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ANALYTICAL APPROACH OF KINETIC-SPECTROPHOTOMETRIC AND REDOX TITRATION METHODS IN THE QUANTITATIVE DETERMINATION OF TICARCILLIN

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This article explores the search for new analytical reactions and the determination of optimal conditions that can serve as a basis for the quantitative analysis of penicillins. Two unified procedures have been developed for the quantitative determination of ticarcillin in pure substance and pharmaceutical formulations using kinetic-spectrophotometric and redox titration methods with potassium hydrogenperoxomonosulphate. A chemical transformation scheme of ticarcillin with potassium hydrogenperoxomonosulphate has been proposed. The kinetics of the coupled reactions of S-oxidation and perhydrolysis of ticarcillin in an alkaline medium were studied by measuring the increase in light absorbance of the reaction product at 295 nm. The appearance of a new absorption band enables the development of a novel procedure for the quantitative determination of ticarcillin. The reaction rate was monitored spectroscopically and displayed in real time. A differential variation of the tangent method was used to process the kinetic data.

Keywords: antibiotic, ticarcillin, kinetic-spectrophotometric method, redox titration method, perhydrolysis, potassium hydrogenperoxomonosulphate.

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Introduction

The properties of ticarcillin's antibiotics arise from their ability to prevent cross-linking of peptidoglycan during cell wall synthesis, when the bacteria try to divide, causing cell death. Ticarcillin (Tic), like penicillin, contains a β-lactam ring that can be cleaved by b-lactamases, resulting in inactivation of the antibiotic [1].

Tic belongs to the carboxy penicillin family, the only difference to carbenicillin being a group of a side chain. Tic is inactivated through β-lactamase. Its main clinical use is as an injectable antibiotic for the treatment of Gram-negative bacteria, particularly *Pseudomonas aeruginosa* and *Proteusvulgaris.* Tic is also one of the few antibiotics capable of treating *Stenotrophomonas maltophilia* infections. Tic is provided as a white or pale-yellow powder [2].

In a highly acidic environment (pH<3), penicillins undergo a number of chemical reactions that lead to the formation of inactive decomposition products. Figure 1 shows the first stage, where penicilloic acid is formed. The process is initiated by protonation of the nitrogen atom of the lactam ring.

β-Lactam antibiotics are among the most important and widely used antimicrobials worldwide and they are comprised of a large family of compounds, obtained by chemical modifications of the common scaffolds. Usually, these modifications include the addition of active groups, but less frequently, molecules were synthesized in which either two β-lactam rings were joined to create a single bifunctional compound, or the azetidinone ring was joined to another antibiotic scaffold or another molecule with a different activity, in order to create a molecule bearing two different pharmacophoric functions [3].

Another way of hydrolysis is the transformation

of penicilloic acid into penillic acid followed by decarboxylation and hydrolytic ring opening and the formation of Penilloic acid (Fig. 2).

Tic shown in Fig. 3 is chemically known as by IUPAC Name: 2S,5R,6R)-6-[[(2R)-carboxy-3-thienylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid disodium salt; 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-(carboxy-3-thienylacetyl)amino-3,3-dimethyl-7-oxo-, disodium salt, [2S-2a,5a,6 b (S*)]-; N-(2-carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0]-hept-6-yl)-3-thiophenemalonamic acid disodium salt.

Ticarcillin is used in the clinics primarily because of its low toxicity and its utility in treating urinary tract infections due to susceptible Pseudomonas species. Its low potency, low oral activity, and susceptibility to bacterial beta-lactamases make it vulnerable to replacement by agents without these deficits. One contender in this race is ticaricillin. Its origin depended on the well-known fact that a divalent sulfur is roughly equivalent to a vinyl group. Figure 4 shows the synthesis scheme of Tic.

Ticarcillin disodium salt is a white or yellowish-white crystalline powder. Chemical formula is $C_{15}H_{14}N_2Na_2O_6S_2$. Its molecular weight is 428.39 g·mol^{-1}.

The quantitative determination of drugs 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 [4–6].

