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The Quantitative Determination of Oxacillin Using Kinetic-Spectrophotometric and Redox Titration Methods

Abstract

The search for new analytical reactions and finding out the optimal conditions for their course, which can be used as the basis for quantitative analytical determinations of penicillins, is a very urgent task.

Aim. To develop methods for the quantitative determination of Oxacillin.

Materials and methods. The study object was Oxacillin sodium salt powder in vials for preparing a solution for injections (0.5 g). Peroxomonosulfate acid as triple potassium salt $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$ (Oxone[®]) of “extra pure” grade was used as an oxidant. The methods of kinetic spectrophotometry and redox titration were used.

Results and discussion. A simple procedure for the quantitative determination of the Oxacillin pure substance by the kinetic spectrophotometry and redox titration methods using potassium hydrogen peroxomonosulfate (KHSO_5) has been developed. The results of the drug analysis obtained by newly developed and current methods are in good agreement with each other; δ (correctness) = (0.45–0.86) %.

Conclusions. Using the methods of kinetic spectrophotometric and redox titration, two independent procedures for the quantitative determination of oxacillin in the substance and the drug product have been developed using potassium hydrogen peroxomonosulfate as an analytical reagent (KHSO_5). A relative standard deviation RSD = (1.24–2.17) %.

Keywords: oxacillin; potassium hydrogen peroxomonosulfate; iodometry; kinetic spectrophotometry

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Кількісне визначення оксациліну методами кінетико-спектрофотометрії та окисно-відновного титрування

Анотація

Мета. Пошук нових аналітичних реакцій та з'ясування оптимальних умов їх перебігу, які можуть бути покладені в основу кількісних аналітичних визначень пеніцилінів, є вельми актуальним завданням. Метою цієї роботи було розробити методики кількісного визначення оксациліну.

Матеріали та методи. Об'єктом дослідження був Оксацилін – порошок натрій оксациліну у флаконах для приготування розчину для ін'єкцій (0,5 г). Як окисник використовували потрійну калієву сіль $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$ кваліфікації “extra pure” (Oxone[®]). У дослідженні було задіяно методи кінетико-спектрофотометрії та окисно-відновного титрування.

Результати та їх обговорення. Розроблено процедуру кількісного визначення оксациліну методами кінетико-спектрофотометрії та йодометричного титрування з використанням калій гідрогенпероксомоносульфату. Результати аналізу препарату, одержані за новоопрацьованими та чинними методиками, добре узгоджуються між собою; δ (правильність) = (0.45–0.86) %.

Висновки. За допомогою методів кінетико-спектрофотометрії та йодометричного титрування розроблено дві незалежні методики кількісного визначення оксациліну в субстанції та лікарському препараті з використанням калій гідрогенпероксомоносульфату як аналітичного реагенту (KHSO_5). Відносне стандартне відхилення RSD (1,24–2,17) %.

Ключові слова: оксацилін; калій гідрогенпероксомоносульфат; йодометрія; кінетико-спектрофотометрія

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■ Introduction

Despite the emergence of new groups of antimicrobial agents, antibiotic drugs of the penicillin series continue to occupy a significant place in pharmacy. In particular, hydrolysis-resistant ampicillin preparations have become widespread.

To determine the activity of penicillin preparations, as well as other antibiotics, biological, chemical, and physicochemical methods are used.

The basic method for the quantitative determination of the content of penicillins is the classical method of iodometry of hydrolysis products. Its disadvantage is the duration of at least 40 min, the need to use standard samples and standardization of the determination conditions, as well as its dependence on temperature [1–3].

According to the literature data, various methods are used for the quantitative determinations of antibiotics: chromatographic methods [4–7], chemiluminescent, spectrophotometric [8–11], fluorimetric [12], kinetic [13], voltammetric, methods using ion-selective electrodes, capillary electrophoresis, extraction method [14, 15].

Spectrophotometric methods are also known. They are based on the interaction of penicillins with copper (II) salts. These procedures allow determining penicillins in drugs in the presence of various additional substances.

Despite the fact that many methods are used in the practice of analysis, the task of improving the known and developing new methods for the quantitative determination of penicillins remains relevant. The well-known pharmacopoeial methods for determining drugs of this series are quite difficult, require a lot of time for preparation, and the use of complex equipment [16].

