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Determination of Mequitazine in Tablets by Difference Spectrophotometry Based on the Absorption of its Sulfoxide

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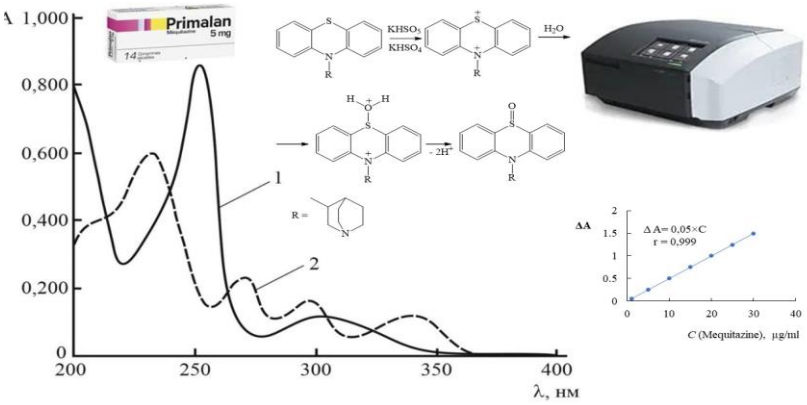
A new method is described for the rapid determination of (R)-(+)-Mequitazine. The drug is determined by a difference spectrophotometric technique based upon the absorbance of its sulphoxide derivative relative to the absorbance of a solution of the underivatized drug. The sulphoxide derivative are formed rapidly and quantitatively at room temperature by the addition of a solution of potassium caroate in form Oxone. The difference absorbance of the solutions is proportional to the concentration of the Mequitazine in the preparation and is specific for the intact drug in the presence of oxidative and photochemical decomposition products and excipients. Linearity range 1.00–35.00 μg/mL. The regression line equation is ΔA (342 nm) =0.05×C (r=0.99) where C is in μg/ml Mequitazine. The limit of quantitation, LOQ (10S), is 1.0 μg/mL. The possibility of quantitative determination of Mequitazin in Primalan 10 mg tablets has been demonstrated. RSD ≤ 1.5%; (($\bar{x}$ – μ) 100%/μ =+0.80%). 'μ' is data of quantitative determination by the reference pharmacopoeial method.

Graphical abstract



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1. Introduction

Mequitazine (trade name Primalan) is an H_1 antagonist and anticholinergic agent of the phenothiazine chemical class. It is used to treat allergies and rhinitis. It was patented in 1969 and has been used in medicine since 1976 [1-3]. The chemical formula of the drug is shown in Fig. 1.

The Japanese Pharmacopoeia recommends using the non-aqueous acidimetry method to determine pure Mequitazine, with the titration limit set potentiometrically, while it is used for the analysis of tablets by direct spectrophotometry using methanol as a solvent after the first isolation. Mequitazine is based on ancillary isolations [4].

In addition to known methods based on non-aqueous

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titrimetry (acidimetry) and direct UV spectrophotometry, many other methods have been proposed for the determination of the antihistamine agent Mequitazine.

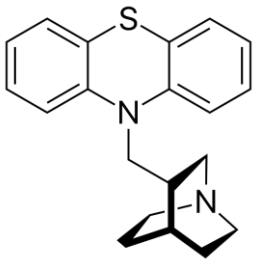

Fig. 1. Chemical structure of Mequitazine

Thus, several selective procedures based on spectrophotometry of the first derivative have been described [5]. A selective method based on the formation of a complex of mequitazine with palladium in the presence of methylcellulose in a buffer or non-buffer medium has also been proposed [6].

Various spectrophotometric methods based on oxidation reactions with the formation of intensely colored radical cations were also used. For example, a simple colorimetric method was described based on the oxidation of an intact phenothiazine preparation with potassium iodate in an acidic medium to form a red intermediate, which is considered to be a free radical of a semiquinoid structure used for its quantitative determination [7].