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). According to the European Pharmacopoeia (EPh), the quantitative determination of penicillin is performed by high performance liquid

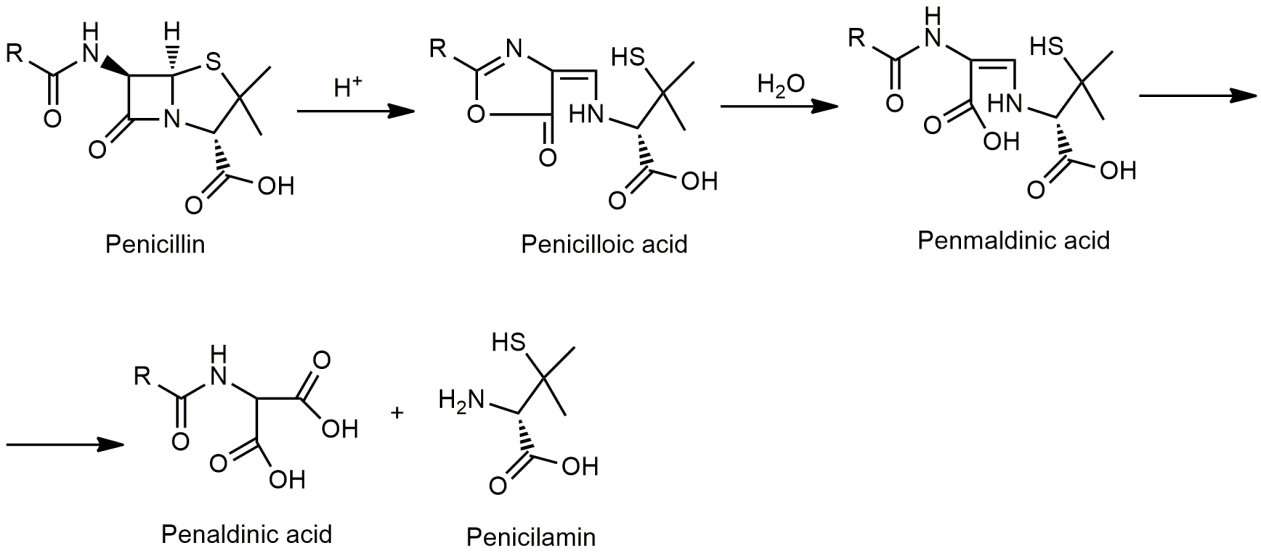

Fig. 1. Stages of formation of penaldinic acid and penicilamin

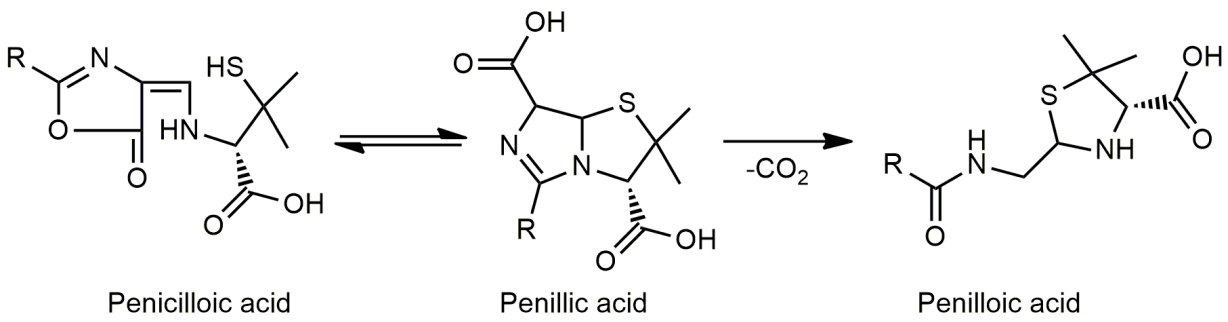

Fig. 2. Stages of formation of penilloic acid

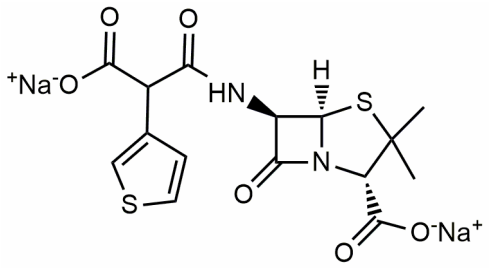

Fig. 3. Chemical structure of ticarcillin disodium salt

chromatography. International Pharmacopoeia recommends to determine penicillin summary in semisynthetic penicillin by neutralization method after preparation hydrolysis by excess of sodium hydroxide titrated solution at heating [7].

