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ORIGINAL ARTICLE

Spectrophotometric determination and thermodynamic studies of the charge transfer complexation of emedastine difumarate with some π-acceptors

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KEYWORDS

Emedastine difumarate;
Spectrophotometry;
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Abstract Spectrophotometric procedures were presented for the determination of antihistaminic drug, emedastine difumarate. The methods are based on the charge transfer complexation reaction of the drug with π-acceptors; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), chloranilic acid (CA) and 7,7,8,8-tetracyanoquinodimethane (TCNQ). Different charge-transfer complexes and colored radical anions were obtained. The formations of the colored complexes were utilized in the development of simple, rapid and accurate spectrophotometric methods for the analysis of emedastine in drug substance and products. Under the optimum reaction conditions, linear relationships with good correlation coefficients (0.9996–0.9999) were found between the absorbance at the relevant maxima and the concentrations of emedastine in the range of 0.8–200 μg mL^{-1}. The limits of detection ranged from 0.06 to 0.76 μg mL^{-1}. The molar absorptivities and association constants for the colored complexes were evaluated using the Benesi–Hildebrand equation. The free energy change ($\Delta G°$) and the enthalpy of formation ($\Delta H°$) as well as the entropy ($\Delta S°$) were also determined. The methods were successfully applied to analyze the drug formulation with mean recovery percentages ± RSD% of 100.04 ± 0.59–100.22 ± 0.72. The results were compared favorably with the official and reported methods.

1. Introduction

Emedastine difumarate is 1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)benzimidazole fumarate (1:2) (The United States Pharmacopeia, 2013). It is a selective H1-receptor antagonist, used in eye drops to treat allergic conjunctivitis (Sweetman, 2007; Lowry et al., 1996; Sharif et al., 1994a,b).

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Few analytical methods were reported for its determination in pharmaceuticals and biological fluids. These include High Performance Liquid Chromatography (HPLC) with tandem mass spectrometry detector using MALDI-TOF MS (Sharif et al., 1994a,b; Takaya et al., 2000) and HPLC – radioreceptor assay (Nihashi and Ishida, 2000).

The aim of the present study is the development of simple and rapid spectrophotometric methods for the analysis of emedastine in its pharmaceutical formulation. The association constant and standard free energy change ($\Delta G°$) were studied using the Benesi–Hildebrand plot. The kinetic study and thermodynamic parameters of the drug with TCNQ were also determined.

2. Experimental

2.1. Instrument

Shimadzu UV-1601 PC and Shimadzu UV–VIS 160 A dual-beam spectrophotometers (Japan), with matched 1 cm quartz cells are used.

2.1.1. Materials and reagents

All solvents used were of spectroscopic grade and bidistilled water was used throughout the work. Emedastine difumarate was kindly supplied from Chem Swiss, SIGMA Co., Egypt. Its purity was found to be 99.00% according to The United States Pharmacopeia (2013). Emedastine 0.05% ophthalmic solution labeled to contain 0.5 mg emedastine difumarate per 1 mL (Batch No., 190409-F_1, manufactured by SIGMA Co. Egypt) was purchased from the local market. DDQ and CA (Aldrich, Germany) 0.2% (w/v), were prepared in acetonitrile and found to be stable for at least one week when stored in refrigerator. TCNQ (Aldrich, Germany) 0.1% (w/v), was freshly prepared in acetonitrile. Acetone, acetonitrile, 1,4-dioxane, ethanol, methanol (Merck Co., Germany), chloroform (Fischer Scientific, UK), anhydrous Na_2SO_4, ammonia solution 33% (Adwic Co., Egypt) were used.

2.1.2. Emedastine difumarate standard solutions

Emedastine difumarate standard solution, 1 mg mL^{-1} was prepared in methanol. This stock solution was subsequently used for preparing working standard solutions, 0.5 mg mL^{-1} for DDQ and, 0.08 mg mL^{-1} for TCNQ using acetonitrile. Emedastine 1×10^{-3} M solution was prepared by dissolving an accurately weighed amount of 53.457 mg in 10 mL methanol. The volume was completed to 100 mL with acetonitrile.

