Chemical Papers
https://doi.org/10.1007/s11696-023-02908-y

ORIGINAL PAPER

Titrimetric determination of Hydroxyzine using Oxone

Ivan Iurchenko[1] · Mykola Blazheyevskiy[2] · Vitaliy Yaremenko[2] · Valeriy Moroz[2] · Oleg Kryskiv[2]

Received: 9 March 2023 / Accepted: 31 May 2023

Abstract

The kinetics of the oxidation reaction of Hydroxyzine hydrochloride with potassium peroxymonosulfate was studied depending on the pH of the medium. It was established for the first time that the kinetics of the reaction of *N*-oxidation of Hydroxyzine obeyed the general laws of the mechanism of specific acid–base catalysis, proceeded quantitatively and stoichiometrically according to the mechanism of nucleophilic substitution of the *β*-oxygen atom of the peroxyacid group of peroxymonosulfate ions. It was shown that quantitative oxidation was achieved in 1–1.5 min at pH 8.0–8.5. The only reaction product was Hydroxyzine *N*-oxide. A scheme of the oxidation process was proposed. Techniques were developed and the possibility of quantitative determination of Hydroxyzine hydrochloride in the substance and tablets of 25 mg by iodometry using Oxone as an analytical reagent was shown. A known excess of reagent was added, and after a predetermined time, the residual reagent was determined iodometrically. RSD ≤ 1.52%. $(\overline{x} - \mu) \cdot 100/\mu < \text{RSD}$. The procedures had several advantages such as speed, simplicity, accuracy, selectivity, and cost-effectiveness, and therefore could be easily adapted by quality control laboratories for routine analysis.

Keywords Acid–base catalysis · Hydroxyzine hydrochloride · Iodometry · *N*-oxidation · Oxone · Quality control

Introduction

Hydroxyzine hydrochloride or Hydroxyzine dihydrochloride (HDH) [2192-20-3], chemically known as (RS)-2-{2-[4-(p-chlorophenylbenzyl)piperazin-1-yl]ethoxy}ethanol dihydrochloride (Fig. 1), is the first-generation antihistamine of the piperazine class that is an H1 receptor antagonist, that exhibits its sedative, anxiolytic, and antiemetic properties (Altamura et al. 2013; Sawantdesai et al. 2016).

Substance of Hydroxyzine hydrochloride is monographed in the Pharmacopoeia [Ph Eur. European Pharmacopoeia 10th Ed 2020), BP 2020 (British Pharmacopoeia Commission 2020), USP 2019 (United States Pharmacopoeia 43 National Formulary 38 2019)]. The pharmacopeial method is based on the potentiometric titration of HDH in non-aqueous medium using perchloric acid (British Pharmacopoeia Commission). The official USP method which is also available for the assay of the drug in tablets employs a chromatographic system equipped with a UV detection, where HDH can be detected at 232 nm (United States Pharmacopoeia 43 National Formulary 38 2019).

Determination of HDH in pharmaceutical preparations is important for pharmaceutical needs, and hence it is crucial to develop simple, sensitive, selective, and cost-effective methods for its determination as apart of compliance of specifications study: specimen quantity, sample homogeneity, and content uniformity in tablets.

Different methods have been used for the determination of the antihistaminic drug HDH including HPLC (Sher et al. 2014), GC (Kintz et al. 1990), spectrophotometry (Rajendraprasad et al. 2011), potentiometry (Anwar 2012), voltammetry (Beltagi et al. 2008), capillary zone electrophoresis using chiral selectors (Saeed and Ali 2011), and titrimetry (Basavaiah and Charan 2002). So, a titrimetric assay of some antihistamines through the determination of the chloride of their hydrochlorides has been reported. The chloride content of the drug is determined by titration with mercury (II) using diphenylcarbazone-BTB as indicator (Basavaiah and Charan 2002). Two simple