The red color of the solution, obtained as a result of the reaction between Mequitazine and potassium iodate, had an absorption maximum at 513 nm. The maximum color intensity was reached after 6 minutes at room temperature, and the resulting color remained unchanged for several minutes. The maximum color intensity is achieved using 0.05 M HCl. A linear concentration dependence was completed in the 5–40 μg/mL range. The regression equation was: A = 0.02138C + 0.0378 (r = 0.999), where A is the light absorption at 513 nm, C is the Mequitazine concentration (μg/mL) and r is correlation coefficient. It is known that the color stability of the radical cation depends mainly on the oxidizing agent used and the acidity of the medium. In the case of a strong oxidizing agent, the color of the radical quickly disappears due to the second stage of the reaction, leading to the formation of a colorless sulfoxide (Fig. 2).

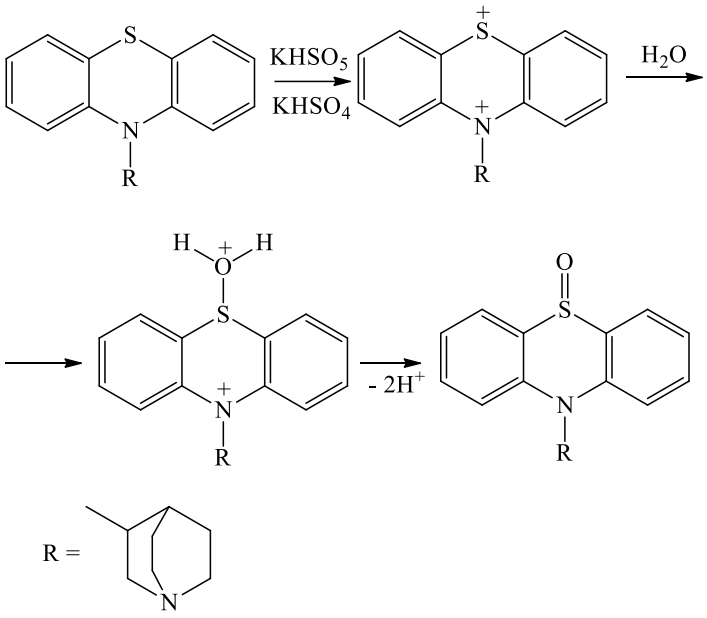

Fig. 2. Scheme of the oxidation process of Mequitazine.

Since the main disadvantage of direct UV spectrophotometry is sensitivity to excipients commonly found in pharmaceutical preparations, methods based on their oxidation reaction may be an alternative. The absorption of the S-oxide of the phenothiazine derivative is less susceptible to spectral interference from other pharmaceutical ingredients. It was considered suitable for the determination of these drugs in the presence of their degradation products formed as a result of oxidation [8].

However, in the article cited, low-stable peroxyacetic acid with a sharp, irritating odor was used as an oxidizing agent.

The aim of our study was to develop a new method for the quantitative determination of Mequitazine (phenothiazine derivative), in tablets using stable Oxone® as an oxidizing agent.

2. Results and Discussion

We have found that Mequitazine in drugs can be determined using a differential spectrophotometric method based on the absorption of the sulfoxide derivative of the drug at 342 nm. The sulfoxide derivative is formed quickly and quantitatively by adding a solution of potassium caroate in the form of "Oxone®", which is a triple potassium salt $2KHSO_5$ $KHSO_4$ K_2SO_4. Oxone has a longer shelf life than potassium peroxymonosulfate [11, 12]. The UV spectra of mequitazine

and its S-oxide mequitazine are shown in Fig. 3.

