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Quantitative Estimation of Dimenhydrinate in Pharmaceuticals Using Redox Reaction with Oxone

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Abstract: The kinetics and mechanism of dimenhydrinate (DMH) oxidation by potassium hydrogen peroxomonosulfate ($KHSO_5$) in aqueous medium were investigated iodometrically at 20°C. The reaction was found to have a stoichiometry of 1:1. The reaction is first order in $KHSO_5$ and diphenhydramine (DPH) concentrations. An increase in the pH from 7.7 to 10.4 causes an increase in the reaction rate. It is shown that the kinetics of the reaction are subject to the mechanism of acid-base catalysis—the proposed reaction kinetic equation. The oxidation product of DPH is DPH *N*-oxide (pDPH). Two analytical methods were developed using $KHSO_5$ as a reagent: a titrimetric method involving N-oxidation with iodometric back titration (method A) and a spectrophotometric method based on the formation of a triiodide chromogen with maximum absorption at 350 nm (method B). Method A was effective for concentrations of 0.5–5.0 mg in 10 mL, while Method B obeyed Beer's law over 0.1–4.1 µg/mL, with a molar absorptivity of 24.4×10^3 L/mol cm. The limits of quantification were 0.05 mg/mL (method A) and 0.11 µg/mL (method B). Both methods were unaffected by common excipients and showed reliability in analyzing bulk DMH s as well as API in Vomacur® and Dramina® tablets of 50 mg and Vomex A® i.v. injection solution of 62 mg/10 mL. Both methods yielded results comparable to official methods, demonstrating their applicability and reliability for quantitatively determining DMH in various pharmaceutical formulations.

Keywords: analytical method; dimenhydrinate; oxone; titrimetry; spectrophotometry.

1. Introduction

Dimenhydrinate (DMH) is a first-generation antihistamine available over the counter. It is used to prevent and relieve nausea and vomiting caused by various factors, including motion sickness. It is also used to treat postoperative nausea [1–8]. DMH is a complex compound (Figure 1), a theoclate salt that is based on a 1:1 ratio of DPH (an ethanolamine derivative) and 8-chlorotheophylline (a chlorinated theophylline derivative) [9–11].

DMH is marketed under many brand names: Driminate (Ukraine), Dramina (Croatia), Vomex (Germany), and Aviomarin (Poland, Slovakia). DMH is currently available in the pharma market as parenteral solutions, rectal suppositories, oral tablets, coated tablets,

suspensions, and solutions. DMH is a white crystalline powder with a pKa of 8.87, and its water solubility equals 3 mg/mL.

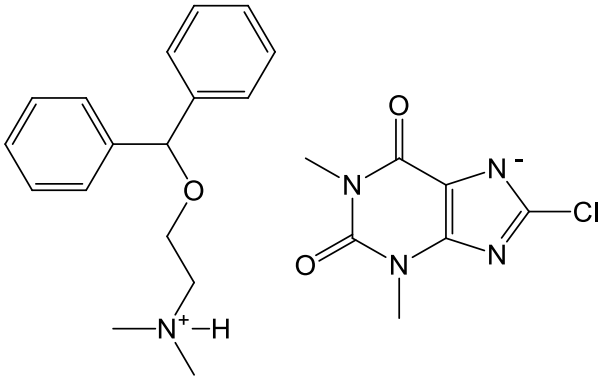

Figure 1. Chemical structure of DMH.

British Pharmacopeia (BPh 2022) recommends a non-aqueous titration as a reference method for the assay of DMH using 0.1 M perchloric acid, determining the end-point potentiometrically [12]. According to the requirements of the BPh, the quantitative determination of DMH in tablets is carried out by back acid-base titration against 2-(diphenylmethoxy)-N, N-dimethylethanamine after its preliminary isolation from an alkalized solution of the drug by the method of ether extraction. To an ethanol solution of 2-(diphenylmethoxy)-N, N-dimethylethanamine, add 50 mL of 0.01M hydrochloric acid and titrate the excess acid with 0.01M sodium hydroxide solution using a solution of methyl red as an indicator [13].

Conversely, the United States Pharmacopeia (USP) recommends a titration procedure for the bulk form and high-performance liquid chromatography (HPLC) for analyzing all DMH dosage forms [14,15].

Some reports have addressed the quantification of DMH in various drug formulations and/or biological samples. Analytical methodologies involving spectrophotometry [16–18], voltammetry [19], in particular, adsorptive stripping voltammetry [20], HPLC with UV-detection [21,22], liquid chromatography-tandem mass spectrometry (LC/MS/MS) [23], HPLC with fluorescence detection [24], high-performance thin-layer chromatography (HPTLC) [25,26], reversed-phase ultra-performance liquid chromatography (RP-UPLC) [27] and others methods [28–33] for determination of DMH either alone or in combination with other drugs and/or impurities were used.

In general, as can be seen, analytical methods for the quantitative determination of DMH are not quite perfect. They require a lot of time and the use of relatively expensive instruments and toxic solvents, which violates the basic principles of “green chemistry”. Therefore, there is a constant need to develop analytical methods such as titrimetry and spectrophotometry that are simple, sensitive, rapid, accurate, precise, and inexpensive and that can be easily adapted in the pharmaceutical industry.