We have developed methods for the quantitative determination of antibiotic oxacillin by two alternative procedures of iodometry and kinetic spectrophotometry using potassium hydrogen peroxomonosulfate (KHSO_5) as an analytical reagent.

■ Materials and methods

Substances and solutions

For the research, oxacillin sodium salt of pharmacopoeial purity (3-phenyl-5-methyl-4-isoxazolylpenicillin sodium salt monohydrate), a dry sterile powder in vials (0.5 g) “OXACILIN-KMP” produced by AT “Kyivmedpreparat”, Kyiv, Ukraine was used. Potassium hydrogen peroxomonosulfate was obtained from commercial sources and used as an oxidant in the form of a triple potassium salt ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$, “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 hydrogen peroxomonosulfate $2 \times 10^{-2} \text{ mol L}^{-1}$.

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

As a standard sample of oxacillin sodium salt, we used the substance of Oxacillin of pharmacopoeial purity with the content of the main substance of 99.1 %.

Standard sample solution of Oxacillin (Oxa), $500 \mu\text{g mL}^{-1}$. A weighed portion of 0.05 g of *Working solution of Oxa* was dissolved in 100.00 mL of distilled water at 20 °C.

Working solutions of Oxa. Seven aqueous solutions of the following concentrations: 80 %; 85 %; 90 %; 95 %; 100 %; 110 %; 120 % were prepared in 100 mL volumetric flasks; the corresponding portions of 0.2289 g; 0.2433 g; 0.2576 g; 0.2718 g; 0.2862 g; 0.3147 g; 0.3433 g of the Oxa substance were weighed.

Sodium thiosulfate solution, $2 \times 10^{-2} \text{ mol L}^{-1}$. 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 °C.

Sodium hydroxide solution, $6.1 \times 10^{-3} \text{ mol L}^{-1}$. 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 Oxa 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 Oxa or double-distilled water (compensation solution).

Titration. The titer of the Oxa solution studied was determined using a 10 mL microburette with an accuracy of $\pm 0.01 \text{ mL}$ filled with a titrant to the zero mark.

Procedures

Kinetic Spectrophotometric Method. 65 mg (accurate weight) of the powder of the Oxa 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 $0.02 \text{ mol L}^{-1} \text{ KHSO}_5$ solution and 3.0 mL of NaOH with the concentration of $6.1 \times 10^{-3} \text{ mol L}^{-1}$ were 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. 450 mg (accurate weight) of the powder of the Oxa sodium salt studied was dissolved in 75 mL of water in a 100 mL volumetric flask at 20 °C, and diluted to the volume. Using a pipette, 10 mL of the resulting Oxa solution was taken and transferred to a 100 mL volumetric flask, 10.0 mL of a $0.02 \text{ mol L}^{-1} \text{ KHSO}_5$ solution was added with stirring, and diluted to the volume with distilled water at 20 °C. Using a pipette, 10 mL of the reaction mixture was taken and transferred to a 100 mL flask, acidified with 1 mL of a $0.1 \text{ mol L}^{-1} \text{ H}_2\text{SO}_4$ 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^{-1} sodium thiosulfate solution. In parallel, under the same conditions, a control experiment is carried out (without the Oxa 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 Oxa solution with KHSO_5 (the stage of the Oxa sulfoxide formation).

Figure 1 shows the electronic light absorption spectra of the reaction product of the alkaline hydrolysis and perhydrolysis of Oxa during the reaction in the A (optical density) – λ (wavelength, nm)

