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Research Article

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Method Development for Quantification of Loratidine and Alverine Citrate by Visible Spectrophotometry

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ABSTRACT

The present work describes on two colorimetric methods based on charge transfer complex reaction of loratidine (LRT) and alverine citrate (ALV) with chloranilic acid in chloroform. The methods were developed on Perkin Elmer LAMBDA 25 UV –VIS spectrophotometer with 1cm quartz cells. The methods were optimised to achieve maximum colour intensity and validated for reliability. The coloured complexes showed maximum absorbance at 538 nm for LRT and 540 nm for ALV. The absorbances were found to increase linearly with increase in concentration which was emphasised by the calculated regression coefficients (0.9998-0.9999). Linearity of standard plot was in the order of 100-700 and 80-560µg/ml for LRT and ALV, respectively. The molar absorptivity, sandells sensitivity, LOD, LOQ and other validation parameters have been assessed extensively and all the parameters seem to comply with the acceptance criteria. The proposed methods were proved to be more accurate, simple, precise and rapid by statistical validation, recovery studies and could be appropriate to employ in regular laboratory analysis.

Keywords: Loratidine (LRT), Alverine citrate (ALV), Chloranilic acid, Chloroform, Charge transfer (CT).

INTRODUCTION

Loratidine, (Fig. 1) ethyl 4-(8-chloro-5, 6-dihydro-11H-benzo [5, 6] cyclohepta [1, 2-b] pyridin-11-ylidene)-1-piperidinecarboxylate, is used in treating allergies such as sneezing, watery eyes, and runny nose. It is also used to treat skin hives and itching in people with chronic skin reactions. It acts as a selective inverse agonist of peripheral histamine H_1 receptors.

Alverine, (Fig. 2) N-Ethyl-3-phenyl-N-(3-phenylpropyl) propan-1-amine, is a drug used for functional gastro-intestinal disorders. It is a smooth muscle relaxant. Alverine acts directly on the muscle in the gut, causing it to relax. This prevents the muscle spasms which occur in the gut in conditions such as irritable bowel syndrome and diverticular disease.

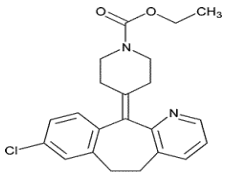

Fig. 1: Structure of LRT

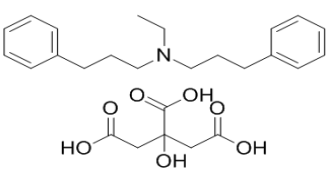

Fig. 2: Structure of ALV

Literature is enriched with several techniques like HPLC and spectrophotometry for the determination of LRT [1-6] and ALV. [7-12] The reported methods suffer from one or more disadvantages such as narrow linear response, lack of sensitivity and selectivity and usage of

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expensive reagents. The need for sensitive, cost effective and reliable spectrophotometric methods for the selected drugs is thus obviously recognized. Spectrophotometry is by far the instrumental technique of choice in the laboratories of under developed and developing nations for the quantification of drugs owing mainly to its simplicity, high sensitivity and selectivity and often demanding low cost equipment. Chloranilic acid and other **π-**acceptors have been extensively used in the spectrophotometric analysis of various drugs which could act as electron donors. CT bands are easily identified because they are very intense, i.e. have a large extinction coefficient, are normally broad and display very strong absorptions that go above the absorption scale (dilute solutions must be used). The appearance of the CT band is attributed to the excitation of an electron from the highest occupied molecular orbital of the donor to the lowest unoccupied molecular orbital of the acceptor. The position and intensity of the CT bands are useful for identification and analysis of the nature of donors and acceptors qualitatively and quantitatively. The electron-rich structure of LRT/ALV was exploited for the quantitative determination by the formation of a stable charge-transfer complex with chloranilic acid via spectrophotometry. The present work was aimed to explore the significance of charge transfer complexation of the drugs with chloranilic acid in polar medium, which was not reported earlier for the quantitative analysis of LRT/ALV and to validate the methods according with ICH guidelines.

MATERIALS AND METHODS

Equipment

Double-beam Perkin Elmer (LAMBDA 25) UV-Vis spectrophotometer with 1 cm matched quartz cells was used for spectral measurements. Samples were weighed using Sartorius electronic balance.

