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RESEARCH ARTICLE

Spectrophotometric Method for Determination of Meclizine in Pure and Dosage form Via Ion Pair Complex Formation Using Eosin Y

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Abstract: ***Objective:*** Simple and sensitive UV method was developed and validated for the determination of meclizine hydrochloride in formulation, based on binary complex formation with eosin Y.

Method: The absorbance of the formed complex was measured at 540 nm. Beer's law was obeyed in the range of 5-25 µgmL^{-1} with r^2 value 0.9960.

Results: The method showed good value of accuracy and precision (%RSD=1.096), and the limits of detection and quantification of the method were 0.76 and 2.29 µgmL^{-1}, respectively. The analytical performance of the method was fully validated, and the results were satisfactory. The method can be applied successfully for the assay of meclizine hydrochloride in commercial tablets containing the drug alone or in combination.

Conclusion: This method provides a valid alternative of reported methods for the determination of meclizine in formulations as it's a simple, less time and cost consuming and can be applied for pharmaceutical analysis in pharmaceutical industries.

Keywords: Meclizine hydrochloride, eosin Y, binary complex, spectrophotometric method, stoichiometry, ion-pairing.

1. INTRODUCTION

Meclizine (Fig. **1**) is classified as first generation piperazine antihistamine, usually used to prevent vomiting, nausea and dizziness caused by motion sickness [1]. Anti-motion sickness medications are usually divided into two groups; central acetylcholine inhibitors and norepinephrine and/or dopamine positive modulators [2]. Meclizine is believed to relief motion sickness through its anti-cholinergic effect rather than its anti-H1 effect [3]. It controls vomiting by its action on trigger zone and vomiting center located in medulla oblongata [4].

In particular, meclizine exhibits very low solubility at pH values greater than 2.0 [5]. Due to its physicochemical properties, meclizine has slow onset of action of about one hour [5]. Meclizine possesses one chiral center and can exist as R- or S- configuration, therapeutically however it is used as racemic mixture [6]. Meclizine can be found in various combinations with other agents; *e.g*. meclizine with pyridoxine (Navidoxin®), with nicotinic acid and caffeine. The aim of such combinations is either to increase the anti-motion sickness effect or to reduce side effects [7].

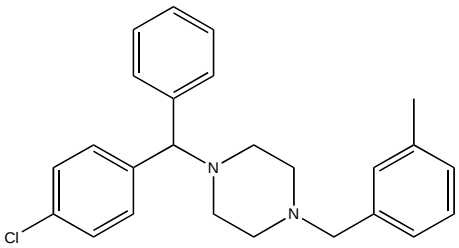

Fig. (1). Molecular Structure of Meclizine.

Several methods have been reported for the determination of meclizine hydrochloride by spectrophotometric as well as HPLC techniques (Table **1**). The determination of meclizine was reported based on ion-pair extraction using methyl orange [8]. Masthanamma *et al*., reported the estimation of meclizine in dosage form and bulk using absorption maxima, first order derivative and Area Under Curve (AUC) [9]. Gas Liquid Chromatography (GLC) was also used for the determination of meclizine in tablet formulations [10]. Reverse phase liquid chromatography was on the other hand used for the determination of meclizine in dosage form and in human serum [11]. Derivative spectrophotometric method has been reported for the determination of meclizine with caffeine in their binary mixture [12].

Eosin Y (Fig. **2**) is an acidic dye that has been useful for the determination of several basic drugs through the formation of binary or ternary complexes [13]. It consists of an

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Table 1. Comparison of precision of proposed method with other methods in literature.

