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Iodometric determination of quinine sulfate in tablets using N-oxidation with diperoxysebacic acid

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Abstract

Using diperoxysebacic acid as an example, it was shown the interaction of diperoxycarboxylic acids with quinine alkaloid in an aqueous medium by kinetics method. The reaction proceeds quantitatively by the mechanism of nucleophilic substitution of β-peroxide oxygen atom in diperoxycarboxylic acid with the formation of the corresponding N-oxide, and the kinetics of the process is a subject to general rules of specific acid-base catalysis. New iodometric methods were developed, and the possibility of quinine sulfate quantification in pure form 'Quinine sulfate', as well as in the combined dosage form 'Limpar® N 200 mg' (Cassella Med GmbH, Germany) and in 'Quinine sulfate 200 mg Tablets' (Accord Healthcare Ltd, UK) by the reaction of oxidation with diperoxycarboxylic acid. They are characterized by high selectivity, and rate, simplicity of performing, and good accuracy. No toxic reagents or special conditions required. RSD ≤1.6% (δ =+0.40..+0.72%), LOQ=0.01 mg.

Keywords: Diperoxysebacic acid; Iodometric titrimetry; Quinine; Quinine-N-oxide

1. Introduction

Quinine is the main alkaloid of cinchona tree bark with antimalarial, antipyretic, analgesic, anti-inflammatory and anticancer effects [1], as well as anti-SARS-CoV-2 activity [2]. *L*-stereoisomer of quinidine is characterized by a bitter taste. Quinine contains a quinoline group with a methoxy side chain, attached through a secondary alcohol linkage to a vinyl quinuclidine ring [3]. The chemical description of the sulfate salt form is (8",9R)-6'-methoxycinchonan-9-ol sulfate dihydrate (2:1) (salt) [4], with the molecular formula $(C_{20}H_{24}N_2O_2)_2{\cdot}H_2SO_4{\cdot}2H_2O$ (molar mass is 783.0 g/mol, melting point is approximately 225 ◦ C) [5]. The structure of quinine sulfate is given in Figure 1.

Quinine was the first an antimalarial drug, which continues to be effectively used in critical situations of tropical malaria, especially given the rapid emergence of malaria plasmodia (*Plasmodium falciparum*) resistance to most of the newest medications [6-8]. Quinine is also a component of some soft drinks, in particular, non-alcoholic soda drink – tonic (or Indian tonic water) [9]. Quinine is a diprotic weak base. It possesses pKa values of 8.5 (quinuclidinyl group) and 4.1 (quinolone group) at 20 ◦ C. Its solubility is 1:810 in water (or 1:32 in boiling water) and 1:120 in ethanol; slightly soluble in chloroform and ether; readily soluble in a 2:1 mixture of chloroform and dehydrated alcohol [10, 11]. Pharmaceutical form is powder, tablets of quinine sulfate, 0.25 and 0.5 g. Since Quinine has a strong antiarrhythmic activity, it is effective in various types of arrhythmia, but relatively often causes side effects. However, in a number of cases, when other antiarrhythmic agents are insufficient, and it is safe with the correct dosage, the substance is useful.

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It belongs to class IA antiarrhythmics. It is also used for the treatment and prevention of nocturnal leg cramps in adults and elderly [12-14].

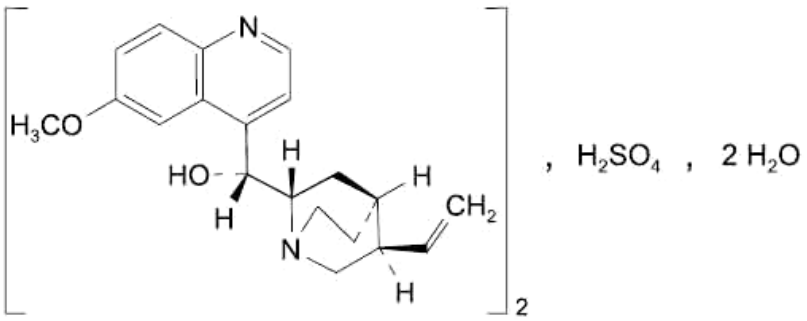

Figure 1 Chemical structure of quinine sulfate

Quantitative determination of individual quinine salts is carried out by gravimetry of the base isolated from the salt solution after adding sodium hydroxide. This free base is extracted by chloroform (distille off after), dried and weighed [11].

A simple non-aqueous titration method has been devised for determining the sulphates of quinine and quinidine. The sulphate is precipitated by addition of excess of barium perchlorate solution in acetic and the liberated alkaloid is then titrated in 1:2 anhydrous acetic-dioxan mixture, with an acetic acid solution of perchloric acid. The end-point is determined either visually with crystal violet as indicator or potentiometrically with a glass-Ag/AgCl combination electrode. The method is accurate, precise and suitable for routine analysis of pure materials and tablets [15].