✉ Ivan Iurchenko
ivan.iurchenko@umanitoba.ca

[1] College of Pharmacy, University of Manitoba, Winnipeg, Canada

[2] National University of Pharmacy, Kharkiv, Ukraine

Published online: 16 June 2023

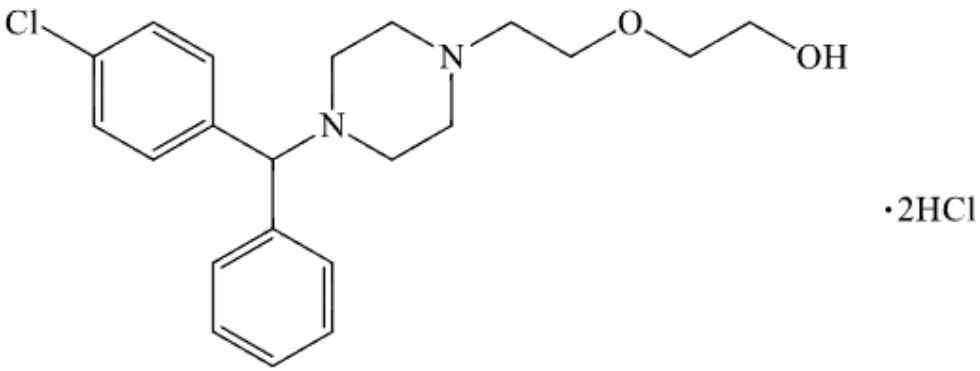

Fig. 1 Chemical formula of Hydroxyzine dihydrochloride

titrimetric methods have been developed for the determination of HDH in pure form and in tablets. The principle of the methods is simple acid–base reactions in which the hydrochloride content of the drug was determined by titrating with an aqueous standardized NaOH solution either visually using phenolphthalein as indicator (method A) or potentiometrically (method B) using glass-calomel electrode system. The methods were applicable over the range of 2–20 mg HDH.

The procedures were also applied for the determination of HDH in its dosage forms and the results were found in good agreement with those obtained by the reference method (Rajendraprasad et al. 2010). Two simple, rapid, reliable, precise, and accurate and cost-effective non-aqueous titrimetric procedures have been developed for the determination of HDH in bulk drug and its pharmaceutical formulations. The methods are based on the titration of the drug in glacial acetic acid in the presence of mercuric acetate with acetous perchloric acid to the visual end point using crystal violet as indicator (Rajendraprasad and Basavaiah 2013).

An inspection of most of the available methods for the above-mentioned drug reveals that most of them are either cumbersome or time-consuming or involve the use of expensive equipment and reagents. On the other hand, titrimetry is the simplest analytical techniques extensively used in the drug standardization laboratories.

Redox titrimetry may serve as useful alternative to many of the aforesaid sophisticated techniques because of their cost-effectiveness, ease of operation, sensitivity, remarkable accuracy and precision, and wide applicability.

The present investigation aims to develop simple, sensitive, and cost-effective method for the determination of HDH in pure form and tablets using redox titrimetric technique. The method involves the use of potassium peroxymonosulfate ($KHSO_5$, PMS) in form Oxone (the triple salt $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) as the titrant.

Experimental

Materials and methods

Chemicals

Hydroxyzine hydrochloride—Sigma-Aldrich, Synonym: Hydroxyzine dihydrochloride. Empirical Formula: $C_{21}H_{27}ClN_2O_2{\cdot}2HCl$. CAS Number: 2192-20-3; Molecular Weight: 447.83 g/mol; Certificate data: 99.6% (purity by perchloric acid titration according to document No. H8885/05/07/08/1).

ATARAX® film-coated tablets 25 mg, No. 25 tablets in a blister, Series of medicinal product No. 313517. Manufacturer USB Pharma S.A., Belgium. Analysis certificate: 98.5%, lot: 313517. *Excipients*: microcrystalline cellulose (Avicel PH102®), colloidal silicon anhydride (Aerosil 200®), magnesium stearate, lactose monohydrate, Opadry® Y-1-7000 (titanium dioxide, hydroxypropyl methylcellulose 2910, macrogol 400).

OXONE®, monopersulfate compound—Sigma-Aldrich; CAS Number: 70693-62-8; Molecular Weight: 307.38 g/mol; % of Active Oxygen (A.O.) = 4.5 (titration by $Na_2S_2O_3$). A stable 2:1:1 ternary compound of this salt, potassium hydrogen sulfate, and potassium sulfate that is available under the trade names Oxone and Caroate is frequently employed as a source of the peroxymonosulfate.

Solution of potassium peroxymonosulfate ($KHSO_5$), 0.04 mol/l

About 1.4 g of $KHSO_5$ powder was dissolved in 70 ml of double-distilled water in a 100-ml volumetric flask, made up to the mark with water and mixed thoroughly. The exact concentration was determined by iodometric titration.

For this 10 ml of the solution was taken with a pipette and transferred into a 100-ml volumetric flask. The volume was brought to the mark with double-distilled distilled water. Then, 10.00 ml of the resulting solution was taken and transferred to a 100 ml conical Erlenmeyer flask, 1 ml of a 0.01 mol l^{-1} H_2SO_4 solution was added and, with vigorous stirring, 2 ml of a 5% KI solution. The released free iodine was immediately titrated with 0.01 mol/l sodium thiosulfate solution. Based on the results of three repeated experiments, the molar concentration of $KHSO_5$ was calculated using the formula:

$$c(\mathrm{KHSO_5}) = V(\mathrm{Na_2S_2O_3}) \times 0.0100 \times 100.00/10.00 \times 10.00 \times 2.$$

Solutions of $c(Na_2S_2O_3, f=1)=0.1$ mol/l of sodium thiosulfate and $c(H_2SO_4)=1$ mol/l of sulfuric acid were prepared from fixanals of the standard titer. A 0.02 mol/l sodium thiosulfate solution was used as a titrant, which was prepared by the appropriate dilution of the original solution with distilled water. To measure the titrant volume with an accuracy of ±0.01 ml, a 10-ml class 2 microburette was used. A 5% solution of potassium iodide was produced by the volume-weight method.

