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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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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.

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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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