Quantitative analysis of quinine sulfate in tablets is recommended to be performed by acidimetry in a non-aqueous medium: aliquots of 20 tablets crushed to powder, equivalent to 100 mg of quinine sulfate, gently stirred for 15 min in 40 ml of acetic anhydride R and 40 ml of anhydrous acetic acid, and titrated with perchloric acid (0.1 mol/l) using crystal violet as indicator (from violet to blue and apple green). Each milliliter of perchloric acid (0.1 mol/l) is equivalent to 26.10 mg of quinine sulfate [$(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$]. The amount of quinine sulfate should be not less than 90.0% and not more than 110.0% [16].

For quantification of the active ingredient in the substance of quinine sulfate, the European Pharmacopoeia suggests using acidimetry in non-aqueous medium with the determination of the endpoint by the potentiometry method: 0.300 g of the substance is dissolved in a mixture of 10 ml of chloroform and 20 ml of acetic anhydride. Titrate with 0.1 M perchloric acid solution. The end-point is determined by potentiometric method [17].

For the determination of quinine sulfate in tablets, the British Pharmacopoeia proposes acidimetry in non-aqueous medium with visual determination of the endpoint. Weigh and crush to powder 20 tablets and dissolve as completely as possible, using heat, a quantity of the powdered tablets containing 0.4 g of quinine sulphate in 40 ml of acetic anhydride. Carry out Method I for titration in non-aqueous medium, using crystal violet as indicator. Each ml of 0.1M perchloric acid VS is equivalent to 26.10 mg of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ [18]. Content of quinine sulphate, $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ should be 95.0 to 105.0% of the stated amount.

Quantitative determination of quinine using bromatometry is based on the bromination of vinyl radical in the quinuclidine fragment [19]. The International Pharmacopoeia regulates the simultaneous determination of quinine forms by two methods: acid-base titration in a non-aqueous medium and bromatometry. The first method determines quinine in total with a possible impurity - dihydroquinine (it has a limiting ethyl radical in the quinuclidine fragment), and the second one determines quinine only. The difference in the results obtained by the two methods shows the content of the dihydroquinine impurity in the preparation [20].

For the analysis of quinine sulfate tablets, the US Pharmacopoeia recommends using of high performance liquid chromatography with UV detection [21].

To date, there are various methods for the quantitative determination of quinine, not only in pharmaceutical forms, but also in food products and biological fluids [22-24]. Many works describe determination of quinine by electrophoretic method [25-27].

Also, there are works about determination of quinine in soft drinks by voltammetry [28, 29].

Most publications are devoted to chromatographic methods for the determination of quinine with various detection methods [30-33]. A method for the determination of quinine in beverages by combining online capillary isotachophoresis with capillary zone electrophoresis with UV spectrophotometric detection is described [34].

The most popular method for determining quinine in beverages is fluorimetry [35-37]. These techniques are highly sensitive and widely used. The main disadvantage is relatively high cost of instrumentation and rather complicated sample preparation.

In general, analytical methods for the quantitative determination of quinine sulfate are not entirely perfect: they require a lot of time for sample preparation, using of relatively expensive instruments, and toxic solvents, which violates the basic principles of "green chemistry".

The quality of these drugs must be routinely monitored and assured with simple, sensitive, and accurate methods. Redox titrimetry can be a useful alternative to many of the above relatively complex methods due to its cost-effectiveness, simplicity, sufficient sensitivity, exceptional accuracy, and wide applicability.

The aim of the work was to study the kinetics and mechanism, as well as to determine the stoichiometry of the oxidation reaction of quinine with diperoxysebacic acid, as well as to develop method for the analysis of the active ingredient and tablet dosage forms of quinine sulfate by iodometry in accordance with the oxidant consumption.

2. Experimental Method

Quinine powder (used as a standard) was obtained from Chemsavers, Inc. (USA).

Quinine sulfate dihydrate; **CAS:** 6119-70-6 Molecular formula $C_{40}H_{48}N_4O_4 \cdot H_2SO_4 \cdot 2H_2O$; Melting Point (°C) 233–235. Molecular weight 782.96 g· mol^{-1}. *Certificate of Analysis*: Assay (anhydrous base) 99.7% (titration with $HClO_4$). Water 4.11 % (K.F.); Specific optical rotation -242.1° (20°C, 589 nm) (*c*=2, 0.1N HCl) (on anhydrous base).

Limpar® N 200 mg Cassella Med GmbH, Köln, Germany Filmtablets 7 tablets, PS: 04150154062167; SN: 5GMRY8FFV51P, Ch.-B.: 191708. 1 film-coated tablet contains 200 mg of quinine sulfate (Ph.Eur.), which is equivalent to 165.7 mg of quinine.

