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QUANTITATIVE DETERMINATION OF PIPERACILLIN BY IODOMETRIC METHOD USING POTASSIUM PEROXOMONOSULFATE

Svitlana P. Karpova *, Mykola Ye. Blazheyevskiy, Olena O. Mozgova, Yulia Yu. Serdiukova, Maryna M. Ivashura and Irina Yu. Petukhova

Department of Physical and Colloid Chemistry, National University of Pharmacy, Pushkinska Street, Kharkiv, Ukraine.

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Correspondence to Author:
Svitlana P. Karpova

Department of Physical and Colloid Chemistry, National University of Pharmacy, Pushkinska Street, Kharkiv, Ukraine.

E-mail: za9594506@gmail.com

ABSTRACT: Kinetics and stoichiometry S-oxidation reaction of sodium piperacillin by means of potassium hydrogen peroxomonosulfate in aqueous solutions using iodometric titration were studied. Zopercin® – powder in vials for piperacillin injection solution in the combined form with tazobactam (piperacillin 4.0 g and tazobactam 0.5 g) was used for analysis. A new iodometric method for quantitative determination of sodium piperacillin in Zopercin® preparation using potassium hydrogen peroxomonosulfate ($KHSO_5$) as analytical reagent was proposed. Peroxomonosulfate acid as triple potassium salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Oxone®) of "extra pure" qualification was used as oxidant. At pH 2-4 for 1 mole of penicillin, 1 mole of $KHSO_5$ is consumed; the quantitative interaction is achieved within a time of more than 1 minute (observation time). The results were obtained by the recommended procedure for seven replicate titrations of mixtures containing the three species at various concentrations. RSD = 1.15 %, δ = (+0.2) %. It can be seen that piperacillin can be determined successively with good accuracy and reproducibility. The new procedure was developed and ability of quantitative determination of penicillin in pharmaceutical preparation Zopercin® by iodometric method using potassium hydrogen peroxomonosulfate ($KHSO_5$) as analytical reagent was shown.

INTRODUCTION: By the chemical structure penicillins are medicinal substances that belong to derivates of 6-aminopenicillanic acid (6-APA). It is a condensed system of tiazolidin and four section azetedin (β - lactam) heterocycles that differs in radical R connected with 6-APA amino group. Their characteristic feature is a rapid bactericide effect on the stage of micro-organisms growth and insignificant side effects on human organism. Decomposition of one of the heterocycles leads to complete loss of activity meaning allergic action.

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Piperacillin/tazobactam is a combination antibiotic containing the extended-spectrum penicillin anti-biotic piperacillin and the β-lactamase inhibitor tazobactam and used to reduce the development of drug-resistant bacteria. [2S-[2a,5a,6b(S)]]-6-[[[(4-ethyl-2,3-dioxo-1-piperazinyl) carbonyl] amino] phenil-acetyl]amino-3,3dimthyl-7-oxo-4-thia-1-aza bicyclo-[3.2.0]heptanes-carboxylic acid (Piperacillin) belongs to the ureidopenicillin class and it is used for the treatment of serious infections caused by susceptible strains of microorganisms.

Tazobactam (2S,3S,5R)-3-methyl-7-oxo-3-(1H-1,2, 3-triazolylmethyl)-4-thia-1-azabicyclo-[3.2.0] hept-nes-2-carboxylic acid-4,4-dioxide is used in combination with beta-lactamase antibiotic as antibacterial. Literature review revealed enormous analytical method were reported for the estimation of piperacillin and tazobactam individually or in

combination with other drugs. Classical iodometry of hydrolysis products is determined to be a basic method of penicillin summary quantitative determination. It's disadvantage is duration at least 40 min, and the necessity in standard samples and in rigid conditions standardization, as iodine interaction with hydrolysis products of penicillin reaction doesn't proceed strictly stoichiometrically: iodine expense, and also the quantity of substance that is equivalent to 1.00 ml 0.005 mol/l (f=1/2, I_2) of iodine, depend on the reaction medium temperature [1].

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 [2]. According to State Pharmacopoeia of Ukraine (SPhU) and European Pharmacopoeia (EPh) penicillin quantitative determination is performed by high performance liquid chromatography (HPLC). The following quantitative procedures of penicillin determination are described: using potentiometry titration and ionometry, spectrophotometry, extraction photometry, voltammetry and polarography, micelle electrokinetic capillary and paper chromatography, chemiluminescense, electrophoresis and kinetic analysis methods [3 - 14].

A new procedure for the quantitative determination of piperacillin sodium in the Zopercin® preparation by the method of back iodometric titration using potassium hydroperoxymonosulfate ($KHSO_5$) as an analytical reagent was developed.