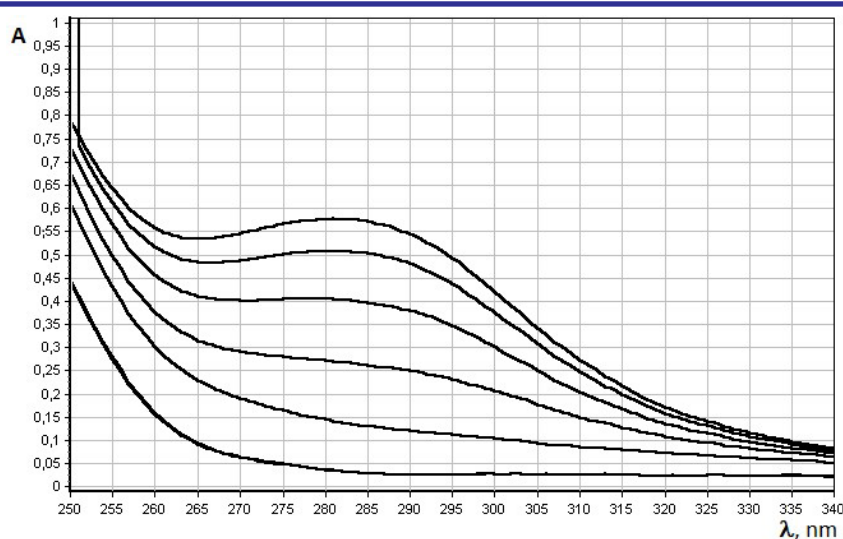


Figure 1. Electronic light absorption spectra of the reaction product of alkaline hydrolysis and Oxa perhydrolysis of the sodium salt over time. $c(\text{NaOH}) = 6.1 \times 10^{-3} \text{ mol L}^{-1}$; $c(\text{KHSO}_5) = 1.2 \times 10^{-3} \text{ mol L}^{-1}$; $c(\text{Oxa}) = 30 \text{ mg mL}^{-1}$

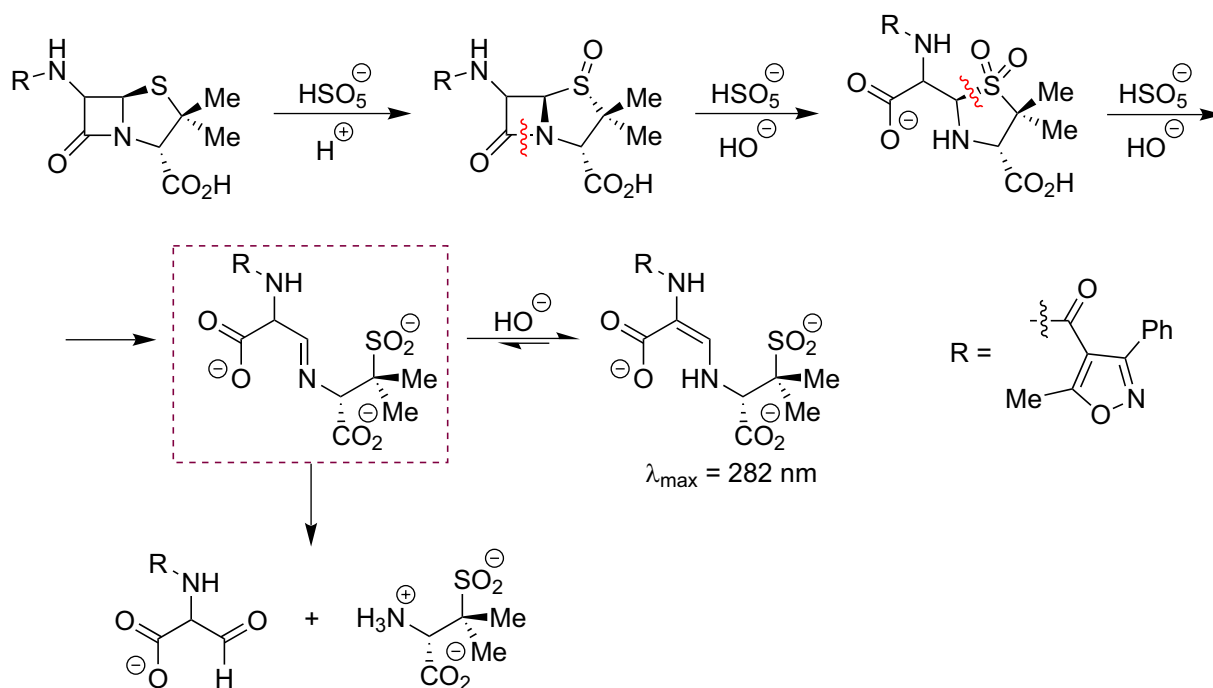


Figure 2. The scheme of coupled reactions of peroxyacid oxidation and perhydrolysis of sulfon Oxa with the formation of a substituted derivative of N-acryl- β -penicillamine sulfate

coordinates. The maximum absorption of the product formed was observed at 282 nm. Therefore, at the given wavelength, the kinetics of the analytical reaction was studied.