Analytes	λ_{max} nm	Mobile phase Composition (v/v)	%RSD	References
HPLC methods				
Meclizine	230	30%, ACN	0.84	[24]
Meclizine Buclizine Pyridoxine	230	80: 20 ACN: H_2O	1.1-3.9	[11]
Meclizine Pyridoxine	253	H_2O, ACN, MeOH CH_3COOH, THF	1.67	[25]
Meclizine Pyridoxin	254	30: 70: 0.1 B: ACN: CF_3COOH	<2	[26]
Meclizine	229	65: 35 H_2O: MeOH	<2	[27]
Spectrophotometric methods				
Complexing reagent				
Meclizine	422	Methyl orange	1.6	[8]
Meclizine	510 484	Cerric sulphate N-Bromoscuccinamide	0.59 0.62	[28]
Meclizine	417 412	bromocressol green bromophenol blue	0.59 0.46	[29]
Meclizine Pyridoxine	231		<0.826	[30]
Meclizine	540	Eosin Y	1.09	(Present method)

ACN=acetonitrile, MeOH= methanol, B= buffer

anionic halo fluorescein [14], and forms an ion pair complex in the presence of acetate buffer [13]. The maximum absorption of the eosin Y alone is observed at 515 nm [15]. Usually water solubility of the formed ion pair complex is weak and can be enhanced by the addition of the nonionic surfactant such as methyl cellulose [13]. Many methods have been reported for the analysis of different drugs using eosin Y. An example of using eosin Y for the determination of basic drugs is the method reported for the determination of four macrolide antibiotics (roxithromycin, clarithromycin, azithromycin, erythromycin) and applied to spiked human urine and plasma [14]. Dothiepin was determined by using formation of a binary complex with eosin through spectrophotometric method at 540 nm in acetate buffer and by spectrofluorimetric method based on the quantitative quenching effect of dothiepin on the native fluorescence of eosin at 543 nm after excitation at 304 nm [16]. Another example is the use of eosin for the determination of verapamil in a 1:1 ratio [15]. A simple and rapid spectrophotometric method was also reported for the determination of tizanidine and orphenadrine via ion pair complex with eosin Y. This method was applied for the determination of these drugs in formulation and for content uniformity test [17]. Amlodipin

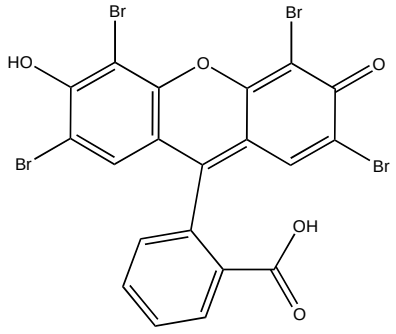


Fig. (2). Molecular Structure of Eosin Y.

and nicerdapin were also determined by forming binary complex with eosin in bulk powder and formulation [18]. Mebeverine [13], carvidilol and nebivolol [19] were all determined by rapid and simple methods based on forming binary complex with eosin Y.

Present study deals with the analysis of meclizine using ion pair complex with eosin Y. The method was developed for validation of drug in very short time. It is an economical method. The proposed method can be easily applied at any

Table 2. λ_{max} **of surfactants.**

Surfactant	λ_{max} nm
Tween 80	540
Tween 20	545
Carboxymethyl cellulose	546
Polyvinyl alcohol	547
Methyl cellulose	549

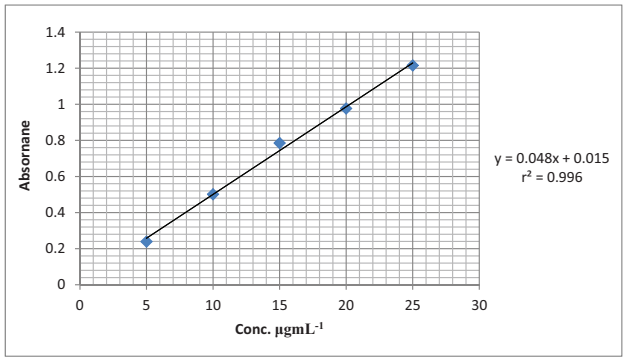


Fig. (3). Linearity of proposed method.

analytical laboratory. Moreover, it does not require tedious steps such as extraction processes or any other solvent preparation steps.