Previously, one of the authors proposed a method for the quantitative determination of DPH in dosage forms based on its *N*-oxidation with an excess of diperoxydicarboxylic acid followed by the determination of unreacted diperoxyacid by the iodometric method [34]. A little later, this laboratory developed a new photometric technique for the DPH quantitative determination in a solution for injection using peroxomonosulfuric acid as an oxidant [35]. However, the proposed approach to the analysis was not extended to other drugs, in particular to DMH.

The current work aims to implement the mentioned approach to analysis using KHSO5 as a stable triple salt of Oxone® as an analytical reagent and to establish two straightforward, fast, accurate, and low-cost techniques for the estimation of DMH in pharmaceutical formulations.

2. Materials and Methods

Dimenhydrinate ($C_{17}H_{21}NO \cdot C_7H_7ClN_4O_2$) was purchased from Sigma-Aldrich Chemie GmbH, CAS 523-87-5. M. w. 469.98 g/mol. Diphenhydramine hydrochloride (DPH·HCl, 2-(diphenylmethoxy)-N, N-dimethylethanamine chloride), a pharmacopeia standard, was used (SE «Ukrainian Research Center Pharmacopoeial quality of drugs» series 2).

Dramina® tablets 50 mg blister, No. *5* (Jadran-Galenski Laboratorij d.d., Croatia). Composition: active substance – dimenhydrinate; 1 tablet contains 50 mg; excipients – microcrystalline cellulose; magnesium stearate; lactose monohydrate; povidone; crospovidone. Series: 212133. Certificate № 170000034953. Assay of DMH (UV-spectrophotometry): 97.8 % (48.9 mg/tablet). Requirements: 95.0-105.0 % of the stated amount (47.5-52.5 mg/tablet).

Vomex A® i.v. injection solution contains: the active ingredient is dimenhydrinate, 1 ampoule with 10 mL i.v. injection solution contains 62 mg. The other ingredient is Water for injections. Clear glass ampoules with a clear, colorless solution. One pack contains 3 ampoules of 10 mL each, by Klinge Pharma GmbH (Germany). Ch. 157336A Zul. Nr. 6581008.00.00

Vomacur® 50 mg tablets (Certificate of conformity, Manufacturers: Hexal AG PZN: 03815234 Zur. – Nr. 1879.99.98 Ch.B. LT2117). Active ingredient: dimenhydrinate, 1 tablet contains 50 mg of dimensions. The other ingredients: calcium hydrogen phosphate dihydrate, sodium carboxymethyl starch (type A) (Ph.Eur.), microcrystalline cellulose, lactose-monohydrate (38 mg Lactose), magnesium stearate (Ph. Eur.), high disperse silicon dioxide, and 50 mg dimenhydrinate.

Also, all of the specified excipients of medicines were purchased from local commercial sources.

Potassium peroxomonosulfate, $KHSO_5$ (ACROS Organics™), is a component in the commercial product called Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$). CAS 70693-62-8, extra pure, min 4.5% active oxygen, formula weight is 614.78 g/mol. Moreover, it is considered a "green"-oxidizing agent because of its nontoxic effects. Oxone has a longer shelf life than potassium peroxomonosulfate [36]. A white, water-soluble solid, oxone, loses <1% of its oxidizing power within a month. The standard electrode potential for potassium peroxomonosulfate is +1.81 V with a half-reaction to form hydrosulfate (pH = 0) [37].

Sodium thiosulphate standard solution, $c(Na_2S_2O_3 \cdot 5H_2O)$ = 0.1 mol/L, was prepared with 0.1 mol/L Normadose® (standard titer) in the freshly boiled and cooled double-distilled water with the addition of 0.5 g sodium carbonate in a 1 L volumetric flask. It is then filled with the same solvent to the mark at 293 K.

Potassium iodide, 5 % solution. 5.0 g of potassium iodide was dissolved in 50 mL of freshly boiled and cooled water. It is then filled with the same solvent to 100 mL. The solution should be colorless. Hydrochloric acid and sulfuric acid solutions were prepared with 0.1 mol/L Normadose® (standard titer).

The preparation of pH buffer solutions. 0.2 mol/L solution of potassium pyrophosphate: dissolve 66.067 g potassium pyrophosphate (potassium diphosphate) in 1 L of double-distilled water (pH 9.2). The preparation method of pH buffers with 7.7 and 8.6 values included dripping diluted hydrochloric acid into an aqueous solution of 0.2 mol/L solution of potassium

pyrophosphate while measuring the pH with a pH meter. The preparation method of pH buffers with 10.4 values included dripping 5% sodium hydroxide solution into an aqueous solution of 0.2 mol/L potassium pyrophosphate while measuring the pH with a pH meter. The pH value of the solutions was controlled using a glass electrode ESL-43-07 on an "Ionomer laboratory I-160M" (Belarus) paired with an Ag/AgCl (saturated with 3 mol/L KCl) reference electrode EVL-1M3.1.

