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DEDUCTIVE APPROACH TO REDOX TITRATION AND KINETIC-SPECTROPHOTOMETRIC METHODS FOR QUANTITATIVE DETERMINATION OF AMPICILLIN

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The article considers the search for new analytical reactions that can be the basis of quantitative analytical determinations of penicillins. The optimal conditions for these reactions were determined. We developed two unified procedures have been and established the possibility of quantitative determination by the methods of kinetic-spectrophotometry and redox titration of ampicillin in a pure substance and drug by using potassium caroate. The scheme of the chemical transformation of ampicillin with the reaction of potassium caroate was proposed. The kinetics of the conjugated reactions of S-oxidation and perhydrolysis of ampicillin with potassium caroate in alkaline medium was studied by an increase in the light absorbance of the reaction product at 290 nm. The appearance of a new wave in kinetic-spectrophotometry created the possibility of developing a new procedure for the quantitative determination of ampicillin. The reaction rate was monitored spectrally and displayed in real time. A differential variation of the tangent method was used to process the kinetic data.

Keywords: antibiotic, ampicillin, kinetic-spectrophotometry method, redox titration method, potassium caroate.

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Introduction

Ampicillin (Amp), commonly known as a broad-spectrum penicillin, is a type of aminopenicillin, a semisynthetic group of β-lactams that were developed against both gram-negative and gram-positive organisms. Amp is a penicillin in which the substituent at position 6 of the penam ring is a 2-amino-2-phenylacetamido group [1].

Amp is an amphoteric compound and it behaves essentially as an aliphatic amino acid. Being amphoteric, Amp in solution exists mainly in three different forms: cation (XH_2^+) in acid, zwitterions ($HX^{\pm}$) in neutral and anion (X^-) in alkaline medium (Fig. 1).

Amp has two dissociation constants: K_1 (pK_1=2.55) that corresponds to the dissociation of cation and K_2 (pK_2=7.14) that corresponds to the dissociation of zwitterion. At pH>7.5, the data indicated that only one type of reaction was responsible for the reaction rate, which is the hydroxyl ion interacting with the anionic form of ampicillin. In the basic solution, the hydrolytic rate of ampicillin is almost 1400 times faster than that in the acid solution (average values of kH^+ and kOH^- are 1.38 L/mol·h and 1945 L/mol·h, respectively). Both α-aminobenzylpenicilloic acid (a) and α-fminobenzylpenilloic acid (b) are formed in a basic solution. In the strong basic solution, only α-

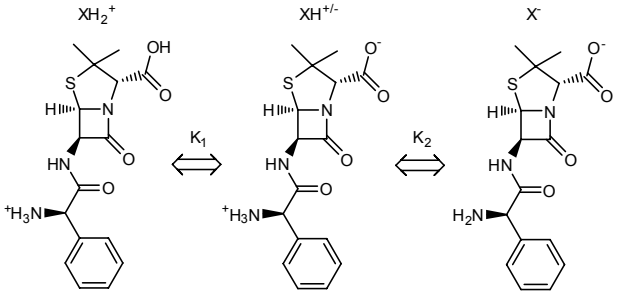

Fig. 1. Dissociation of ampicillin

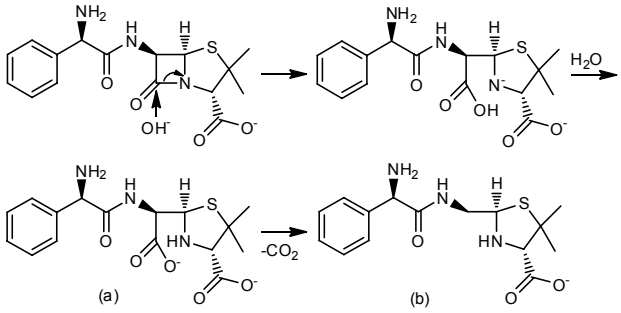

Fig. 2. Degradation of ampicillin in a basic solution

aminobenzylpenilloic acid, a decarboxylated product, is formed (Fig. 2).