Chemicals

Pharmaceutical grade LRT and ALV was graciously donated by Aurobindo Pharma Ltd, Hyderabad. Chloranilic acid and chloroform of AR grade were used for the experimental work. Double distilled water was used in the preparation of solutions. All the preparations were prepared a fresh daily.

Preparation of 0.1% chloranilic acid

50 mg of chloranilic acid was dissolved in 5 ml isopropyl alcohol and made up to 50 ml with chloroform.

Preparation of stock solution for estimation of LRT

125 mg of LRT was weighed and transferred to a 25 ml volumetric flask, dissolved and diluted to final volume with chloroform. The resulting solution has a concentration of 5 mg/ml.

Preparation of stock solution for estimation of ALV

25 mg of ALV was weighed and transferred to a 25 ml volumetric flask, dissolved and diluted to final volume with chloroform. The resulting solution has a concentration of 1 mg/ml.

Procedure for calibration plot of LRT (Method A)

In to a series of 5 ml volumetric flasks, 0.1-0.7 ml (1 ml=5 mg/ml) of working standard solution of LRT was pipetted out and 1.5 ml of (0.1 %) chloranilic acid was added and made to 5 ml with chloroform. The absorbance of the purple coloured chromogen was measured at 538 nm against reagent blank. The amount of LRT present in the sample solution was computed from its calibration curve.

Procedure for calibration plot of ALV (Method B)

In to a series of 5 ml volumetric flasks, 0.4-2.8 ml (1 ml=1 mg/ml) of working standard solution of ALV was pipetted out and 1.5 ml of (0.1 %) chloranilic acid was added and final volume was made to 5 ml with chloroform. The absorbance of the purple coloured chromogen was measured at 540 nm against reagent blank. The amount of ALV present in the sample solution was computed from its calibration curve.

Assay procedure for LRT

Twenty tablets of commercial samples (Loratin 10 mg) of LRT were accurately weighed and powdered. Tablet powder equivalent to 125 mg of LRT was dissolved in chloroform and the final volume was made up to 25 ml with chloroform and the assay was carried out by the above procedure.

Assay procedure for ALV

Twenty tablets of commercial samples (Gastrim plus 60 mg) of ALV were accurately weighed and powdered. Tablet powder equivalent to 25 mg of ALV was dissolved in chloroform and the final volume was made up to 25 ml with chloroform and the assay was carried out by the above procedure.

RESULTS AND DISCUSSION

The drugs LRT/ALV on reacting with chloranilic acid produced characteristic colours attributed to the formation of CT complexes. Both the reacted products exhibit one CT band each in the wavelength region where neither of the components have any absorption. The benzo-cylcohepta-pyridine structure of loratidine and tertiary amino group of alverine are electron rich and good electron donors.

Optimisation of the Method

The method was optimised by selecting the proper solvent, chromogen, and concentration of the reagent, order of addition, selection of the wavelength and stability of the coloured product.

Solvent selection

Several solvents were used for the solubility of the drugs like water, HCl, sodium hydroxide, ethanol, methanol, chloroform etc, and found that both LRT and ALV were soluble in chloroform. So, finally chloroform was used as diluent throughout the procedure.

Effect of chloranilic acid concentration

It was studied by treating the fixed volume of LRT/ALV concentration and in-turn varying the volume of choranilic acid from 0.1-0.7 ml for LRT and 0.4-2.8 ml for ALV. The results for both methods were depicted in Table 1.

Effect of time/temperature on reaction

The effect of time and temperature on the formation of the coloured complex was studied for all the methods. The complex formation was complete in 10 min time interval at room temperature and found stable up to 1 h for both drugs. Above 30ºC the colour intensity of the complex decreases. Fig. 3 and 4 represents the effect of temperature and time on colour development process of LRT and ALV.

Method validation

Both methods were validated for accuracy, precision, linearity, LOD, LOQ, ruggedness and robustness and the results were found to be satisfactory.

Linearity and range

At the described experimental conditions for LRT/ALV standard calibration curves were constructed by plotting an increase in absorbance with concentration (Fig. 5 and 6). A linear correlation was found between absorbance and concentration of LRT/ALV and all the parameters regarding linearity were given in Table 2.

Table 1: Order of addition/concentration of reagents for the proposed methods.