Stock standard solution of 0.02 M $KHSO_5$. About 0.7 g of oxone was dissolved in 70 mL of double-distilled water in a 100 mL volumetric flask, made up to the mark with the same solvent, and mixed thoroughly. The exact concentration was determined by iodometric titration, as described in our previous works [38–41].

Working standard solution of $KHSO_5$. 10 mL of 0.02 M $KHSO_5$ stock standard solution was accurately transferred into 100 mL volumetric flasks and completed to volume with double-distilled water.

All other chemicals used throughout this study were of analytical grade. All solutions were prepared using double-distilled water.

2.1. Titrimetric assay.

2.1.1. Procedure for quantitative determination of the DMH content in DPH pure substance.

An accurately weighed portion (about 0.25 g) of the DMH pure substance was transferred into a 100 mL calibrated flask, dissolved in 70 mL of double-distilled water, and made up to the mark with the same solvent. An aliquot of solution 20.0 mL was taken and transferred into a 100 mL calibrated flask to flask 30 mL of a buffer mixture with a pH of 9.2 and 10.0 mL of a 0.02 mol/L solution of $KHSO_5$ was added, and the content was diluted to the mark with double distilled water and mixed thoroughly; the mixture was set aside for 5 min. Then, 10.0 mL of the solution was taken and placed in a conical flask for titration; 2 mL of 0.1 mol/L sulfuric acid solution and 1 mL of 5% potassium iodide solution were added. Released iodine was immediately titrated with 0.02 mol/L sodium thiosulfate solution. Starch was added at the end of the titration. In parallel, a control experiment was conducted under similar conditions (in the absence of DMH, with the same amount of 0.02 mol/L reagent solution).

The DPH ($C_{17}H_{21}NO$) content in the DMH pure substance, calculated with reference to the dried substance, % (X), was calculated according to the formula (1):

$$X = \frac{(V_0 - V) \times K \times T \times V_m \times 10 \times 100 \times 100\%}{m \times V_a \times (100 - w)} \qquad (1)$$

where V_0 is the volume of standard 0.02 mol/L sodium thiosulfate solution used for titration in the control experiment, mL; V is the volume of standard 0.02 mol/L sodium thiosulfate solution used for titration in the working experiment, mL; K is the concentration correction factor of the standard solution of sodium thiosulfate to 0.0200 mol/L; T is the amount of DPH, $C_{17}H_{21}NO$, which corresponds to 1.00 mL of a standard 0.0200 mol/L sodium thiosulfate solution, g⁄mL; V_m is calibrated flask volume, mL; V_a is the volume of the solution of the dosage form taken for analysis, mL; m is weight of dosage form, g; w is water content in the substance, %; 10 is the dilution factor.

1.00 mL of a standard 0.0200 mol/L solution of sodium thiosulfate is equivalent to 0.00255355 g of DPH($C_{17}H_{21}NO$).

DMH contains not less than 53.0 % and not more than 55.5 % of DPH, calculated with reference to the dried substance.

2.1.2. Procedure for injections.

An accurately measured volume of 7.00 mL of test solution for injections was transferred into a 100 mL calibrated flask. To a flask, 20 mL of a phosphate buffer mixture with a pH of 9.2 and 10.0 mL of 0.02 mol/L solution of $KHSO_5$ were added and diluted to the mark with double-distilled water and mixed thoroughly; a mixture was set aside for 5 min. Then, continue as indicated in the procedure for quantitative determination of the DMH content in a pure DPH substance. The content of DMH in the injection solution, in mg/10 mL (*X*), was calculated by the formula:

$$X = \frac{(V_0 - V) \times T \times 10 \times K}{V_a} \qquad (2)$$

where V_0 is the volume of standard 0.02 mol/L sodium thiosulfate solution used for titration in the control experiment (reagent blank), mL; *V* is the volume of standard 0.02 mol/L sodium thiosulfate solution used for titration in the working experiment, mL; *K* is the concentration correction factor of the standard sodium thiosulfate solution to 0.0200 mol/L; *T* is the amount of DMH corresponding to 1 mL of standard 0.02 mol/L sodium thiosulfate solution, mg⁄mL; V_a is the volume of the solution of the dosage form of one series taken for analysis, mL; *10* is the dilution factor.

1.00 mL of a standard 0.0200 mol/L sodium thiosulfate solution corresponds to 4.6998 mg of DMH ($C_{17}H_{21}NO \cdot C_7H_7ClN_4O_2$), which should be 58.9...65.1 mg/10 mL in the preparation.

