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## IODOMETRIC METHOD FOR THE DETERMINATION OF MEZLOCILLIN

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**ABSTRACT:** Kinetics and stoichiometry S-oxidation reaction of sodium monohydrate Mezlocillin (Mezl) using potassium hydrogen peroxomonosulfate in aqueous solutions using iodometric titration were studied. Baypen®-powder Mezl sodium monohydrate in flacons for preparation of solution for injections (Mezl 1.0 g). A new iodometric method for the quantitative determination of sodium monohydrate Mezl in Baypen® preparation using potassium hydrogen peroxomonosulfate (KHSO<sub>5</sub>) as analytical reagent was proposed. Peroxomonosulfate acid as triple potassium salt 2KHSO<sub>5</sub>·KHSO<sub>4</sub>·K<sub>2</sub>SO<sub>4</sub> (Oxone®) of “extra pure” qualification was used as the oxidant. At pH 1-4 for 1 mole of penicillin, 1 mole of KHSO<sub>5</sub> is consumed, the quantitative interaction is achieved within a time of more than 1 min (observation time). The results were obtained by the recommended procedure for seven replicate titrations of mixtures containing the three species at various concentrations. RSD = 2.01%, δ = (+ 0.51) %. It can be seen that Piperacillin can be determined successively with good accuracy and reproducibility. The new procedure was developed, and the ability of quantitative determination of penicillin in pharmaceutical preparation Baypen® by an iodometric method using potassium hydrogen peroxomonosulfate (KHSO<sub>5</sub>) as analytical reagent was shown.

**INTRODUCTION:** By the chemical structure Penicillins are medicinal substances that belong to derivatives of 6-amino penicillanic acid (6-APA). It is a condensed system of thiazolidine and four-section azetidone ( $\beta$ -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 microorganism's growth and insignificant side effects on the human organism. Decomposition of one of the heterocycles leads to complete loss of activity meaning allergic action.

Mezlocillin is a 4<sup>th</sup> generation penicillin antibiotic which kills certain bacteria that cause infection or stops their growth. It treats many kinds of infections including those of the skin, blood, CNS, respiratory tract, sinuses. It also treats gynecological infections in women. This drug is discontinued in the US.

Mezl has *in-vitro* activity against gram-positive and gram-negative aerobic and anaerobic bacteria. The bactericidal activity of Mezlocillin results from the inhibition of cell wall synthesis and is mediated through Mezlocillin binding to penicillin-binding proteins (PBPs). Mezl is stable against hydrolysis by a variety of beta-lactamases, including Penicillinases, and cephalosporinases and extended spectrum beta-lactamases. Mezl can be used to treat susceptible strains of *H. influenzae*, *Klebsiella species*, *Pseudomonas species*, *Proteus mirabilis*,

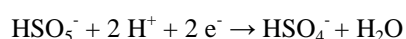
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*E. coli*, *Enterobacter species*, *Streptococcus faecalis*, *Peptococcus species*, *Peptostreptococcus species*, *Bacteroides species*, *Serratia species*, *P. vulgaris* and *Providencia rettgeri*. Classical iodometry of hydrolysis products is determined to be a basic method of Penicillin summary quantitative determination. Its disadvantage is duration at least 40 min, and the necessity in standard samples and 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, depending on the reaction medium temperature<sup>1</sup>.

International Pharmacopoeia recommends determining Penicillin summary in semi-synthetic penicillin by neutralization method after preparation hydrolysis by an excess of sodium hydroxide titrated solution at heating<sup>2</sup>. 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, chemiluminescence, electro-phoresis, and kinetic analysis methods<sup>3-14</sup>. A new procedure for the quantitative determination of MezI in the Baypen® preparation by the method of back iodometric titration using potassium hydroperoxymonosulfate ( $KHSO_5$ ) as an analytical reagent was developed.

**MATERIALS AND METHODS:** Peroxomonosulphate acid as triple potassium salt  $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$  (Oxone®) of "extra pure" qualification was used as the 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<sup>15</sup>.

0.1 mol/l standard sodium thiosulphate solution was prepared using the standard titer 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. The solution of potassium iodide (5%) was prepared by dissolving 5.0g of potassium iodine in just boiled distilled water transferring the solution into a 100 ml volumetric flask, diluting to volume and mixing. The standard sulphuric acid solution was prepared using the standard titre fixanal ampoule on the double-distilled water.  $c(H_2SO_4) = 0.1$  mol/l.

Titration volume is determined by 10 ml micro burette with precise  $\pm 0.01$  ml.

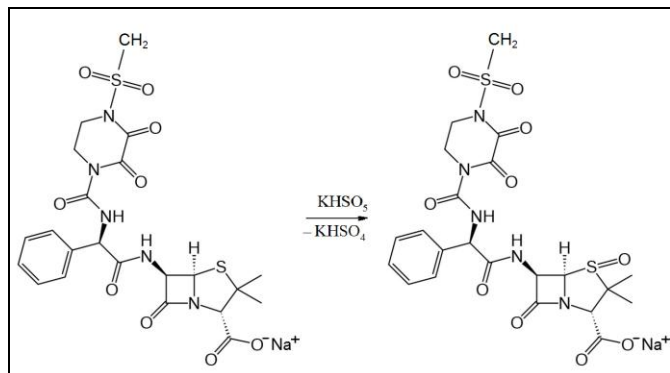
The solution of potassium hydrogen peroxomonosulfate (0.02 mol/l) in water was prepared by dissolving 0.615 g of potassium hydrogen peroxomonosulfate in double distilled water, transferring the solution into a 100 ml volumetric measuring flask, diluting to volume and mixing at +20 °C. Solution concentration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