Other ingredients: gelatin, magnesium stearate (Ph.Eur.), microcrystalline cellulose, colloidal anhydrous silicon dioxide, carmellose sodium, talc, poly [butyl methacrylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate] (1:2:1), refined castor oil.

Pharmaceutical form. Quinine sulfate 200 mg Film-coated 28 tablet tablets. Accord Healthcare Ltd, UK; PC: 05012617009982; lot: EHYPRWTE9Z1Y; ID 1542311000001109

Quinine sulfate tablets contain the active ingredient quinine sulfate (200 mg); excipients: sodium lauryl sulfate, povidone, microcrystalline cellulose (E460), croscarmellose sodium, magnesium stearate, hydrogenated vegetable oil. The coating contains hypromellose, hydroxypropyl cellulose, medium chain triglycerides, macrogol 3350, titanium dioxide (E171).

Only analytical grade chemicals were used for all analyses.

The maintenance of the required acidity of the medium (pH of the solution) was kept by buffer solutions based on borax, as well as KH_2PO4 and K_2HPO4 in accordance with Green Chemistry [38].

Phosphate buffer, pH 8.3: 7.8 ml of a 0.1 $mol \cdot l^{-1}$ solution of hydrochloric acid was added to 250.0 ml of a 0.2 $mol \cdot l^{-1}$ solution of disodium phosphate.

Excipients presented in quinine sulfate solid pharmaceutical form for oral use, with a permission for sale in Germany and the United Kingdom, as well as the minimum and maximum amount of this auxiliary substance present in a dosage unit of solid medicinal products for oral use are given in table. 1.

Table 1 Excipients presented in Quinine Sulfate IR Solid Oral Drug Products with a Marketing Authorization (MA)† in Germany (DE) [39], United Kingdom (UK) [40] and the minimum and maximum amount of those excipients per one dosage unit in solid oral drug products with a MA

Excipient	**Medicinal Products Containing an Excipient with an MA Granted by the Named Country**	**Range Present in Solid Oral Dosage Forms with a MA in the US (mg)**
Carmellose sodium DE(1), 2.2–160	Carmellose sodium DE(1), 2.2–160	Carmellose sodium DE(1), 2.2–160
Cellulose, microcrystalline DE(1), UK(2) 4.6–1385a	Cellulose, microcrystalline DE(1), UK(2) 4.6–1385a	Cellulose, microcrystalline DE(1), UK(2) 4.6–1385a
Croscarmellose sodium UK(2) 2–180	Croscarmellose sodium UK(2) 2–180	Croscarmellose sodium UK(2) 2–180
Gelatin DE(1) 1–756a	Gelatin DE(1) 1–756a	Gelatin DE(1) 1–756a
Lactose UK(2) 23–1020a	Lactose UK(2) 23–1020a	Lactose UK(2) 23–1020a
Magnesium stearate DE(1), UK(2) 0.15–401a	Magnesium stearate DE(1), UK(2) 0.15–401a	Magnesium stearate DE(1), UK(2) 0.15–401a
Povidone UK(2) 0.17–80	Povidone UK(2) 0.17–80	Povidone UK(2) 0.17–80
Silica DE(1) 0.50–100	Silica DE(1) 0.50–100	Silica DE(1) 0.50–100
Sodium laurilsulfate UK(2) 0.65–52	Sodium laurilsulfate UK(2) 0.65–52	Sodium laurilsulfate UK(2) 0.65–52
Sodium starch glycolate UK(2) 2–876a	Sodium starch glycolate UK(2) 2–876a	Sodium starch glycolate UK(2) 2–876a
Starch UK(2), 0.44–1135a	Starch UK(2), 0.44–1135a	Starch UK(2) 0.44–1135a
Talc DE (1) 0.10–220a	Talc DE (1) 0.10–220a	Talc DE (1) 0.10–220a
Vegetable oil, hydrogenated UK(2) 2–261	Vegetable oil, hydrogenated UK(2) 2–261	Vegetable oil, hydrogenated UK(2) 2–261

(1) Limptar *R*® N Filmtabletten 200mg; (2) Quinine Sulfate Tablets 200mg (Accord Healthcare Ltd); † The approval of a drug product by the local regulatory authority. Also the terms drug approval and registration are used.; ‡ FDA's inactive ingredient database, http://www.fda.gov/Drugs/InformationOnDrugs/ucm113978.htm (version date 31-12-2010).; a The upper range value reported is unusually high for solid oral dosage forms and the authors doubt its correctness.

Diperoxysebacic acid was prepared by the reaction with excess 50% H_2O_2 and the corresponding dicarboxylic acid in sulfuric acid as described by Swern [41]. The content of the basic substance in the products in accordance with iodometric titration was 96-98%.

Diperoxysebacic acid (diperoxydecanedioic acid, DPSA), chemical structure: $HO_3C(CH_2)_8CO_3H$, melting point, 96°C (dec.). The active oxygen content (AOC), % (Theor.) 13.5 (13.7), molar mass is 234.1 g·mol^{-1}). pK_{H2An} = 7.68; pK_{HAn^-}= 8.35 [42].