Ampicillin trihydrate is a white, practically odorless, crystalline powder. Ampicillin sodium is a white to off-white, odorless or practically odorless, crystalline, hygroscopic powder.

Chemical formula is $C_{16}H_{19}N_3O_4S$. Molecular weight is 349.40476 g/mol.

Amp shown in Fig. 3 is chemically known according its IUPAC name: (2*S*, 5*R*, 6*R*)-6-([(2*R*)-2-amino-2-phenylacetyl]amino)-3,3-dimethyl-7-oxo-4-thia-1-azabicycloheptane-2-carboxylic acid. Dicloxacillin (DX) shown in Fig. 1 is chemically known as (2*S*, 5*R*, 6*R*)-6-{[3-(2,6-dichlorophenyl)-5-methyloxazole-4-carbonyl]amino}-3,3-dimethyl-7-oxo-4-thia-1-azabicycloheptane-2-carboxylic acid. Both of them are used alone and in constant dose combinations as antimicrobial and antibacterial agents (1, 2). 6-Aminopenicillanic acid (APA) shown in Fig. 3, is chemically known as (2*S*, 5*R*, 6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo heptane-2-carboxylic acid.

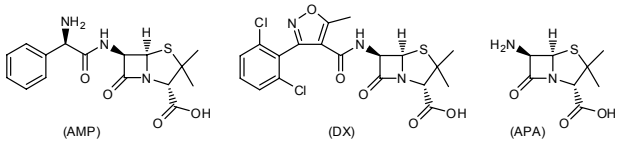

Fig. 3. Chemical structures of AMP, DX and 6-APA

The quantitative determination of drugs from penicillin series 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 has 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). European Pharmacopoeia (EPh) penicillin quantitative determination is performed by high performance liquid chromatography. International Pharmacopoeia recommends determining penicillin summary in semisynthetic penicillin by neutralization method after preparation hydrolysis by excess of sodium hydroxide titrated solution at heating[1].

Analysis of literary data shows that a promising direction of scientific research is to find out the possibility of carrying out the analysis of penicillins. The methods that are currently used to determine penicillins in pharmaceutical preparations have been reviewed in the literature. They include analytical measurement and appliance, equipment designed to perform a specific task in dependency of detection methods.

Published works described the methods of potentiometry titration [2], amperometry [3], high-performance liquid chromatography [4], voltammetry [5], polarography [6], micelle electrokinetic capillary method [7], spectrophotometry [8], chemi-luminescense [9], iodometry [10], and other methods [4,11,12] for the quantitative determination of penicillin drugs.

The issue of quantitative determination of penicillins does not lose its relevance. Most of the known methods for the quantitative determination of penicillins are reduced to the determination of the final products of their hydrolytic cleavage, which are obtained at the previous stage of analysis. They are long-lasting and require heating.

The methods for determining ampicillin developed by us have a number of advantages over the already known ones: they allow determining ampicillin in much smaller quantities, do not require long-term heating of the reaction mixture and are simpler and faster than the analogues.

The developed spectrophotometric method is time saving, simple, accurate, economic, sensitive and reproducible; it can be used in quality control laboratories. In addition, the suggested method is rapid and precise enough comparing with other known methods.

Thus, this article is devoted to the search for an analytical reaction and finding out the optimal conditions for its course, which can be used as a basis for the quantitative determination of Amp using

[1] United States Pharmacopeial Convention, Rockville, Maryland. 2015, 4. https://www.worldc at.org/title/united-at.org/title/united-states-pharmacopeia-the-nationa l-formulary/oclc/933365422.

potassium caroate.

Experimental

Peroxomonosulphate acid as triple potassium salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Oxone®) of «extra pure» qualification was used as oxidant. Active oxygen content was 4.3% (Acros Organics). The reagent is used due to its availability, good solubility and stability in water and its relatively high oxidation ability. The standard electrode potential for half-reaction $HSO_5^- + 2H^+ + 2e^- \rightarrow HSO_4^- + H_2O$ is 1.81 V.

