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DEVELOPMENT AND VALIDATION OF SPECTROPHOTOMETRIC DETERMINATION OF LORATADINE THROUGH CHARGE-TRANSFER COMPLEXATION WITH IODINE AND CHLORANIL

Niranjani S.[1], Muthukumaran M.[2], Samuel Barnabas K.[3],* Dr. K. Venkatachalam[2], *Dr. T. Raju[2]

[1]SDNB Vaishnav College for Women, Chromepet, Chennai-44.

[*,2]Department of Analytical Chemistry, University of Madras, Guindy Campus, Chennai-25.

[3]Orchid Pharmaceutical Ltd, Sholinganalur, Chennai-119.

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***Corresponding Author**
Dr. Raju T, Dr. Venkatachalam K.
Department of Analytical Chemistry, University of Madras, Guindy Campus, Chennai-25.

ABSTRACT

Two simple, sensitive and inexpensive spectrophotometric methods have been described for the determination of loratadine, an antiallergic drug. The procedure was based on the formation of coloured charge-transfer complexes of loratadine acting as an n-electron donor with iodine acting as σ-acceptor in chloroform (method A) and 2,3,5,6-tetrachloro-1,4-benzoquinone (p-chloranil) acting as π-acceptor in dimethyl sulfoxide (method B). The optimizations of various experimental conditions and the mole ratio were studied. The charge-transfer complexes formed were found to absorb at 399 nm and 528 nm. Beer's law was obeyed for these methods in a concentration range of 6.5-78 mM and 0.2-6 µg ml^{-1} with correlation coefficients 0.9999 and 0.9993. Application of these methods to the assay of loratadine in tablet form was described and the results were statistically validated. The results of analysis of commercial formulations and the recovery study of the drug suggested that there was no interference from any excipients, which were present in pharmaceutical formulations.

KEYWORDS: loratadine; spectrophotometry; iodine; chloranil; charge-transfer complexes.

INTRODUCTION

The molecular interactions between electron donors and acceptors are generally associated with the formation of intensely coloured charge-transfer complexes which absorb radiation in

the visible region. The photometric methods based on these interactions are usually simple and convenient because of the rapid formation of the complexes.[1]

Loratadine (LOR, figure 1), ethyl-4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridine-11-ylidene)-1-piperidinecarboxylate is a tricyclic, piperidine derivative of antihistamine H1 receptor. It belongs to the second generation antihistamines, so it has non–sedating properties. It is applied in the treatment of allergies. They prevent symptoms such as itching, congestion, rhinorrhoea, tearing and sneezing. LOR belongs to Class II of the BCS. LOR is official in the undermentioned pharmacopoeias: British Pharmacopoeia 2012, The United States Pharmacopoeia 34 - National Formulary 29, European Pharmacopoeia 7.4.

