

Original Research Article

Thermodynamic and Spectrophotometric Studies of Electron Donor-Acceptor Complexation Between Loratadine and Chloranilic Acid

Kenneth C Ofokansi¹ and Philip F Uzor^{2*}

¹Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, ²Department of Pharmaceutical and Medicinal Chemistry, University of Nigeria, Nsukka 41001, Nigeria

*For correspondence: E-mail: philuzor4u@yahoo.com; Tel: +234-803-7008 294

Received: 10 May 2012

Revised accepted: 29 January 2013

Abstract

Purpose: To developing a simple, rapid and reliable analytical method for loratadine based on charge transfer complexation with chloranilic acid.

Methods: The complex between loratadine and the complexing agent, chloranilic acid, was formed by mixing appropriate volumes of their solutions in non-aqueous media. Some features of the formed complex, such as molar ratio of the reaction and effect of time, were determined spectrophotometrically. Thermodynamic parameters were determined as well, the method was utilized in the assay of the drug in both bulk and tablet dosage forms.

Results: The complex showed a wavelength of maximum absorption (λ_{max}) at 527 nm (λ_{max} of loratadine alone was 440 nm). Beer's law was obeyed in the concentration range of 3.2 - 28.8 mg% ($r^2 = 0.9997$). The stoichiometry of the complex was 2:1 (loratadine: chloranilic acid) and the complex was stable for over 60 min. Thermodynamic results show that as temperature changed from 30 to 70 °C, enthalpy change (ΔH) was steady at $-0.254 \text{ kcal.mol}^{-1}$ while the free energy (ΔG) changed from -3.904 to $-4.450 \text{ kcal.mol}^{-1}$. The complex appeared to be more stable at the slightly elevated temperature of 50 °C with a value of 757.14 mol^{-1} . Analysis of the drug in both bulk and dosage forms showed good accuracy and precision with recovery ranging from 99.98 ± 1.00 to $100.94 \pm 2.39 \%$.

Conclusion: Charge transfer complexation method with chloranilic acid was successfully developed for the simple, rapid and accurate determination of loratadine.

Keywords: Charge transfer, Complexation, Loratadine, Spectrophotometry, Electron donor-acceptor, Chloranilic acid.

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bionline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Drug substances and drug products are routinely analyzed for impurities and related substances and for assay of active pharmaceutical ingredient (API) content to ensure efficacy and safety of the pharmaceutical product. One of the simplest methods of drug analysis is the formation of charge transfer complexes between the drug acting as electron donor and various electron

deficient reagents acting as electron acceptors [1]. Molecular interactions between electron donors and acceptors are generally associated with the formation of intensely colored charge-transfer complexes, which absorb radiation in the visible region where many of the common excipients used in the formulation of the drug products do not absorb light. 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 colorimetric methods [1-3].

Loratadine ((Ethyl-4-(8-chloro-5,6-dihydro-11H-benzo(5,6) cyclohepta (1,2-b) pyridine-1-piperidine carboxylate) is a second generation, non-sedating, long-acting antihistamine which is employed in the symptomatic relief of allergies such as hay fever, urticaria and seasonal allergic rhinitis and it elicits this effect by selective and peripheral antagonistic action on histamine -1 receptors [4]. Several methods have been reported for the determination of loratadine in pharmaceutical preparations including spectrophotometry [5], polarography [6], densitometry [7], capillary electrophoresis [8], gas chromatography [9], high performance liquid chromatography [10], liquid chromatography-tandem mass spectrophotometry [11], spectrofluorimetric and potentiometric methods [12]. Many of these methods require expensive equipment and/or are time-consuming [12]; hence the need to develop a method that is simple, sensitive and fast, yet reliable and reproducible. Since there is a basic centre in the chemical structure of loratadine (Fig 1a) which is a potential electron donating site, charge transfer complexation with an electron acceptor, as a colorimetric method, is considered such a simple method for fast and reliable assay of the drug. The present study was aimed at investigating this complexation reaction using chloranilic acid (CAA, Fig 1b) as a π -acceptor, with the expectation of developing a new analytical method for loratadine. The thermodynamic parameters of the formed complex were determined as well.