The optimal concentrations of alkali and KHSO_5 were $6.1 \cdot 10^{-3} \text{ mol L}^{-1}$ and 0.02 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 necessary excess of KHSO_5 can be explained by the influence of further hydrolytic decomposition of S-oxide Oxa 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 (Figure 2). 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 [17].

Plotting a calibration graph. Using a microburette, 0.50; 2.50; 3.00; 4.00; 5.00; 7.50 mL samples of the standard Oxa solution were added to 50 mL volumetric flasks followed by 5 mL of $2 \cdot 10^{-2} \text{ mol L}^{-1}$ KHSO_5 solution put to each flask, and the content was shaken thoroughly. 5.0 mL of $6.1 \cdot 10^{-3} \text{ mol L}^{-1}$ 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 started. The resulting solutions were photometered in a quartz cuvette with a thickness of 1 cm at 282 nm against distilled water (compensation solution) for 10 minutes every minute at 20°C , and kinetic curves of the dependence of the optical density on time were plotted. According to the slope of the linear sections of the kinetic curves, a calibration dependence of tga on the concentration of Oxa (C , $\mu\text{g mL}^{-1}$) was constructed.

Figure 3 shows a calibration graph for determining Oxa, according to which, the dependence of concentration on tga is linear in the range of 5 to $50 \mu\text{g mL}^{-1}$. This makes it possible to determine the quantitative content of Oxa in the given concentration range by the standard method.

The content of $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_4\text{S}$, in mg in one vial, (X_{Oxa}) was calculated by the formula:

$$X_{\text{Oxa}} = \frac{\alpha_{st} \cdot \text{tga} \cdot w \cdot 0.9094 \cdot a}{a \cdot \text{tga}_{st}}$$

where: α_{st} – is the mass of a standard sample of oxacillin sodium salt, mg;
 tga_{st} – is the tangent of the angle of the slope of the kinetic curve in the study with the standard solution of oxacillin sodium salt, min^{-1} ;
 w – is the content of $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_4\text{S}$ oxacillin sodium salt in the standard sample of Oxa, in mass fractions;

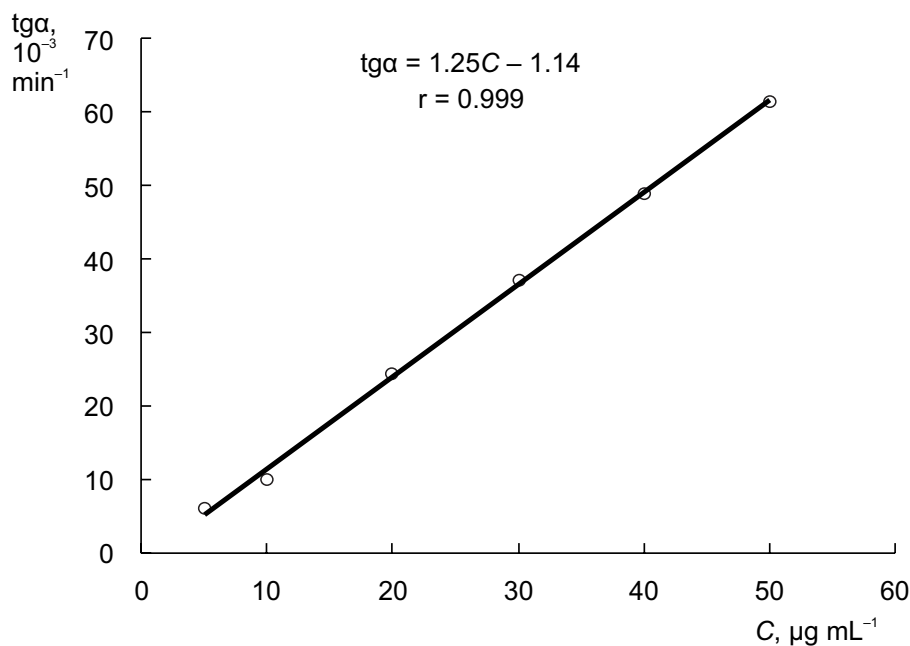


Figure 3. The calibration graph for the quantitative determination of Oxa, $c(\text{KHSO}_5) = 2 \times 10^{-3} \text{ mol L}^{-1}$; $c(\text{NaOH}) = 6.1 \times 10^{-3} \text{ mol L}^{-1}$