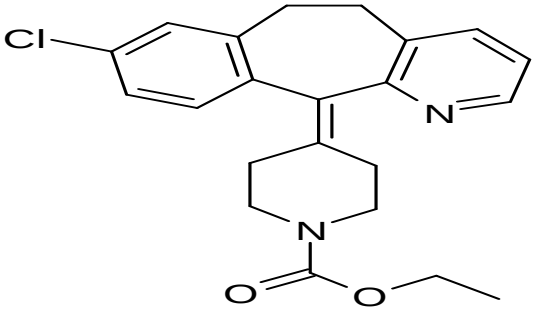


Figure 1. Chemical structure of loratadine

Owing to its great therapeutic importance and widespread use, several procedures have been reported for its determination in pharmaceutical preparations and biological fluids. Loratadine was determined in body fluids using LC.[2] HPLC.[3] GCMS.[4] UV spectrophotometric methods were done to the determination of LOR hydrochloride in tablets and suspension.[5] LOR and pseudoephedrine sulfate were determined by first-, second- and ratio spectra derivative spectrophotometric methods[6]. Stability-indicating methods reported for the determination of LOR in the presence of its degradation products developed by 1D ratio spectra at 236, 262.4 and 293.2 nm and by second derivative spectrophotometry at 266 nm.[7] Visible spectrophotometric method developed for estimation of LOR from tablet formulation via formation of chloroform extractable colored complex with bromophenol blue at 413 nm and with cobalt thiocyanate at 624.5 nm.[8] El-Kousy and Bebawy.[9] developed a method for the determination of KET and LOR based on the formation of radical ion using 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ), the color formed was absorbed at 588 nm. LOR was analysed by charge-transfer complex formation with chloranilic acid as a π-acceptor and the resultant complex was measured at 520 nm.[10]

Charge-transfer complexation reactions have been extensively utilised for the determination of electron-donating basic nitrogenous compounds using σ-acceptor iodine[11] and chloranil[12] in organic solvents. In this paper, spectrophotometric methods based on these reactions developed for the determination of loratadine drug. Chloroform (method A) and dimethyl sulfoxide (method B) was the most suitable solvent as they dissolved loratadine and are a suitable medium for charge-transfer complexation reactions leading to radical ion formation.

EXPERIMENTAL

Instrument

An ELICO SL-218 double beam spectrophotometer equipped with 1 cm matched quartz cells was used for all the spectral measurements.

Reagents and materials

Pharmaceutical grade LOR (99.8% purity) was gifted from Orchid Pharmaceuticals, Chennai. Iodine bought from SD FINE CHEM INDIA LTD and chloranil from SIGMA-ALDRICH. Lorfast Meltab and Lorinol-10 tablets manufactured by CADILA and MICROLAB got from the local pharmacy (Chennai, Tamilnadu). The solvents used were of analytical grade.

Working standard solution of loratadine

An accurately weighted amount of LOR equivalent to 5g was dissolved in 10 ml of chloroform and made upto the mark into a 100 mL calibrated flask using the same solvent. This concentration (0.13M) was used for method A. For method B, 10mg of LOR was dissolved in 10ml of DMSO and made up in 100ml using the same solvent. This concentration (100 µg/ml) was diluted to 10 µg/ml and used for method B.

Iodine and chloranil solution (0.1%)

These solutions were prepared by dissolving 0.1 g of iodine and chloranil in 100 ml of chloroform and DMSO respectively. 0.13 M iodine and 4×10^{-3} M of both LOR and chloranil solutions were also prepared for Job's and mole-ratio methods. Chloranil solutions were prepared fresh daily.

Analysis of tablets

Twenty tablets were finely powdered in a mortar and mixed. An accurately weighed quantity equivalent to LOR concentration mentioned was transferred to a 100 ml beaker and the drug

was extracted with three 10 ml portions of chloroform and DMSO and filtered using a Whatman filter paper-41. The residue was washed with 10 ml of chloroform and DMSO and the volume was finally made up to 100 ml calibrated flask with the corresponding solvents for both the methods.

Procedure for the selectivity study

The selectivity was tested by both placebo blank analysis and recovery studies. Placebo blank, commonly employed excipients added to the formulations, consisting of 40 mg starch, 25 mg lactose, 30 mg acacia, 35 mg calcium gluconate, 30 mg talc, 40 mg magnesium stearate and 30 mg sodium alginate was prepared as described under analysis of tablets and then subjected to analysis. A synthetic mixture was prepared by adding 5g and 10 mg of pure LOR to the above mentioned placebo blank and the mixture was homogenized. Following the same procedure for tablets, the synthetic mixture solutions were prepared and suitable quantities were subjected for the analysis by the proposed methods.

PROCEDURES FOR CALIBRATION GRAPH

Method A (using iodine as acceptor reagent)

A volume of 0.25-3.00 ml of LOR was transferred into a 5ml calibrated flask and the volume was made up to 3.00 ml by adding requisite volumes of chloroform. 2.00 ml of 0.1% iodine solution was added and allowed to stand for 10 min. The absorbance was measured at 399 nm against the reagent blank prepared in the similar way without the drug.