2.1. Preparation of a solution of DPSA with a concentration of 0.02 mol·l^{-1}.

A sample of about 0.2 g of DPSA powder is dissolved in 10-15 ml of ethanol and the volume is brought up to 100 ml with distilled water. The exact content is determined by the method of iodometric titration [43].

$(CH_2)_8(CO_3H)_2 + 4KI + 4HCl = 2I_2 + 2(CH_2)_8(CO_2H)_2 + 4KCl + 2H_2O$

$2I_2 + 4Na_2S_2O_3 = 2Na_2S_4O_6 + 4NaI$

Kinetic measurements. All kinetic measurements were conducted at 293±0.2 K. The reaction of alkaloid quinine sulfate with DPSA was conducted in oxygen-free buffer solution by observing the decrease in DPSA concentration by iodometric titration under the conditions of [DPSA]>[Quinine].

The volume of titrant solution was measured to within ± 0,01 ml using microburette. pH measurements were made using a pH/mv meter Model «Ionometer I-130» equipped with a standardized glass electrode EGL-43-07 at 293 K.

2.2. Synthesis and identification of the reaction product of quinine with DPSA

Using equimolar solutions of DPSA and quinine sulfate in 25 ml of 0.2 mol·l^{-1} phosphate buffer (pH 8.3) and 5 ml ethanol at 30°C, reaction gave quinine *N*-oxide after 20 min. The reaction mixture was diluted in 25 ml of 0.1 mol·l^{-1} sodium hydroxide solution and then extracted 3 times with 30 ml of $CHCl_3$. The organic phase was collected and dried over Na_2SO_4. The residue was then rotary evaporated to obtain yellow foamy oil. After purification, a thick yellow product was obtained (M.p.133-134˚C). The pure product was identified by chromatographic and spectroscopic methods.

Thin layer chromatography using a mixture of methanol-acetone (1:1) as the mobile phase and silica gel Merck plate showed a single spot of the product with a lower R_f (R_f value = 0.3) compared to quinine (R_f value = 0.5).

Spectrometer Specord M40 VEB (Carl Zeiss Jena), Specord M 80 Spectrometer (Carl Zeiss Jena) and Bruker AVANCE500 spectrometer which operated at range 500 MHz (^{1}H).

The result of the UV-Vis spectrum showed two main peaks at wavelength 235 nm and 334 nm.

IR-spectrum (KBr): 3288 (hydroxy group), 3078 (aromatic C-H), 2962 (aliphatic C-H), 1662 (unconjugated alkene), 1508 (ether group), 1469, 1436, 1363, 1305, 1238 (N-O), 1138, 1109, 1074, 1024, 993, 927, 864, 833, 810, 781, 725, 638, 547, 530, 466 cm^{-1}.

^{1}H-NMR -spectrum 500 MHz, $CDCl_3$): 3.21 (1H; ddd; J= 3.1; 6.6; 12.7), 3.72 (1H; dd; J= 11.0; 12.7) , 2.96 (1H; m, 1.95 (1H; m, 2.03 (1H; m), 2.39 (1H; m), 3.43 (1H; m), 4.17 (1H; m, 1.71 (1H; m), 2.43 (1H; m), 3.46 (1H; dd, J= 5.5; 11.0, 6.23 (1H; br s), 5.79 (1H; ddd; J= 7.0; 10.3; 17.2), 5.02 (1H; dd; J= 0.9; 10.3), 5.08 (1H;dd; J= 0.9; 17.2), 8.68 (1H; d; J= 4.6, 7.78 (1H; d; J= 4.6), 7.83 (1H; d; J= 2.7), 7.40 (1H; dd; J= 2.7; 9.2), 7.93 (1H; d; J= 9.2), 3.94 (3H; br s).

3. Results and Discussion

A plot of $\log_{10} C_t/ [C_{Am} - 2(C_0 - C_t)]$ on time is kept linear up to 100% conversion, that shown to second kinetic order of reaction and practical absence of influence of the formed products on her velocity (Fig. 2).