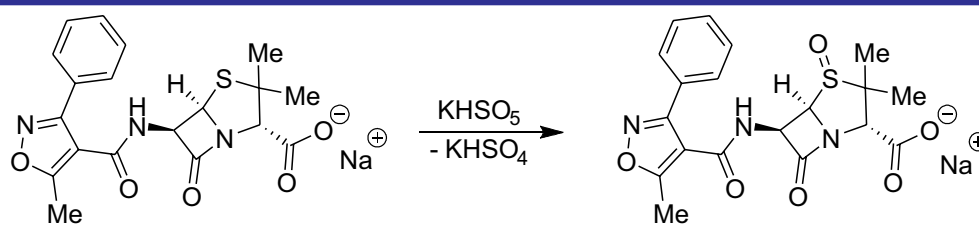


Figure 4. The scheme of S-oxidation of Oxa by Potassium hydrogen peroxomonosulfate

α – is the weighed portion of the powder of oxacillin sodium salt studied, mg;

$\bar{\alpha}$ – is the average weight of the drug in the vial, mg;

tga – is the tangent of the angle of the slope of the kinetic curve in the study with the test solution of oxacillin sodium salt, min^{-1} ;

0.9094 – is the calculation coefficient of oxacillin sodium salt to oxacillin.

The results of the analysis of the Oxa drug by kinetic spectrophotometric method are shown in

Table 1. The relative standard deviation did not exceed 1.7 % ($\delta = -1.35$ %).

Redox titration method

By the method of reverse iodometric 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 Oxa, and the interaction between them occurred for 1 min. The analytical reaction underlying the method is shown in Figure 4.

Table 1. Results of the quantitative determination of oxacillin by the kinetic spectrophotometric method in the Oxa drug according to the reaction with potassium hydrogen peroxomonosulfate ($P = 0.95$, $n = 7$)

Oxacillin taken, mg	Found		Results of processing statistical data
	mg	%	
503.1 ^[a]	494.2	98.8	$\bar{x} = 496.3$ (99.3 %) $S = \pm 8.41580$ $S_{\bar{x}} = \pm 3.18087$ $\Delta\bar{x} \pm 7.79314$ $\text{RSD} = \pm 1.7$ % $\epsilon = \pm 1.57$ % $\delta^{[b]} = -1.35$ %
	491.7	98.3	
	495.3	99.1	
	505.8	101.2	
	498.1	99.6	
	506.6	101.3	
	482.2	96.4	

Note: [a] The Oxa content indicated in the quality certificate (m);
[b] $\delta = \bar{x} - \mu \times 100 \% \times \mu^{-1}$

Table 2. Results of the quantitative determination of oxacillin by redox titration in the Oxa drug by the reaction with Potassium hydrogen peroxomonosulfate ($P = 0.95$, $n = 7$)

Oxacillin taken, mg	Found		Results of processing statistical data
	mg	%	
503.1 ^[a]	498.5	99.7	$\bar{x} = 500.1$ (100.02 %) $S = \pm 1.43228$ $S_{\bar{x}} = \pm 0.54135$ $\Delta\bar{x} \pm 1.32631$ $\text{RSD} = \pm 0.29$ % $\epsilon = \pm 0.27$ % $\delta^{[b]} = -0.60$ %
	501.2	100.2	
	499.3	99.9	
	502.1	100.4	
	499.6	99.9	
	501.4	100.3	
	498.7	99.7	

Note: [a] The Oxa content indicated in the quality certificate;
[b] $\delta = \bar{x} - \mu \times 100 \% \times \mu^{-1}$

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

$$X = \frac{0.02 \cdot K \cdot 423.43 \cdot (V - V_0) \cdot 100 \cdot 100 \%}{2 \cdot 1000 \cdot m_s \cdot (100 - w_{H_2O})}$$

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;

423.43 – is the molar mass of oxacillin (anhydrous), $g \cdot mol^{-1}$;

K – is the correction coefficient for the concentration of sodium thiosulfate solution to $0.0200 \text{ mol L}^{-1}$;

m_s – is the weighed portions of Oxa, g.

The results of the analysis of the Oxa drug by redox titration are shown in Table 2. The relative standard deviation did not exceed 0.3 % ($\delta = -0.60 \%$).

■ Conclusions

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

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