2.1.3. Procedure for tablets.

20 tablets were weighed and ground into a very fine powder. A precisely measured amount of the substance (approximately 0.23 g), equal to 50 mg of the DMH, was transferred into a 100 mL calibrated flask and diluted to the mark with double-distilled water. The powder was completely disintegrated using a mechanical stirrer, and the solution was filtered. An aliquot of solution 50.0 mL was taken and transferred into a 100 mL calibrated flask to flask 30 mL of a buffer mixture with a pH of 9.2 and 10.0 mL of a 0.02 mol/L solution of $KHSO_5$ was added, the content was diluted to the mark with double distilled water and mixed thoroughly; the mixture was set aside for 5 min. Then, continue as indicated in the Procedure for quantitative determination of the DMH content in DPH pure substance. The content of DMH in tablets, *X*, in mg/tablet, was calculated according to the formula (3):

$$X = \frac{(V_0 - V) \times T \times \bar{m} \times 100 \times 10 \times K}{m \times 50} \qquad (3)$$

where V_0 is the volume of standard 0.02 mol/L sodium thiosulfate solution used for titration in the control experiment (reagent blank), mL; *V* is the volume of standard 0.02 mol/L sodium thiosulfate solution used for titration in the working experiment, mL; *K* is the concentration correction factor of the standard sodium thiosulfate solution to 0.0200 mol/L; *T* is the amount of DMH corresponding to 1.00 mL of standard 0.0200 mol/L sodium thiosulfate solution, mg/mL; $\bar{m}$ is the average weight of one tablet, g; *50* is the test solution volume taken

for analysis, mL; *m* is the powder mass of crushed tablets, taken for analysis, g; *100* is the measuring flask volume, mL.

1.00 mL of a standard 0.0200 mol/L solution of sodium thiosulfate corresponds to 4.6998 mg/mL of DMH ($C_{17}H_{21}NO \cdot C_7H_7ClN_4O_2$), which should be 95.0-105.0 % of the stated amount (47.5 ... 52.5 mg/tabl).

The titrimetric method (A) was applicable over the concentration range of 0.5-5.0 mg to an end volume of 10 mL. The limit of quantification was calculated to be 0.05 mg/mL.

2.2. Spectrophotometric assay.

2.2.1. Procedure for DMH pure substance.

The standard solution of pure DMH with a concentration of 3.0 mg/ mL was prepared by carefully weighing 300 mg of pure DMH using an analytical scale, inserting it into a 100 mL measuring flask, then partially adding double-distilled water, then sonication, and subsequently adding water until the boundary mark. An accurately measured volume was appropriately diluted to get 30 µg/mL of DMH solution.

Aliquots (1.00-17.00 mL) of standard DMH solution (30.0 µg/mL) were transferred separately into 25 mL calibrated flasks. To each flask, 5 mL 0.2 mol/L $K_4P_2O_7$ (pH 9.2) and 2.5 mL 5×10^{-4} mol/L of PMS were added, and the contents were diluted to the mark with double-distilled water and mixed. Each mixture was set aside for 30 minutes. After aliquots, 5.00 mL of each mixture was transferred separately into 25 mL calibrated flasks. To each flask, 1.5 mL of 1:4 sulfuric acid and 2 mL of 5% KI solution were added, and the contents were diluted to the mark with double-distilled water and mixed; the absorbance values at λ_{max} = 350 were measured against water. In parallel, a control experiment (reagent blank). A control measurement was carried out similar to the working experiment, with the difference that double-distilled water was used instead of the investigated drug solution. The difference in optical densities obtained in the control and working experiments, respectively (ΔA), was plotted versus the concentration of DMH.

2.2.2. Procedure for tablets.

20 tablets were weighed and ground into a very fine powder. A precise amount of the powder, equivalent to 50 mg of the DMH, was put into a 100 mL calibrated flask. Then, it was diluted to the mark volume with double-distilled water. Using a mechanical stirrer, the powder was completely disintegrated, and the solution was filtered. After aliquoting 10.00 mL of the mixture, it was transferred into a 200 mL calibrated flask, and the content was diluted to the mark with double-distilled water and mixed. An appropriate amount of this solution within the individual DMH working range was then treated according to the recommended procedure.

2.2.3. Procedure for injections.

A precisely measured volume was suitably diluted to achieve 31.0 µg/mL of the DMH solution. The recommended procedure for analyzing drug content was followed using a proper aliquot of the solution.

2.3. Identification of reactive species in reaction systems.

2.3.1. Synthesis of DPH N-oxide.

A 0.291 g (0.001 mol) aliquot of DPH·HCl powder was mixed with 5 mL of 1 M sodium hydroxide solution to liberate the free base, which was then extracted by ether, followed by spontaneous vaporization of the solvent. The obtained base was suspended in 5 mL of a 12 % solution of oxone, pre-adjusted to pH 9.3 with sodium hydroxide. After 30 minutes, a clear solution was formed, which was left to stand at room temperature for another 30 minutes, and then water was removed from the mixture by evaporation under vacuum, and the residue was taken up with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and filtered. Distillation of the filtrate under reduced pressure gave pDPH, which solidified on m.p. 153-155 °C (dec.). After crystallization from an aceton–ether mixture, the solid product melted at 131 °C (dec.). The oxidation product powder was identified by IR-spectrometry, where the appearance of strong bands corresponding to the *N*-oxide group at 955 cm^{-1} and at 901 cm^{-1} in the IR spectrum of pDPH (Figure 2), which is absent in the IR spectrum of DPH is evidence of the oxidation to the *N*-oxide form of the drug under the stated conditions as shown in Figure 3.