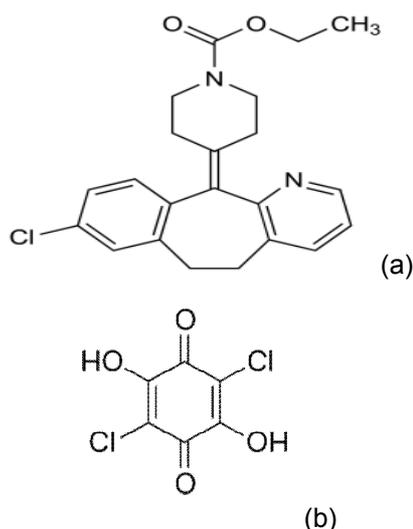


Fig 1: Structure of (a) loratadine and (b) chloranilic acid (CAA)

EXPERIMENTAL

Materials

The following materials were procured from their local suppliers: loratadine tablet dosage forms, Loratyn 10[®] (Hovid, Malaysia) and Lotin[®] (Medreich Ltd, India). Other materials used were 1, 4-dioxan (Merck, Germany), chloroform (May and Baker, England). Loratadine bulk powder was a kind donation by Juhel Nig Ltd. All other reagents and solvents were of analytical grade and were used as such. All laboratory reagents were freshly prepared. Distilled water was collected from an all-glass still.

Preparation of standard solutions

A stock solution of CAA with a concentration of 3.34×10^{-3} M was prepared by dissolving 0.069 g of accurately weighed CAA powder in 1, 4-dioxan and making up to 100 mL with the same solvent. Similarly a stock solution of loratadine in chloroform was prepared by accurately weighing 0.064 g of loratadine into a 100 mL volumetric flask and making up to volume with chloroform to provide a 1.67×10^{-3} M solution. Other concentrations were similarly prepared or diluted from the stock with the appropriate solvent.

Absorption spectra of loratadine and chloranilic acid

Loratadine stock solution (2 mL) was mixed with 3 mL of chloroform and the solution scanned in a spectrophotometer (UNICO 2102 PC, USA) over a wavelength range of 400-700 nm to determine its wavelength of maximum absorption (λ_{max}) against a blank made up of 5 mL of chloroform. Similar procedure was followed in the scanning of the solution of CAA in 1,4-dioxan over the same wavelength range.

Determination of absorption spectrum of loratadine-chloranilic acid complex

CAA stock solution (2 mL) was mixed with 2 mL of loratadine stock solution in a flask and the contents were left at room temperature for 1 h. A colour developed and the complex formed was scanned against the blank of equal volumes of dioxan and chloroform over a wavelength range of 400-700 nm using the spectrophotometer as above.

Evaluation of chromogen concentration effect on complex formation

To determine the optimum concentration of the chromogen (CAA) to form the complex, a fixed

volume of loratadine stock solution (2 mL) was added to various volumes (0.5, 1.0, 1.5...2.5 mL) of CAA stock solution, and the absorbance was monitored to determine the chromogen concentration which yielded maximum complexation with loratadine.

Construction of standard plot for loratadine-chloranilic acid complex

Serial concentrations of 0.2, 0.4.....1.8 mL of loratadine stock solution in 0.2 mL steps were transferred to different test tubes. Sufficient volume of chloroform was added to bring the volume in each test tube to 2 mL. Then 2 mL of CAA stock solution was added to each of the test tubes to afford the final concentrations of loratadine ranging from 8.35×10^{-5} M to 7.52×10^{-4} M. The contents were mixed and left at room temperature for 1 h. The absorbance of each sample was determined at 527 nm against a blank made up of equal volumes of chloroform and 1, 4-dioxan.

Evaluation of time - absorbance relationship

A time - absorbance relationship was established for the complex to determine the time required for the complex to develop fully. Equal volumes (2 mL each) of the two stock solutions were mixed and the absorbance measured at various time intervals from zero to 180 min at 527 nm.