Method A	LRT + 1.5 ml chloranilic acid (0.1%) + chloroform
Method B	ALV + 1.5 ml chloranilic acid (0.1%) + chloroform

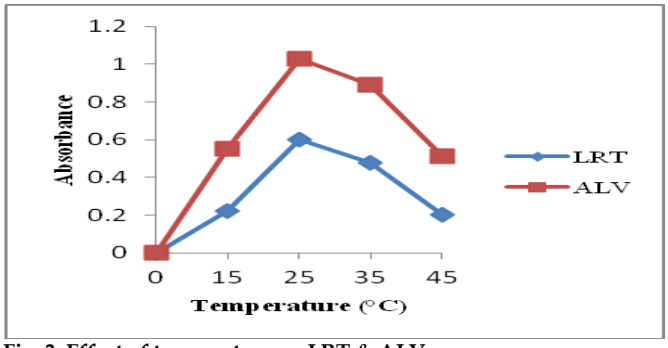

Fig. 3: Effect of temperature on LRT & ALV

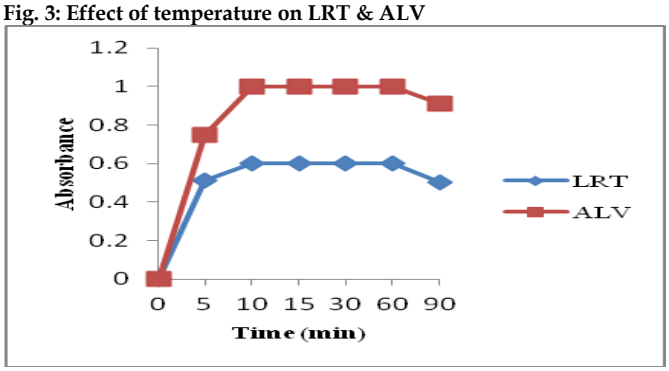

Fig. 4: Effect of time on LRT & ALV

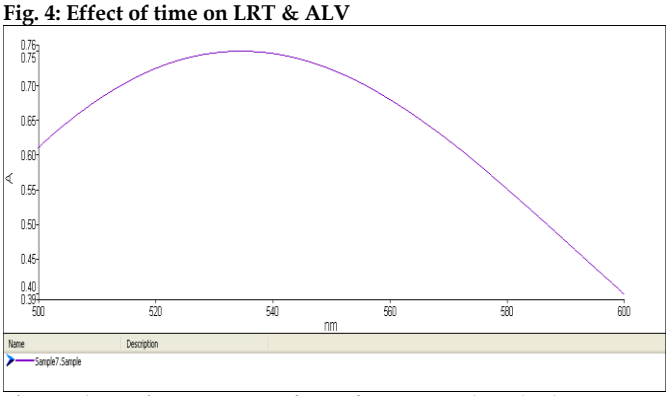

Fig. 5: Absorption spectrum of LRT for proposed method A

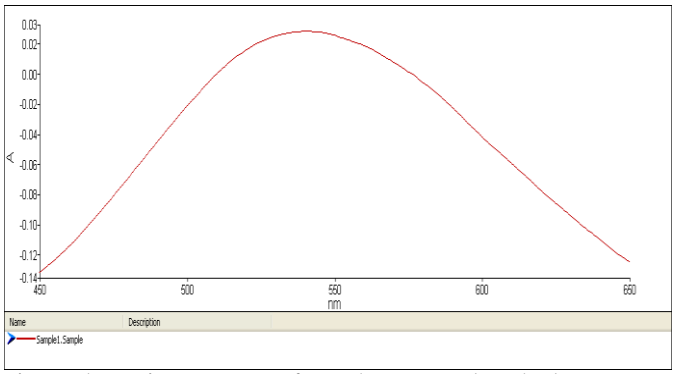

Fig. 6: Absorption spectrum of ALV by proposed method B

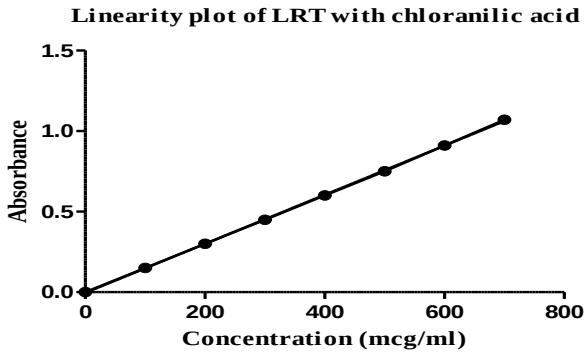

Fig. 7: Linearity plot of LRT

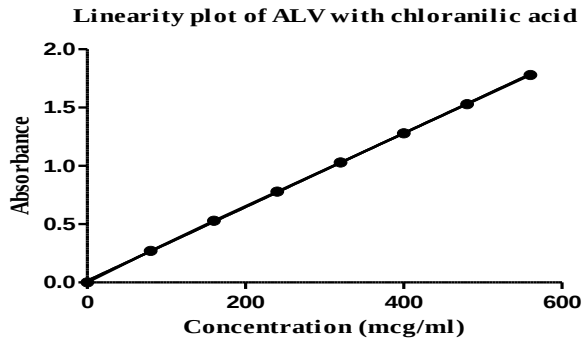

Fig. 8: Linearity plot of ALV

The statistical parameters given in the regression equation were calculated from the calibration graphs. The high values of the regression coefficients and low values of y-intercepts of the regression equations, proved the linearity of the calibration curves.

Precision

The precision of the proposed methods were assessed by determining the relative standard deviation (RSD) of six replicate analyses on the same solution containing fixed concentration of LRT/ALV (within Beer's law limit). The low % RSD of the intraday and interday repeatability studies corroborates precision of the method. Table 3 represents the results of precision studies.

Robustness

Robustness was checked by narrow alteration of the optimized parameters and the % RSD were found to be satisfactory.

Limit of detection (LOD) and limit of quantification (LOQ)

LOD and LOQ were determined by analysing progressively lower concentrations of standard

solutions using optimized conditions and the results were presented in Table 2.

Accuracy

The validity and accuracy of the proposed methods were further assessed by recovery studies using the standard addition technique. For this purpose, a known amount of pure drug at three different levels was spiked to the fixed and known quantity of pre analyzed formulation samples and the nominal value of drug was estimated by the proposed methods. The results given in Table 4 establish that the methods were reproducible by low SD and % RSD. No interference was evidenced from the commonly encountered formulation excipients.