Substances and solutions

For the research, ampicillin sodium salt of pharmacopoeial purity (2*S*, 5*R*, 6*R*)-6-[(2*R*)-2-amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate), a dry sterile powder in vials (1.0 g) «MR Ampicillin sodium» produced by «MERRYMED FARM», Namangan, Republic of Uzbekistan was used. Potassium caroate was obtained from commercial sources and used as an oxidant in the form of a triple potassium salt ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, «Oxone») of «extra pure» grade with an active oxygen content of 4.5%. The choice of the reagent was due to its availability, fairly good solubility and stability in aqueous solutions, and a relatively high oxidizing ability.

Working solution of potassium caroate $2 \cdot 10^{-2}$ mol/L

A weighed portion of 0.6148 g of the salt was dissolved in 100.0 mL of double-distilled water at 20^0C. The solution concentration was controlled by iodometric titration.

As a standard sample of ampicillin sodium salt, we used the substance of Ampicillin of pharmacopoeial purity with the content of the main substance of 98.8%.

Standard sample solution of Ampicillin (Amp), 1000 mg/mL

A weighed portion of 0.1 g of working solution of Amp was dissolved in 100.00 mL of distilled water at 20^0C.

Working solutions of Amp

Seven aqueous solutions of the following concentrations (%): 70; 90; 100; 110; 120; 130; and 150) were prepared in 100 mL volumetric flasks; the corresponding portions of 0.2446; 0.3145; 0.3494; 0.3843; 0.4193; 0.4542; and 0.5241 of the Amp substance were weighed (g).

Sodium thiosulfate solution, $2 \cdot 10^{-2}$ mol/L

An ampoule of a standard titer of sodium thiosulfate with an exact concentration of 0.1 mol/L was diluted five times with distilled water.

Solution of potassium iodide, 5%

A weighed portion of 5.0 g of potassium iodide was dissolved in 50 mL of distilled water, and the solution was diluted to the volume in a 100 mL volumetric flask at 20^0C.

Sodium hydroxide solution, $4.88 \cdot 10^{-3}$ mol/L

The sodium hydroxide solution was prepared according to Hillebrant by diluting the saturated solution with freshly distilled water.

Sulfuric acid, 0.1 mol/L

An ampoule of a standard titer of sulfuric acid with an exact concentration of 0.1 mol/L was diluted with distilled water.

Equipment

Spectrophotometry

The spectra of solutions of Amp and its oxidation products were recorded, and the light absorption of solutions in a quartz cuvette per 1 cm was measured on an Evolution 60S UV-Visible Spectrophotometer Thermo-Scientific (USA) against the solution without Amp or double-distilled water (compensation solution).

Titration

The titer of the Amp solution studied was determined using a 10 mL microburette with an accuracy of ±0.01 mL filled with a titrant to the zero mark.

Procedures

Kinetic spectrophotometric method

Close 50 mg (accurate weight) of the powder of the Amp sodium salt studied was transferred into a 100 mL volumetric flask, dissolved in 50 mL of distilled water, the solution was diluted to the volume, and the content was mixed. 5.00 mL of the solution obtained was transferred into a 50 mL volumetric flask, 3.0 mL of a 0.02 mol/L $KHSO_5$ solution and 3.0 mL of NaOH with the concentration of $4.88 \cdot 10^{-3}$ mol/L was added. The resulting solution was exposed to photometric measurements for 10 min in a 1 cm quartz cuvette at 282 nm using distilled water as a compensation solution.