2. MATERIALS AND METHODS

Meclizine hydrochloride (≥97%) European pharmacopeia reference standard (Council of Europe- EDQM CS 30026F-67081 Strasbourg Cedex) and analytical reagent grades of eosin Y, acetic acid, anhydrous sodium acetate and hydrochloric acid used were purchased from Merck, Darmstadt, Germany. Meclizine tablets (labeled to contain 12.5 mg) were obtained from commercial sources in the local market. Cary 60 UV–visible spectrophotometer of Agilent Technologies was used to record the absorption spectra. Cary WinUV version 5.0.0.999 software (Agilent Technologies) was utilized for data acquisition.

2.1. Standard Solutions

Stock solutions of 100 μgmL^{-1} of meclizine were prepared by dissolving 10 mg of drug in 100 mL of 0.1 N HCl. More dilute solutions were obtained by appropriate dilutions. Eosin Y 4×10^{-3} M aqueous solution was prepared in distilled water. Acetate buffer, pH 4 was prepared by mixing volumes of 0.4 M acetic acid and 0.4 M sodium acetate solutions as reported in literature [17]. Methyl cellulose (0.25%) was prepared by adding appropriate amount in distilled water.

2.2. Procedures for Calibration Graph

Different aliquots of the stock solution transferred accurately into a series of 10 mL volumetric flasks and diluted to 6 mL with distilled water. 0.5 mL of 4×10^{-3} M of eosin Y solution and 1 mL of methyl cellulose was added to each flask and solutions were well mixed before addition of acetate buffer (pH 4) as the volume was brought to the mark. The absorbance was measured at 540 nm against prepared reagent blank. To get the standard calibration graphs, the values of the absorbance were plotted against the final concentration in μgmL^{-1}, and the regression equations were derived (Fig. **3**).

2.3. Procedure for Tablet

10 tablets were weighted and powdered. From the mixed contents of 10 pulverized tablets an amount equivalent to 10.0 mg of drug was transferred into 100 mL volumetric flasks and makeup the volume upto the mark with 0.1 N HCl. The contents of the flask were stirred for 60 min and filtered. A required amount of filtrate was diluted to the desired range and the same procedure was applied described in calibration curve. The nominal contents were calculated using the corresponding regression equations of calibration graphs.

2.4. Validation

Validation of the present method was carried out for specificity, linearity, precision, accuracy, LOD and LOQ according to ICH guidelines [20]. The linearity of the present method was assessed at different concentration levels with each level analyzed repeatedly for three times. Standard meclizine hydrochloride solution at three concentration levels was used to evaluate the precisions and accuracy of the method.

2.5. Linearity

Linearity was assessed by using calibration curves of the standard solution of meclizine. Linear regression equations were used to calculate slope and the other statistics of the calibration curves (Table **3**) and correlation coefficient obtained was 0.9960 for drug.

2.6. Accuracy and Precision

Independent stock solutions of drugs were used to analyze the intraday accuracy of the method as the mean %recovery (Table **4**). Three different concentration levels, *i.e.* 8, 10, 12 μgmL^{-1} were used to evaluate the accuracy of the proposed method with all samples. Relative standard deviation (%RSD) of meclizine at three independent replicates was used to scrutinize the precision of the method. The results of %RSD value of the drug sample of 20 μgmL^{-1} are shown in Table **3** that are very low (*i.e.* 1.096) and illustrate that the method possesses excellent precision values.

2.7. Specificity

Table **5** shows the mean recovery values of the drug in formulation that is found to be satisfactory. The absence of any interfering peak from excipients may be attributed to the fact that excipients lack amino group due to which the reaction proceeds.

Table 3. Linear regression functions and their statistical parameters.

Drug	Meclizine
λ_{max} (nm)	540
Regression parameters	
Intercept	0.015
Slope	0.048
Calibration range (μgmL^{-1})	5-25
r^2	0.9960
LOD (μgmL^{-1})	0.76
LOQ (μgmL^{-1})	2.29
Precision (%RSD)	1.096

Table 4. Accuracy of method.

Analyte	Measuring Concentration (μgmL^{-1})	Measured Concentration (μgmL^{-1})	Accuracy %
Meclizine	8	8.06	100.75
	10	10.40	103.99
	12	12.19	101.58

Table 5. Determination of the meclizine in formulation.

