdelmageeda OH, Attiaa TZ. Kinetic spectrofluorimetric determination of certain cephalosporins in human plasma. Talanta 2009;77(4):1394-1404.

[36] Ilyas SA, Imran Md, Kumar N, Shah J, Jan MR, Kousar Z, Aslam M. Development of Spectrophotometric Method for Determination of Ceftriaxone Sodium in Different Brands of Pharmaceutical Preparation Involving Diazotization. International Journal of Pharmaceutical Sciences And Research 2015;6(12):5164-73.

[37] Majani AV, Paradkar MU. Development and Validation of UV Spectrophotometric Method for the Estimation of Ceftriaxone Sodium in Nanoparticles. Der Pharma Chemica. 2018;10(3):151-157.

[38] Patel S, Patel N, Patel M. Spectrophotometric estimation of cefotaxime and ceftriaxone in pharmaceutical dosage forms. Indian Journal of Pharmaceutical Sciences 2006;68(1):101.

[39] Hassan EM, Mahrous MS, Shdeed RN. Stability-Indicating Spectrophotometric Methods for The Determination of Ofloxacin and Ceftriaxone and Their Degradation Products. J. Pharm. Biomed.Sci. 2012;18(03):99-110.

[40] Blazheyesvky MYe, Labuzova YuYu. Kinetychne spektrofotometrychne vyznachennia tsefazolinu za produktom reaktsii peroksykyslotnoho okysnennia ta perhidrolizu. Pharm. J. 2012;4:76-80.

[41] Blazheyevskiy MYe, Labuzova YuYu.. Kinetic spectrophotometric determination of cefadroxil in pure substance and pharmaceutical dosage form. J. Chem. Pharm. Res. 2013;5(8):115-121.

[42] Blazheyesvky MYe, Labuzova YuYu. Kinetychne spektrofotometrychne vyznachennia tsefaleksynu za produktom reaktsii peroksokyslotnoho okysnennia ta perhidrolizu. News Pharm. 2010;6(22):30-33.