MATERIALS AND METHODS: Peroxomonosulfate 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 is 4.5 % (Acros Organics). The reagent is used due to its availability, good solubility and stability in water, also its relatively high oxidation ability. Standard electrode potential for semi reaction is 1.8 V [15].

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

0.1 mol/l standard sodium thiosulphate solution was prepared using the standard titre fixanal ampoule on the double-distilled water. Titrated 0.02 mol/l thiosulphate solution was prepared through the corresponding dilution of the initial solution in the newly boiled double-distilled water with the addition of chemically pure sodium carbonate.

Solution of potassium iodide (5%) was prepared by dissolving 5.0 g of potassium iodine in just boiled distilled water transferring the solution into a 100-ml volumetric flask, diluting to volume and mixing.

Standard sulfuric acid solution was prepared using the standard titre fixanal ampoule on the double-distilled water. $c(H_2SO_4)$ = 0.1 mol/l.

Titrant volume is determined by 10 ml micro burette with precise ±0.01 ml.

Solution of potassium hydrogen peroxomonosulfate (0.02mol/l) in water was prepared by dissolving 0.615 g of potassium hydrogen peroxomonosulfate in double distilled water, transferring the solution into a 100-ml volumetric measuring flask, diluting to volume and mixing at +20°C. Solution concentration is determined by iodometric titration. 10.00 ml of prepared solution was transferred to 100-ml measuring flask, diluted. 10.00 ml of prepared solution was transferred into titration flask, 1 ml of 0.1 sulfuric acid solution and 1 ml of 1 % potassium iodide were added. The excess of iodine was titrated with 0.02 mol/l sodium thiosulphate.

Piperacillin sodium salt substance (CAS Number 59703-84-3) sodium (2*S*,5*R*,6*R*)-6-{[(2*R*)-2-[(4-ethyl-2,3-dioxo-piperazine-1-carbonyl)amino]-2-phenyl-acetyl]amino}-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate ($C_{23}H_{26}N_5NaO_7S$).

Zopercin® powder in vials for piperacillin injection solution in the combined form with tazobactam (piperacillin 4.0g and tazobactam 0.5g). Manufacturer Orchid Healthcare (office Orchid Chemicals and Pharmaceuticals Limited, India), series No. UA/5033/01/01 **Fig. 1**.

The preparation Piperacillin sodium standard solution. 0.53954 g Piperacillin sodium salt substance was transferred to 100-ml measuring flask, dissolve in 50 ml of double distilled water and to bring the final volume of solution to the mark by double distilled water.

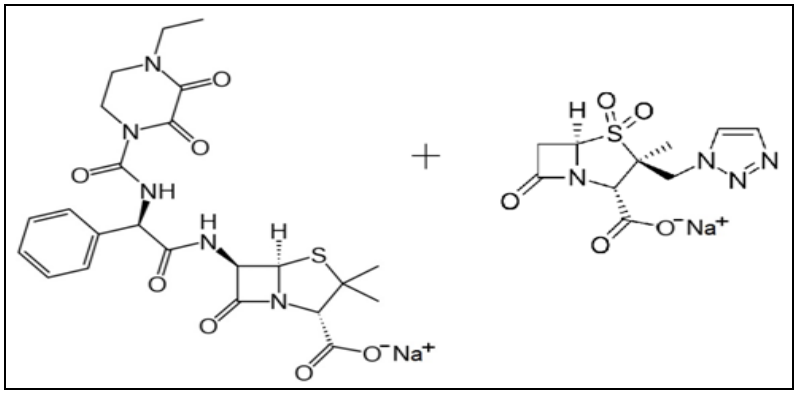

FIG. 1: CHEMICAL FORMULAS OF ZOPERCIN PREPARATION CONTENT

RESULTS AND DISCUSSIONS: By the method of back iodometric titration of $KHSO_5$ residue was determined that 1 mol of $KHSO_5$ is used per 1 mol of penicillin. The reaction finishes during 1 min and stays for 30 min (observation time at pH 2-3). The transformation scheme of analytical determination of piperacillin is given on **Fig. 2**.