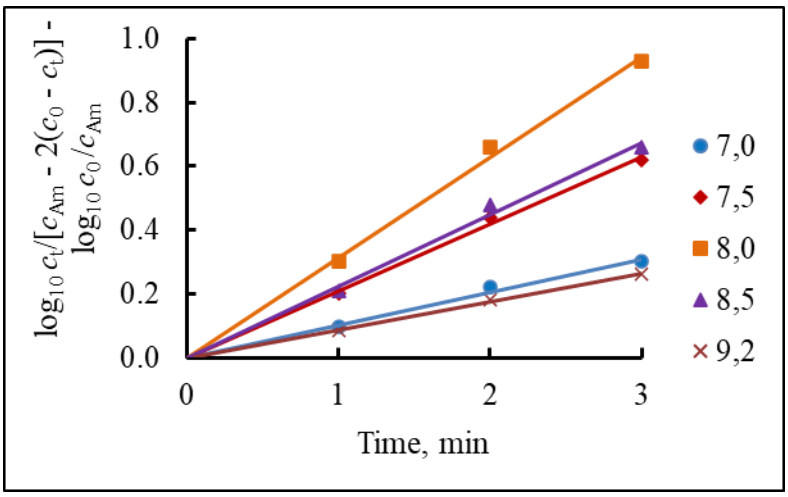

Figure 2 Semi-logarithmic plots of $\log_{10} c_t/ [c_{(Am)} - 2(c_0 - c_t)] - \log_{10} c_0/c_{(Am)}$ vs. time *N*-oxidation of quinine by DPSA for different pH. *c*(Am)=1.0·10^{-3} mol L^{-1}; *c*(DPSA)=1.5·10^{-3} mol·l^{-1}. pH 7.0–9.2.

Dependence of the apparent second-order rate constants on pH has form of curves with maximum, corresponding to the values of p*Ka* salt form of alkaloid and indicate the ionic nature of the reaction (Fig. 3 «*a*»).

Based on the hypothesis that the transitional state of reactions involves a undissociated form of acid (H_2An), its monoanion (HAn^-) and base form of quinine (tertiary amine) (Am), the kinetic equation that establishes a connection between by the apparent rate constant k_{obs} and the second-order rate constant, K was obtained:

$k_{obs} = K \cdot \alpha_{Am} (\alpha_{H2An} + \alpha_{HAn^-})$,

where, α_{Am} is molar fraction of alkaloid base, $(\alpha_{H2An} + \alpha_{HAn^-})$ is sum of molar fractions of protonated form of diperoxycarboxylic and its mono anion (HAn^-) particles.

Molar fractions that correspond to acid-base forms at different concentrations of H^+ ions were calculated by known formulas:

$\alpha_{Am} = K_a / \{(K_a + [H^+]\}$;

$\alpha_{H2An} = [H^+]^2 / \{[H^+]^2 + K_{H2An} \cdot [H^+] + K_{H2An} \cdot K_{HAn^-}\}$;

$\alpha_{HAn^-} = K_{H2An} \cdot [H^+] / \{[H^+]^2 + K_{H2An} \cdot [H^+] + K_{H2An} \cdot K_{HAn^-}\}$,

where K_a is dissociation constant of acid of salt forms of alkaloid;

K_{H2An} is dissociation constant protonated form diperoxycarboxylic acid;

K_{HAn^-} is constant of acid dissociation of acid salt (of monoanion) diperoxycarboxylic acid.

Obtained plots well agree with the experimental results. k_{obs} was a linear function vs. the product of molar fractions α_{Am} $(\alpha_{H2An} + \alpha_{HAn^-})$ in the pH range studied (r=0.985), which confirms the adequacy of the proposed above equation experimentally obtained dependence (Fig. 3 «*b*»).