2.2. General analytical procedures

2.2.1. Construction of calibration curves

Aliquots equivalent to 50.0–1000.0 μg or 200.0–2000.0 μg of emedastine difumarate working standard solutions (0.5 or 1 mg mL^{-1}) were transferred into two separate series of 10 mL volumetric flasks. To each series, 2.5 mL of each; 0.1% DDQ or 0.1% CA was added separately. Then the volume was completed with acetonitrile. The absorbance was measured after about 20 and 5 min at 457 and 519 nm of DDQ and CA, respectively, against the appropriate reagent blank. Plots of absorbance against drug concentration were plotted and regression parameters were computed.

For TCNQ, into a series of stopper test tubes, aliquots of working drug solution (0.08 mg mL^{-1}) equivalent to 8.0–160.0 μg of emedastine were transferred, followed by 2.5 mL of 0.1% of TCNQ solution and 2 mL acetonitrile. The tubes were heated in a thermostatic water bath at 60 °C for 30 min then cooled and the content of each tube was transferred quantitatively into a 10 mL volumetric flask and completed to the mark with acetonitrile. The absorbance was measured at 841 nm against a reagent blank treated similarly. The absorbance was plotted against corresponding drug concentration and the regression equations were calculated.

2.2.2. Determination of stoichiometry of the charge transfer complex by Job's method of continuous variation

Three series of 2 mL quantities of mixtures of equimolar solutions of emedastine difumarate-DDQ, emedastine difumarate-CA and emedastine difumarate-TCNQ were made. The first and third series were made from 1×10^{-3} M of each DDQ and TCNQ and acceptor by compromising complementary proportions of the two solutions (0.2:1.8, 0.4:1.6,.., 1.8:0.2) in 10 mL volumetric flasks and stopper test tubes for the first and third series, respectively. The second series was made by the same procedure, using solutions of emedastine difumarate and CA each of, 5×10^{-3} M in 10 mL volumetric flasks. Then the detailed procedures described under, "Construction of calibration curves", were followed. The absorbance was measured, at 457, 520 and 481 nm for the charge transfer complexes of DDQ-emedastine, CA-emedastine and TCNQ-emedastine, respectively each against its appropriate blank.

2.2.3. Determination of stability constant, molar absorptivity and standard free energy change

Different volumes; 0.1–0.5 mL of 1×10^{-3} M solution of emedastine in acetonitrile were transferred into a series of 10 mL volumetric flasks. To each flask, 5 mL of 10^{-4} M DDQ or CA in acetonitrile was added separately. For TCNQ, different volumes; 0.1–0.5 mL of 1×10^{-3} M drug solution in acetonitrile were transferred into a series of 10 mL stopper test tubes. Then 2 mL of 10^{-4} M TCNQ in acetonitrile was added. The detailed procedures described under, "Construction of calibration curves", were followed for each method.

2.2.4. Determination of thermodynamic parameters of emedastine-TCNQ complex

Into a series of stopper test tubes, aliquots of working solutions of emedastine equivalent to 80 μg of emedastine were transferred, followed by 2.5 mL of 0.1% TCNQ and 2 mL of acetonitrile. The tubes were heated in a thermostatic water bath at different temperatures (40, 50, 60 °C) for different time intervals. At the specified time intervals, the tubes were cooled and the content of each tube was transferred quantitatively to 10 mL volumetric flasks. Then the detailed procedures described under "Construction of calibration curves", were followed.

2.2.5. Application to pharmaceutical formulations

An accurately measured volume of the mixed emedastine eye drop solution (five bottles) equivalent to 10 mg of emedastine

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difumarate was quantitatively transferred into a beaker and evaporated under vacuum, then dissolved in 5 mL methanol and transferred quantitatively to 10 mL volumetric flask and completed with acetonitrile, then filtered and completed to 10 mL with acetonitrile. The procedure described under, ''Construction of calibration curves'', was followed.