Preparation of 0.2 mol L^{-1} Phosphate buffer solution (pH 8.3) 35.75 g Crystallized disodium hydrogen phosphate dodecahydrate ($Na_2HPO_4 \cdot 12H_2O$) was dissolved in 500 mL flask using double-distilled water. 19 mL of 0.1 M solution of hydrochloric acid solution was added. pH of the final solution was controlled potentiometrically.

Sodium Phosphate dibasic, $Na_2HPO_4 \bullet 12H_2O$, CAS-7558-79-4, produced by «ReaChem», Kharkiv, Ukraine.

Sodium hydroxide solutions were prepared by diluting a previously obtained concentrated (50% w/w) solution with distilled water.

Other chemicals and reagents such as hydrochloric acid and potassium iodide used were of analytical grade from Qualigens. All reagents and solutions were prepared using this distilled water.

The reaction product was identified by reacting a desired quantity of Hydroxyzine with potassium peroxymonosulfate in a sodium bicarbonate solution and allowing the reaction mixture to sit for one hour to complete the reaction. One of the products was extracted with ether, and the organic layer obtained was separated and treated with distilled water. The ether layer was evaporated and dried to get the product.

Methods

Method for the quantitative determination of HDH in model (reference) solutions

An aliquot of 1.00–10.00 ml of a solution containing 2.5–25 mg of HDH was placed with a pipette into a 100 ml Erlenmeyer flask; after that, 1 ml of NaOH (0.02 M), 5.0 ml of 0.2 M buffer solution (pH 8.3), 5.00 ml of $KHSO_5$ (0.008 M) were successively added and left for a certain time (1 min) at room temperature to complete the oxidation of the drug. To lower the pH, 1.0 ml of 1.0 M H_2SO_4 solution and then 2 ml of 5% potassium iodide were added while stirring the contents of the flask. The mixture was again left for about 10 s, and the liberated iodine was titrated with 0.01 M thiosulfate, while 1 ml of 1% starch solution was added near the end point. The whole procedure was also applied in a blank determination on water.

Method for quantitative determination of the content of the main substance in HDH substance

An accurate weight of 0.22392 g of the powder of HDH substance with a known content of the main substance was dissolved in 70 ml of double-distilled water in a 100-ml volumetric flask, diluted with water to the mark and mixed well. A 20.00 ml aliquot of the drug solution was transferred into a 100-ml volumetric flask, 60 ml of pH 8.3 buffer solution and 5.00 ml of $KHSO_5$ (0.04 M) were successively added, the volume was finally diluted with water to 100 ml and mixed well. After 1 min, an aliquot of the reaction mixture (10.00 ml) was quickly added to Erlenmeyer flask, which already contained 1 ml of 1 M H_2SO_4 solution, and immediately after that, 1 ml of 5% potassium iodide solution was added with shaking. The mixture was again left for about 5–10 s and the released iodine was titrated with 0.01 M thiosulfate with the addition of 1 ml of 1% starch solution near the end point. Similarly, a blank determination was performed with water instead of a solution of the analyzed substance.

The content of the main substance in the substance of HDH in terms of dry matter (w, %) was found by the formula:

$$w = \frac{(V_0 - V) \cdot T \cdot 100 \cdot 100 \cdot 100\% \cdot 100\%}{10 \cdot 20 \cdot a(100 - w(\mathrm{H_2O}))},$$

where V_0 is the volume of standard 0.0100 mol/l sodium thiosulfate used for titration in the control experiment, ml; V is the volume of standard 0.0100 mol/l sodium thiosulfate used for titration in the experiment, ml; 100 and 100 is volumes of volumetric flasks, ml; 20 is taken for the analysis of the volume of the solution of the dosage form, m; a is the mass of the sample of the substance, g; w (H_2O) is moisture content in the substance (mass loss upon drying), %; 10 is the volume of the reaction mixture taken for titration, ml.

T is HDH ($C_{21}H_{29}Cl_3N_2O_2$) amount, which corresponds to 1 ml of a standard 0.0100 mol/l thiosulfate solution, g/ml; 1.00 ml of standard 0.0100 mol/l sodium thiosulfate corresponds to 0.00223915 g/ml of HDH

($C_{21}H_{29}Cl_3N_2O_2$), which should be 99–101% in a dosage form in terms of anhydrous substance.