Method B (using chloranil as acceptor reagent)

A volume of 0.1-3.0 ml of LOR was transferred into a 5ml calibrated flask and the volume was made up to 3.0 ml by adding requisite volumes of DMSO. 2.0 ml of 0.1% chloranil solution was added and heated the solution to 50ºC for 1min. The solution was allowed to stand for 1 h at room temperature to develop the full colour. The absorbance was measured at 528 nm against the reagent blank prepared in the similar way without the drug.

The calibration graph in each instance was prepared by plotting the measured absorbance versus concentration of drug. The concentration of the unknown was read from the calibration graph or computed from the regression equation.

RESULTS AND DISCUSSION

Absorption spectra

The reaction between LOR and iodine to form charge transfer complex was studied and the absorption spectrum was recorded at 200-800 nm against the reagent blank. Spectrum of LOR-I_2 was characterized by the appearance of a new band at 399 nm. It was evident that the broad band located at 512 nm that was due to the absorption of free iodine exhibits a hypsochromic shift due to complexation with LOR. Thus, the new band located at 399 nm was assigned as a CT band (figure 2).

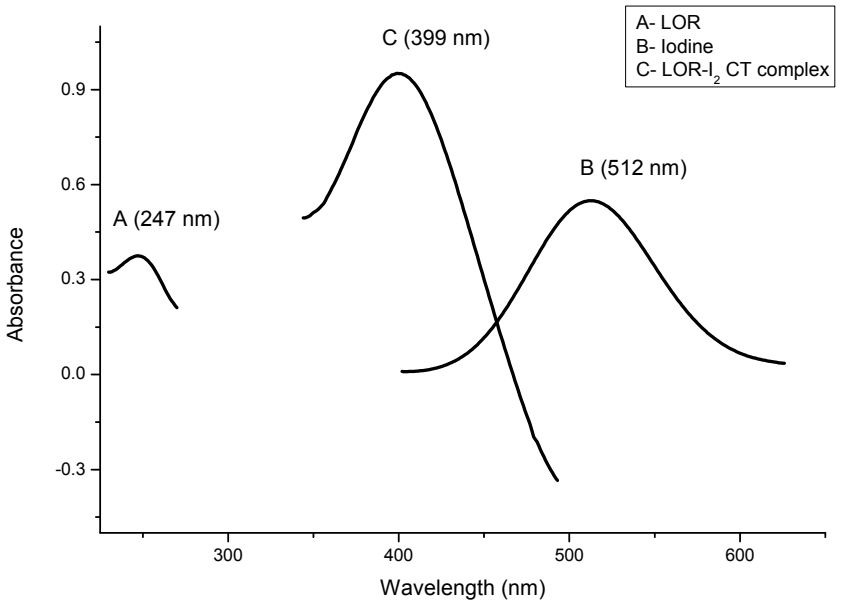


Figure 2. Absorption Spectra of LOR-I_2 CT complex (LOR-I_2 CT concentration-78mM; I_2 – 2ml of 0.1% iodine)

For the reaction of LOR with chloranil, figure 3 shows the absorption spectrum recorded in the region of 200-800 nm. A strong change in color was observed upon mixing and heating the solution at 50ºC. Red color indicates the formation of LOR-chloranil charge-transfer complex and it is associated with the electronic absorption at 528 nm.