Reduction-oxidation (redox) titration method

Close 910 mg (accurate weight) of the powder of the Amp sodium salt studied was dissolved in 75 mL of water in a 100 mL volumetric flask at 20^0C, and diluted to the volume. Using a pipette, 10 mL of the resulting Amp solution was taken and transferred to a 100 mL volumetric flask, 10.0 mL of a 0.02 mol/L $KHSO_5$ solution was added with stirring, and diluted to the volume with distilled water at 20^0C. Using a pipette, 10 mL of the reaction mixture was taken and transferred to a 100 mL flask, acidified with 1 mL of a 0.1 mol/L H_2SO_4 solution, and 2 mL of a 5% potassium iodide solution was added with vigorous stirring. The displaced iodine was immediately titrated with a standard 0.02 mol/L sodium thiosulfate solution. In parallel, under the

same conditions, a control experiment is carried out (without the Amp solution studied).

Results and discussion

Kinetic spectrophotometric method

As a result of the study, it was found that the order of mixing the solutions significantly affected the kinetics and the yield of the reaction product: the highest rate of the product formation was after the preliminary mixing of the Amp solution with $KHSO_5$ (the stage of the Amp sulfoxide formation).

Figure 4 shows the kinetic curves of Amp oxidation with potassium caroate.

Figure 5 shows the electronic light absorption spectra of the reaction product of the alkaline hydrolysis and perhydrolysis of Amp during the reaction in the *A* (absorbance) vs. λ (wavelength, nm) coordinates. The maximum absorption of the product formed was observed at 290 nm. Therefore, at the given wavelength, the kinetics of the analytical reaction was studied.

The optimal concentrations of alkali and $KHSO_5$ were $4.88 \cdot 10^{-3}$ mol/L and $2.0 \cdot 10^{-2}$ mol/L, respectively, at which the reaction rate of the perhydrolysis product formation was the highest.

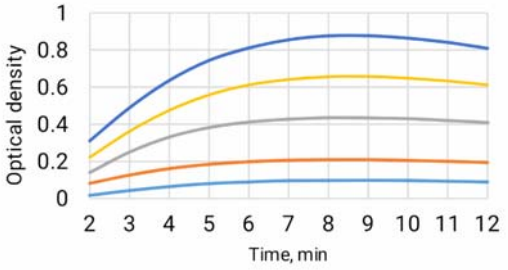

Fig. 4. Kinetic curves of oxidation Amp $KHSO_5$. *c*(Amp), μg/mL: 1 – 5; 2 – 10; 3 – 20; 4 – 30; and 5 – 40. *c*(NaOH)=$4.88 \cdot 10^{-3}$ mol/L; *c*($KHSO_5$)=$2.0 \cdot 10^{-2}$ mol/L

Without $KHSO_5$ under the above conditions, no reaction product was formed for 30 min. The necessary excess of $KHSO_5$ can be explained by the influence of further hydrolytic decomposition of S-oxide Amp in the alkaline medium (nucleophilic catalysis of the hydrolysis of the·β-lactam and thiazolidine cycles). Due to the alpha effect, $KHSO_5$ is a stronger nucleophile than hydroxide ion by many times (Fig. 6).

PMS-induced oxidation of β-lactam antibiotics was proposed to proceed through a non-radical mechanism involving direct two-electron transfer along with the heterolytic cleavage of the PMS peroxide bond. The product analysis indicated oxidation of β-lactam antibiotics to two stereoisomeric sulfoxides [13].

Plotting a calibration graph

Using a microburette, 0.50; 2.50; 3.00; 4.00; and 5.00 mL samples of the standard Amp solution were added to 50 mL volumetric flasks followed by

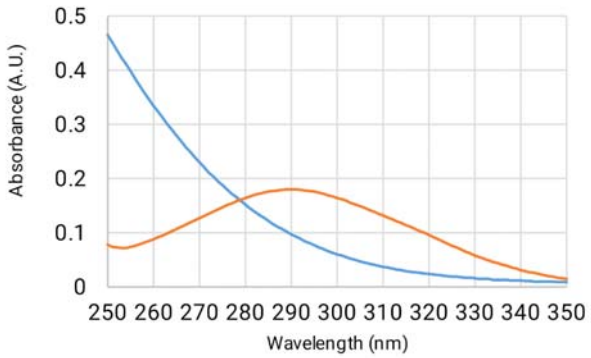

Fig. 5. Electronic light absorption spectra of the reaction product of alkaline hydrolysis and Amp perhydrolysis of the sodium salt over time. *c*(NaOH)=$4.88 \cdot 10^{-3}$ mol/L; *c*($KHSO_5$)=$2.0 \cdot 10^{-2}$ mol/L; *c*(Amp)=20 μg/mL