Method for the quantitative determination of HDH in tablets of 0.25 g

Twenty tablets were accurately weighed and ground into a fine powder. An accurately weighed amount of ground powder, equivalent to 250 mg of HDH, was transferred into a 100-ml volumetric flask. 60 ml of water was added, and the contents were thoroughly shaken for 15–20 min to extract the drug into the liquid phase, the volume was finally adjusted to the mark with water, mixed well and filtered using Whatman No. 42 filter paper. An aliquot of the filtrate (25 mg/ml) was used for the method described above (see "*Method for the determination of HDH in model (reference) solutions*").

Instruments and measurements

The product obtained is Hydroxyzine *N*-oxide with a melting point of 170–172 °C (decomposition). Its identity has been confirmed by IR- and 1H NMR spectroscopy.

The melting point was determined by the open capillary method on a PTP-M instrument (instrument for determining the melting point of solids).

The pH value of the solutions was controlled using a glass electrode ESL-43-07 with "Ionomer laboratory I-160 M" ionometer (Belarus) paired with an argentum chloride electrode EVL-1M3.1 saturated with potassium chloride.

Method for registration of IR spectra. IR spectra were recorded at 650–4000 cm^{-1} with SPECORD M-80 spectrometer (Zeiss, Jena, Germany). Tablets were prepared by mixing 200 mg of potassium bromide and 2 mg of the test compound (1% concentration) followed by compression in the standard manner.

Infrared spectrum of isolated Hydroxyzine oxidation product shows principal peaks at wavenumbers: 2825, 1685.5, 1591, 1488, 1454, 1367, 1127, 939 (N + –O–), 804, 761, 721, 703, 665 cm^{-1} (KBr disk).

The NMR measurements were carried out with 400 MHZ Varian spectrometer (Varian, USA). The NMR spectra were measured in D_2O.

The ^1H NMR spectrum of isolated Hydroxyzine oxidation product was compared to NMR of Hydroxyzine (Odeneal et al. 2004). The number of protons in the aromatic region of the ^1H NMR of the degradation product was similar to that of Hydroxyzine, indicating formation of *N*-oxide. The *N*-oxide effect can be observed by the difference in the chemical shifts of the proximal protons adjacent to the *N*-oxide carbons (Fig. 2). The deshielding influence of the *N*-oxide function, generated on the nitrogen bearing the ethoxyethanol chain, causes a down-field shift of the piperazine ($\Delta\delta = 0.2$) and ethoxy ($\Delta\delta = 0.5$) protons.

Results and discussion

Study of the kinetics of the *N*-oxidation of Hydroxyzine with potassium peroxymonosulfate in aqueous medium

The results of studying the kinetics of the reaction of *N*-oxidation of Hydroxyzine with potassium peroxymonosulfate by the method of iodometric titration (according to the consumption of the oxidizing agent) depending on pH are shown in Fig. 3.

$$c(\mathrm{Hyd}) = 1.35 \cdot 10^{-3}\ \mathrm{mol\ l^{-1}}; c\left(\mathrm{KHSO_5}\right) = 2.05 \cdot 10^{-3}\ \mathrm{mol\ l^{-1}}$$

The dependence of the observed second-order constant of the reaction of *N*-oxidation of Hydroxyzine with potassium peroxymonosulfate on the pH of the medium is shown in Fig. 4.

As it can be seen, the maximum rate of the reaction of *N*-oxidation of Hydroxyzine with potassium peroxymonosulfate is reached at pH 8.3. It can be assumed that the nonprotonated form of the tertiary Nitrogen of Hydroxyzine base (Hyd_0) and peroxymonosulfate monoanion (HSO_5^-) reacted. Based on this assumption, we derived the kinetic equation for the reaction:

$$\mathrm{Rate} = k_{\mathrm{obs}} \cdot c(\mathrm{Hyd_0}) \cdot c(\mathrm{KHSO_5})$$

$$k_{\mathrm{obs}} = k\alpha(\mathrm{Hyd_0}) \cdot \alpha(\mathrm{HSO_5^-})$$

where, α (Hyd_0) is the mole fraction of the Hydroxyzine base; α (HSO_5^-) is the molar fraction of peroxymonosulfate monoanion; which are respectively equal to:

$$\begin{aligned}\alpha(\mathrm{Hyd^0}) &= \mathrm{Ka}/(\mathrm{Ka} + [\mathrm{H^+}]) = \alpha(\text{L-}\mathrm{Hyd^0}) \\ &= 10^{-7.4}/\left(10^{-7.4} + 10^{-\mathrm{pH}}\right); \\ \alpha(\mathrm{HSO_5^-}) &= \left(10^{-0.4} \cdot 10^{-\mathrm{pH}}\right)/[\left(10^{-\mathrm{pH}}\right)^2 \\ &\quad + \left(10^{-0.4} \cdot 10^{-\mathrm{pH}}\right) + \left(10^{-0.4} \cdot 10^{-9.4}\right);\end{aligned}$$

*K*a is the dissociation constant of the acid form of Hydroxyzine;

It should be considered that $\mathrm{pH} = -\lg [\mathrm{H^+}]$, and $[\mathrm{H^+}] = 10 - \mathrm{pH}$.