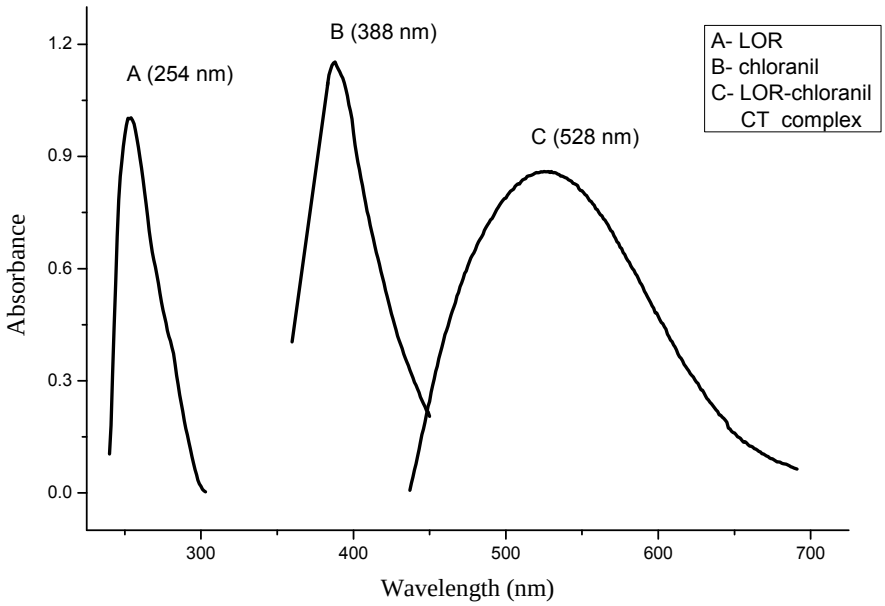


Figure 3. Absorption Spectra of LOR-chloranil CT complex (LOR-chloranil CT concentration -5.5 µg/ml; chloranil -2ml of 0.1% chloranil)

Reaction Mechanism

UV–visible study of the interaction between LOR and I_2 as σ-acceptor

Absorption spectra of chloroform solution of LOR-I_2 CT complex show the triiodide bands[13-15] located at 290 and 385 nm. This means that in LOR-I_2 interactions the first appeared CT band diminishes meanwhile the triiodide band appears. Generally, transformation of the CT complex characterized with the first appeared CT band to the corresponding triiodide complex with its characteristic bands may occur instantaneously on mixing the donor with the acceptor or takes several minutes or hours to occur depending mainly on the strength of the donors and on several factors such as polarity of the used solvent, the reaction temperature and other reaction conditions. Herein, absorption spectral tracking of the LOR-I_2 mixture solution in $CHCl_3$ has shown that the primarily formed CT band, located at 399 nm, gradually shifts toward lower wavelengths, hypsochromic shift, through lapse of time (figure 4). Thus, the destination of the gradual shift of the first formed CT band is directed toward the wavelength region near to that characterizing to the triiodide ions (I_3^-)[13-15] at 385 nm in $CHCl_3$, meanwhile a parallel gradual diminishment of the primary formed CT band is observed through that time, which is due to a decrease in the concentration of the CT complex (figure 4).