The 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. They include analytical measurement and appliance, equipment designed to perform a specific task in dependency of detection methods.

There are a number of well-described methods for the quantitative determination of penicillin drugs: potentiometry titration, amperometry, high-performance liquid chromatography, voltammetry, polarographic analysis, micelle electrokinetic capillary, spectrophotometry, chemiluminescense, iodometry, etc. [6,8–13]. Nevertheless, 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.

We developed the methods for determining Tic that have a number of advantages over the already known ones: they allow determining Tic in much smaller quantities, do not require long-term heating of the reaction mixture.

The developed spectrophotometric method is time saving, simple, accurate, economic, sensitive and reproducible, can be used in quality control laboratories. In addition, the principal advantages of the present method are that it is rapid and enough precise comparing with other methods of assay.

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 Tic using potassium hydrogenperoxomonosulphate.

Experimental

Peroxomonosulphate acid as triple potassium salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Oxone) of «extra pure» grade was used as oxidant. Active oxygen content is 4.3% (Acros Organics). The reagent is used due to its availability, good solubility and stability in water, as well as its relatively high oxidation ability. The standard electrode potential for the following half-reaction

$$HSO_5^- + 2H^+ + 2e^- \rightarrow HSO_4^- + H_2O$$

is 1.81 V.

Substances and solutions

Ticarcillin disodium salt of pharmacopoeial purity, a dry sterile powder in vials (0.5 g) «Ticarcillin disodium salt» produced by «Carl Roth GmbH+Co. KG» (Karlsruhe, Germany) was used. Potassium hydrogenperoxomonosulphate was 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 hydrogenperoxomonosulphate $2 \cdot 10^{-2}$ mol L^{-1}

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.

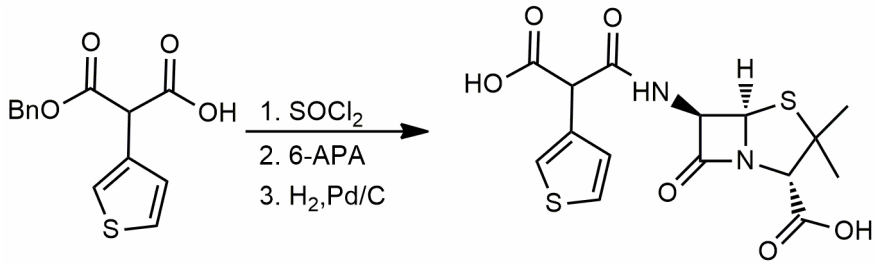

Fig. 4. TIC synthesis

As a standard sample of ticarcillin disodium salt, we used the substance of Tic of pharmacopoeial purity with the content of the main substance of 97.5%.

Standard sample solution of Ticarcillin (Tic), 500 mg μL^{-1}

A weighed portion of 0.05 g of working solution of Tic was dissolved in 100.00 mL of distilled water at 20^0C.

Working solutions of Tic

Seven aqueous solutions were prepared in 100 mL volumetric flasks with the following concentrations (%): 60; 80; 100; 120; 130; 140; and 150. The corresponding portions of 0.2570; 0.3427; 0.4284; 0.5141; 0.5569; 0.5998; 0.6426 of the Tic substance were weighed (g).

Sodium thiosulfate solution, $2 \cdot 10^{-2}$ mol L^{-1}

An ampoule of a standard titer of sodium thiosulfate with an exact concentration of 0.1 mol·L^{-1} 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, $5.05 \cdot 10^{-3}$ mol L^{-1}

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

Sulfuric acid, 0.1 mol L^{-1}

An ampoule of a standard titer of sulfuric acid with an exact concentration of 0.1 mol L^{-1} was diluted with distilled water.

Equipment

Spectrophotometry

The spectra of solutions of Tic 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 Tic or double-distilled water (compensation solution).

Titration

The titer of the Tic solution under study 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 Ticarcillin disodium salt under study was transferred to 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 to a 50 mL volumetric flask, 4.0 mL of a 0.02 mol L^{-1} $KHSO_5$ solution and 4.0 mL of NaOH with the concentration of $5.05 \cdot 10^{-3}$ mol L^{-1} was added. The resulting solution was exposed to photometric measurements for 10 min in a 1 cm quartz cuvette at 295 nm using distilled water as a reference solution.