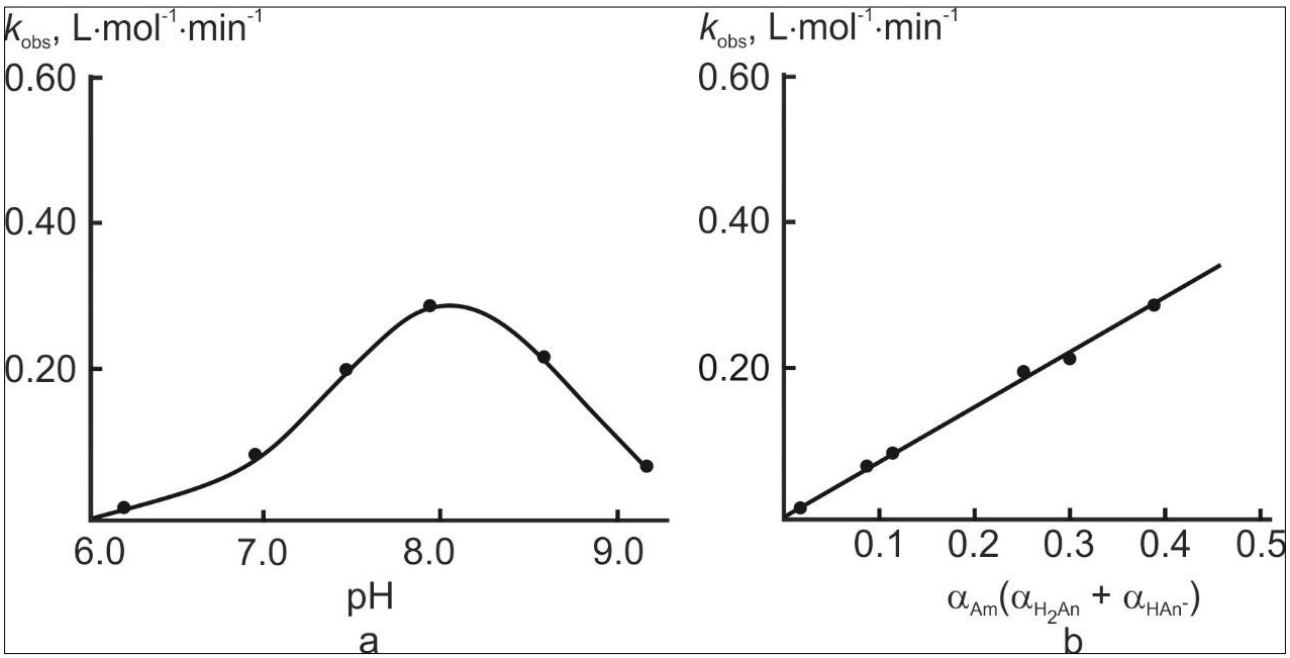

Figure 3 The apparent second-order rate constant for the *N*-oxidation of quinine by DPSA as a function of pH (*a*) and vs. $\alpha_{Am} \cdot (\alpha_{H2An} + \alpha_{HAn^-})$ (*b*): $C_{Am} = 1.0 \cdot 10^{-3}$ mol L^{-1}; *c*(DPSA) = $1{,}5 \cdot 10^{-3}$ mol·l^{-1}. 293 K

All spectroscopic data, including UV-Vis, IR and ^{1}H-NMR and comparation data with literature revealed that the product is quinine-*N*-oxide [44].

The product was identified by TLC: a single spot was detected from the product which has a lower R_f (R_f value = 0.3±0.05) than that of the quinine (R_f value = 0.5±0.04). This indicates that a more polar product had been synthesized. Furthermore, the melting point of the product was 133-134˚C corresponding to quinine-*N*-oxide [46].

The result of the UV-Vis spectrum showed two main peaks at wavelength 235 nm and 334 nm. These are specific for an aromatic resonance of quinoline and forbidden transition of a lone pair of electrons of tertiary Nitrogen.

The IR spectrum identifies a nitrogen oxide stretch at the wave number of 1238 cm^{-1}. The rest signals corresponded to unconjugated alkene (1622 cm^{-1}), hydroxyl group (3200-3300 cm^{-1}), aromatic C-H (3078 cm^{-1}), aliphatic C-H (2962 cm^{-1}) and ether group (1508 cm^{-1}) were observed.

The NMR data also exhibited typical structural units that could be identified as the units of quinine-*N*-oxide. Five aromatic signals appeared at 7.39, 7.78, 7.92, 7.83 and 8.67 ppm are signals for quinoline ring unit. Vinyl group signals appeared at 5.02 ppm and 5.08 ppm for geminal proton and 5.81 ppm for methyne proton. This methyne signal was multiplet due to cis and trans coupling from its two-proton neighbor. There were four deshielding methylene signals, 3.21; 3.45; 3.72 and 4.15 ppm that showed inductive effect from Oxygen. This indicates that quinine was oxidized at the tertiary Nitrogen of quinuclidine ring.

Based on the obtained results, the process of *N*-oxidation of quinine by means of DPSA can be represented by the scheme (Fig. 4):

