Journal of Molecular Liquids 243 (2017) 750–760

Contents lists available at ScienceDirect

Journal of Molecular Liquids

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

Development and validation of fluorescence spectrophotometric method: Quantitation of chlorpheniramine maleate in pharmaceutical formulations

Syed Najmul Hejaz Azmi *, Shamsa Said Khalfan Al-Hadhrami, Bashair Mohammed Rashid Al-Marhoubi, Safa Saleh Said Al-Sulaimi, Zainab Darwish Said Al-Shamoosi

Department of Applied Sciences, Chemistry Section, Higher College of Technology, P.O. Box 74, Al-Khuwair-133, Muscat, Oman

ARTICLE INFO

Article history:
Received 11 July 2017
Received in revised form 14 August 2017
Accepted 22 August 2017
Available online 26 August 2017

Keywords:
Chlorpheniramine maleate
Eosin Y
Static quenching
Stern-Volmer equation
Pharmaceutical formulations

ABSTRACT

Ion-pair complex of the chlorpheniramine maleate with eosin Y was achieved because of the interaction of protonated drug with dianionic eosin Y. The stoichiometry of the reaction was studied by mole ratio method which showed 2:1 ratio for drug and eosin Y. This lead to the quenching of eosin Y which was the basis for the quantitation of chlorpheniramine maleate by fluorescence spectrophotometry. The fluorescence intensity was recorded at 544.02 nm after excitation at 257.96 nm. The linear dynamic range was obtained in the concentration range of 1–8 μg mL^{-1}. The quenching rate constant was calculated and found to be 8.2×10^{13} L mol^{-1} s^{-1} which is more than 2×10^{10} L mol^{-1} s^{-1} indicated that the proposed method has followed static quenching. The enthalpy change and Gibb's free energy were calculated and found to be negative. The same results were also obtained by computational calculations using Gaussian. Various variables such as reaction time, temperature, buffer solution and solvent were optimized and the proposed method was successfully applied for the assay of active chlorpheniramine maleate in commercial tablets.

1. Introduction

Chlorpheniramine maleate is chemically known as (3*RS*)-3-(4-Chlorophenyl)-*N*,*N*-dimethyl-3-(pyridin-2-yl)propan-1-amine hydrogen (*Z*)-butenedioate (CAS: 113-92-8; M.W.: 390.9). The drug is freely soluble in water with molecular formula of $C_{20}H_{23}ClN_2O_4$ [1]. The drug is a first-generation antihistamine and used in the treatment of allergic conditions such as rhinitis and uticaria. The usual recommended dose of tablets for adults and children older than 12 year is 4 mg orally for every 4–6 h, (should not exceed from 24 mg in 24 h) [2]. Injections of chlorpheniramine maleate are used as an adjunct to adrenaline (epinephrine) in the emergency treatment of anaphylaxis and angioedema [3]. The sedative action of the drug is relatively weak compared to other first-generation antihistamines. This sedating activity is sometimes used to manage the pruritus associated with some allergies [3].

The preparation of drug formulations with active chlorpheniramine maleate along with excipients is very important for accurate action of chlorpheniramine maleate. In high doses, abnormal heart rhythms have occurred and in some cases cause excitement, agitation, hallucinations and convulsions. Therefore the quality, quantity, purity and safety of chlorpheniramine maleate in pharmaceutical formulations are the main idea behind this research project. The importance of analytical techniques in the quality control of active pharmaceutical ingredients in pharmaceutical formulations has been discussed in recent reviews [4,5].

The literature survey revealed assay of chlorpheniramine maleate by potentiometric titration in BP monograph [1] and high performance liquid chromatographic method in USP monograph [6].

With increasing regulatory strictness and owing to the reason of quality control, various analytical methods have been developed in pure and dosage forms including thin layer chromatography [7], gas chromatography [8], high performance liquid chromatography [9–25], micellar electro-kinetic chromatography [26] differential pulse voltammetry [27–28], derivative spectrophotometry [29,30] and spectrophotometry [31–33]. Some of the above methods are labour-intensive, require high and expensive instrumentations and tedious post-processing. Fluorescence spectrophotometric methods analysis assay are good choice of analysis because of high selectivity, good sensitivity, simple operation, rapid and accurate determination. As per literature survey and gathered information, there is no spectrofluorimetric method based on Stern-Volmer equation for quantitation of chlorpheniramine maleate.

Eosin Y is chemically known as 2,4,5,7-tetrabromofluorescein can exist in 4 different structures [34]: spirocyclic form, neutral form, monoanionic form and dianioinic form (Fig. 1). Eosin Y contains 2 relatively acidic protons (pKa 2, 3.8 in water) [34] which can be easily abstracted to give dianionic form. Eosin Y is a xanthene polyprotic acid dye with strong green fluorescence ($\lambda_{excitation}$ = 257.96 nm and emission = 544.02 nm) and has been used for determination of doxepin

* Corresponding author.
E-mail address: syed-azmi@hct.edu.om (S.N.H. Azmi).