$\mathrm{p}K\mathrm{a} = -\log K\mathrm{a}$, and $K\mathrm{a} = 10^{-\mathrm{p}K\mathrm{a}}$.

For Hydroxyzine, pKa = 7.4.

For Caro's acid, pKa1 = 0.4 and pKa2 = 9.4.

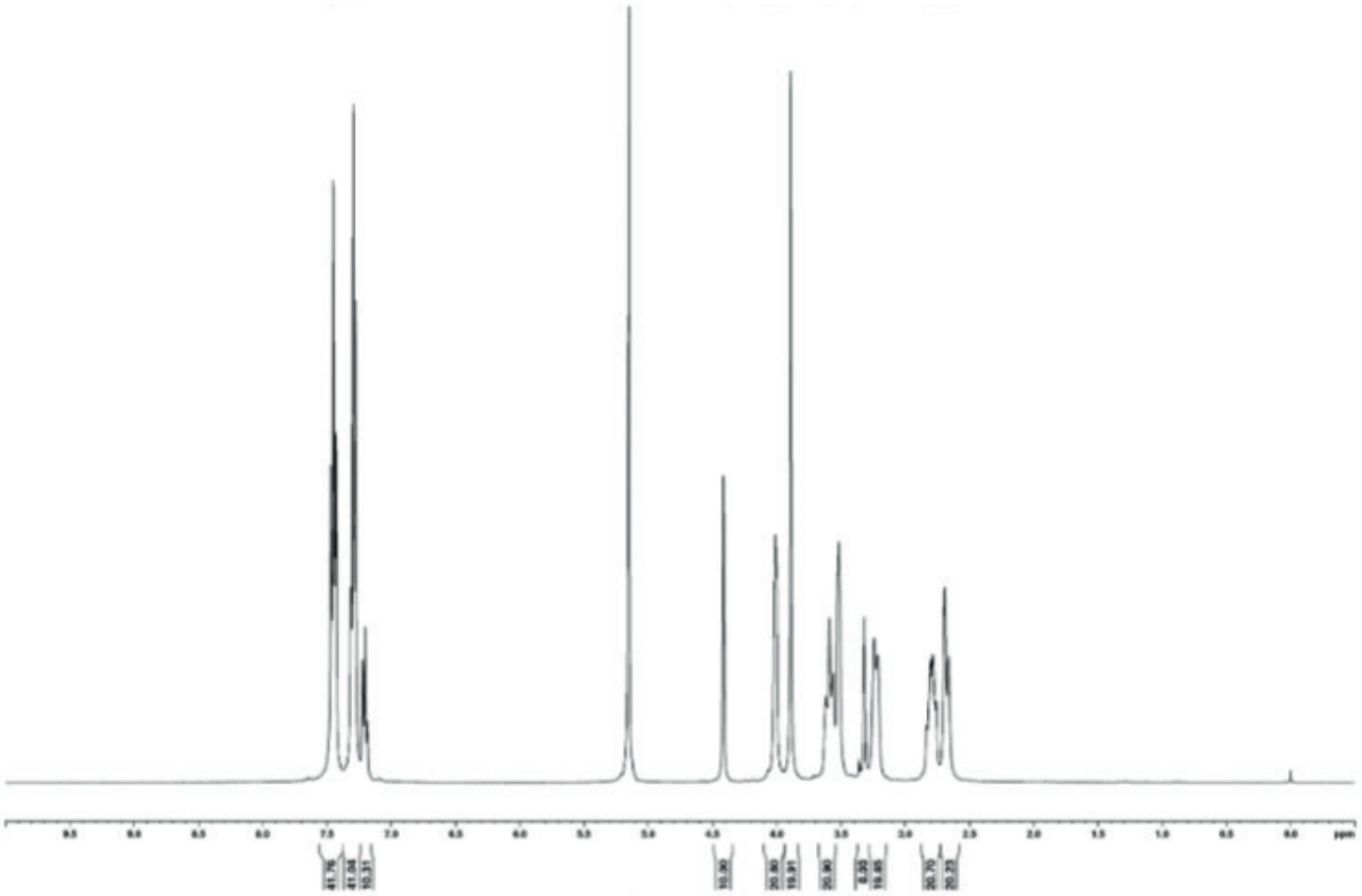

Fig. 2 The proton NMR spectrum of isolated Hydroxyzine oxidation product

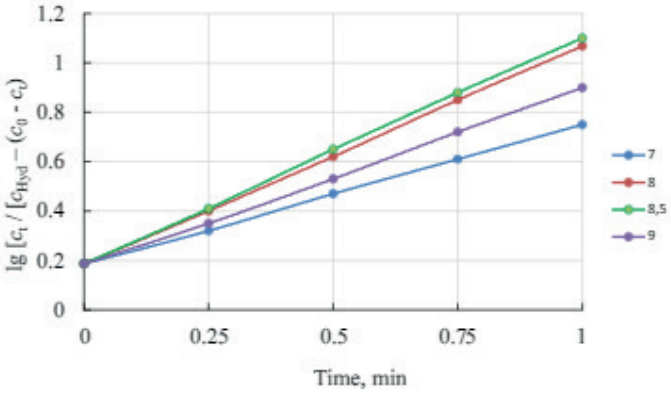

Fig. 3 Semi-log anamorphoses of the kinetic curves *N*-oxidation of Hydroxyzine with potassium peroxymonosulfate depending on pH

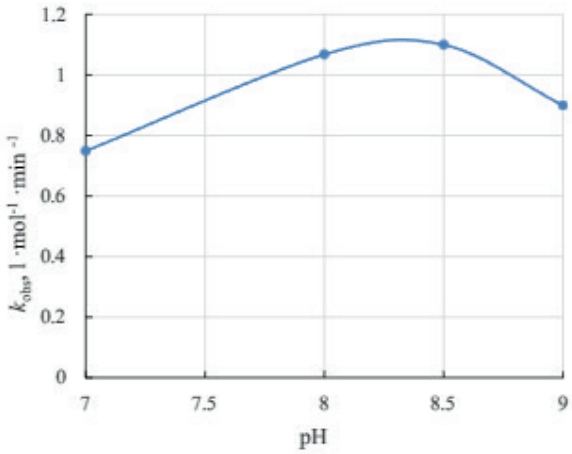

Fig. 4 The dependence of the observed second-order constant of the reaction of *N*-oxidation of Hydroxyzine with potassium peroxymonosulfate on the pH of the medium

The linear dependence with k_{obs} on the production of molar fractions of the Hydroxyzine base and the HSO_5^- monoanion (Fig. 5) indicates the correct assumption that it is the Hydroxyzine base and mainly the peroxymonosulfate acid monoanion that take part in the reaction (correlation coefficient $R = 0.93$, which is close to 1).

The scheme of the process of oxidation of Hydroxyzine potassium peroxymonosulfate is shown in Fig. 6.