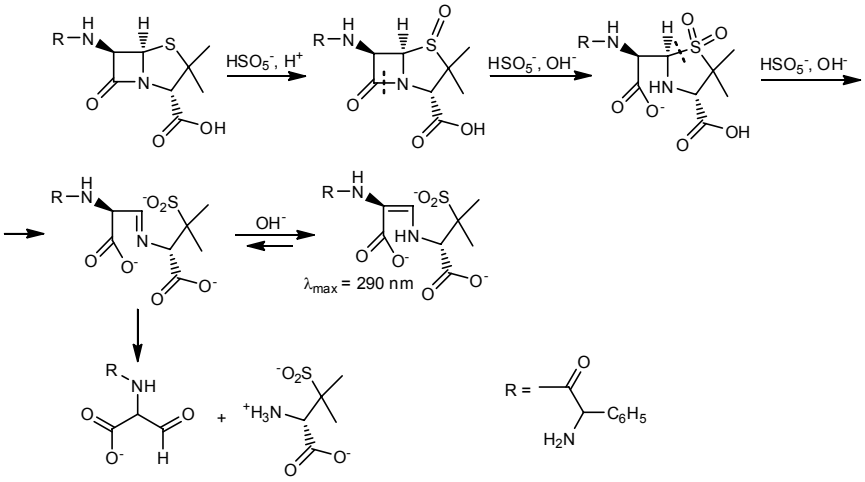

Fig. 6. The scheme of coupled reactions of peroxyacid oxidation and perhydrolysis of sulfon Amp with the formation of a substituted derivative of N-acryl-β-penicylamine sulfate

5 mL of $2 \cdot 10^{-2}$ mol/L $KHSO_5$ solution put to each flask, and the content was shaken thoroughly. 5.0 mL of $4.88 \cdot 10^{-3}$ mol/L NaOH solution were sequentially poured into each flask; the solution was diluted to the volume with distilled water and thoroughly mixed. After adding alkali to the solution, the stopwatch was started. The resulting solutions were photometered in a quartz cuvette with a thickness of 1 cm at 290 nm against distilled water (compensation solution) for 10 minutes every minute at 20^0C, and kinetic curves of the dependence of the absorbance on time were plotted. According to the slope of the linear sections of the kinetic curves, a calibration dependence of tgα on the concentration of Amp (c, μg/mL) was constructed.

Figure 7 shows a calibration graph for determining Amp, according to which, the dependence of concentration on tgα is linear in the range of 5 to 40 μg/mL. This allows determining the quantitative content of Amp in the given concentration range by the standard method.

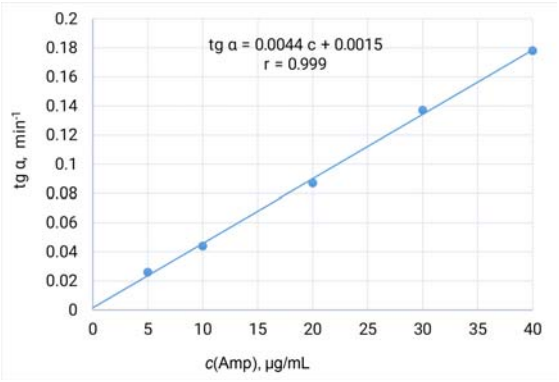

Fig. 7. The calibration graph for the quantitative determination of Amp, c(NaOH)=$4.88 \cdot 10^{-3}$ mol/L; c($KHSO_5$)=$2.0 \cdot 10^{-2}$ mol/L