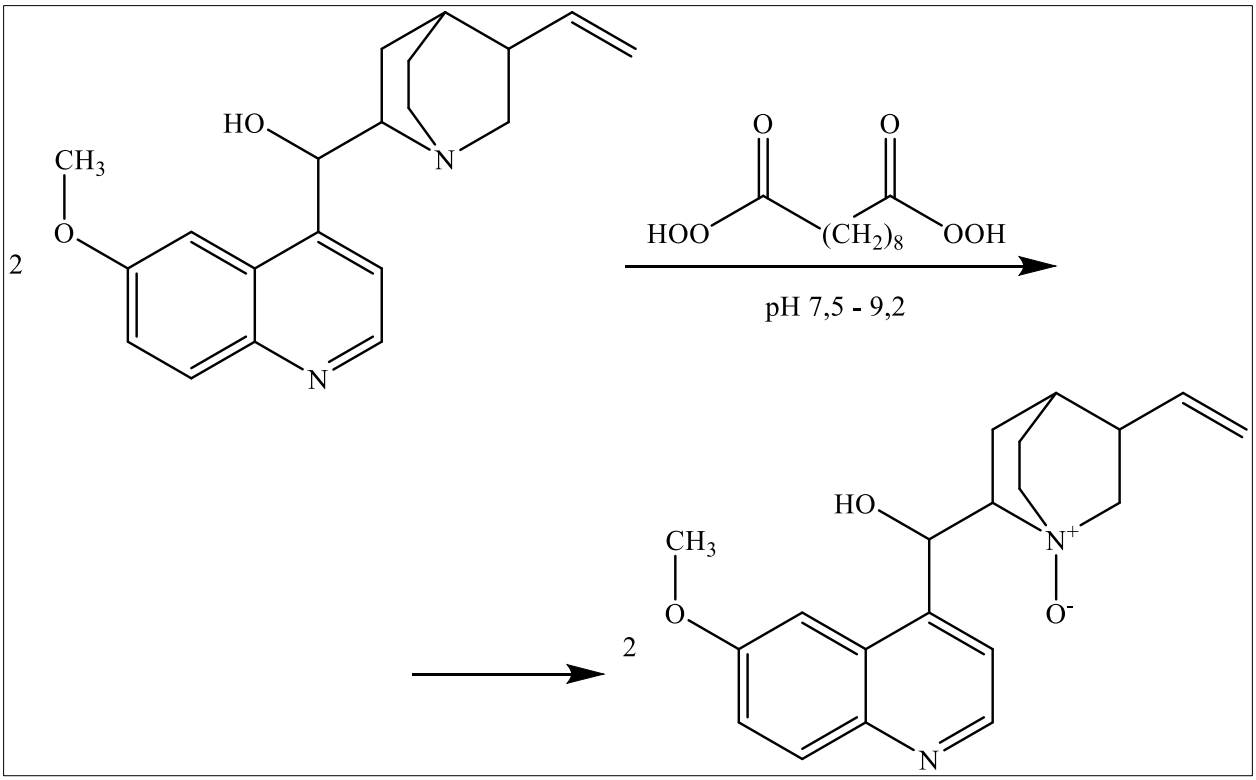

Figure 4 Scheme of the process of *N*-oxidation of quinine by DPSA

3.1. Quantitative determination of the content of the main substance in the quinine sulfate substance.

3.1.1. Analysis procedure

Preparation for analysis — accurately weighed portion of the powder, approximately 200 mg of quinine sulfate substance, quantitatively transfer the volumetric flask to 100 ml, add 80 ml of methanol and shake the flask mechanically until complete dissolution. Dilute to the mark with methanol.

Transfer 10.0 ml of the filtrate to a 100-ml volumetric flask, 10.0 ml of a 0.02 mol·l^{-1} solution of DPSA, and 50 ml of phosphate buffer solution with pH 8.3 were sequentially added and the volume was diluted to 100.00 ml with distilled water and thoroughly mixed. After 10 minutes, 20.0 ml of the solution was taken, transferred to a conical flask for titration, 5 ml of 0.02 mol·l^{-1} sulfuric acid solution and 2 ml of 5% potassium iodide solution were added. The released iodine was titrated by 0.02 mol·l^{-1} sodium thiosulfate solution. A control experiment was conducted in parallel (in the absence of tested sample solution). The content of the main substance in the substance of quinine sulfate in terms of anhydrous substance W, %, was calculated according to the formula:

$$W = \frac{(V_0 - V_1)\cdot K\cdot T\cdot 5\cdot 10\cdot 100\cdot 100\%}{g\cdot(100 - w_{H2O})}$$

where, V_0 is volume of standard 0.02 mol·l^{-1} sodium thiosulfate solution used for titration in the control experiment, ml; V_1 is volume of standard 0.02 mol·l^{-1} sodium thiosulfate solution used for titration in the working experiment, ml; K is concentration correction coefficient of the standard solution of sodium thiosulfate to 0.0200 mol·l^{-1}; 10, 5 are dilution coefficients; w_{H2O} is water content determined by the Karl Fischer method, %; T is quantity of quinine sulfate corresponding to 1.00 ml of standard 0.0200 mol·l^{-1} sodium thiosulfate solution, g·ml^{-1};1.00 ml of a standard 0.0200 mol·l^{-1} sodium thiosulfate solution corresponds to 0.00373465 g of quinine sulfate ($C_{40}H_{48}N_4O_4\cdot H_2SO_4$).

3.1.2. Analysis of tablets

Assay preparation— Weigh and finely powder not less than 20 tablets. Transfer an accurately weighed portion of the powder, equivalent to about 200 mg of quinine sulfate, to a 100 ml volumetric flask, add 80 ml of methanol, and shake the flask by mechanical means for 30 minutes. Dilute with methanol to volume, and filter, discarding the first 10 ml of the filtrate.