Redox titration method

Close 490 mg (accurate weight) of the powder of the Tic disodium salt under study was dissolved in 75 mL of water in a 100 mL volumetric flask at 20^0C, and then diluted to the required volume. Using a pipette, 10 mL of the resulting Tic solution was taken and transferred to a 100 mL volumetric flask; 10.0 mL of a 0.02 mol L^{-1} $KHSO_5$ solution was added at 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^{-1} H_2SO_4 solution, and 2 mL of a 5% potassium iodide solution was added at vigorous stirring. The displaced iodine was immediately titrated with a standard 0.02 mol L^{-1} sodium thiosulfate solution. In parallel, under the same conditions, a control experiment is carried out (without the Tic solution studied).

Results and discussion

Kinetic spectrophotometric method

We 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 Tic solution with $KHSO_5$. Figure 5 shows the kinetic curves of Tic oxidation with potassium hydrogenperoxomonosulphate. The optimal concentrations of alkali and $KHSO_5$ were $5.05 \cdot 10^{-3}$ mol L^{-1} and $2.0 \cdot 10^{-2}$ mol L^{-1}, respectively, at which the reaction rate of the perhydrolysis product formation was the highest.

Without $KHSO_5$ under the above conditions, no reaction product was formed for 30 min. The

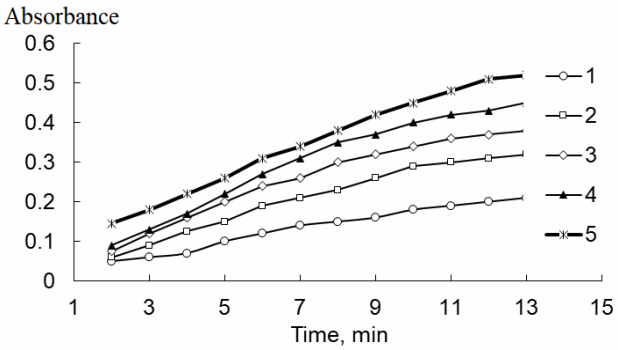

Fig. 5. Kinetic curves of Tic oxidation with $KHSO_5$. c(Tic), μg mL^{-1}: (1) 5; (2) 10; (3) 20; (4) 30; and (5) 40. c(NaOH)=$5.05 \cdot 10^{-3}$ mol L^{-1}; c($KHSO_5$)=$2.0 \cdot 10^{-2}$ mol L^{-1}

necessary excess of $KHSO_5$ can be explained by the influence of further hydrolytic decomposition of S-oxide Tic 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 [14].

Plotting a calibration graph

Using a microburette, 0.50; 2.50; 3.00; 4.00; 5.00 mL samples of the standard Tic solution were added to 50 mL volumetric flasks followed by 5 mL of $2{\cdot}10^{-2}$ mol L^{-1} $KHSO_5$ solution put to each flask, and the content was shaken thoroughly. 5.0 mL of $5.05{\cdot}10^{-3}$ mol L^{-1} 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 turned on. The resulting solutions were photometered in a quartz cuvette with a thickness of 1 cm at 295 nm against distilled water (a reference solution) at 20^0C every minute for 10 minutes, and the kinetic curves as the time dependences of absorbance were plotted. According to the slope of the linear sections of the kinetic curves, a calibration dependence of tgα on the concentration of Tic (c, μg mL^{-1}) was plotted.

Figure 7 shows a calibration graph for determining Tic, according to which, the dependence of tgα on concentration is linear in the range of 5 to 50 μg mL^{-1}. This allows determining the quantitative content of Tic in the given concentration range by the standard method.

The content of $C_{15}H_{14}N_2Na_2O_6S_2$, in mg in one vial, ($X_{Tic}$) was calculated by the following formula:

$$X_{Tic} = \frac{\alpha_{st} \cdot tg\alpha \cdot \overline{\alpha} \cdot w}{\alpha \cdot tg\alpha_{st}}, \quad (1)$$

where a_{st} is the weight of a standard sample of Tic disodium 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 Tic disodium salt, min^{-1}; w is the content of $C_{15}H_{14}N_2Na_2O_6S_2$ Tic disodium salt in the standard sample of Tic, mass fractions; a is the weighed portion of the powder of Tic disodium salt studied, mg; $\overline{a}$ 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 Tic disodium salt, min^{-1}.

