Spectrochimica Acta Part A 74 (2009) 740–745

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Photodegradation and photostability-indication of mequitazine

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ARTICLE INFO

Article history:
Received 5 January 2009
Received in revised form 5 July 2009
Accepted 5 August 2009

Keywords:
Colorimetry
Mequitazine
Photodegradation
Stability

ABSTRACT

The photochemical behavior is investigated for mequitazine (MQ) illustrating possible mechanisms and photodegradation products formed. Accelerated photolysis is done for MQ under justified stress conditions by subjecting aqueous drug solutions to radiation for specified period of time. Synthesis of the main photodegradants, the sulfoxide, is achieved. Selective quantification of MQ, singly in bulk form, pharmaceutical formulations and/or in the presence of its photodegradants is demonstrated.

The indication of stability has been undertaken under conditions likely to be expected at normal storage conditions using a simple colorimetric method based on oxidation of the intact phenothiazine drug by potassium iodate in acid medium to form a red colored product adequate for quantitative estimation of the studied drug.

1. Introduction

Phenothiazines exert photosensitization, where, their photodecay may occur either by a free-radical chain process, *i.e.* autooxidation, and/or by involving excited singlet molecular oxygen, *i.e.* oxygenation [1,2]. Formation of the corresponding sulfoxide was reported to be the primary decay product [3]. A number of other photodecomposition products including N-oxides, hydroxyl derivatives, dimeric or polymeric products, excited monomers (excimers), in addition to sulfones, of various phenothiazines were isolated and characterized [4–6]. The molecular characteristics–phototoxicity relationship demonstrated that the tricyclic moiety is essential for the phototoxic activities.

Mequitazine (MQ) is 10-(1-Azabicyclo[2.2.2]oct-3-yl-methyl)-10H-pheno-thiazine (Fig. 1). It is an antihistaminic phenothiazine drug prescribed for treating allergic rhinitis and urticaria [7].

MQ was determined by a number of spectrophotometric and spectrofluorometric methods [8–10]. Assay of MQ was done based on complex formation with palladium in the presence of methylcellulose [11]. Chemiluminescence of MQ, utilizing single photoelectron counting apparatus was carried out [12]. Determination of MQ by GC/MS [13–16] and by HPLC methods was described [17–19].

A possible photochemical process leading to photosensitivity due to MQ was studied in comparison with that of chlorpromazine [20] while the phototoxic potential of MQ was determined by the photosensitizing action on microbial systems [21].

In modern analytical laboratory, there is always a need for significant stability-indicating methods of analysis. The present work aimed to study the photodegradation of MQ and to develop a simple colorimetric method for its quantification in pure form or even in the presence of its photolytic degradants in bulk powder as well as in pharmaceutical preparations.

2. Experimental

2.1. Instruments

- High-pressure mercury lamp, Hanau, (Germany), 12.5 W short/long wavelengths (254 nm and 365 nm) equipped with a quartz glass cooling mantle.
- Xenon lamp for suntest, Vilber Laurmat, providing UV–vis light in the range of 300–800 nm, equipped with a quartz glass cooling mantle.
- Spectrophotometer: Shimadzu UV-1601 PC, dual-beam UV–vis spectrophotometer (Japan), with matched 1-cm quartz cells, connected to an IBM-compatible PC. Bundled, UV-PC personal spectroscopy software version 3.7 was used to process the absorption spectra. The spectral band width was 2 nm with wavelength-scanning speed of 2800 nm min^{-1}.
- IR spectrophotometer: Mattson Genesis II FTIR™ (USA), sampling was undertaken as potassium bromide discs.
- Precoated TLC-plates, silica gel 60 F_{254} (20 cm × 20 cm, 0.25 mm), E. Merck, (Germany).
- Gas chromatograph coupled to a mass spectrophotometer: GC–MS-QB 1000 EX, Finnigan nat (USA).
- pH-meter, Digital pH/MV/TEMP/ATC meter, Jenco Model-5005 (USA).