Mezlocillin sodium monohydrate substance (CAS Number 59798-30-0) was used in the experiment. Its chemical structure is following (2S, 5R,6R)-3, 3-dimethyl-6 -[(2R)-2 -[(3-methylsulfonyl)-2 -oxoimidazolidine-1-carbonyl) amino]-2-phenylacetyl] amino]-7-oxo-4-thia-1-azabicyclo[3.2.0] heptan-2-carboxylate ( $C_{21}H_{24}N_5NaO_8S_2$ ). Baypen®-powder MezI sodium monohydrate in flacons for preparation of solution for injections (MezI 1.0 g). Manufacturer Bayer Aktiengesellschaft (Germany) was studied in the presented work as a medical preparation.

The procedure of preparation MezI sodium monohydrate standard solution is following. 0.59348 g MezI sodium monohydrate 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.

**RESULTS AND DISCUSSION:** By the method of back iodometric titration of  $\text{KHSO}_5$  residue was determined that 1 mol of  $\text{KHSO}_5$  is used per 1 mol of penicillin. The reaction finishes during 1 min and stays for 30 min (observation time at pH 1-4). The transformation scheme of analytical determination of MezI is given on **Fig. 1**.



**FIG. 1: SCHEME OF MEZLOCILLIN S-OXIDATION BY MEANS OF POTASSIUM HYDROGEN PEROXOMONOSULPHATE**

**TABLE 1: DETERMINATION OF MEZLOCILLIN BY IODOMETRIC METHOD WITH USE  $\text{KHSO}_5$  AS OXIDIZING AGENT**

Taken, g	Determined by kinetic method,* $\bar{X} \pm \Delta \bar{X}$	RSD (%)	$\delta = x - a / a \times 100$	Recovery kinetic method (%)
1.286	$1.29 \pm 0.039$	2.89	+0.31	100.31
2.735	$2.75 \pm 0.041$	1.36	+0.55	100.55
5.126	$5.13 \pm 0.047$	0.73	+0.08	100.08

\* Average of seven determinations ( $P = 0.95$ ).

MezI content in the acidic form ( $\text{C}_{21}\text{H}_{25}\text{N}_5\text{O}_8\text{S}_2$ ) in one flacon, X g, was calculated using the equation:

$$X = \frac{0.02 \cdot K \cdot 539.578 \cdot (V_0 - V) \cdot 100 \cdot \bar{m} \cdot 100}{m_w \cdot 20 \cdot 20 \cdot 2}$$

Where  $V_0$  - Sodium thiosulphate volume used for titration in blank determination, ml;  $V$  - Sodium thiosulphate volume used for titration in procedure,

ml; 539.578 - Mezlocillin (anhydrous) molar mass, g/mol; K- correction factor of 0.0200 mol/l thiosulphate solution concentration;  $\bar{m}$  - Flacon average mass, g;  $m_w$  - Weight mass, g.

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

**TABLE 2: RESULTS OF QUANTITATIVE MEZLOCILLIN IN BAYPEN® DOSAGE FORM DETERMINATION BY MEANS OF POTASSIUM HYDROGENPEROXOMONOSULFATE ( $P=0.95$ ,  $n=7$ )**

Nominal Piperacillin mass, g	Actual		Metrological characteristics
	g	%	
<b>BAYPEN® BAYER (GERMANY)</b>			
1.001*	1.0028	100.18	$\bar{x} = 1.0061(100.51\%)$
	1.0139	101.29	$S = \pm 0.02026$
	0.9821	98.11	$S_x = \pm 0.00766$
	1.0396	103.86	$\Delta \bar{x} = \pm 0.01876$
	1.0102	100.92	$RSD = 2.01$
	1.0128	101.18	$\delta = + 0.51 \%$
	0.9810	98.00	

\*As given in the certificate Orchid Healthcare (determined by BPh, 2016<sup>16</sup>).

**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 MezI could be determined successively with good accuracy and reproducibility.

**Analysis of Mezlocillin Powder:** MezI sodium monohydrate (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  $\text{KHSO}_5$  solution was added, diluted to the 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 sulphuric acid solution and 2 ml of 5% potassium iodide were added. The excess of iodine was titrated with 0.02 mol/l sodium thiosulphate using 10 ml micro burette. The blank determination was performed.

**CONCLUSION:** Kinetics and stoichiometry of S-oxidation reaction of sodium Mezlocillin by means of potassium hydrogen peroxomonosulfate in aqueous solutions at pH 1-4 using iodometric titration method were studied. For 1 mole of penicillin, 1 mole of  $\text{KHSO}_5$  is consumed, the quantitative interaction is achieved within a time of more than 1 min (observation time). The new procedure was developed, and the ability of quantitative determination of penicillin in pharmaceutical preparation Baypen® by an iodometric method using potassium hydrogen peroxomonosulfate ( $\text{KHSO}_5$ ) as analytical reagent was shown.  $\text{RSD} = 2.01\%$ ,  $\delta = (+0.51)\%$ .

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**CONFLICT OF INTEREST:** The authors do not have any conflict of interest.

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