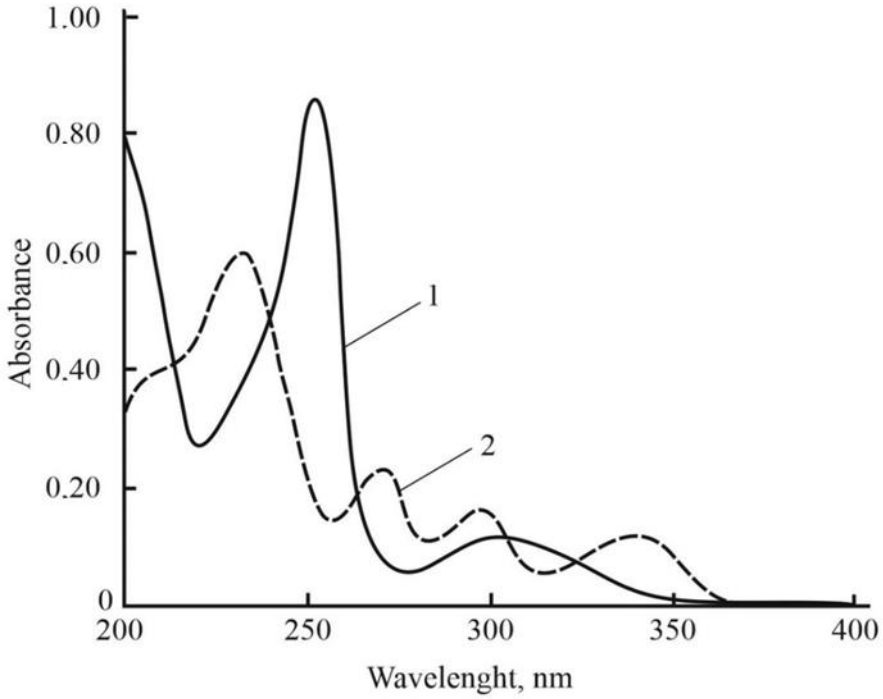

Fig. 3. UV spectra of mequitazine (1) and mequitazine S-oxide (2), each at 10 μg/mL.

The molar coefficient of light absorption (the slope of the dependence A on the concentration Mequitazine is 4.19×10^3 $L\times mol^{-1}\times cm^{-1}$.

Additional selectivity of the proposed method can be achieved by measuring the absorbance of the formed sulfoxide derivative at 342 nm with respect to the absorbance of the non-derivatized drug solution, i.e. by performing the determination by the differential method. The difference in the absorption of solutions is proportional to the concentration of the phenothiazine derivative in the preparation and specific for the intact preparation in the presence of oxidative and photochemical decomposition products and excipients (flavors, etc.). Linearity range 1.00–35.00 μg/mL. The regression line equation is: ΔA=0.05×C (r=0.999) where C is in μg/mL Mequitazine (Fig. 4).

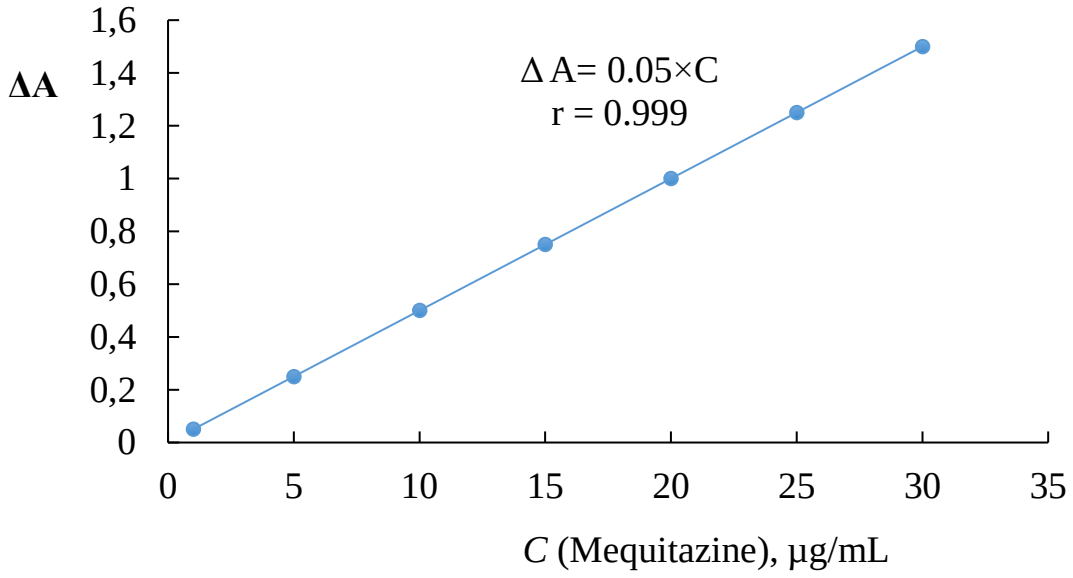

Fig. 4. Absorption of Mequitazine sulfoxide versus Mequitazine concentration. λ = 342 nm; the path length is 5 cm.