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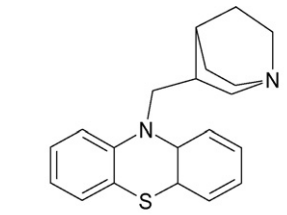
doi:10.1016/j.saa.2009.08.006



$C_{20}H_{22}N_2S$ (M.W. 322.47)

Fig. 1. Structural formula of mequitazine.

o Graffin melting point apparatus model SMP1, Stuarts Scientific Co. Ltd. (UK).

2.2. Materials and reagents

2.2.1. Materials

Reference MQ standard was kindly supplied by Rhone-Poulanc-Rorer (France). Its potency was found to be 99.70 ± 0.39% (n = 6), according to a reference spectroscopic method [22].

2.2.2. Pharmaceutical formulations

Primalan® tablets (5-mg per tablet) and Primalan® syrup (0.5 mg mL^{-1}) were kindly supplied by Amriya for Pharmaceutical Industries (Egypt).

Pure drug, utilized without further treatments, and pharmaceutical formulations were kept always protected from light.

2.2.3. Standard solutions

o Mequitazine hydrochloride (MQ·HCl) standard solution (1 mg mL^{-1}, as free base) was prepared by adding 3.1 mL of 0.1N HCl to 100 mg of MQ free base, dispersed in 70 mL distilled water, in 100-mL volumetric flask. Shaking was done till complete dissolution then the volume was completed with distilled water.
o Photodegraded MQ·HCl working solution (1 mg mL^{-1}, as free base) was prepared by complete photolysis of the corresponding solution by the aid of stress ultraviolet illumination in a UV-cabinet. Complete photolysis was achieved after 24 h, as shown by TLC-fractionation. The aqueous degraded solution was evaporated under vacuum in a N_2-atmosphere till dryness and quantitatively transferred with distilled water into 100-mL flask. The volume was completed with distilled water.

All calculations and samples preparation for reference material and pharmaceutical formulation were done on MQ free base. Solutions were always freshly prepared on the day of analysis and stored in a refrigerator, protected from light, to be used within 24 h.

2.2.4. Reagents

o Hydrochloric acid, chloroform, aqueous ammonia solution (25%, w/v) and *n*-butanol: ADWIC, El-Nasr Pharm. Co. (Egypt).
o Potassium iodate: E. Merck (Germany).
o De-ionized water: bi-distilled from "Aquatron" Automatic Water Still A4000, Bibby Sterillin Ltd. (UK).

2.3. Procedures

2.3.1. Accelerated photolysis of an aqueous solution of the drug

Safety measures should be taken to avoid exposure of eyes and skin to direct UV-irradiation. Solutions of MQ·HCl in water (1 mg mL^{-1}, free base) were irradiated by exposure to UV light (254 nm) in an open container (12 cm Ø, 2 cm height) at a small angle (~60°) to the surface of the solution. The distance from the surface of the solution to the UV-lamp was ~30 cm. The temperature was controlled to be 35 °C using cooling mantle. Continuous mixing was done without interrupting the irradiation using long glass rod, just to minimize the local thermal effect. Irradiation was carried out for different time intervals (up to 180 min). At different specified time intervals, a sample (5-mL) was withdrawn from the vessel using a graduated pipette after short pre-stirring. Each taken sample was placed into a test tube protected from light by careful wrapping with aluminum foil. Protection measurement should be pre-taken to avoid any possible long exposure of eyes and skin to direct UV-irradiation. A part of the solution was protected from the light source and was considered as a blank. Long-period irradiation was interrupted by short dark phases to save the lamp-life. The irradiated drug solution was fractionated by TLC on silica gel 60 F_{254} plates using *n*-butanol + water + 25% (w/v) aqueous ammonia (17:2.8:0.2, by volume) as a developing solvent. The ultraviolet spectrum was monitored for the withdrawn samples during irradiation.