Thus, it has been established that the reaction kinetics obeys the general laws of specific acid–base catalysis. The stoichiometric ratios and interaction time in the reaction

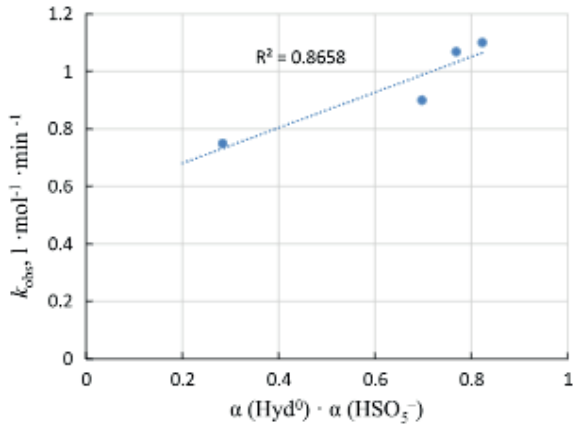

Fig. 5 Dependence of the observed second-order rate constant (k_{obs}) of the reaction of *N*-oxidation of Hydroxyzine with potassium peroxymonosulfate on the product of the molar fractions of the Hydroxyzine base and HSO_5^- monoanion

were established: 1 mol of $KHSO_5$ is consumed per mol of HDH; stoichiometric consumption of the oxidizing agent at pH 8–8.5 is achieved in 1–1.5 min.

The obtained results of studying the reaction kinetics were used by us as the basis for the development of a new method for the quantitative determination of Hydroxyzine by the *N*-oxidation reaction using potassium peroxymonosulfate as an analytical reagent.

The results of the titrimetric determination of HDH in model solutions using Oxone are given in Table 1. For HDH levels of 2.24 mg and 22.40 mg, the relative standard deviation is 2.5% and 0.43%, respectively. $\delta < RSD$.