The results of the analysis of the Tic drug by kinetic spectrophotometric method are shown in Table 1. The relative standard deviation did not exceed 1.91% (δ=−0.65%).

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 Tic, and

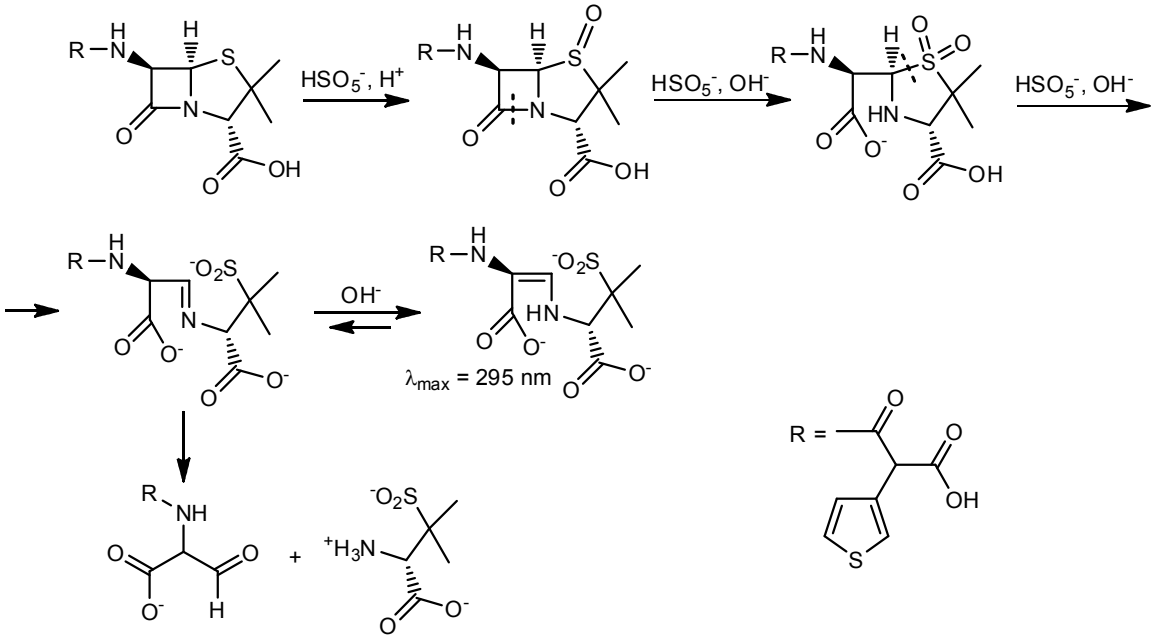

Fig. 6. The scheme of coupled reactions of peroxyacid oxidation and perhydrolysis of sulfon Tic with the formation of a substituted derivative of N-acryl-β-penicylamine sulfate

the interaction between them occurred for 1 min. The analytical reaction underlying the method is shown in Fig. 8.

The content of $C_{15}H_{14}N_2Na_2O_6S_2$ (X, in %) was calculated by the following formula:

$$X = \frac{0.02 \cdot K \cdot 428.40 \cdot (V_0 - V) \cdot 100 \cdot 100\%}{2 \cdot 1000 \cdot m_s \cdot (100 - w_{H_2O})}, \quad (2)$$

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; 428.40 is the molar mass of Ticarcillin disodium salt anhydrous, g mol^{-1}; K is the correction coefficient for the concentration of sodium thiosulfate solution to 0.0200 mol L^{-1}; and m_s is the weighed portions of Tic, g.

The results of the analysis of the Tic drug by redox titration are shown in Table 2. The relative standard deviation did not exceed 0.74% (δ=+1.56%).