2.3.2. Suntest on MQ

The dry powder of MQ was placed in pyrex vial, where, it was subjected to direct irradiation using xenon lamp that provides UV–vis light in the range 300–800 nm (having the same spectral distribution of sunlight). The irradiance level is adjusted at 510 W h m^{-2}. A dose of 45.7 W h m^{-2} could be permitted in the UV (300–400 nm) and 112.5 k lx in the visible range (400–800 nm). Accordingly, the samples were exposed to light for 15 h providing an overall illumination of 200 W h m^{-2} (near-UV energy) and 1.2 million lx h (visible energy), according to ICH guidelines.

The protected samples, wrapped with aluminum foil and placed alongside the authentic samples, were considered as the dark controls. To minimize the thermal effect, possibly caused by the xenon lamp, the temperature was adjusted at the minimum value (35 °C) and the lamp was switched off for 10 min per an illumination hour.

The treated drug powder after running the suntest was fractionated by TLC on silica gel 60 F_{254} plates using the previously described developing solvent. The ultraviolet spectral monitoring was performed on the treated powder after running the suntest.

2.3.3. Synthesis of MQ sulfoxide

The preparation of pure phenothiazine sulfoxide was possible by aqueous nitrous acid oxidation of the drug at room temperature [23]. Accurate mass (1×10^{-2} M) of MQ (3.22 g) was suspended in 250 mL of distilled water, in a flask. Then ~50 drops of HCl were added with magnetic stirring. Excess of aqueous sodium nitrite solution (120 drops, 0.1 g mL^{-1}) was carefully added. Nitrogen was bubbled through the solution for ~2 h to remove the resulted nitrogen oxide gas. The reaction product was extracted twice with chloroform to remove any foreign materials. Chloroform was discarded and conc. ammonia solution (100 drops) was added to reach pH 10 and allow sulfoxide separation. The liberated base sulfoxide was extracted with chloroform and washed with water. The chloroformic extract was evaporated to dryness under nitrogen gas and the residue was crystallized by cooling the solution overnight in a refrigerator (~5 °C). The product was purified using preparative TLC, where the synthesized sulfoxide was characterized by determination of its m.p., TLC-fractionation, UV, IR spectrometry and GC/MS.

2.3.4. Colorimetric determination of MQ using potassium iodate

Aliquots equivalent to (0.5–4 mL) of MQ·HCl standard solution (1 mg mL^{-1}, as free base) were separately transferred to 100-mL volumetric flask. For each flask 5 mL of aqueous potassium iodate solution (0.1%, w/v) was added and then the volume was completed with 0.05N HCl. The absorption spectrum of the color developed

was recorded at 513 nm against the corresponding reagent blank after 6 min. Effect of potassium iodate concentration, acid concentration and temperature were studied. The regression equation was then computed and used for determination of unknown samples containing MQ.

2.3.5. Assay of laboratory prepared mixtures containing different ratios of MQ and its photodegradants using the proposed method

Aliquots of intact drug were mixed with portions of photodegraded drug (as prepared in Section 2.2.3) to prepare different mixtures containing 10–90% (w/w) degradation products, and proceed as mentioned under the described method. Calculate the concentration from the computed regression equation.

2.3.6. Assay of pharmaceutical formulations

o *Primalan® tablets*

At least twenty tablets were weighed to determine the average weight per tablet. The tablets were powdered well and homogeneously mixed. A mass of powdered tablets equivalent to 50 mg of MQ is transferred into a 100-mL flask. Extraction with 2 × 30 mL of 0.05N HCl was done by vigorous shaking for ~10 min, the volume was completed with the same solvent. The well-mixed extract was filtered through Whatman filter paper (No. 42). The solutions were diluted to the same concentrations of the standard stock solution and analyzed as mentioned by the proposed method.

o *Primalan® syrup*

Portions of the syrup solution were diluted with 0.05N HCl and completed as mentioned under the proposed method (in Section 2.3.4).