Table 1 Results of titrimetric determination of HDH in model solutions using Oxone ($n=7$; $P=0.95$)

Taken HDH, mg	Found HDH $\bar{x} \pm \Delta\bar{x}$ (mg)	RSD, %	Accuracy (%), $\delta = \frac{(\bar{x}-\mu)}{\mu^*}100\%$
2.24	2.25 ± 0.05	2.50	−0.45
4.48	4.51 ± 0.06	1.49	+0.67
8.96	8.97 ± 0.07	0.87	+0.11
22.40	22.41 ± 0.10	0.43	+0.05

*μ is true content of HDH (taken) (mg)

Table 2 Results of titrimetric determination of the content of the main substance in the API HDH substance using Oxone ($n=7$; $P=0.95$)

Content indicated in the certificate analysis (w, %)	Found ($\bar{x} \pm \Delta\bar{x}$), (%)	RSD, %	$\frac{(\bar{x}-\mu)}{\mu^*}100$ (%)
99.6*	99.2 ± 0.44	0.48	−0.40

*Average HDH content data of the official method BPh (based on the potentiometric titration of HDH in non-aqueous medium using perchloric acid), μ

Results of titrimetric determination of the content of the main substance in HDH substance using Oxone are given in Table 2: RSD = 0.48%. $|(\bar{x} - \mu) \cdot 100)/\mu| < RSD$.

The results of the analysis of ATARAX® tablets, 25 mg each according to the proposed method ($n=5$; $P=0.95$) are shown in Table 3. RSD ≤ 1.52%. $|(\bar{x} - \mu) \cdot 100)/\mu| < RSD$.

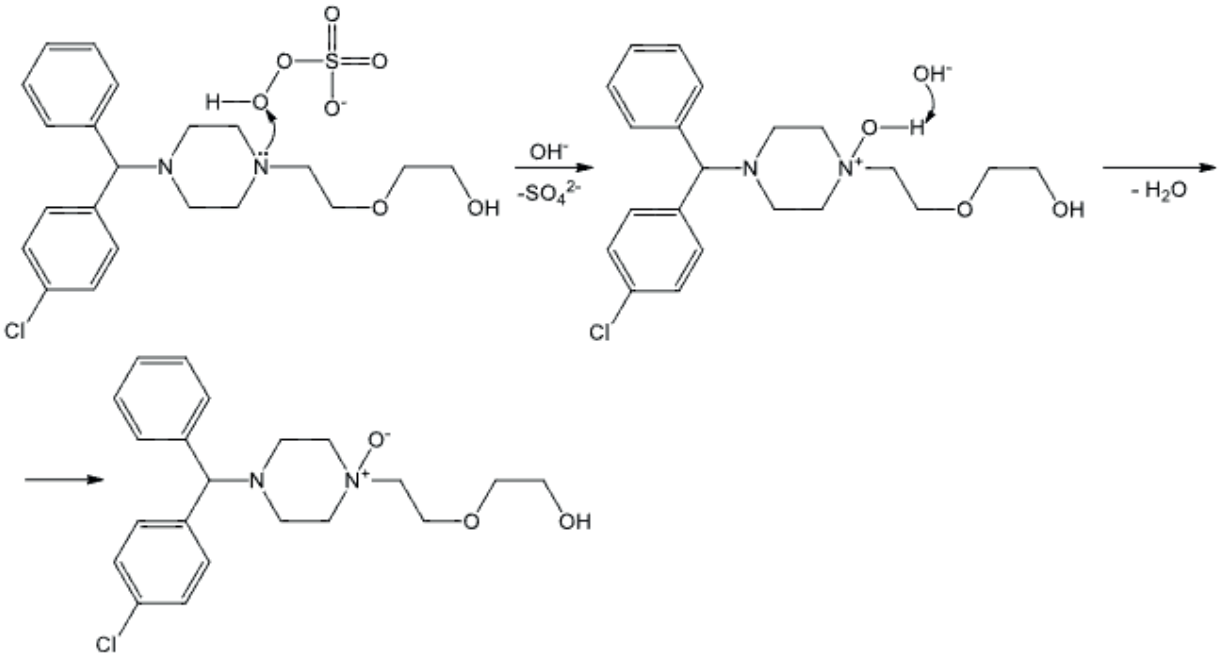

Fig. 6 Scheme of the oxidation process of Hydroxyzine with potassium peroxymonosulfate

Table 3 The results of the analysis of ATARAX® tablets, 25 mg each according to the proposed method ($n=5$; $P=0.95$)