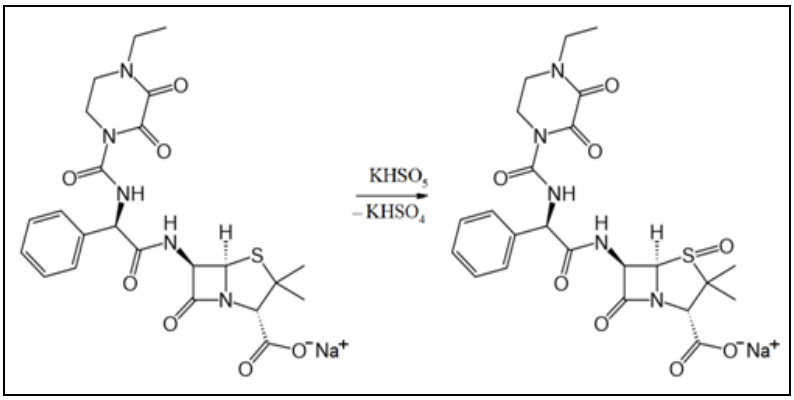

FIG. 2: SCHEME OF PIPERACILLIN S-OXIDATION BY MEANS OF POTASSIUM HYDROGEN PEROXOMONOSULPHATE

$$KHSO_5 + 2HCl + 2KI = KHSO_4 + 2KCl + I_2 + H_2O$$

$$HSO_5^- + 2H^+ + 3I^- = HSO_4^- + I_3^- + H_2O$$

$$I_2 + 2Na_2S_2O_3 = 2NaI + Na_2S_4O_6.$$

Table 1 shows the results obtained by the recommended procedure for seven replicate titrations of mixtures containing the three species at various concentrations. It can be seen that piperacillin could be determined successively with good accuracy and reproducibility.

Analysis of Piperacillin Powder*:* Piperacillin sodium (ca 600 mg) was weighed accurately, dissolved in water and diluted to 100 ml. 10.00 ml of prepared piperacillin solution using pipette was transferred to 100 ml volumetric flask, 20.00 ml of 0.02 mol/l $KHSO_5$ solution was added, diluted to volume at +20 °C and mixed. After 2 min 20.00 ml of repapered solution was transferred into 100 ml volumetric flask, 2 ml of 0.1 mol/l sulfuric acid solution and 2 ml of 5 % potassium iodide were added. The excess of iodine was titrated with 0.02 mol/l sodium thiosulphate by means of 10 ml micro burette. Blank determination was performed.

Piperacillin content in acidic form ($C_{23}H_{27}N_5O_7S$) in one flacon, X g, was calculated using the equation:

$$X = \frac{0{,}02 \cdot K \cdot 517{,}555 \cdot (V_0 - V) \cdot 100 \cdot m \cdot 100}{m_w \cdot 20 \cdot 20 \cdot 2}$$

where V_0 – sodium thiosulphate volume used for titration in blank determination, ml; V – sodium thiosulphate volume used for titration in procedure, ml; 517.555 – piperacillin (anhydrous) molar mass,

g/mol; K – correction factor of 0.0200 mol/l thiosulphate solution concentration; $\overline{m}$ – flacon average mass, g; m_w – weight mass, g.

Zopercin® dosage form analysis results are given in **Table 2**. (P=0.95, n=7).

TABLE 1: DETERMINATION OF PIPERACILLIN BY IODOMETRIC METHOD WITH USE $KHSO_5$ AS OXIDIZING AGENT

Taken mg	Determined by kinetic method,* $X \pm \Delta X$	RSD (%)	$\delta = \frac{x-a}{a} \times 100\%$	Recovery kinetic method (%)
1.349	1.35±0.036	2.88	+0.07	100.07
2.698	2.71±0.040	1.60	+0.07	100.44
5.395	5.40±0.045	0.90	+0.09	100.09

* Average of seven determinations (P = 0.95)

TABLE 2: RESULTS OF QUANTITATIVE PIPERACILLIN IN ZOPERCIN® DOSAGE FORM DETERMINATION BY MEANS OF POTASSIUM HYDROGENPEROXOMONOSULFATE (P=0.95, n=7)

Nominal piperacillin mass, g	Actual		Metrological characteristics
	g	%	
Zopercin® Orchid Healthcare (India)			
4.001*	4.0160	100.37	$\overline{x}$= 4.0078 (100.17%)
Series No. UA/5033/01/01	4.0763	101.88	S = ±0.0028
	3.9557	98.87	S_x = ±0.0011
	3.9858	99.62	$\Delta\overline{x}$ = ±0.0010
	3.9557	98.87	RSD = 1.15
	4.0135	100.31	δ = +0.2 %
	4.0515	101.26	

*As given in the certificate Orchid Healthcare (determined by BPh, 2016 [16])

CONCLUSION: Kinetics and stoichiometry of S-oxidation reaction of sodium piperacillin by means of potassium hydrogen peroxomonosulfate in aqueous solutions at pH 2-3 using iodometric titration method were studied. For 1 mole of penicillin, 1 mole of $KHSO_5$ is consumed; the quantitative interaction is achieved within a time of more than 1 minute (observation time). The new procedure was developed and ability of quantitative determination of penicillin in pharmaceutical preparation Zopercin® by iodometric method using potassium hydrogen peroxomonosulfate ($KHSO_5$) as analytical reagent was shown. RSD =1.15 %, δ = (+ 0.2) %.

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CONFLICT OF INTEREST: Nil

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