3. Results and discussion

3.1. Accelerated photolysis of an aqueous solution of MQ

The aim of the work was to investigate the photodegradation possibly occurring as a result of the UV-irradiation of aqueous solutions of the selected phenothiazine drug.

3.1.1. Spectral changes

Accelerated drug photolysis was carried out for MQ by irradiating its aqueous solution (1 mg mL^{-1}, free base), utilizing a 12.5-W UV-lamp (254 nm) at a specified distance and angle in an open container. The color of irradiated MQ solution changed gradually from colorless to faint pink and finally reddish-brown by the end of irradiation period. The spectral monitoring revealed an increase in the light absorption at ~513 nm inducing the red coloration. The intensity of the formed color was time-dependent; the more the exposure, the more intense was the color. Generally, the principal photodegradation products of the phenothiazines are reported to be the corresponding sulfoxides, as the major photodegradates. Felmeister and Disher [5] studied the photodegradation of chlorpromazine (CPZ) and the production of a stable red radical, CPZ$^{\bullet+}$ upon UV-irradiation. The observed red color in the case of MQ may be attributed to a similar stable red radical. Such radicals decompose on heating; so upon heating the colored drug solution, color fainting then total discharging was observed.

The distribution of electrons in the MQ molecule, like other phenothiazines, may lead to the formation of many radical forms, such as at S-atom, at N_{10}-atom and between S- and N-atoms in the phenothiazine ring, as a result of possible resonances [1]. The possibility of formation of MQ radical at the S-atom is expected under the influence of short lasting UV-irradiation.

Fig. 2 shows the ultraviolet absorption spectra resulting upon irradiation of MQ·HCl at different time intervals. The ultraviolet

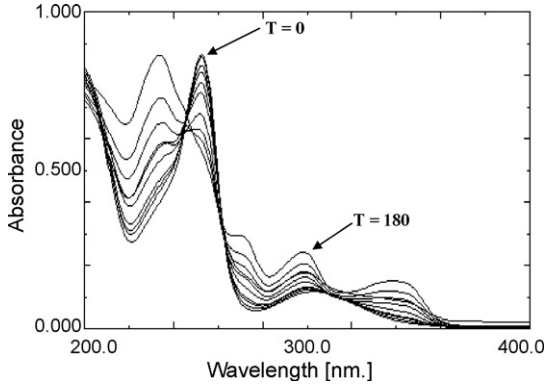


Fig. 2. Absorption spectra of MQ·HCl (10 μg mL^{-1}) irradiated for different time intervals (0–180 min).

irradiated phenothiazines degrade *via* a semiquinone free-radical intermediate. Disproportionation of these free radical results in the formation of the phenothiazine sulfoxide as indicated in Scheme 1 that shows the mechanism illustrating the formation of the phenothiazine sulfoxide from the parent phenothiazine compound during the ultraviolet irradiation.

As shown in Fig. 2, peaks characteristic for intact drug appear at 253 nm and 302 nm. During irradiation, the peak at 253 nm exhibited a hypochromic shift and then disappeared after irradiation for about 180 min. On the other hand, formation of new peaks was observed at 232 nm, 271 nm, 198 nm and 342 nm, which are the characteristic maxima of the corresponding sulfoxide.