Analysis of Primalan® Tablets

Weighed at least twenty tablets to determine the average weight of one tablet. The tablets were well crushed and homogeneously mixed.

A weight of powdered tablets equivalent to 50 mg Mequitazine was transferred to a 100 mL flask. Was extracted

with 2×30 mL of 0.1 M HCl with vigorous shaking for ~10 min, the volume was adjusted with the same solvent. The well-mixed extract was filtered through filter paper (red ribbon). The solutions were diluted to the same concentrations as the standard stock solution, and analyzed as indicated in the method, according to the proposed method.

Quantitative determination of Mequitazine tablets, 10 mg Primalan®

Add 75 mL of 0.1 M perchloric acid solution to the powder of 5 tablets, shake for 10 minutes, sonicate for 1 minute, dilute with 0.1 M perchloric acid solution to obtain a solution containing 0.05 (w/v) Mequitazine and filter (solution A). Dilute 5.00 mL of solution A to 100 mL with 0.1 M perchloric acid solution (solution B). To another 5 mL of solution A add 50 mL of 0.2 M hydrochloric acid solution, 2.00 mL of 0.005 M potassium caroate solution, mix, leave for 5 minutes and add enough water to make 100 mL (solution C).

Measure the absorbance of solution C at a maximum at 342 nm using solution B in the reference cuvette, and measure the absorbance of solution B at the same wavelength using water in the reference cuvette. Repeat the procedure using 0.050% (w/v) Mequitazine solution in 0.1 M perchloric acid instead of solution A, starting with "Dilute 5.00 mL of solution A to 100 mL..." and calculate the $C_{20}H_{22}N_2S$ content using the reported $C_{20}H_{22}N_2S$ content of Mequitazine PCO. The test is invalid if the absorbance of solution B is greater than 0.10.

Mequitazine standard solution. About 50 mg (accurately weighed) of the working standard sample of Mequitazine is placed in a volumetric flask with a capacity of 100 mL, dissolved in 30 mL of a 0.1 M solution of perchloric acid and the volume of the solution is adjusted to the mark with the same solvent to obtain a solution with 0.050% of Mequitazine (solution A).

5.00 mL of a working standard solution of Mequitazine is placed in a volumetric flask with a capacity of 100 mL and the volume of the solution is adjusted to the mark with a 0.1 M solution of perchloric acid (solution B).

To another 5 mL of solution A add 50 mL of 0.2 M hydrochloric acid solution, 2.00 mL of 0.005 M potassium caroate solution, mix, leave for 5 minutes and add enough water to make 100 mL (solution C).

Results processing

The content of Mequitazine ($C_{20}H_{22}N_2S$) in tablets as a percentage of the declared amount (X) is calculated by the formula:

$$X = \frac{A_1 \cdot a_0 \cdot P \cdot G}{A_0 \cdot a_1 \cdot L},$$

where A_1 is the optical density of the test solution;

A_0 is the optical density of the solution of Mequitazine;

a_1 is weighed powder of crushed tablets, mg;

a_0 is sample of Mequitazin, mg;

P is content of Mequitazin in a sample of Mequitazin, %;

G is average weight of one tablet, mg;

L is the declared amount of Mequitazin in one tablet, mg.

Table 1. The results of the analysis of tablets Primalan® "Pierre Fabre", France, 10 mg each according to the proposed method (*number of trials (n)* was 5; *probability (p) was* 0.95).