Determination of stoichiometry of the complex

The Job's method of continuous variation was employed for the determination of the stoichiometry of the reaction [13]. Equimolar concentrations (3.34×10^{-3} M) of solutions of loratadine and CAA were used for the experiment. A series of 5 mL volumes of mixtures of the above solutions comprising complementary proportions of the two solutions corresponding to 0.5:4.5; 1:4; ...4.5:0.5 of loratadine: CAA solutions were transferred into different test tubes and the complex formed for each reaction mixture was allowed to stand for 1 h at room temperature before analysis at 527 nm. A blank solution consisting of 1, 4-dioxan and chloroform was used.

Determination of stability constant, molar absorptivity and other thermodynamic parameters

Serial volumes of the stock solution of loratadine ranging from 0.4 to 2.4 mL in 0.4 mL steps were transferred to different test tubes. The solutions were diluted to 3 mL with chloroform and 1 mL of

the stock solution of CAA was added to each test tube. The contents were capped and mixed by gentle shaking. The test tubes were allowed to stand for 1 h at room temperature (30 °C), and absorbance measurements were taken with a spectrophotometer at 527 nm against a blank of chloroform and dioxan. Further analyses of the reaction mixtures were done at elevated temperatures of 50 and 70 °C.

Assay procedure for loratadine in tablet dosage form and in bulk form

One hundred loratadine tablets were ground and thoroughly mixed by trituration in a mortar and an amount equivalent to 0.064 g of active drug was accurately weighed. This was dissolved in a 100 mL flask with 70 mL of chloroform and shaken for 30 min to extract the active drug. The suspension was filtered to remove the excipients and the latter washed with 20 mL of chloroform. The filtrate was thereafter made up to 100 ml with chloroform to provide a theoretical concentration of 1.67×10^{-3} M solution of loratadine. Serial volumes of 0.2, 0.4..... 2.0 mL of loratadine solution in 0.2 mL steps of the solution were transferred into different test tubes. Sufficient chloroform was added in each case to bring the volumes to 2.5 mL. Then 2.5 mL of 3.34×10^{-3} M CAA solution was added in each case to bring the final volume to 5 mL. The contents were mixed and left for 1 h at room temperature after which their absorbances were determined at 527 nm against a blank of chloroform and dioxan. The procedure was carried out in four replicates. Percentage recoveries of loratadine from the dosage form were calculated by reference to the Beer's plot. For the bulk loratadine sample, the experiment above was repeated except that there was no prior extraction from the tablet dosage form.

Statistical analysis

The data were expressed as mean \pm standard deviation (SD, n = 4). Statistical significance of difference between brands of the drug was determined by Student's 't' test followed by one-way analysis of variance (ANOVA) and $p < 0.05$ was considered as statistically significant. Data were analyzed with SPSS 16.0 software.

RESULTS

Absorption spectra

Chloranilic acid (CAA) solution in 1, 4-dioxan gave a yellow colour with an absorption maximum (λ_{max}) at 430 nm while loratadine had λ_{max} at 440 nm. On addition of a solution of

loratadine in chloroform to CAA solution, the colour changed to purple and a bathochromic shift to a longer wavelength (λ_{max} of 527 nm) was obtained at room temperature (Fig. 2). Measurements were carried out at 527 nm. The different variables were studied and optimized.

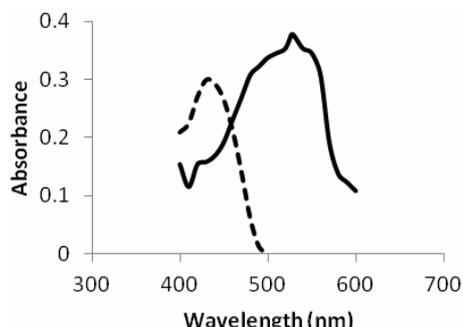


Fig 2: Absorption spectra of chloranilic acid (.....) and loratadine-chloranilic acid complex (—)

Effect of chromogen concentration on complex formation

A mixture of 1, 4-dioxan and chloroform was found to be an ideal solvent for the formation of the complex. The optimum volume of CAA was found to be 2.0 mL which was taken at the highest absorbance reading of 0.235. This volume was used throughout the whole experiment for the formation of the complex.