3.1.2. TLC-fractionation

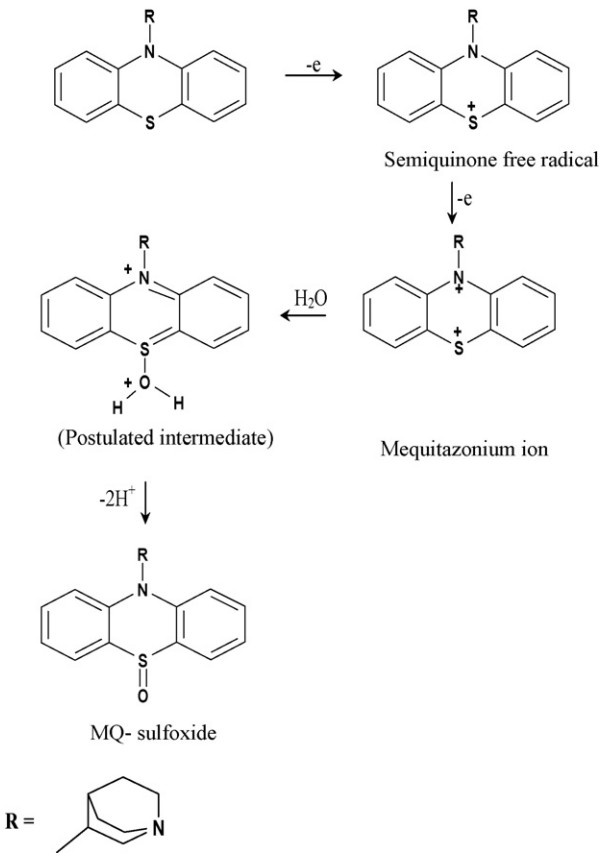
Working standard solution of MQ·HCl (1 mg mL^{-1}, free base) after irradiation time of 180 min was evaporated to dryness under reduced pressure in rotavapor, in an atmosphere of nitrogen gas. The obtained residue was dissolved in the least amount of distilled water. Fractionation of the components of the drug degradation was done on thin layers of silica gel F_{254} using *n*-butanol + water + 25% (w/v) aqueous ammonia solution (17:2.8:0.2, by volume) as the developing solvent. The developed plate was visualized under short UV-lamp and/or by subjecting it to iodine vapors. TLC-fractionation of photodegraded MQ·HCl (irradiated for 3 h) showed seven photodegradates (with R_f-values 0.05–0.2) separated from the intact drug (its R_f-value = 0.26). Like other phenothiazines, MQ undergo a series of molecular breakdown. Some of the less stable primary photolytic products may be easily converted to different stable secondary photodegradants on longer exposure to light. Early investigations on phenothiazines' photoxidation indicated the formation of the corresponding sulfoxides as the major products [5].

3.1.3. pH profiling

The change in the pH-value was determined during different time intervals of UV-irradiation for MQ·HCl. A significant increase in hydrogen ion concentration, *i.e.* decrease in the pH-value, on irradiation was noticed. It can be explained on the basis of the reaction of the short-lived phenazathionium ion with water to yield the S-oxide (Scheme 1). Two hydrogen ions result for each molecule of the S-oxide formed. Thus, on irradiation of MQ·HCl solution pH-value decreased from 3.1 to 2.8.

3.1.4. The kinetic order

Estimation of the kinetic order of the photodegradation of MQ·HCl solution could be done by calculating the percentage of the remaining drug concentration (C_t/C_i) %, and its logarithmic value at different time intervals during the irradiation, where C_t (is the con-



Scheme 1. Possible reaction mechanism for the oxidation of mequitazine by potassium iodate.

centration at time t) and C_i is the initial concentration. Assay of MQ was carried out by adopting the developed potassium iodate colorimetric method. Plotting the percentage of the remaining drug concentration (C_t/C_i) %, *versus* time showed curved correlation indicating the complicity of the photolysis process. Some of the less stable primary photolytic products may be easily converted to different stable secondary degradation compounds on longer exposure to light. The photodegradation process of MQ·HCl followed first order kinetics during early stages of photodegradation as indicated by the straight line relationship between log the % of the remaining drug concentration *versus* time, the linear correlation extends from the beginning of the irradiation process till 60 min, *i.e.* at the early illumination periods, then linearity is deformed, shown in Fig. 3).

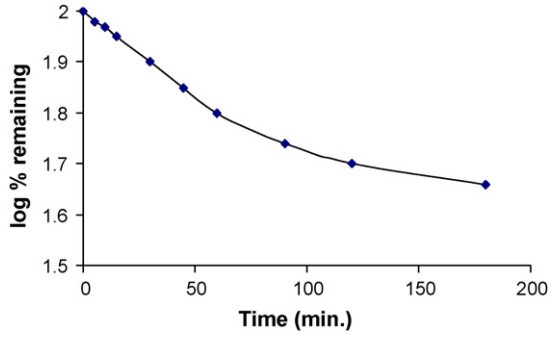


Fig. 3. Plotting of log the % remaining (C_t/C_i) % of photolyzed solution (1 mg mL^{-1}) of MQ·HCl.