3. Results and discussion

The molecular interactions between electron donors and electron acceptors are generally associated with the formation of intensely colored charge-transfer complexes, which absorb radiation in the visible region (Hamada et al., 1989). A variety of electron donating compounds have been reported to yield charge-transfer complexes leading to their utility in the development of simple and convenient spectrophotometric methods (Foster, 1969; Mohamed et al, 2007; Hasani and Akbari, 2007; Wu and Du, 2007; Khaked, 2008; El-Zaria, 2008; El-Bagary et al, 2012; Raza and Zia-Ul-Haq, 2011).

The molar absorptivities and association constants for the colored complexes were evaluated using the Benesi–Hildebrand equation (Benesi and Hidelbrand, 1949).

The standard free energy was also calculated. The color reaction between the studied drug and TCNQ is heat dependant. Therefore, kinetic and thermodynamic parameters were studied to establish the stability of the complex and the optimum conditions for the complex formation. The values obtained for these thermodynamic parameters indicated that the complex formed between these two chemical entities (Emedastine and TCNQ) is highly stable.

3.1. Spectral characteristics of the reaction

The absorption spectra of, emedastine difumarate in acetonitrile are shown in Fig. 1, where emedastine exhibits strong band at 283 nm. The interaction of emedastine with the π acceptors DDQ, CA and TCNQ yields charge transfer complexes which are converted to intensity colored radical ions in the polar solvent used acetonitrile. They are absorbed maximally at 457, 519 and 841 nm, respectively, according to the following scheme:

$$D + A \rightarrow \underset{\text{Complex}}{(D - A)} \longrightarrow \underset{\text{Radical ions(in polar solvent)}}{D^{*+} + A^{*-}}$$

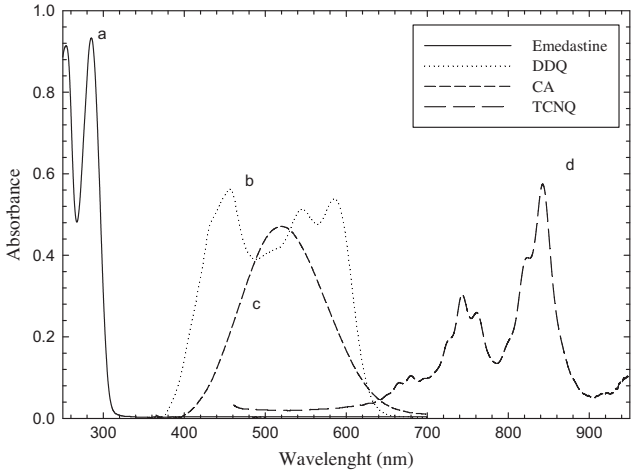

Figure 1 Zero order absorption spectra of, (a) emedastine difumarate in acetonitrile (50 μg mL^{-1}), (b) emedastine difumarate-DDQ CTC (50 μg mL^{-1}), (c) emedastine difumarate-CA CTC (100 μg mL^{-1}) and (d) emedastine difumarate-TCNQ CTC (8 μg mL^{-1}).

3.2. Optimization of reaction conditions

3.2.1. Effect of reagent volume

Different volumes; 0.5–3.0 mL of each DDQ and CA (0.2% w/v) and TCNQ (0.1% w/v) were studied. Highest absorbance at the relevant maxima was obtained upon using 2.5 mL of each.

3.2.2. Effect of solvents

Different solvents were tried for the complexation reaction. Acetonitrile afford maximum color intensity, which may be attributed to its high dielectric constant that promotes maximum yield of radical anions, and its high solvating power for π acceptors (Geffken and Salem, 2006).

3.2.3. Effect of time and temperature

Complete color development was attained instantaneously at room temperature between drug and CA, which remained stable for further 1 h. For DDQ maximum absorbance was developed after 20 min and remained stable for further 15 min.

However, with TCNQ the complex formation was slow over a period of two hr, which suggests heating at different temperatures (40–60 °C). The highest color intensity was attained, after heating at 60 °C for 30 min and remained stable for further 25 min.