Effect of time on complex formation

The optimum reaction time was determined from the absorbance readings and by monitoring the color development at room temperature (30 ± 2 °C). The absorbance of the complex increased gradually from zero to 60 min and remained fairly constant up till 90 min after the commencement of the experiment. After this period there was a gradual decline in absorbance. Absorbance reading ranged between 0.220 and 0.240 (Fig. 3). Also complete colour development was attained at 60 min and the colour of the complex remained fairly stable until 90 min. Absorbance measurements were therefore taken 60 min after mixing the reagents.

Beer's plot for loratadine-chloranilic acid complex

The regression equation for the plot of absorbance of complex formed against loratadine concentration was derived using the least-square method as:

$$A_{527\text{ nm}} = 0.011x + 0.0018 \dots\dots\dots (1)$$

where x is the concentration (mg%) of loratadine. At 527 nm, Beer's law was obeyed by the complex; the plot was linear with very small intercept. A good correlation coefficient ($r^2 =$

0.9997) was obtained between the absorbance and the concentration over the entire range studied (3.2-28.8 mg% of loratadine).

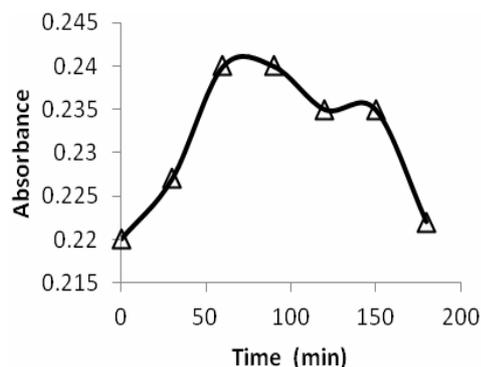


Fig 3: Time absorbance relationship for the loratadine-chloranilic acid complex at room temperature

Job's plot for loratadine-chloranilic acid complex

The stoichiometry of the complex, according to Job's plot, was found to be 2:1 (loratadine: CAA, Fig 4).

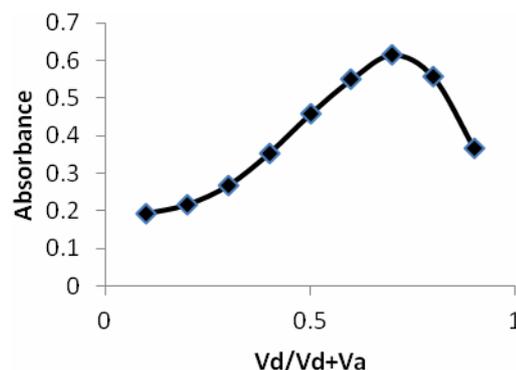


Figure 4: Job's plot of continuous variation for loratadine-chloranilic acid complex Key: Vd = volume of loratadine; Va = volume of CAA

Stability constant, molar absorptivity and other thermodynamic parameters

The molar absorptivity (ϵ), association constant and other thermodynamic parameters for the loratadine-CAA complex were evaluated using the Benesi-Hildebrand equation, Eq 2 [14].

$$\frac{[A_0]}{A_\lambda^{[A:D]}} = \frac{1}{E_\lambda^{[A:D]}} + \frac{1}{[E_\lambda^{[A:D]}][K_c^{[A:D]}] \times \frac{1}{[D_0]}} \dots\dots\dots (2)$$

where $[D_0]$ and $[A_0]$ are initial concentrations of the reactants, $A_\lambda^{[A:D]}$ is the absorbance of the complex at 527 nm, $E_\lambda^{[A:D]}$ is the molar absorptivity of the complex at 527 nm, and $K_c^{[A:D]}$ is the stability constant. The intercepts and slopes of the regression lines from a plot of

proposed method gave true values according to the label claims and this suggests the accuracy of the method. The results were not affected by the presence of excipients in the tablets since the excipients were removed before analysis and could not absorb at 527 nm. The proposed method is simple, fast, accurate and precise.

CONCLUSION

The reaction between loratadine and chloranilic acid was spontaneous and yielded a complex which was quite stable for over one hour, giving enough time for the analysis. This complexation reaction was successfully employed in the assay of loratadine in both bulk and in tablet dosage forms with good precision and accuracy. It is recommended that the accuracy and precision of the proposed method be validated using larger number of dosage forms of the drug and comparing inter-laboratory results.