3.2. Suntesting on MQ

Suntesting for MQ was carried out to study its photostability in the solid form and compare it with the photostability of the solution form.

Pure powder of MQ free base was subjected in heat resistant pyrex vials to the Xenon lamp. After subjecting the dry MQ powder to the irradiation dose (for 15 h), the vials were then opened and the contents were examined. Irradiated MQ powder was still white in color but with melting point of 150 °C, instead of 130 °C for the non-irradiated drug. The ultraviolet spectra, shown in Fig. 4 show quite difference from the corresponding spectrum of the original non-irradiated pure MQ. Such findings indicate that a possible decomposition could be occurred.

TLC-fractionation of the photolyzed samples was applied, where, only few photodegradates (including the sulfoxide) were observed. MQ showed certain stability when present in the solid form more than that if it was in solution but still photo-labile in both cases.

3.3. Synthesis of MQ sulfoxide

Sulfoxidation resulting in 5-sulfoxide metabolite is a common bio-transformation pathway for all phenothiazines and it is the main photodegradate formed during ultraviolet irradiation [24].

MQ sulfoxide could be obtained synthetically by nitrous acid oxidation. It is yellowish-orange crystalline powder (melting range of 214–218 °C). The synthesized sulfoxide is bitter in taste and freely soluble in dilute acids and in methanol, but practically insoluble in water. TLC-fractionation shows the MQ sulfoxide with retention value of 0.1, using the specified conditions mentioned

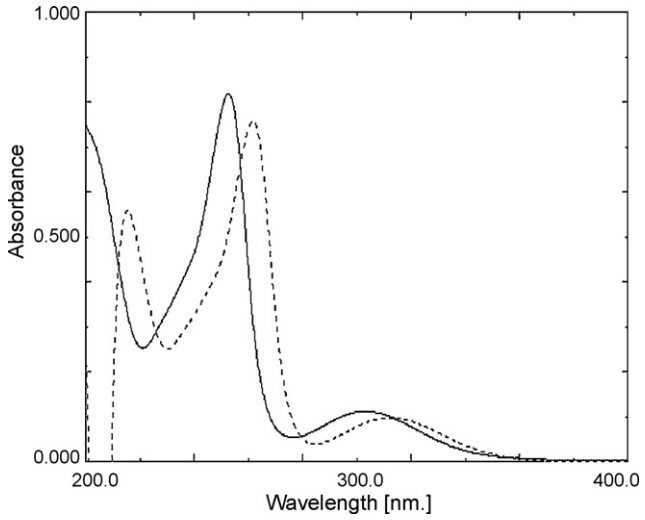


Fig. 4. Absorption spectra of pure (––) and suntest irradiated (. . . . . .) mequitazine (10 μg mL^{-1}).

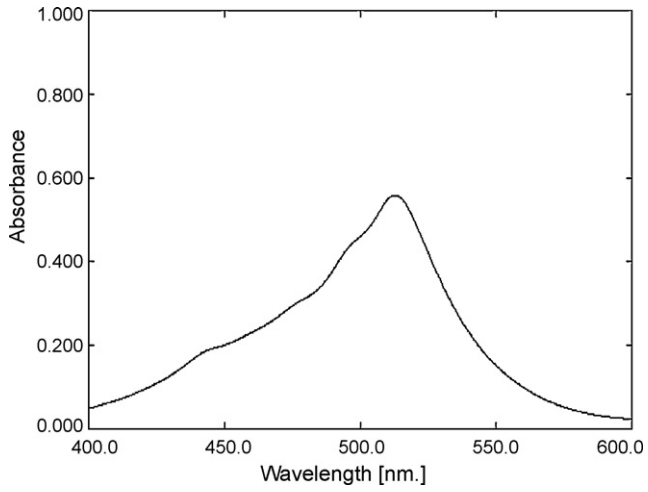


Fig. 6. Spectrum of the reaction product obtained from the reaction between 30 μg mL^{-1} mequitazine and potassium iodate.