Conclusions

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

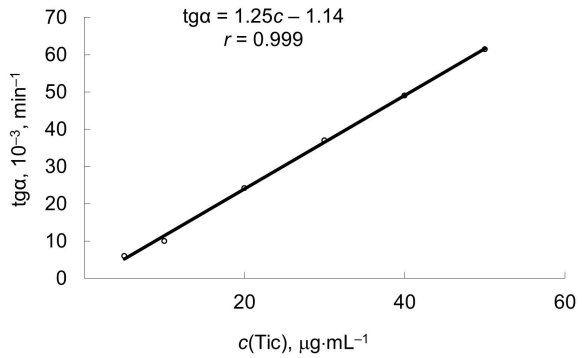

Fig. 7. The calibration graph for the quantitative determination of Tic. c(NaOH)=5.05·10^{-3} mol L^{-1}; c($KHSO_5$)=2.0·10^{-2} mol L^{-1}

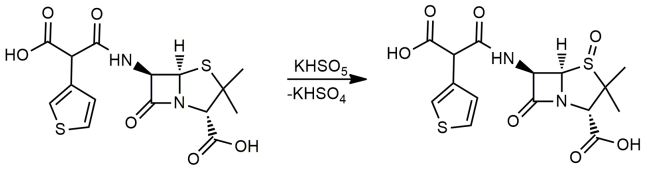

Fig. 8. The scheme of S-oxidation of Tic by potassium hydrogenperoxomonosulphate

Table 1

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

Ticarcillin taken, mg	Found		Results of processing statistical data
	μμg	%	
475.4*	464.5	92.9	$\bar{x}$ = 472.3 (94.5%)
	475.6	95.1	S=±9.04212
	465.3	93.1	S_x=±3.41760
	477.8	95.6	$\Delta\bar{x}$ = ±8.37313
	486.7	97.3	RSD=±1.91%
	461.2	92.2	ε=±1.77%
	475.3	95.1	δ**=–0.65%

Notes: * – the Tic content indicated in the quality certificate (m);** – $\delta = (\bar{x} - \mu) \cdot 100\% \cdot \mu^{-1}$.

Table 2

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

Ticarcillin taken, mg	Found		Results of processing statistical data
	μg	%	
475.4*	481.2	96.2	$\bar{x}$ = 482.8 (96.6%)
	486.1	93.5	S=±3.58306
	479.5	95.9	S_x=±1.35427
	487.6	97.5	$\Delta\bar{x}$ = ±3.31796
	484.3	96.9	RSD=±0.74%
	477.6	95.5	ε=±0.69%
	483.4	96.7	δ**=+1.56%

Notes: * – the Tic content indicated in the quality certificate (m);** – $\delta = (\bar{x} - \mu) \cdot 100\% \cdot \mu^{-1}$.

The developed methods of quantitative determination of Ticarcillin 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.

REFERENCES

1. *The odd* couple(s): an overview of beta-lactam antibiotics bearing more than one pharmacophoric group / De Rosa M., Verdino A., Soriente A., Marabotti A. // Int. J. Mol. Sci. – 2021. – Vol.22. – Art. No. 617.

2. *Role* of β-lactamase inhibitors as potentiators in antimicrobial chemotherapy targeting gram-negative bacteria / Zhang S., Liao X., Ding T., Ahn J. // Antibiotics. – 2024. – Vol.13. – No. 3. – Art. No. 260.

3. *United* States Pharmacopeial Convention. – Rockville, Maryland: United States Pharmacopeial Convention, 2015.

4. *Ismail F., Adeloju SB.* Galvanostatic entrapment of penicillinase into polytyramine films and its utilization for the potentiometric determination of penicillin // Sensors. – 2010. – Vol.10. – No. 4. – P.2851-2868.

5. *Amperometric* pH-sensing biosensors for urea, penicillin, and oxaloacetate / Stredansky M., Pizzariello A., Stredanska S., Miertus S. // Anal. Chim. Acta. – 2000. – Vol.415. – No. 1-2. – P.151-157.

6. *Chromatographic* methods for quantitative determination of ampicillin, dicloxacillin and their impurity 6-aminopenicillanic acid / Abdelrahman M.M., Naguib I.A., Elsayed M.A., Zaazaa H.A. // J. Chromatogr. Sci. – 2018. – Vol.56. – No. 3. – P.209-215.

7. *El-Desoky H.S., Ghoneim E.M., Ghoneim M.M.* Voltammetric behavior and assay of the antibiotic drug cefazolin sodium in bulk form and pharmaceutical formulation at a mercury electrode // J. Pharm. Biomed. Anal. – 2005. – Vol.39. – No. 5. – P.1051-1056.