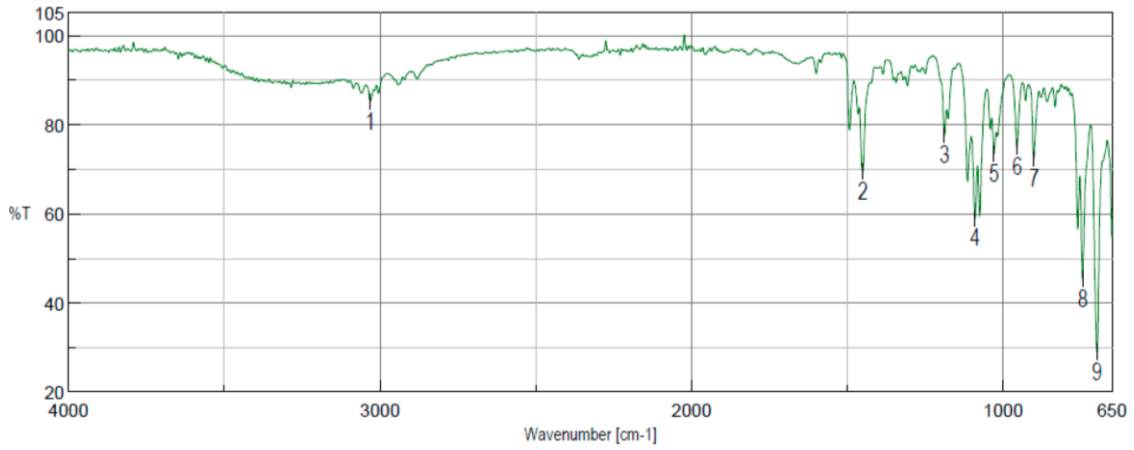

Figure 2. IR-spectrum of DPH *N*-oxide.

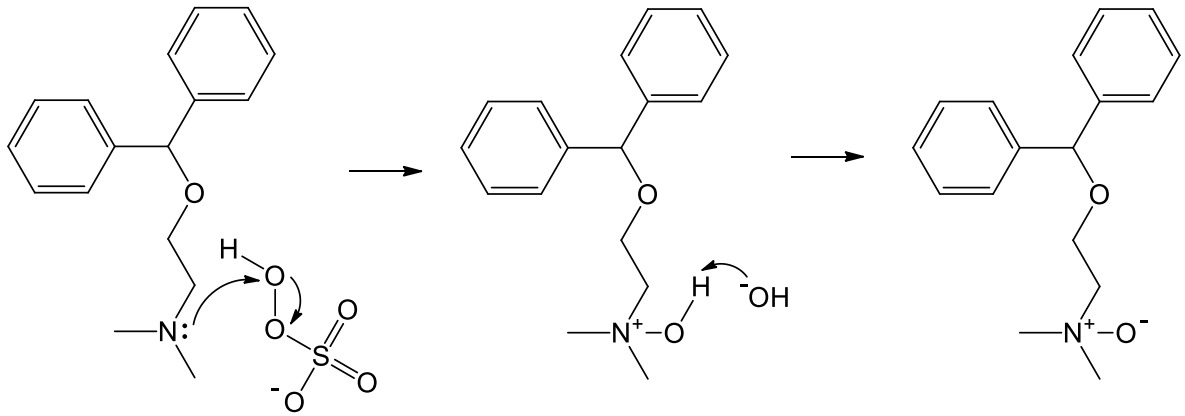

Figure 3. Scheme of the oxidation process of DPH (diphenhydramine) with $KHSO_5$.

Elemental analysis for $C_{17}H_{21}NO_2$ (271.35) was calculated: 75.26 % (C); 7.80 % (H); 5.16% (N). Found: 74.99 % (C); 7.90 % (H); 5.09% (N).

TLC measurements were performed in the conditions: SiO_2: Dichloromethane: Methanol: Ammonium hydroxide = 9:1:0.2, visualization with UV, one spot, R_f = 0.40.

2.3.2. Polarographic measurements.

Polarographic measurements were performed on a Universal polarograph MTech POL-20 (MTech Lab, Ukraine) with a three-electrode electrolytic cell (dropping mercury electrode (DME) as working electrode, saturated calomel electrode (SCE) as a reference and platinum electrode as auxiliary one) in aqueous medium of phosphate buffer solutions under an argon atmosphere in a thermostated vessel. Temperature was maintained at 20°C ±0.1°C. Characteristics of DME: m = 5.9×10^{-4} g/s. Dissolved oxygen from the electrolytic cell was removed with purified argon for 10–15 min. τ_k = 10 s in a 0.2 M NH_4Cl solution without applying a polarization voltage. The potential was applied at a rate of V = 0.5 V/s. The accuracy of the potential measurement is 1 mV. The uncertainty of the current measurement is 0.1%. Single irreversible peaks occurred at E = –0.98 V and E = –1.23 V vs SCE, respectively, using phosphate buffers with pH 4.0 and pH 7.0 as supporting electrolytes.