before. The scanned spectrum of MQ sulfoxide demonstrates the characteristic maxima of the sulfoxide at 232 nm, 271 nm, 298 nm and 342 nm (Fig. 5). The prepared sulfoxide was characterized by IR spectroscopy showing a peak at 1020 cm^{-1} corresponding to sulfoxide stretching which is absent in the spectrum of pure MQ. GC/MS-spectrum shows a peak at *m*/*z* 338 corresponding to molecular ion of MQ sulfoxide with a molecular formula of $C_{20}H_{22}N_2SO$.

3.4. Colorimetric determination of MQ using potassium iodate

Different colorimetric methods have been reported for the determination of phenothiazines. The general method of Cavatorta [25] to quantitate unoxidized phenothiazine derivatives by color complex formation with palladium chloride has been reported. Phenothiazines react with ceric ammonium sulfate, first by forming a red colored semiquinone free radical followed by colorless sulfoxide derivative [26].

Ellaithy et al. [27] observed that chlorpromazine, promethazine and fluphenazine hydrochlorides undergo one-electron oxidation with potassium iodate in acid medium to a red intermediate which is believed to be a free radical with a semiquinoid structure. The stability of the red color obtained depends on the concentration of acid, oxidizing agent and concentration of the phenothiazine drug. When a large excess of oxidizing agent was added the red color was quickly destroyed leaving colorless sulfoxide (Scheme 1).

Only intact MQ is oxidized in the proposed method by potassium iodate in acid medium. The isolated photodegradates of MQ and the chemically prepared sulfoxide derivative fail to produce the red color obtained by adopting the proposed colorimetric method. It could be considered therefore, stability-indicating method for estimating MQ in the presence of its photodegradants weather in solution or solid forms.

The red color produced from the reaction between MQ and potassium iodate shows absorption maxima at 513 nm, as shown in Fig. 6. Optimization of the reaction conditions was done and it was found that maximum color intensity was attained after 6 min at room temperature using 5 mL of aqueous potassium iodate solution of concentration of 0.1% (w/v) and the obtained color remains stable for few minutes. Maximum color intensity was attained when using 0.05N HCl and temperature between 10 and 30 °C *i.e.* room temperature. The studied range for potassium iodate solution concentration was 0.05–0.5% (w/v), while the studied range for the acid concentration was 0.02–0.5N HCl. The temperature effect was investigated in the range of 10–70 °C.

A linear relationship was obtained in the range of 5–40 μg mL^{-1} of MQ. The regression equation was computed and found to be:

$$A = 0.02138C + 0.0378 \quad (r = 0.999)$$

where *A*: absorbance at 513 nm, *C*: concentration of MQ (μg mL^{-1}), and *r*: the correlation coefficient.

The precision of the proposed method was confirmed by the analysis of different concentrations of pure samples. The mean percentage recovery was found to be 100.12 ± 0.679.