Detected substance/ - analyzed drug	Found ($\bar{x} \pm \Delta\bar{x}$), mg/tabl.	RSD %	Certificate data (μ *) mg per tablet	$\frac{(\bar{x} - \mu)}{\mu *} 100$ (%)
Mequitazin/ - Primalan® "Pierre Fabre", France, 10 mg, No. 14;	9.98±0.19 (99.80±1. 90 %)	1.5	9.90	+0.80

* Calculated using mean (μ) analysis data according to JP XVII (Japanese Pharmacopoeia. 17th edition). Mequitazine tablets must contain at least 95.0% and not more than 105.0% of the stated amount of mequitazine ($C_{20}H_{22}N_2S$: 322.47 g/mol)

3. Material and Methods

Reagents and instruments

Mequitazine, pure sample. Its purity was checked by determining its m.p. (130–131 °C) [9] and by the reference spectroscopic method using A (1%, 1 cm) [10]. The content of the main substance was 99.71 ± 0.40% (*n* = 7).

A standard solution of mequitazine hydrochloride (1 mg/mL, as free base) was prepared by adding 3.1 mL of 0.1 M HCl to 100 mg of Mequitazine free base dispersed in 70 mL of distilled water in a volumetric 100 mL flask. It was shaken until complete dissolution, then the volume was supplemented with distilled water.

"Primalan" 10 mg tab. No. 14, manufacturer "JSC Pierre Fabre", France. The active pharmaceutical ingredient (API) of the drug is Mequitazine, excipients: lactose; starch; acacia gum; colloidal silicon; talc; sodium carmellose; magnesium stearate; in a blister pack 14 pcs.; in a pack of cardboard 1 pack. Lot: 6118000011323.

Mequitazine tablets contain not less than 95.0% and not more than 105.0% of the indicated amount of Mequitazine ($C_{20}H_{22}N_2S$: 322.47) [4].

S-oxidation product identification

Synthesis of Mequitazine sulfoxide

Obtaining pure Mequitazine sulfoxide was made possible by the oxidation of the drug with an aqueous solution of Oxone at room temperature. An exact weight (0.01 mol) of Mequitazine (3.22 g) was added with stirring with a magnetic stirrer to a 250 mL flask containing 200 mL of distilled water, 2.5 mL of HCl and 0.012 mol (calculated as potassium caroate) Oxone. After 30 min, the reaction product was extracted twice with chloroform after adding ammonia solution to reach pH 10. The liberated mequitazine sulfoxide base in chloroform was washed with water, dried by adding anhydrous sodium sulfate, and the extract was evaporated to dryness under nitrogen atmosphere; the residue was crystallized by cooling the solution overnight in a refrigerator (~5°C). We obtained a yellowish-orange crystalline powder with a melting point of 215–218°C (according to the literature, 214–218°C).

The scanned UV spectrum of Mequitazine sulfoxide shows characteristic sulfoxide maxima at 232 nm, 271 nm, 298 nm and 342 nm (Fig. 3).