Active substance, analyte	Found $(\bar{x}\pm\Delta\bar{x})$, mg/tabl Percentage of declared (% *Re*covery)	RSD, %	Average content analysis certificate data (μ^*) mg/tab	Accuracy, $\frac{(\bar{x}-\mu)}{\mu^*}100$ (%)
Hydroxyzine—ATARAX® film-coated tablets *25 mg;* Series no 313517 Manufacturer USB Pharma S.A., Belgium	25.10 ± 0.38 $RE=100.4\pm1.5$	1,52	24.63 (98.5%)	+0.50

*Data from official BPh method (based on the potentiometric titration of HDH in non-aqueous medium using perchloric acid), μ

Conclusions

The kinetics of the oxidation reaction of Hydroxyzine dihydrochloride with potassium peroxymonosulfate was studied depending on the pH of the medium. It has been established that the reaction kinetics obeys the general laws of specific acid–base catalysis. Techniques have been developed and the possibility of quantitative determination of Hydroxyzine dihydrochloride in substance and tablets of 25 mg by iodometry using Oxone as an analytical reagent has been shown. RSD ≤ 1.52%. δ < RSD.

Author contributions II and MB conducted the experiments and analyzed the data. VY, VM, OK assisted in the experiments and discussed the results. MB and II wrote the manuscript and drew the graphs. VM, OK revised the manuscript. All authors read and approved the final manuscript.

Funding No funding was received.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval and consent to participate Not applicable.

References

Altamura AC, Moliterno D, Paletta S, Maffini M, Mauri MC, Bareggi S (2013) Understanding the pharmacokinetics of anxiolytic drugs. Expert Opin Drug Metab Toxicol 9(4):423–440. https://doi.org/10.1517/17425255.2013.759209

Anwar A (2012) Wassel characteristic of membrane sensors for the selective determination of some antihistaminic pharmaceutical formulations. Anal Bioanal Electrochem 4(1):17–31

Basavaiah K, Charan VS (2002) Charan Titrimetric and spectrophotometric assay of some antihistamines through the determination of the chloride of their hydrochlorides. Il Farmaco 57(1):9–17. https://doi.org/10.1016/S0014-827X(01)01151-X

Beltagi AM, Abdallah OM, Ghoneim MM (2008) Development of a voltammetric procedure for assay of the antihistamine drug Hydroxyzine at a glassy carbon electrode: quantification and pharmacokinetic studies. Talanta 74(4):851–859. https://doi.org/10.1016/j.talanta.2007.07.009

British Pharmacopoeia Commission (2020) British Pharmacopoeia. Stationery Office, London. Available from: https://www.pharmacopoeia.com/

European Pharmacopoeia 10th Ed (2020) European directorate for the quality of medicines, Strasbourg. Available from: https://pheur.edqm.eu/home

Kintz P, Godelar B, Mangin P (1990) Gas chromatographic identification and quantification of Hydroxyzine: application in a fatal self-poisoning. Forensic Sci Int 48:139–143. https://doi.org/10.1016/0379-0738(90)90106-9

Odeneal NG II, Casale JF, Wojno HL (2004) Technical Note. Hydroxyzine: an analytical profile. Microgram J. 2:17–21

Rajendraprasad N, Basavaiah K, Vinay K (2011) Optimized and validated spectrophotometric methods for the determination of Hydroxyzine hydrochloride in pharmaceuticals and urine using iodine and picric acid. J Serb Chem Soc 76:1551–1560. https://doi.org/10.2298/jsc101007138r

Rajendraprasad N, Basavaiah K (2013) Titrimetric assay of hydroxyzine dihydrochloride in pharmaceuticals and formulations in non-aqueous medium. Int J Chem Tech Res 5(1):105–111

Rajendraprasad N, Basavaiah K, Vinay B (2010) Acid-base titrimetric assay of Hydroxyzine dihydrochloride in pharmaceutical samples. Chem Ind Chem Eng Q 16(2):127–132. https://doi.org/10.2298/ciceq090929014r

Saeed N, Ali RF (2011) Chiral separation and quantitation of cetirizine and Hydroxyzine by maltodextrin-mediated CE in human plasma: effect of zwitterionic property of cetirizine on enantioseparation. Electrophoresis 32:764–771. https://doi.org/10.1002/elps.201000607

Sawantdesai NS, Kale PP, Savai J (2016) Evaluation of anxiolytic effects of aripiprazole and Hydroxyzine as a combination in mice. J Basic Clin Pharm 7(4):97–104. https://doi.org/10.4103/0976-0105.189429

Sher N, Siddiqui FA, Fatima N, Perveen S, Shafi N (2014) New method development for Hydroxyzine determination: application in stability studies, pharmaceutical formulations, and humane serum. J Liq Chromatogr Relat 38(8):911–918. https://doi.org/10.1080/10826076.2014.991871

United States Pharmacopoeia 43 National Formulary 38 (2019) United States pharmacopeial convention, Rockville. Available from: https://www.usp.org/