8. *Voltammetric* methods for the determination of prarmaceuticals / Dubenska L.O., Blazhejevskyj M.Ye., Plotycya S.I., Pylypets M.Ya., Sarahman O.M. // Methods Objects Chem. Anal. – 2017. – Vol.12. – No. 2. – P.61-75.

9. *Zadorozhnii P.V., Kiselev V.V., Kharchenko A.V.* In silico ADME profiling of salubrinal and its analogues // Future Pharmacol. – 2020. – Vol.2. – P.160-197.

10. *Asan A., Seddiq N.* A simple spectrophotometric determination of amoxicillin in drug samples // J. Turk. Chem. Soc. A. Chem. – 2022. – Vol.9. – No. 2. – P.423-432.

11. *Chemiluminescence* assay for Listeria monocytogenes based on Cu/Co/Ni ternary nanocatalyst coupled with penicillin as generic capturing agent / Zhang Y., Cui G., Meng Y., Wang Y., Hun X. // Luminescence. – 2021. – Vol.36. – No. 1. – P.11-19.

12. *Karpova S., Krutskikh T., Mozgova O.* Iodometric method for the determination of mezlocillin // Int. J. Pharm. Sci. Res. – 2019. – Vol.10. – No. 5. – P.2358-2361.

13. *Recent* progress in the development of immobilized penicillin G acylase for chemical and industrial applications: a mini-review / Li K., Mohammed M.A.A., Zhou Y., Tu H., Zhang J., Liu C., et al. // Polym. Adv. Technol. – 2020. – Vol.31. – P.368-388.

14. *Oxidation* of fluoroquinolone antibiotics by peroxymonosulfate without activation: kinetics, products, and antibacterial deactivation / Zhou Y., Gao Y., Pang S.Y., Jiang J., Yang Y., Ma J., et al. // Water Res. – 2018. – Vol.145. – P.210-219.

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АНАЛІТИЧНИЙ ПІДХІД МЕТОДІВ КІНЕТИКО-СПЕКТРОФОТОМЕТРИЧНОГО ТА РЕДОКС-ТИТРУВАННЯ ПРИ КІЛЬКІСНОМУ ВИЗНАЧЕННІ ТИКАРЦИЛІНУ

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У статті розглянуто пошук нових аналітичних реакцій і визначення оптимальних умов їх перебігу, що може бути основою для кількісного аналітичного визначення пеніцилінів. Розроблено дві уніфіковані методики для кількісного визначення тикарциліну в чистій субстанції та препараті за допомогою кінетико-спектрофотометричного методу та редокс-титрування з використанням калій гідрогенпероксомоносульфату. Запропоновано схему хімічного перетворення тикарциліну. Досліджено кінетику спряжених реакцій S-окиснення та пергідролізу тикарциліну в лужному середовищі шляхом вимірювання світлопоглинання продукту, що утворюється, при 295 нм. Поява нової хвилі дозволяє розробити нову методику кількісного визначення тикарциліну. Швидкість реакції контролювали спектрально та відображали в реальному часі. Для оброблення кінетичних даних використовувався диференціальний варіант методу дотичної.

Ключові слова: антибіотик, тикарцилін, кінетико-спектрофотометричний метод, редокс-титрування, калій гідрогенпероксомоносульфат, пергідроліз.

ANALYTICAL APPROACH OF KINETIC-SPECTROPHOTOMETRIC AND REDOX TITRATION METHODS IN THE QUANTITATIVE DETERMINATION OF TICARCILLIN

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This article explores the search for new analytical reactions and the determination of optimal conditions that can serve as a basis for the quantitative analysis of penicillins. Two unified procedures have been developed for the quantitative determination of ticarcillin in pure substance and pharmaceutical formulations using kinetic-spectrophotometric and redox titration methods with potassium hydrogenperoxomonosulphate. A chemical transformation scheme of ticarcillin with potassium hydrogenperoxomonosulphate has been proposed. The kinetics of the coupled reactions of S-oxidation and perhydrolysis of ticarcillin in an alkaline medium were studied by measuring the increase in light absorbance of the reaction product at 295 nm. The appearance of a new absorption band enables the development of a novel procedure for the quantitative determination of ticarcillin. The reaction rate was monitored spectroscopically and displayed in real time. A differential variation of the tangent method was used to process the kinetic data.