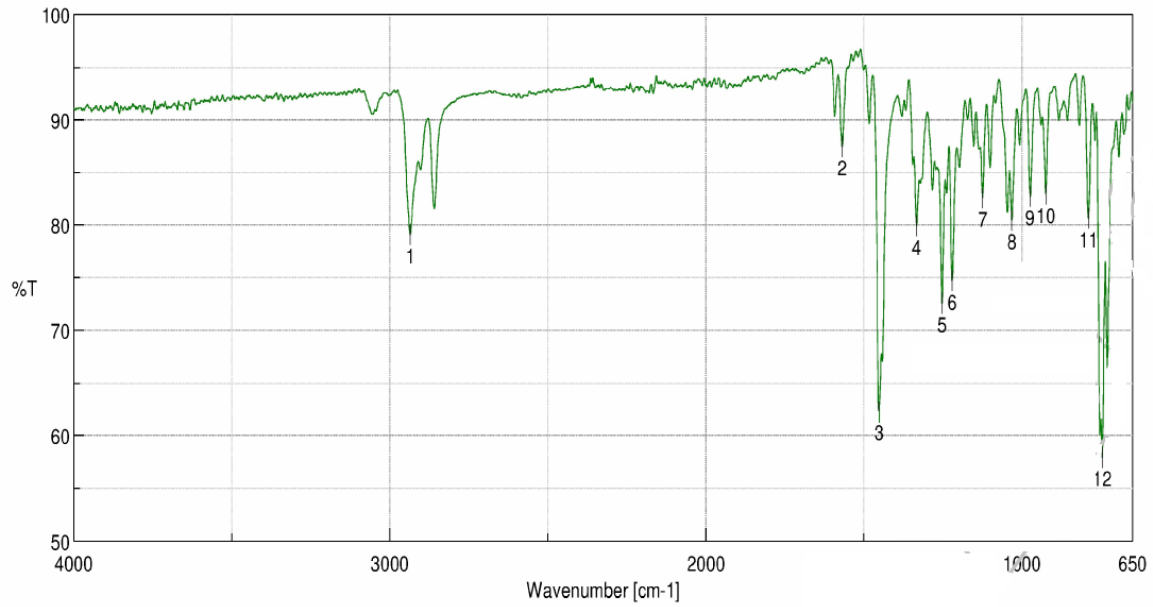

Fig. 5. IR spectrum Mequitazine sulfoxide.

Tab. 2. Results of Peak Find.

No.	Position	Intensity
1	2935.13	79.0055
2	1568.81	87.4393
3	1452.14	79.8315
4	1333.53	62.2225
5	1252.54	72.5116
6	1220.72	74.6537
7	1124.30	82.4876
8	1020.00	80.3782
9	973.87	82.6308
10	924.70	82.8161
11	789.70	80.5661
12	746.31	57.8901

The resulting sulfoxide was also characterized by IR spectroscopy: the IR spectrum shows a characteristic peak at 1020 cm^{-1} corresponding to the sulfoxide group (Fig.5, Tab. 2), which is absent in the spectrum of pure MEQUITAZINE [7].

The oxidant was Oxone®, i.e., a triple potassium salt of Caro's acid, $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Acros Organics).

Preparation of a solution of potassium hydrogen peroxomonosulfate 0.005 mol/L. A portion of about 0.15-0.2 g of Oxone was dissolved in 100 mL of double-distilled water. The exact content of potassium caroate was determined by iodometric titration. 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 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: $c(KHSO_5)$ = $V(Na_2S_2O_3)$ ×0.0100×100.00/ 10.00×10.00×2.

A double-beam Shimadzu UV-Visible spectrophotometer, with spectral bandwidth of 1 nm wavelength accuracy ±0.5 nm, Model – UV 1800 (Japan), Software UV-Probe 2.62, and a pair of 1 cm matched quartz cells, as well as in a cuvette with an absorbing layer thickness of 50 mm on a Speckol-11 spectrophotometer (Carl Zeiss Jena) with the prefix EC 5 were used to measure absorbance of the resulting solution.

4. Conclusions

In contrast to the recommended procedure by direct UV spectrophotometry, our proposed indirect spectrophotometric method is simpler. The reagent used in the proposed method is cheap and available. The developed technique does not involve any critical conditions or tedious sample preparation. This method of spectrophotometric analysis is of great interest to analytical pharmacy because it allows the quantitative determination of Mequitazin in its pharmaceutical formulations without interference from excipients and degradation products. The proposed method of quantitative determination allows you to determine Mequitazine in the concentration range of 1-35 μg/mL. The limit of quantitation, LOQ (10S), is 1.0 μg/mL. A new spectrophotometric technique has been developed and the possibility of quantitative determination of Mequitazin in Primalan 10 mg tablets has been demonstrated. RSD ≤ 1.5%; $((\bar{x})-\mu)$ 100%/μ = +0.80%). μ is data of quantitative determination by the reference pharmacopoeial method.

Author Contributions

MB: Conceptualization, Methodology, Writing – original draft. II: Formal analysis, Resources, Writing – review & editing, Project administration.

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