3.2.4. Stoichiometry of the reaction

On studying the molar ratio between drug and each of, DDQ, CA and TCNQ, using Job's method of continuous variation for; 1×10^{-3} M solutions for DDQ, CA or TCNQ it was found to be 1:1 (Rose, 1964), this indicates that only one site is responsible for the formation of the complex and a univalent charged species, is the possible site of the charge transfer process.

3.2.5. Association constants and standard free energy

The association constants were calculated for the interaction of emedastine with either DDQ, CA or TCNQ, using the Benesi–Hildebrand equation (Benesi and Hidelbrand, 1949) which depends on the experimental conditions that one of the two component species should be present in large excess, so that its concentration is virtually unaltered on formation of the complex.

$$\frac{[A_o]}{A^{AD}} = \frac{1}{\varepsilon^{AD}} + \frac{1}{\varepsilon^{AD} K_C^{AD}} X \frac{1}{[D^o]}$$

where $[A_O]$ and $[D_O]$ are the total concentrations of the interacting species (acceptor and donor, respectively), A^{AD} is the absorbance of the complex, ε^{AD} is the molar absorptivity of the complex and K_C^{AD} is the association constant of the complex.

On plotting the values of $[A_O]/A^{AD}$ versus $1/[D_O]$ straight line was obtained (Fig. 2) whose intercept and the slope were calculated and the following equations were obtained:

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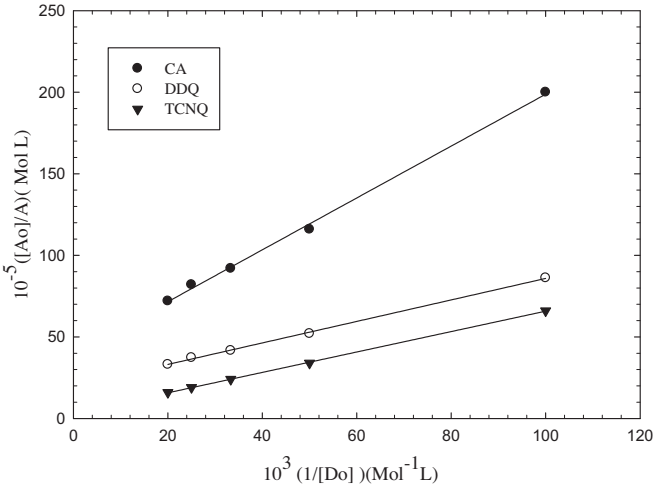

Figure 2 Benesi–Hildebrand plot for DDQ, CA and TCNQ complexes.

$$\frac{[Ao]}{A_{\lambda}^{AD}} = 19.95 \times 10^{-5} + 7 \times 10^{-8} \times \frac{1}{[D_0]} \quad \text{DDQ complex}$$

$$\frac{[Ao]}{A_{\lambda}^{AD}} = 39.79 \times 10^{-5} + 1.6 \times 10^{-8} \times \frac{1}{[D_0]} \quad \text{CA complex}$$

$$\frac{[Ao]}{A_{\lambda}^{AD}} = 3.221 \times 10^{-5} + 6 \times 10^{-8} \times \frac{1}{[D_0]} \quad \text{TCNQ complex}$$

The standard free energy change of complexation (ΔG^{o}) is related to the association constant by the following equation (Vogel's, 1989; Martin and Swarbrick, 1969).

$$\Delta G^{\circ} = -2.303\ RT \log \quad K_C^{AD}$$

where ΔG^{o} is the standard free energy of the complex (kcal/mol), R is the gas constant (1.987 cal mol^{-1} deg^{-1}), T is the temp in Kelvin (273 + °C) and K_C^{AD} is the association constant of complex (L/mol), (K_C^{AD}), (ε^{AD}) and (ΔG^{o}) were calculated and the results are represented in Table 1.

3.3. Method validation (ICH Q2A, 1994; ICH Q2B, 1996)

3.3.1. Linearity and sensitivity

Under the specified optimum reaction conditions, the calibration curves for emedastine difumarate with the different Pi acceptors employed in the present work were constructed.