2.3.3. Fourier transform infrared (FT-IR) spectral analysis.

Samples were scanned at the functional group region (4000-650 cm^{-1}) using a Shimadzu FT-IR spectrometer (Shimadzu, Kyoto, Japan). 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. FTIR-ATR Spectrum shows characteristic principal peaks at wavenumber, cm^{-1} (KBr disk): 689, 744, 901, 955 (N^+—O^-), 1029, 1090, 1188, 1450, 3032. Principal peaks at wavenumbers, cm^{-1} (KBr disk): 713, 754, 991, 1103, 1017, 1180 (DPH·HCl). In the IR spectrum of pDPH (Figure 2), in contrast to the spectrum of the corresponding DPH, a doublet of new bands belonging to ν(N—O) appeared at 955-900 cm^{-1}. Both bands were sharp and of approximately the same average intensity: at 955 cm^{-1} (number 6) and 901 cm^{-1} (number 7). The position and shape of these bands were in accordance with the literature data for amine oxides [42].

3. Results and Discussion

Conditions for oxidimetric determination of the drug were preliminarily established, and the effect of pH medium on the kinetics of DMH oxidation was studied. The research results showed that the latter oxidizes the fastest in a medium with a pH of 9.2-10.4, and the reaction is completed in 5 minutes (Figure 4). The stoichiometry of the reaction was determined. It was found that one mole of DMH consumes one mole of $KHSO_5$ (1:1).

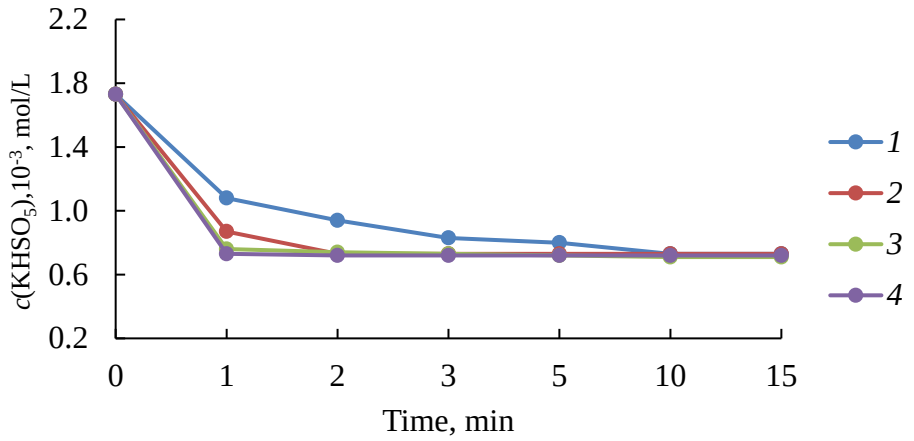

Figure 4. Kinetic curves of the *N*-oxidation reaction of DMH by $KHSO_5$ depending on the pH. *c*(DMH) = 1×10^{-3} mol/L; *c*($KHSO_5$) = 1.73×10^{-3} mol/L; pH: *1* – 7.7; *2* – 8.6; *3* – 9.2; *4* – 10.4.

3.1. Reaction mechanism.

3.1.1. Identification of reactive species in reaction systems.

If we assume that the non-protonated form of the tertiary nitrogenous base DPH (DPH^0), the monoanionic of hydrogen peroxomonosulfate (HSO_5^-), and the dianion of peroxomonosulfate (SO_5^{2-}) are involved in the reaction, then the kinetic equation of the reaction can be presented in the following form:

$$\text{Rate} = k_{obs} \times c(DPH^0) \times c(KHSO_5) \quad (4)$$

$$k_{obs} = K_a \times \alpha(DPH^0) \times [\alpha(HSO_5^-) + \beta \times \alpha(SO_5^{2-})] \quad (5)$$

where K_a is a dissociation constant of the DPH acidic form, it should be taken into account that $pH = -\lg[H^+]$ and $[H^+] = 10^{-pH}$, $pK_a = -\lg K_a$ and $K_a = 10^{-pKa}$, $pK_a(DPH) = 9.1$; $KHSO_5$ has two dissociation constants, expressed by the following pK_a values: $pK_{a1} = 0.4$ and $pK_{a2} = 9.4$; β is the ratio of the oxidation of DPH by the dianion and the monoanionic rate constants: $\beta = (k\ SO_5^{2-}/DPH^0):(k\ HSO_5^-/DPH^0)$; $\alpha(DPH^0)$ is a mole fraction of DPH base, $\alpha(HSO_5^-)$ is a mole fraction of monoanionic, $\alpha(SO_5^{2-})$ is a mole fraction of dianion, which are respectively equal to:

$$\alpha(DPH^0) = K_a/(K_a + [H^+]) = 10^{-9.1}/(10^{-9.1} + 10^{-pH}); \quad (6)$$

$$\alpha(HSO_5^-) = (10^{-0.4} \times 10^{-pH})/[(10^{-pH})^2 + (10^{-0.4} \times 10^{-pH}) + (10^{-0.4} \times 10^{-9.4}); \quad (7)$$

$$\alpha(SO_5^{2-}) = (10^{-0.4} \times 10^{-9.4})/[(10^{-pH})^2 + (10^{-0.4} \times 10^{-pH}) + (10^{-0.4} \times 10^{-9.4}). \quad (8)$$

The transformation of the H_1-antihistamine DPH by direct $KHSO_5$ oxidation was recently investigated in [43]. The parent compounds and $KHSO_5$ transformation product pDPH were measured, with the HPLC signal proportional to concentration plotted as a function of treatment time.