Analyte	Measuring Concentration (μgmL^{-1})	Mean recovered Concentration %
Meclizine	8	97.56
	10	102.46
	12	99.05

2.8. Limit of Detection and Quantification (LOD and LOQ)

LOD and LOQ were corresponding to ICH definitions [20]. They were assessed using 3.3 σ/s and 10 σ/s, respectively. Here σ represents mean standard deviation of replicate determination values, and s is the sensitivity, namely the slope of the calibration graphs (Table **3**).

2.9. Application of the Method

The proposed method was applicable for the quantification of meclizine in dosage forms as shown in Table **4**. Suitable amount of the powdered tablets equivalent to 10 mg of meclizine was accurately weighed and dissolved in 100 mL of 0.1 N HCl. Then the filtered and diluted to the mark as working solutions for the assay and procedure described above was applied to the determination of meclizine in pharmaceutical formulations. Three replicate averages were used to calculate the average percent recoveries at different concentrations levels (Table **4**).

2.10. Stoichiometry

The stoichiometry of the reaction between the studied drugs and eosin Y was determined by continuous variation method (Job's method) [21] using equimolar solutions of the drug and the reagent.

3. RESULTS

Present work deals with the establishment of a simple spectrophotometric method for the determination of meclizine hydrochloride in active and in dosage form without prior extraction. The method developed here is based on the formation of ion pair complex between the meclizine and eosin Y in acidic medium. The method was validated according to ICH guidelines [20] in terms of linearity, specificity, accuracy, precision, limit of detection and quantification. The method was linear over a range of 5-25 μgmL^{-1} with r^2 value 0.9960. The low value of %RSD (*i.e*. 1.096) demonstrates that the method possesses excellent precision values while limits of detection and quantification of the method were found to be 0.76 and 2.29 $\mu g\ mL^{-1}$, respectively.

3.1. Optimization of the Reaction Conditions

The assay procedure was developed by studying and optimizing all the factors responsible for the binary complex formation between meclizine and eosin Y. To obtain the accurate and precise result, it was observed to be difficult due to the low solubility of the complex formed in aqueous solutions. To avoid the precipitation of complex, dilute the sample to the maximum before adding the eosin Y and mixing well before the addition of acidic buffer as also reported by Walash *et al*., [17]. This pattern provided the accurate results with good precision values. It was found that by increasing the reagent concentration, the absorbance gradually increased. Maximum values were obtained when eosin Y was 4×10^{-3} M. Further increase or decrease in concentration of eosin Y led to decrease in the obtained results. The pH influence over a pH range of 3 to 5 using McIlvaine buffer, acetate buffer etc on the absorbance of the binary complex showed maximum absorbance values at pH 4 of the reaction mixtures. The absorbance was found to remain constant at room temperature which showed that reaction between the drug and dye was completed immediately after the mixing of the solution. The ion pair complex remained stable for at least 1 h.

3.2. Discussion

A spectrophotometric analysis of binary complexes formed by reaction of eosin and basic compounds with amine containing drugs has been reported in literature [13-15, 17, 18, 22, 23]. Meclizine possessing tertiary amine group offers a basic characteristic to the drug. The drug is protonated in the presence of buffer solution of pH 4. Eosin Y has good hydrophilicity and can easily dissolve in aqueous solution. The formation of complex between the tertiary amino groups in meclizine and the anionic functional group

of eosin Y results from electrostatic interaction forces under acidic pH. The absorption maxima of the pink colored complex was at 540 nm which was absent in drug or eosin Y as shown in Fig. (**4**). The complex formation took place instantaneously, with color formation in few seconds.

Eosin Y, utilized as an ion-pairing agent, has pK_{a1} and pK_{a2} of 2.6 and 3.6 [15], while in presence of methyl cellulose are 2.10 and 2.85, respectively [13] and exists in monovalent anionic form in weak acidic solutions as in pH 4. The two possible ionic forms of eosin Y may results from dissociation of the hydroxyl and carboxylic groups. Due to the presence of two strong electron withdrawing bromo groups near the hydroxyl group the charge density at oxygen atom of hydroxyl is reduced and eosin Y monovalent anion is formed [15].