The content of $C_{16}H_{19}N_3O_4S$, in mg in one vial, (X_{Amp}) was calculated by the following formula:

$$X_{Amp} = \frac{a_{st} \cdot tg\alpha \cdot 0.9408 \cdot \bar{a} \cdot w}{a \cdot tg\alpha_{st}}, \quad (1)$$

where a_{st} is the mass of a standard sample of Amp sodium salt, mg; $tg\alpha_{st}$ is the tangent of the angle of the slope of the kinetic curve in the study with the standard solution of Amp sodium salt, min^{-1}; w is the content of $C_{16}H_{19}N_3O_4S$ Amp sodium salt in the standard sample of Amp, in mass fractions; a is the weighed portion of the powder of Amp sodium salt studied, mg; $\bar{a}$ is the average weight of the drug in the vial, mg; tgα is the tangent of the angle of the slope of the kinetic curve in the study with the test solution of Amp sodium salt, min^{-1}; and 0.9408 is the calculation coefficient of Amp sodium salt to Amp.

The results of the analysis of the Amp drug by kinetic spectrophotometric method are shown in Table 1. The relative standard deviation did not exceed 1.3% (δ=+0.43%).

Table 1

Results of the quantitative determination of Ampicillin by the kinetic spectrophotometric method in the Amp drug according to the reaction with potassium caroate (P=0.95, n=7)

Ampicillin taken, mg	Found		Results of processing statistical data
	mg	%	
991.4[a]	993.5	99.4	$\bar{x}$ =995.7 (99.6%)
	1013	101.3	S=±12.74029
	985.6	98.6	S_x=±4.81538
	977.8	97.8	$\Delta\bar{x}$ =±11.79768
	996.7	99.7	RSD=±1.28 %
	1011	101.1	ε=±1.18%
	992.2	99.2	δ^b=+0.43%

Notes: [a] – the Amp content indicated in the quality certificate (μ); [b] – $\delta=(\bar{x}-\mu)\cdot 100\% \cdot \mu^{-1}$.

Redox titration method

By the method of reverse redox titration of the $KHSO_5$ excess, it was found that in the reaction studied 1 mol of $KHSO_5$ was consumed by 1 mol of Amp, and the interaction between them occurred for 1 min. The analytical reaction underlying the method is shown in Fig. 8.

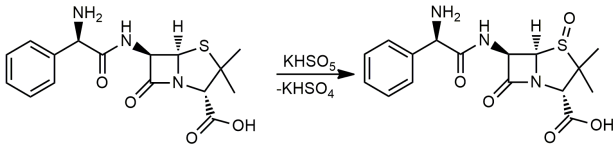

Fig. 8. The scheme of S-oxidation of Amp by potassium caroate

The content of $C_{16}H_{19}N_3O_4S$ (X, in %) was calculated by the following formula:

$$X = \frac{0.02 \cdot K \cdot 349.40 \cdot (V_0 - V) \cdot 100 \cdot 100\%}{2 \cdot 1000 \cdot m_s \cdot (100 - w_{H_2O})}, \quad (2)$$

where V_0 is the volume of sodium thiosulfate solution in the control experiment, mL; V is the volume of sodium thiosulfate solution studied, mL; 349.40 is the molar mass of Ampicillin (anhydrous), g/mol; K is the correction coefficient for the concentration

of sodium thiosulfate solution to 0.0200 mol/L; and m_s is the weighed portions of Amp, g.

The results of the analysis of the Amp drug by redox titration are shown in Table 2. The relative standard deviation did not exceed 0.7% (δ=−0.22%).