Transfer 10.0 ml of the filtrate to a 100 ml volumetric flask, 10.0 ml of a 0.02 mol·l^{-1} solution of DPSA, and 50 ml of phosphate buffer solution with pH 8.3 were sequentially added and the volume was diluted to 100.00 ml with distilled water and thoroughly mixed. After 10 minutes, 20.0 ml of the solution was taken, transferred to a conical flask for titration, 5 ml of 0.02 mol·l^{-1} sulfuric acid solution and 2 ml of 5% potassium iodide solution were added. The released iodine was titrated by 0.02 mol·l^{-1} sodium thiosulfate solution. A control experiment was conducted in parallel (in the absence of tablet solution). The content of quinine sulfate in tablets X, in g, was calculated by the formula:

$$X = \frac{(V_0 - V_1)\cdot K\cdot T\cdot 5\cdot 10\cdot \bar{m}}{g}$$

where, V_0 is volume of standard 0.02 mol·l^{-1} sodium thiosulfate solution used for titration in the control experiment, ml; V_1 is volume of standard 0.02 mol·l^{-1} sodium thiosulfate solution used for titration in the working experiment, ml; K is concentration correction coefficient of the standard solution of sodium thiosulfate to 0.0200 mol·l^{-1}; 10, 5 are dilution coefficients; $\bar{m}$ is average weight of the tablet; g is weight of the powder of crushed tablets, g; T is quantity of quinine sulfate corresponding to 1.00 ml of standard 0.0200 mol·l^{-1} sodium thiosulfate solution, g/ml; 1.00 ml of a standard 0.0200 mol·l^{-1} sodium thiosulfate solution corresponds to 0.0039148 g of quinine sulfate $(C_{40}H_{48}N_4O_4)_2\cdot H_2SO_4\cdot 2H_2O$) which is equivalent 0.0032425 g of quinine base $(C_{20}H_{24}N_2O_2)_2$.

Quinine sulfate tablets contain amounts of quinine sulfate and dihydroquinine sulfate totaling not less than 90.0 percent and not more than 110.0 percent of the labeled amount of quinine sulfate, calculated as $(C_{20}H_{24}N_2O_2)_2\cdot H_2SO_4\cdot 2H_2O$.

It was established in separate experiments the excipients from the tablets (see Tabl. 1) do not affect the stoichiometry of the analytical reaction. It was proved by the results of the analysis of tablets containing several different ingredients. The results of the determination of quinine sulfate in the pure substance and "Quinine sulfate 200 mg" tablets are presented in Table 2.

Table 2 The results of the determination of the content of quinine in the substance of quinine sulfate and in the tablets quinine sulfate 0.2 g

Taken for analysis	**Found content**	**Characteristics of statistical processing of results**
0.2005 g (99.7%*) Substance of quinine sulfate	%	P=0,95
	100.09 99.65 99.90 97.95 100.81	$\bar{x} \pm \Delta\bar{x}$ = 99.68±1.32% *S* = 1.059; *RSD* = 1.06% (δ = – 0.02%)
0.2812 g (Quinine sulfate 0.2051 g)* Limpar® N 200 mg Cassella Med GmbH, Köln, Germany; lot: 5GMRY8FFV51P	g/tablet	(*P*=0.95)
	Quinine sulfate 0.2081 0.2102 0.2014 0.2072 0.2086	$\bar{x} \pm \Delta\bar{x}$ = 0.2066±0.004 g *S* = 0.0033; *RSD* = 1.59%; δ** = +0.72%
0.2980 g (Quinine sulfate 0.2060 g)* Quinine sulfate 200mg Accord Healthcare Ltd, UK; lot: EHYPRWTE9Z1Y	Quinine sulfate 0.2100 0.2071 0.2012 0.2086 0.2072	$\bar{x} \pm \Delta\bar{x}$ = 0.2068±0.004 g *S* = 0.0033; *RSD* = 1.62%; δ** = +0,40%

* The amount of quinine sulfate, calculated as $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ is specified in the Certificate of Analysis (μ). ** $\delta = (\bar{x} - \mu)\ 100\%/\ \mu$.

They testify that the newly developed methods make it possible to quantitatively determine the content of the main substance in the quinine sulfate substance with RSD = 1.06 (δ = +0.57). In the analysis of "Quinine sulfate 200 mg" tablets RSD = 1.6% (δ = +0.4…+0.7). Since δ < RSD, it can be concluded that the results are correct. The limit of quantification (LOQ) for both substances is 0.01 mg.

4. Conclusion

By kinetic method and on example of DPSA, it has been shown that interaction of diperoxycarboxylic acids with *quinine* in aqueous medium takes place quantitatively by nucleophilic substitution mechanism at *β*-peroxide atom of diperoxyacid oxygen with the formation of corresponding *N*-oxide, while reaction kinetics agrees with laws of specific acid-base catalysis. It was developed analytical techniques and it was demonstrated possibility of analyzing the active ingredient in pure form and tablets of quinine sulfate by the method of back iodometric titration. They are characterized by sufficiently high selectivity, rate and simplicity of performing and good accuracy. No toxic reagents or special conditions required. RSD ≤1.6% (δ =+0.40..+0.72%), LOQ=0.01 mg.

Compliance with ethical standards

Disclosure of conflict of interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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