The regression equations for the results were derived using the least-squares method. In all cases, Beer's law plots were linear in the concentration range of 5.0–100.0, 20.0–200.0, and 0.8–16.0 μg mL^{-1}, for emedastine difumarate with DDQ, CA and TCNQ, respectively with very small intercepts and good correlation coefficients in the specified concentration range (Table 2). For accurate determination, Sandell sensitivities were calculated which reflected the sensitivity and accuracy of the proposed methods. The limits of detection (LOD) and quantification (LOQ) were determined, using the formula: LOD = 3.3 σ/S and LOQ = 10 σ/S, where σ = the standard deviation of the intercepts of regression lines, S = the slope of the calibration curve.

Table 1 Association constant, molar absorptivity values and calculated free energy from Benesi–Hildebrand plots for the complexes formed.

Parameters	DDQ	CA	TCNQ
K_c ^{AD}(L/mol)	2.8×10^4	2.5×10^4	5.33×10^4
^{AD}(L.mol^{-1} cm^{-1})	5.01×10^3	2.5×10^3	3.11×10^4
ΔG (kcal/mol)	−6.09	−10.14	−7.3

3.3.2. Accuracy and precision

The accuracy was evaluated by performing analysis of quality control samples with known concentration level of emedastine difumarate. The concentrations of the drug were calculated from slope and intercept obtained from the corresponding regression equation of the standard calibration curve. The recovery percentages and the mean recovery were then calculated. Statistical comparison between the proposed spectrophotometric and the official or manufacturer's methods using student's t-test and F-ratio at the 95% confidence level reveals an insignificant difference (Table 3). The accuracy was also assessed by applying the standard addition technique. Satisfactory results were obtained in good agreement with the labeled claim (Table 3).

The precisions of the assays (repeatability and intermediate precision) were determined for emedastine difumarate concentrations. Repeatability was assessed by analyzing five concentration levels in triplicates, using the proposed procedures, where RSD were 0.427–0.82% (intra-assay precision). Intermediate precision was evaluated by assaying the same concentrations in triplicate on three successive days. The assays gave satisfactory results; the relative standard deviations (RSD) were less than 2% (Table 2). This level of precision of the proposed methods was adequate for the quality control analysis of emedastine.

3.3.3. Ruggedness and robustness

The ruggedness of the proposed methods was assessed by applying the procedures using two different instruments in

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Table 2 Spectral data and validation results for the reaction of emedastine difumarate with DDQ, CA and TCNQ.

Parameters	DDQ	CA	TCNQ
λ_{max} (nm)	457	519	841
Beer's law limits ($\mu g\ mL^{-1}$)	5–100	20–200	0.8–16
Molar absorptivity ($L\ mol^{-1}\ cm^{-1}$)	4.97×10^3	2.4×10^3	3.54×10^4
Sandell sensitivity ($\mu g\ cm^{-2}$)	0.107	0.223	0.015
Accuracy, $n = 5$, (mean ± RSD%)	100.24 ± 0.50	100.21 ± 0.47	99.78 ± 0.75
Precision, $n = 15$ Repeatability (mean ± RSD%)	99.88 ± 0.43	100.14 ± 0.60	100.67 ± 0.82
Intermediate precision (mean ± RSD%)	100.35 ± 0.55	100.08 ± 0.86	100.06 ± 0.78
Regression parameters			
Slope ± SD	$0.0094 \pm 8.4 \times 10^{-5}$	$0.0045 \pm 7.1 \times 10^{-5}$	$0.0661 \pm 4.3 \times 10^{-4}$
Intercept ± SD	$-0.0819 \pm 5.5 \times 10^{-4}$	$-0.0055 \pm 8.4 \times 10^{-5}$	$0.00541 \pm 1.1 \times 10^{-4}$
SD of residual (S_{xy})	8.7×10^{-3}	5.6×10^{-3}	3.9×10^{-3}
Correlation coefficient (r)	0.9996	0.9998	0.9999
LOD ($\mu g\ mL^{-1}$)	0.31	0.76	0.06
LOQ ($\mu g\ mL^{-1}$)	1.03	2.53	0.21

Table 3 Statistical analysis of the results obtained by the proposed charge transfer and official or manufacturer procedures for the determination of emedastine difumarate in its drug substance and pharmaceutical formulation.