The individual rate constants (k_{ij}, 1/M s) of the interaction of the DPH base with the monoanion of hydrogen peroxomonosulfate (HSO_5^-) and the dianion of peroxomonosulfate (SO_5^{2-}) were estimated, respectively. It is shown that $k\ HSO_5^-/\ DPH^0 = 175 \pm 15.9 > k\ SO_5^{2-}/\ DPH^0 = 31.5 \pm 4.00$ 1/M s. The ratio of the oxidation of DPH by the dianion and the monoanion rate constants was taken by us as $\beta = (k\ SO_5^{2-}/DPH^0):(k\ HSO_5^-/DPH^0) = 31.5/175 \approx 0.2$. Such a mechanism was further supported by the *N*-oxide product identified by mass spectrometry and nuclear magnetic resonance (NMR) analyses [43].

pDPH was identified by us as a product of the oxidation of the DMH base by oxone without isolating it from the reaction mixture by the polarographic method by comparing the peak value of the reduction potential with this value of the reduction potential of the previously obtained pDPH by the reaction of oxidation of DPH by oxone [44]. pDPH was also identified by IR spectrometry and elemental analysis; purity was assessed by thin-layer chromatography (see *Experimental part*). So, the interaction of DPH with $KHSO_5$ can be represented by a scheme (Figure 3).

The titrimetric method (A) was based on the *N*-oxidation reaction involving using $KHSO_5$ and subsequent iodometric back titration of a known residual reagent. The spectrophotometric method (B) was based on the derivatization of DMH with $KHSO_5$ in the presence of iodide to produce a chromogen (triiodide) with a wavelength of maximum absorption at 350 nm.

3.2. Specificity.

A number of substances that may be present in preparations with DMH as excipients were studied under analytical conditions, comparing the difference in titrant volumes V_0–V (see analysis method) in the absence and presence of their regulated quantities. The following substances in the indicated quantities had virtually no effect on the difference (V_0 – V) and therefore do not interfere with the analysis: calcium hydrogen phosphate dihydrate – 10 mg, sodium carboxymethyl starch (type A) – 5 mg, microcrystalline cellulose – 60.8 mg, lactose-monohydrate (38 mg Lactose), magnesium stearate – 1.6 mg, high disperse silicon dioxide – 1.6 mg, povidone – 10 mg, crospovidone – 10 mg, to 50 mg of dimenhydrinate.

Fig. 5 shows the linear calibration for the spectrophotometric method. Characteristics of the linear regression equation curve calibration graph are shown in Table 1. Beer's law was observed within the concentration range of 0.1-4.1 μg/mL, exhibiting a molar absorptivity of 24370 L/mol cm. The limit of quantification was calculated to be 0.1 μg/mL.

Table 1. Characteristics of linear regression equation curve calibration graph

Characteristics	***Parameters***
$y = bx + a$	$y = (0.2439\times10^5)x - 0.0003$
Correlation coefficient (r)	0.999
Linear regression equation	$\Delta A = 2.44\times10^4\times c$
Slope (b±Δb)	$(0.2439\pm0.0027)\times10^5$
Intercept (a±Δa)	–0.0003±0.0016
SD of slope (Sb)	0.001×10^{-5}
SD of intercept (Sa)	0.0006
LOD (3.3Sa/b), mol/L	7.65×10^{-8} (0.036 μg/mL)
LOQ (10Sa/b) , mol/L	2.32×10^{-7} (0.11 μg/mL)

LOD is limit of detection, LOQ is limit of quantification, SD is standard deviation.

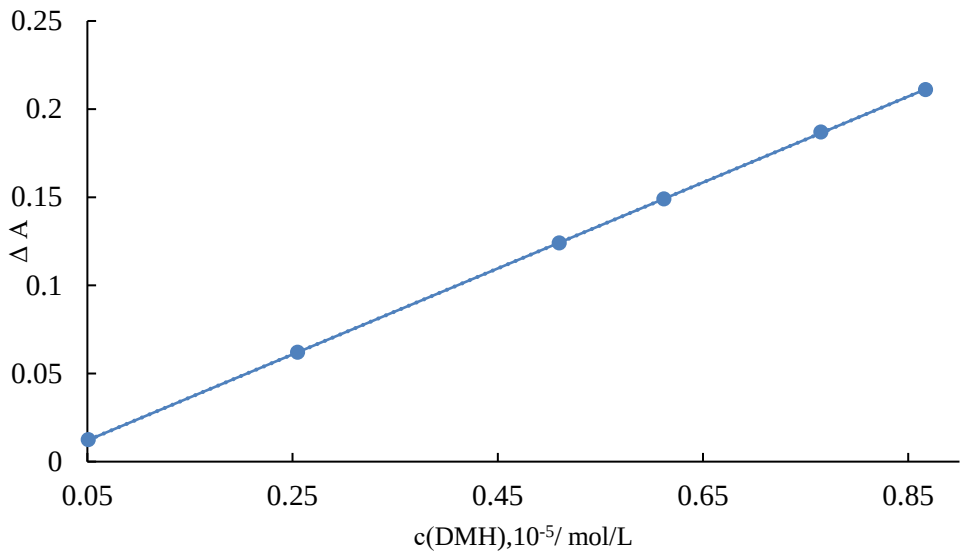

Figure 5. Calibration graph for the spectrophotometric determination of DMH.