http://dx.doi.org/10.1016/j.molliq.2017.08.081
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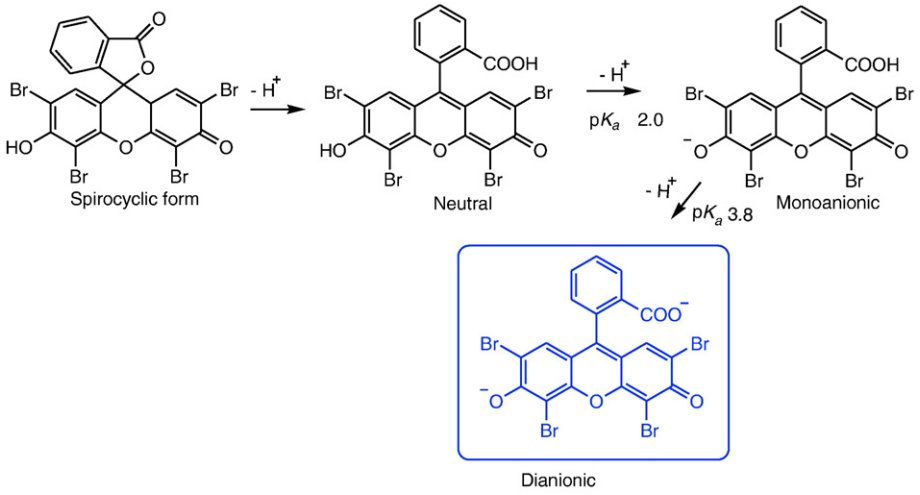

Fig. 1. Prototropic forms of eosin Y.

[35], citalopram HBr [36], clindamycin HCl [37] and carbazochrome [38]. In this study, Eosin Y was chosen as a fluorescent probe sensor. Under the optimized conditions, chlorpheniramine maleate could quench the fluorescence of eosin Y in the presence of sodium acetate-acetic acid buffer solution of pH 3.72 while the fluorescence of eosin Y remained unchanged in the presence of buffer solution alone (Fig. 2). Therefore, a simple and effective spectrofluorimetric assay method for quantification of chlorpheniramine maleate in pharmaceutical preparations could be developed on the basis of the quenching of the fluorescence of eosin Y using Stern-Volmer equation. Moreover, the factors affecting the quenching of fluorescence of eosin Y were carefully investigated and optimized. The proposed method was validated as per the International Conference on Harmonization guidelines [39]. Computational studies via Gaussian 16 Revision-A.03 and GaussView 6.0 softwares are instrumental in exploring the binding affinity and the binding sites between dyes and the quencher [40,41]. In the present study, the reasons behind the quenching of eosin Y with chlorpheniramine were investigated. Various possible interactions between eosin Y and chlorpheniramine were modeled and the energetics were studied.

2. Experimental

2.1. Apparatus

An Agilent Cary Eclipse Fluorescence Spectrophotometer (Thermo Scientific, Australia) equipped with a xenon 150 W arc lamp and fluorescence cell UV 10 mm 3.5 mL stopper was used to record fluorescence spectra and fluorescence intensity with slit widths of 10 nm.

High performance liquid chromatography was performed in the isocratic mode on Dionex-Ultimate 3000 high performance liquid chromatography (Thermo Scientific, Australia). The system consists of a pump (HPG 3200 SD) with an injection capacity of 20 μL sample injection loop (manual). The detector consists of a photodiode array detector (WDM 3000 photodiode array UV–Visible detector) and an Acclaim 120 C18 (25 cm × 4.6 mm, i.d. 5 μm) column. The equipment was controlled by a PC work station equipped with Ver. 5.80 SR11 chromeleon Data System Software. A Helios and evolution 300 series UV–Visible double beam spectrophotometer (Thermo electron Corporation, England) were employed with a spectral band width of 1 nm using a pair of 1-cm matched quartz cells.

A Hanna pH meter (USA) was used to adjust pH values for sodium acetate-acetic acid buffer solutions. IR spectra were recorded on an IR Affinity-1 spectrophotometer (Shimadzu, Kyoto, Japan) was used to record FTIR spectra in the range of 4000–400 cm^{-1}.

Gaussian 16 Revision-A.03 and GaussView 6.0 softwares (USA) were used in this study. All geometry optimizations were carried out using DFT calculations for the singlet ground states. Geometry optimization on all structures were performed using Becke, 3-parameter, Lee-Yang-Parr (B3LYP) [42,43] functional and 3-21G* basis set. Stationary points were characterized and validated by frequency calculations. Calculations were performed using Gaussian16W program package [44] where as structures were modeled and visualized using GaussView 6.0 [45].

2.2. Reagents and standards

All reagents and solvents were AR grade. 0.015% eosin Y disodium salt (CAS: 17372-87-1, M.W.: 691.85, Fluka Chemie AG, Switzerland) solution was freshly prepared in distilled water.

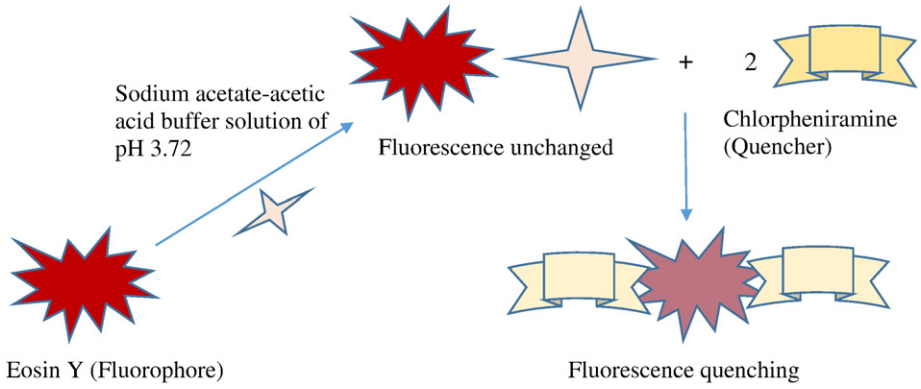

Fig. 2. Model for the interaction of chlorpheniramine and eosin Y.