Values	Drug substance				Emedin eye drop			
	DDQ	CA	TCNQ	Official method[a]	DDQ	CA	TCNQ	Manufac. method[b]
Mean	100.24	100.21	99.78	100.30	100.22	100.04	100.08	100.60
SD	0.498	0.497	0.746	0.819	0.589	0.680	0.719	0.938
SE	0.223	0.222	0.334	0.367	0.263	0.304	0.322	0.419
Variance	0.248	0.247	0.112	0.671	0.347	0.463	0.517	0.879
n	5	5	5	5	5	5	5	5
t-test (2.306)[c]	0.139	0.210	1.055		0.767	1.08	0.984	
F-test (6.400)[c]	2.71	2.73	5.99		2.53	1.89	1.70	
Standard addition mean ± RSD%					100.14 ± 0.96	100.67 ± 0.39	100.12 ± 0.91	

[a] Official HPLC method (USP 2013).
[b] Manufacturer's HPLC method.
[c] The values between parenthesis are the theoretical values of t and F at ($p = 0.05$).

two different laboratories at different elapsed time. Results obtained from lab-to-lab and day-to-day variations were found to be reproducible as RSD did not exceed 2%. Robustness of the procedures was assessed by evaluating the influence of small variation of experimental variables: concentrations of reagents, and reaction time, on the analytical performance of the method. In these experiments, one experimental parameter was changed while the other parameters were kept unchanged, and the recovery percentage was calculated each time. The small variations in any of the variables did not significantly affect the results; recovery percentages were 99.78 ± 0.746–100.21 ± 0.468%. This provided an indication for the reliability of the proposed methods during routine work.

3.3.4. Application to pharmaceutical formulations

The obtained satisfactory validation results made the proposed procedures suitable for the routine quality control analysis of emedastine. The proposed method was applied for the determination of emedastine in its ophthalmic solution. The obtained mean recoveries ± RSD% ranged from 100.04 ± 0.68 to 100.22 ± 0.59. The methods were also assured by applying the standard addition technique (Table 3). The results were statistically compared with those obtained by the reported method, proving no significant difference with respect to accuracy and precision (Table 3).

3.4. Kinetic and thermodynamic parameters

The kinetic studies were carried out at different temperatures (40, 50, and 60 °C) for emedastine complex with TCNQ. The plot of $\ln\{(A_i - A_t)/(A_i - A_0)\}$ as a function of time produced straight line with slope equal to $-k$. The equation gave the best fit for the experimental data corresponding to first order (Zhai et al., 2006). The straight lines revealed that the reaction followed pseudo first order, and the slope represents rate constants (Fig. 3). Table 4, summaries the calculated k and $t_{1/2}$ at different temperatures, from which it is evident that as the temperature increased the $t_{1/2}$ decreased, proving that at higher temperature the reaction was less time consuming.

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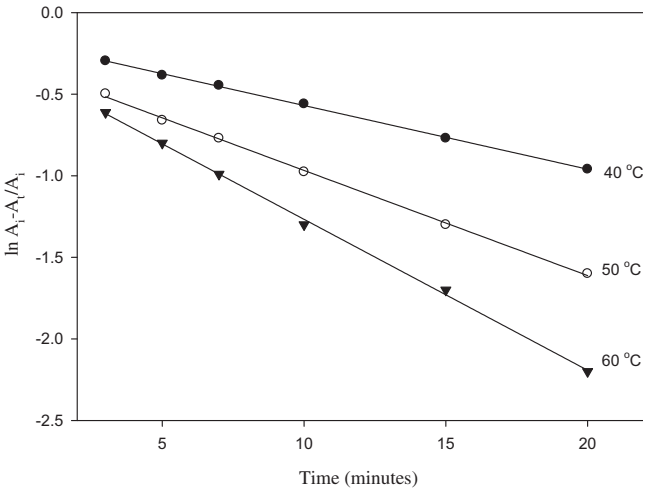

Figure 3 Pseudo first order plots for the reaction of 8.0 μg mL^{-1} emedastine difumarate using 0.1% w/v TCNQ at 841 nm.