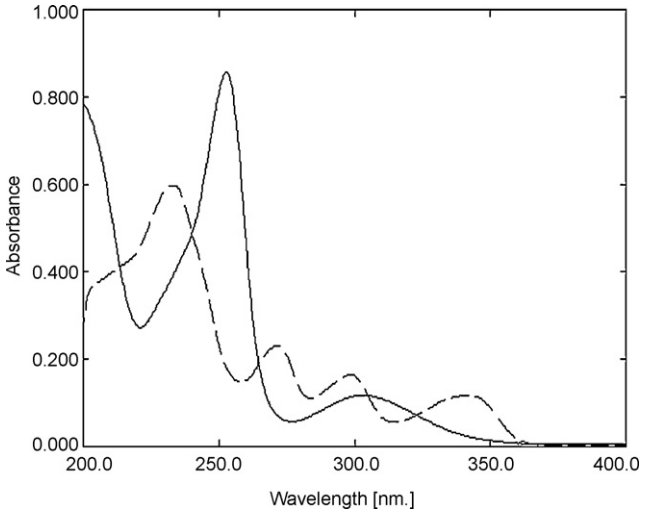


Fig. 5. Spectra of mequitazine (––) and its sulfoxide (—·—) each 10 μg mL^{-1}.

3.5. Stability-indication

To assess the stability-indicating efficiency of the proposed method, the photodegraded MQ was mixed with the pure drug at different ratios and the mixtures were analyzed by the proposed method. Satisfactory selectivity could be confirmed in the determination of MQ even in the presence of up to ~70% (w/w) of its photodegradants by adopting the described colorimetric method. The mean percentage recovery was found to be 100.06 ± 0.724.

Table 1
Determination of mequitazine in its pharmaceutical formulations by the proposed potassium iodate method.

Preparation	Mean ± SD CV
Primalan® tablets	100.06 ± 0.675
BN: 406704	0.675
Primalan® syrup	100.23 ± 0.469
BN: 552302	0.468

Table 2
Statistical comparison for the results obtained by the proposed potassium iodate colorimetric method and the reference method for the analysis of mequitazine.

Parameter	The proposed method	The reference method [22]
Mean	100.12	99.70
SD	0.679	0.396
CV	0.678	0.397
n	8	6
Variance	0.461	0.157
Student's *t*-test	1.511 (2.179)*	
F	2.94 (4.88)*	

* Figures in parentheses are the theoretical *t*- and *F*-values at $P = 0.05$ [28].

Table 3
Assay parameters and method validation for the reaction of mequitazine with potassium iodate.

Parameter	Mequitazine
λ_{max}	513 nm
Linearity range ($\mu g\,mL^{-1}$)	5–40
LOD ($\mu g\,mL^{-1}$)	1.31
LOQ ($\mu g\,mL^{-1}$)	3.96
$A^{1\%}_{1cm}$	213.84
ε(apparent molar absorpitivity)	6895.69
Slope	0.0214
Intercept	0.0378
X	100.12
SD	0.679
CV	0.678
r	0.999
RSD (%)[a]	0.485–0.515
RSD (%)[b]	0.441–0.497

[a]The interday ($n = 6$) and [b]the intraday ($n = 5$) relative standard deviations of samples of concentrations (20 $\mu g\,mL^{-1}$ and 40 $\mu g\,mL^{-1}$) for mequitazine.

3.6. Application of the proposed methods to the pharmaceutical formulations

The suggested method was successfully applied for the determination of MQ in Primalan® tablets and syrup, showing good percentage recoveries. The validity of the suggested methods was further assessed by applying the standard addition technique (Table 1) and the precision was also expressed in terms of relative standard deviation of the inter-day and intra-day analysis results.

3.7. Statistical analysis

Results of the suggested method for determination of MQ were statistically compared with those obtained by applying the reference method [22]. The calculated *t*- and *F*-values [28] were found to be less than the corresponding theoretical ones, confirming good accuracy and excellent precision (Table 2). Assay parameters and method validation are declared in Table 3.

4. Conclusion

Unlike the mostly recommended HPLC-procedures, the proposed colorimetric method is simple and not expensive. The reagents used in the proposed method are cheap and readily available. The procedures applied do not involve any critical reactions or tedious sample preparations. This aspect of spectrophotometric analysis is of major interest in analytical pharmacy since it offers distinct possibility of assaying MQ in its pharmaceutical formulations without interference due to the excipient or the photodegradation products.

The suggested method is found to be simple, accurate, selective and stability-indicative one unlike the reference spectroscopic method [22]. It could be applied for routine analysis of pure drug or in its pharmaceutical formulations.

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