Application of the proposed methods to formulations

To evaluate the proposed methods, they were applied to the determination of LRT/ALV in commercial formulations. The recoveries are close to 100 %, indicating that there is no serious interference in samples. The good agreement between these results and known values indicate the successful applicability of the proposed methods for the determination of LRT/ALV in formulations. The results are given in Table 5.

Table 2: Optical and regression parameters

Parameters	LRT	ALV
λ max, nm	538	540
Beer's law range (µg/ml)	100-700	80-560
Molar absorptivity (L.mole^{-1} .cm^{-1})	1.5×10^{-5}	3.2×10^{-5}
Sandell's sensitivity (µg/cm^2)/0.001 absorbance unit)	4×10^{5}	3.2×10^{5}
LOD, µg/ml	11.62	8.49
LOQ, µg/ml	35.21	25.73
Slope(m)	0.001523	0.003164
Intercept(b)	-0.004167	0.01417
Correlation coefficient(r)	0.9998	0.9999

Table 3: Results of precision studies

Parameter	LRT		ALV	
	Intraday*	Inter day*	Intraday*	Inter day*
Conc	400µg/ml		320µg/ml	
Mean abs	0.61	0.618	1.036	1.026
SD	0.008944	0.007528	0.010328	0.010328
% RSD	1.46	1.21	0.99	0.97

***n=six determinations**

Table 4: Results of accuracy studies by proposed methods

Drug	Drug in formulation (µg)	Std added (µg)	Amt Found (µg)	% Recovered	% RSD N=3
	400	200	598.98	99.83	0.12
LRT	400	400	799.14	99.89	0.036
	400	600	999.33	99.93	0.034
	400	240	639.47	99.91	0.078
ALV	400	400	799.05	99.88	0.030
	400	480	879.50	99.94	0.051

Table 5: Assay results of LRT/ALV

Formulations	Label claim (mg)	Amount found (mg)	% Recovery N=3
Loratin (tablet)	60	59.75	99.58
Gastrim plus (tablet)	10	9.9	99

Two new, cost effective, simple and sensitive visible spectrophotometric methods, using chloranilic acid as reagent, were developed for the determination of LRT and ALV in bulk and in pharmaceutical formulations. The developed methods were also validated. From the statistical data, it was found that the proposed methods were accurate, precise and reproducible and can be successfully applied to the analysis of the same and could make a better alternative to the existing methods.

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