ACKNOWLEDGEMENT

The authors are grateful to Juhel Nig Ltd, Enugu, Nigeria for the kind donation of a pure sample of loratadine.

REFERENCES

1. Khaled E. Spectrophotometric determination of terfenadine in pharmaceutical preparations by charge-transfer reactions. *Talanta* 2008; 75(5): 1167-1174.
2. El-Zaria ME. Spectrophotometric study of the charge transfer complexation of some porphyrin derivatives as electron donors with tetracyanoethylene. *Spect Chim Acta A* 2008; 69(1): 216-221.
3. Ofokansi KC, Adikwu MU. Qualitative detection of some electron donor drugs on thin layer plates: chloranilic acid as the locating reagent in non-aqueous media. *J Pharm Allied Sci* 2004; 2: 226-232.
4. Katzung, BG. *Basic & Clinical Pharmacology*. 9th ed. USA: The McGraw-Hill Companies; 2004; pp 482-495.
5. María JC, Héctor CG. Determination of loratadine and pseudoephedrine sulfate in pharmaceuticals based on non-linear second-order spectrophotometric data generated by a pH-gradient flow injection technique and artificial neural networks. *Anal Bioanal Chem* 2007; 389: 2217-2223.
6. Ghoneim MM, Mabrouk MM, Hassanein AM, Tawfik A. Polarographic behaviour of loratadine and its direct determination in pharmaceutical formulation and human plasma by cathodic adsorptive stripping voltammetry. *J Pharm Biomed Anal* 2001; 25: 933-937.
7. Indrayanto G, Darmawan L, Widjaja S, Noorizka G. Densitometric determination of loratadine in pharmaceutical preparations and validation of the method. *J Planar Chromatogr Modern TLC* 1999; 12: 261-268.
8. Fernandez H, Ruperez FJ, Barbas C. Capillary electrophoresis determination of loratadine and related impurities. *J Pharm Biomed Anal* 2003; 31: 499-506.
9. Johnson R, Christensen J, Lin CC. GC method of loratadine determination. *J Chromatogr Biomed Appl* 1994; 657: 125-134.
10. Ruperez FJ, Fernandez H, Barbas C. LC determination of loratadine and related impurities. *J Pharm Biomed Anal* 2002; 29: 35-41.
11. Sutherland FCW, de Jager AD, Badenhorst D, Scanes T, Hundt HKL, Swart KJ, Hundt AF. Sensitive liquid chromatography-tandem mass spectrometry method for the determination of loratadine and its major active metabolite descarboethoxyloratadine in human plasma. *J Chromatogr A* 2001; 914 (1):37-43.
12. Mashhadizadeh MH, Hadjiakhoondi A, Ahmadaghaei S. A novel PVC membrane sensor for determination of loratadine in pharmaceutical compounds and blood serum. *J Iran Chem Soc* 2011; 8(3): 687-693.
13. Job R. *Advanced Physicochemical Experiments*. London: Pitman; 1964; p 54.
14. Benesi HA, Hildebrand JH. Ultraviolet absorption bands of iodine and aromatic hydrocarbon. *J Am Chem Soc* 1949; 70: 2032-2036.
15. Attama AA, Nnamani PO, Agbo AN. Development of alternative assay technique for cephalexin by charge transfer interaction of the donor: acceptor type with chloranilic acid. *Chinese Pharm J* 2006; 58:11-18.
16. Salem H. Analytical study for the charge-transfer complexes of gabapentin. *Afr J Pharm Pharmacol* 2008; 2 (7): 136-144.
17. Basavaiah K, Charan VS. The use of chloranilic acid for the spectrophotometric determination of three antihistamines. *Turk J Chem* 2002; 26: 653-661.
18. Obonga WO, Omeje EO, Uzor PF, Ugwu MO. Spectrophotometric determination and thermodynamic parameters of charge transfer complexation between stavudine and chloranilic acid. *Trop J Pharm Res* 2011; 10: 817-823.