Table 2

Results of the quantitative determination of Ampicillin by redox titration in the Amp drug by the reaction with potassium caroate (P=0.95, n=7)

Ampicillin taken, mg	Found		Results of processing statistical data
	mg	%	
991.4[a]	982.3	98.2	$\bar{x}$ =989.2 (98.9%)
	985.9	98.6	S=±6.78366
	998.5	99.9	S_x=±2.76942
	995.6	99.6	$\Delta\bar{x}$ =±6.78508
	984.2	98.4	RSD=±0.69%
	994.6	99.5	ε=±0.69%
	983.2	98.3	δ[b]=–0.22%

Notes: [a] − the Amp content indicated in the quality certificate {μ); [b] − $\delta=(\bar{x}-\mu)\cdot 100\%\cdot\mu^{-1}$.

Conclusions

Using the methods of kinetic spectrophotometric and redox titration, two independent procedures for the quantitative determination of ampicillin in the substance and the drug product have been developed using potassium caroate as an analytical reagent ($KHSO_5$).

The suggested methods of quantitative determination of ampicillin can be used to develop analytical regulatory documentation for medicinal products, as well as in the practice of state laboratories for quality control of medicinal products and central factory laboratories of pharmaceutical enterprises.

The proposed methods of performing the analysis do not require the use of expensive devices, as well as toxic chemical reagents. In terms of sensitivity, speed of execution and selectivity, the developed methods of analysis are more perfect and economically profitable than the existing ones.

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ДЕДУКТИВНИЙ ПІДХІД ДО ОКИСНО-ВІДНОВНОГО ТИТРУВАННЯ ТА КІНЕТИКО-СПЕКТРОФОТОМЕТРИЧНОГО МЕТОДІВ ДЛЯ КІЛЬКІСНОГО ВИЗНАЧЕННЯ АМПІЦИЛІНУ

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У статті розглянуто пошук нових аналітичних реакцій, які можуть бути покладені в основу кількісних аналітичних визначень пеніцилінів, та з'ясовано оптимальні умови їх перебігу. Розроблено дві уніфіковані методики і показано можливість кількісного визначення ампіциліну методами кінетико-спектрофотометрії та окисно-відновного титрування в чистій субстанції та препараті з використанням калій кароату. Запропоновано схему хімічного перетворення ампіциліну за реакцією з калій кароатом. Досліджено кінетику сполучених реакцій S-окиснення та пергідролізу ампіциліну калій кароатом у лужному середовищі за збільшенням світлопоглинання утвореного продукту при 290 нм. Поява нової хвилі у випадку кінетико-спектрофотометричного визначення дає можливість розробки нової методики кількісного визначення ампіциліну. Швидкість реакції контролювали спектрофотометрично та відображали в реальному часі. Для обробки кінетичних даних використовували диференціальний варіант методу дотичної. Обидва запропоновані способи є придатними для кількісного визначення ампіциліну.

Ключові слова: антибіотик; ампіцилін; кінетико-спектрофотометричний метод; метод окисно-відновного титрування; калій кароат.

DEDUCTIVE APPROACH TO REDOX TITRATION AND KINETIC-SPECTROPHOTOMETRIC METHODS FOR QUANTITATIVE DETERMINATION OF AMPICILLIN

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The article considers the search for new analytical reactions that can be the basis of quantitative analytical determinations of penicillins. The optimal conditions for these reactions were determined. We developed two unified procedures have been and established the possibility of quantitative determination by the methods of kinetic-spectrophotometry and redox titration of ampicillin in a pure substance and drug by using potassium caroate. The scheme of the chemical transformation of ampicillin with the reaction of potassium caroate was proposed. The kinetics of the conjugated reactions of S-oxidation and perhydrolysis of ampicillin with potassium caroate in alkaline medium was studied by an increase in the light absorbance of the reaction product at 290 nm. The appearance of a new wave in kinetic-spectrophotometry created the possibility of developing a new procedure for the quantitative determination of ampicillin. The reaction rate was monitored spectrally and displayed in real time. A differential variation of the tangent method was used to process the kinetic data.

Keywords: antibiotic; ampicillin; kinetic-spectrophotometry method; redox titration method; potassium caroate.

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