A number of substances that may be present in dosage forms of DMH preparations as excipients was investigated by analyzing the difference in absorbance at the analytical wavelength. Drug excipients in regulated quantities (calcium hydrogen phosphate dihydrate – 10 mg, sodium carboxymethyl starch (type A) – 5 mg, microcrystalline cellulose – 60.8 mg, lactose-monohydrate (38 mg Lactose), magnesium stearate – 1.6 mg, high disperse silicon dioxide – 1.6 mg) give zero difference in absorption and therefore do not interfere with the analysis.

The feasibility of the technique for the analysis of pharmaceutical formulations was investigated. Results of titrimetric and spectrophotometric determination of pure substance, tablets, and injection dosage forms containing DMH using oxone are given in the Table. 2. The suggested technique is discovered to be more straightforward, adequately selective, and extremely sensitive in comparison to several of the documented techniques.

Table 2. Results of titrimetric (method A) and spectrophotometric (method B) determination of pure substance (i) (method A), tablets (ii), and injection (iii) dosage forms (method A, B) containing DMH using oxone.

Statistical parameters	**A. Titrimetric method**				**B. Spectrophotometric method**	
	i. Pure substance (%)		ii. Tablets Dramina® 50 (mg/tablet)	iii. Injection Vomex A® i.v. (mg/per 10 mL)	ii. Tablets Vomacur® 50 (mg/tablet)	iii Injection Vomex A® i.v. (mg/per 10 mL)
Found	%	99.4	48.5	60.6	50.6	60.0
		99.8	48.8	60.5	50.3	60.3
		98.2	49.6	61.3	49.8	61.9
		99.5	50.2	61.5	49.2	61.4
		98.2	48.6	61.7	48.6	62.5
Metrological characteristics (n = 5, p=0.95)	$\bar{x}$	99.0 % (Re:100.0%)	49,1 mg/tabl (Re:98.2%)	61.1 mg/per 10 mL (Re:98.6%)	49.7 mg (Re:99.3%)	61.22 mg/per 10 mL (Re: 98.7%)
	S	0.76	0.72	0.52	0.80	1.07
	$\Delta\bar{x}$	0.95	0.90	0.65	0.99	1.33
	RSD (%)	0.77	1.48	0.86	1.60	1.74
	δ* (%)	+0.53	+0.41	–0.13	–0.48	+0.01

Max. error, δ*: $(\bar{x} - \mu)\ 100/\mu$; μ – current found by standard pharmacopeial procedure; i. The quantitative content of DMH in the substance was 98.5%; ii. According to the quality certificate, the quantitative content DMH in Dramina was 48.9 mg (97.8%); the quantitative content DMH in Vomacur® 50 was 49.9 mg (99.8%); iii. According to the quality certificate, the quantitative content of DMH 10.0 mL of solution for injection contains 61.2 mg of DMH (98.71 %). RSD is Relative standard deviation; DMH is Dimenhydrinate, Re is Recovery

The method is reproducible and accurate, as shown by the statistical parameters and recovery study data. RSD does not exceed 1.7%. $(\bar{x} - \mu) \times 100/\mu < t_{\alpha}\times\text{RSD}/\sqrt{n}$. So, this approach could be used to determine the presence of DMH drugs in quality control labs.

4. Conclusions

Two simple methods for the determination of DMH in tablets and injections were developed. These methods are based on the *N*-oxidation reaction using $KHSO_5$ as an analytical reagent. The iodometric titration method is the first ever documented method for determining DMH, and the spectrophotometric method is the simplest reported method. The titrimetric method can be used over a wide linear dynamic range and was successfully applied to pure substances, tablets, and injections. The statistical characteristics and recovery study information revealed the accuracy and reproducibility of the methods. In addition to the simplicity and sensitivity of the procedures, the affordable cost of the apparatus and reagents is a further advantage. They're also useful because they have a high tolerance level for the usual ingredients that are found in most pharmaceutical blends. The possible application of these methods in routine quality control laboratories is suggested by their merits, which include the use of simple and relatively inexpensive instruments and high selectivity.

Author Contributions

Conceptualization, M.B. and O.M.; methodology, M.B.; software, O.K.; validation, O.M. and I.S.P.; formal analysis, V.M.; writing—original draft preparation, M.B., O.M.; visualization, O.K., V.M.; supervision, M.B., I.S.P. All authors have read and agreed to the published version of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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