Keywords: antibiotic; ticarcillin; kinetic-spectrophotometric method; redox titration method; perhydrolysis; potassium hydrogenperoxomonosulphate.

REFERENCES

1. De Rosa M, Verdino A, Soriente A, Marabotti A. The odd couple(s): an overview of beta-lactam antibiotics bearing more than one pharmacophoric group. *Int J Mol Sci*. 2021; 22: 617. doi: 10.3390/ijms22020617.

2. Zhang S, Liao X, Ding T, Ahn J. Role of β-lactamase inhibitors as potentiators in antimicrobial chemotherapy targeting gram-negative bacteria. *Antibiotics*. 2024; 13(3): 260. doi: 10.3390/antibiotics13030260.

3. United States Pharmacopeial Convention. The United States Pharmacopeia. The National Formulary. Rockville, Maryland: United States Pharmacopeial Convention; 2015. Available from: https://search.worldcat.org/title/The-United-States-pharmacopeia-:-the-national-formulary/oclc/933365422.

4. Ismail F, Adeloju SB. Galvanostatic entrapment of penicillinase into polytyramine films and its utilization for the potentiometric determination of penicillin. *Sensors*. 2010; 10(4): 2851-2868. doi: 10.3390/s100402851.

5. Stredansky M, Pizzariello A, Stredanska S, Miertus S. Amperometric pH-sensing biosensors for urea, penicillin, and oxaloacetate. *Anal Chim Acta*. 2000; 415(1-2): 151-157. doi: 10.1016/S0003-2670(00)00869-2.

6. Abdelrahman MM, Naguib IA, Elsayed MA, Zaazaa HA. Chromatographic methods for quantitative determination of ampicillin, dicloxacillin and their impurity 6-aminopenicillanic acid. *J Chromatogr Sci*. 2018, 56(3): 209-215. doi: 10.1093/chromsci/bmx101.

7. El-Desoky HS, Ghoneim EM, Ghoneim MM. Voltammetric behavior and assay of the antibiotic drug cefazolin sodium in bulk form and pharmaceutical formulation at a mercury electrode. *J Pharm Biomed Anal*. 2005; 39(5): 1051-1056. doi: 10.1016/j.jpba.2005.05.020.

8. Dubenska LO, Blazhejevskyj MYe, Plotycya SI, Pylypets MYa, Sarahman OM. Voltammetric methods for the determination of prarmaceuticals. *Methods Objects Chem Anal*. 2017; 12(2): 61-75. doi: 10.17721/moca.2017.61-75.

9. Zadorozhnii PV, Kiselev VV, Kharchenko AV. In silico ADME profiling of salubrinal and its analogues. *Future Pharmacol*. 2020; 2: 160-197. doi: 10.3390/futurepharmacol2020013.

10. Asan A, Seddiq N. A simple spectrophotometric determination of amoxicillin in drug samples. *J Turk Chem Soc A Chem*. 2022; 9(2): 423-432. doi: 10.18596/jotcsa.978686.

11. Zhang Y, Cui G, Meng Y, Wang Y, Hun X. Chemiluminescence assay for Listeria monocytogenes based on Cu/Co/Ni ternary nanocatalyst coupled with penicillin as generic capturing agent. *Luminescence*. 2021; 36(1): 11-19. doi: 10.1002/bio.3908.

12. Karpova S, Krutskikh T, Mozgova O. Iodometric method for the determination of mezlocillin. *Int J Pharm Sci Res*. 2019; 10(5): 2358-2361. doi: 10.13040/IJPSR.0975-8232.10(5).2358-61.

13. Li K, Mohammed MAA, Zhou Y, Tu H, Zhang J, Liu C, et al. Recent progress in the development of immobilized penicillin G acylase for chemical and industrial applications: a mini-review. *Polym Adv Technol*. 2020; 31: 368-388. doi: 10.1002/pat.4791.

14. Zhou Y, Gao Y, Pang SY, Jiang J, Yang Y, Ma J, et al. Oxidation of fluoroquinolone antibiotics by peroxymonosulfate without activation: kinetics, products, and antibacterial deactivation. *Water Res*. 2018; 145: 210-219. doi: 10.1016/j.watres.2018.08.026.