The two tertiary amino groups present in meclizine get easily protonated in an acidic medium to a positively charged cation. The electrostatic and hydrophobic interaction of the protonated tertiary amino groups of meclizine is responsible for formation of the complex with the ionized hydroxyl group of the eosin Y mono anion.

Demonstrated by using Job's method, the reaction was found to precede in the ratio of 1:2 of drug to eosin Y for meclizine (two basic centers), moreover, the proposed mechanism of the reaction pathway is shown in Scheme **1**.

Different non ionic surfactants were used and their effect on the absorbance intensities was observed. It was found that methyl cellulose at 0.25% was the most effective for showing longer wavelength and preventing precipitation of the complex (Table **2**) [18] while higher concentration showed no effect.

CONCLUSION

A method, based on ion-pair complex formation is described for the quantitative determination of meclizine in

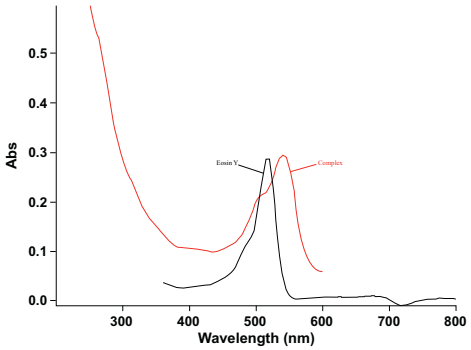
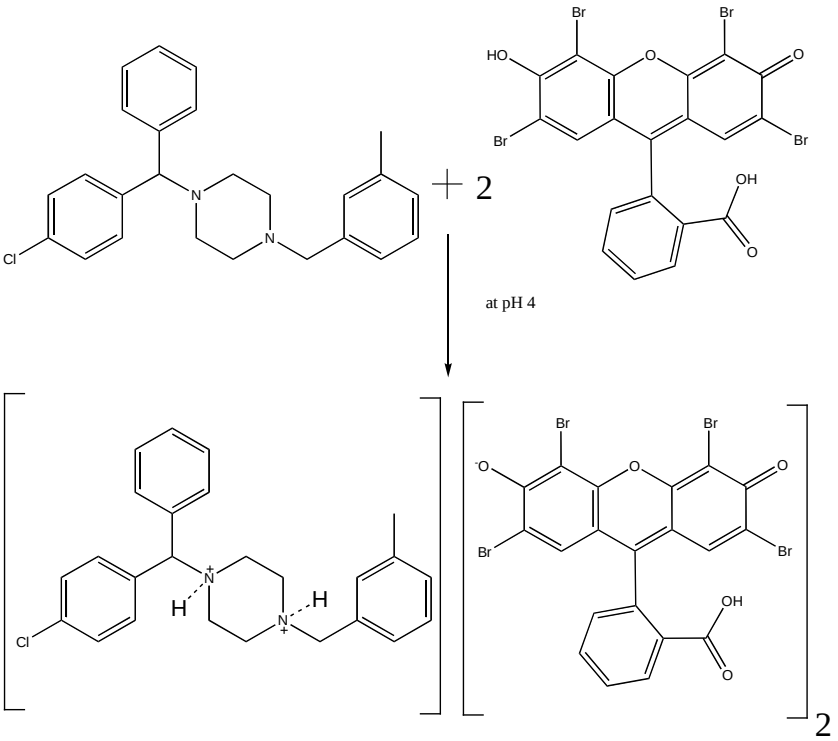


Fig. (4). UV-visible spectrum of eosin Y and binary complex.



Scheme 1. Proposed mechanism for reaction between meclizine with eosin Y.

pharmaceutical dosage form for concentration monitoring. Eosin Y was selected as an ion-pairing agent in order to obtain water soluble and stable ion pair complexes with appropriate and measurable absorbance values. The application of the described method is ascertained since, the determination of meclizine can be done by using this precise, simple and accurate method with no interference from common excipients. The demonstrated method is simple, sensitive, accurate and fast. Moreover, lack of extensive extraction, satisfactory sensitivity and reproducibility makes the method a suitable alternative for routine analysis in laboratories.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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