Table 4 Rate constant and half-life times of the studied reactions at different temperatures.

$T(K)$	k (min^{-1})	Intercept	$t_{1/2}$ (min)	R
313	0.0407	−0.1789	17.027	0.9996
323	0.0614	−0.3229	11.29	0.9995
333	0.0944	−0.3417	7.34	0.9994

Table 5 Kinetic parameters for the reactions of emedastine difumarate with TCNQ at different temperatures.

$T(K)$	ΔS^o (J mol^{-1} K^{-1}).	ΔH^o (kJ mol^{-1})	ΔG^o (kJ mol^{-1})
313			51.26
323			51.84
333	−1.809	4.902	52.42

The relationship between the rate of reaction and temperature is determined by the Arrhenius equation:

$$k = Ae^{-Ea/RT}$$

E_a is the activation energy, $R = 8.314$ J/mol K, T is the absolute temperature in Kelvins, A is frequency factor (Abdellatef, 1998).

$$\ln k = -E_a/RT + \ln A$$

Arrhenius curve for the studied drug with TCNQ was constructed by plotting $\ln k$ versus $1/T$ and it was found to be linear. The value of E_a was found to be 35.75 kJ/mol indicating that the reactions need low activation energy, and $\ln A$ was found to be 10.56. The other activation parameters such as enthalpy, entropy and free energy of activation were calculated using the Eyring equation (Atkins, 1979; Stevens and Phil, 1970) which was applied in the following form;

$$\ln k/T = (-\Delta H^*/R)(1/T) + \ln k_B/h + \Delta S^*/R$$

where k_B is Boltzmann's constant [1.381×10^{-23} J K^{-1}] and h is Plank's constant [6.626×10^{-34} J s], $\ln k_B/h = 10.76$.ΔH (kJ mol^{-1}) is activation enthalpy. ΔS (J mol^{-1} K^{-1}) is activation entropy. ΔG^* (kJ mol^{-1}) is the free activation enthalpy (Gibb's free energy).The Eyring plot of $\ln (k/T)$ versus $1/T$ produces a straight line. Activation parameters such as enthalpy, entropy and free energy of activation of the reaction were calculated and ΔS^* from the intercept of Eyring plot: ΔG^* was calculated by using equation:

$$\Delta G^* = \Delta H^* - T\,\Delta S^* \quad (1)$$

The thermodynamic parameters are presented in Table 5. The negative values of ΔS^* at test reduce the freedom of motion in the transition state and relatively slow the reaction that can be followed spectrophotometrically. The positive values of ΔG^* indicate that the reactions are non-spontaneous.

4. Conclusion

The present work is concerned with the analysis of emedastine difumarate in drug substance and pharmaceutical formulations. In this paper charge-transfer reaction of emedastine as n-electron donor with DDQ, CA and TCNQ as π-acceptors has been investigated, using spectrophotometry methods. The kinetic study of TCNQ by plotting $\ln k$ versus $1/T$ gives straight line, reveals pseudo first order and the thermodynamic parameters reveal that the reaction of drug with TCNQ is non spontaneous. On studying the molar ratio between drug and each of, DDQ, CA and TCNQ, using Job's method of continuous variation, it was found to be 1:1. This indicates that only one site is responsible for the formation of the complex and a univalent charged species, is the possible site of the charge transfer process.

In the literature, there is no other colorimetric method concerned with the analysis of emedastine.

Unlike the most recommended HPLC-procedures, the proposed spectrophotometric methods are simple, rapid and inexpensive. The procedures applied do not involve any critical reactions or tedious sample preparations. This aspect is of major interest in analytical pharmacy.

High values of correlation coefficients and small values of intercepts validated the linearity of the calibration graphs and the obedience to beer's law. The RSD values, the slopes and the intercepts of calibration graphs indicated the high reproducibility of the proposed methods.

From the results obtained, we concluded that the suggested methods showed high accuracy, reproducibility, simplicity and inexpensiveness, permitting their application in quality control laboratories.

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