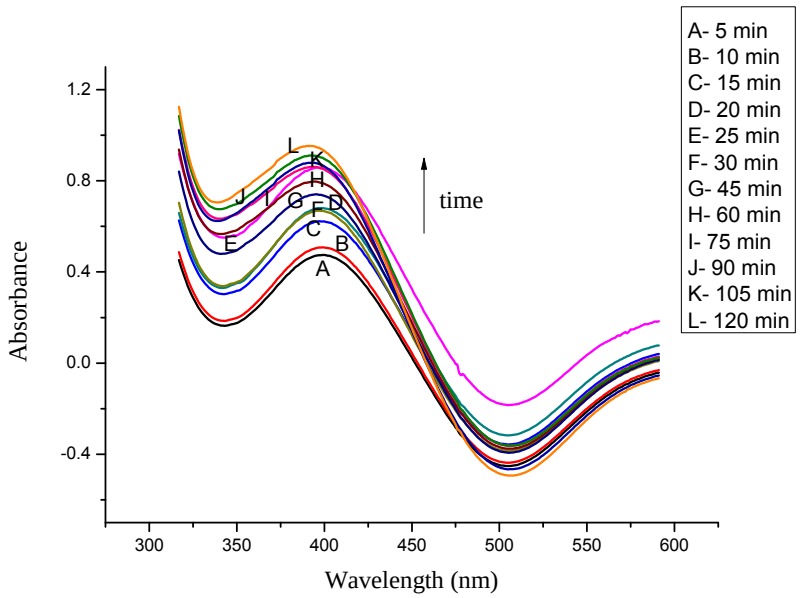


Figure 4. Effect of time on LOR-I_2 CT complex

Formation of the triiodide complexes as a result of the interactions of n-donors (L) with the σ-acceptor (I_2) has been reported[16-18] to follow the following reaction pathway: (1) formation of the associative outer-sphere CT complex L.I_2, where L represents the pyridine ring nitrogen atom acting as n-donor; (2) transformation to the dissociative inner-sphere complex (L+I.I^-); and (3) association with another iodine molecule to form the triiodide complex (L).(L+I.I_3^-). Thus, the following reported reaction pathway given in scheme 1 may represent the interaction of the n-donor (L) with the σ-acceptor (I_2):

$$L + I_2 \rightleftharpoons L \,.\, I_2 \longrightarrow L^+ I \,.\, I^{--}$$

(very fast - outer sphere CT complex) (very slow- inner sphere complex)

$$L^+ I \,.\, I^{--} + I_2 \longrightarrow L^+ I \,.\, I_3^{--}$$

(initially formed complex)

$$L + L^+ I \,.\, I_3^{--} \longrightarrow (L) \,.\, (L^+ I \,.\, I_3^{--})$$

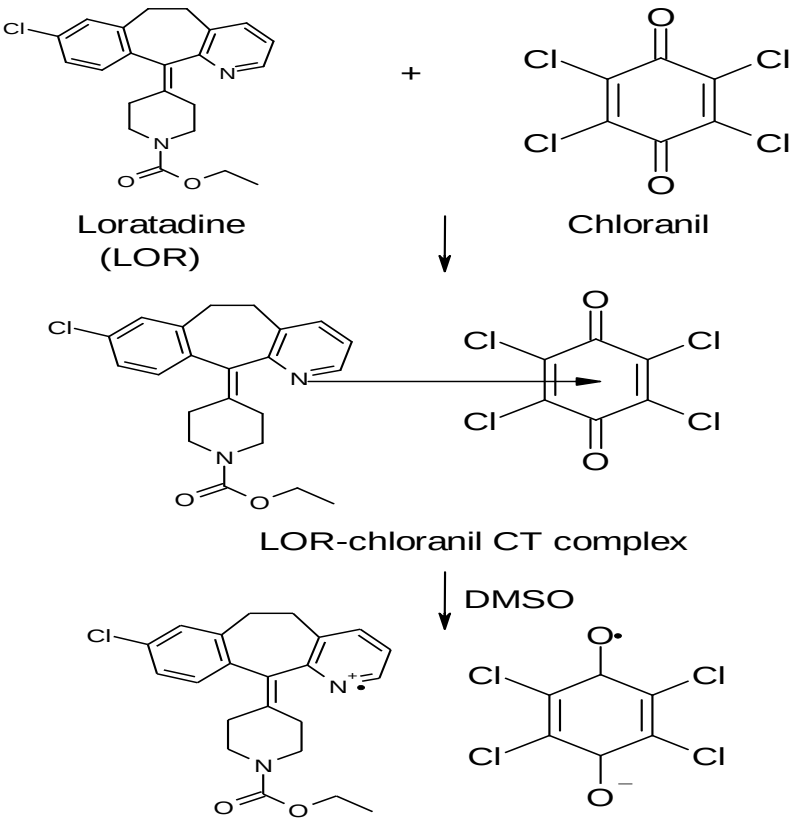
(new acceptor) (CT complex)

Scheme 1. The proposed reaction mechanism between LOR and iodine

UV–visible study of the interaction between LOR and chloranil as π-acceptor

When LOR in DMSO solution was mixed with DMSO solution of chloranil and heated the solution to 50ºC, red colour developed that reached its maximum intensity and stability after

standing for 1 h at room temperature. This finding may be explained in terms of the formation of a charge-transfer complex between LOR as electron donor and π-acceptor chloranil. LOR contains basic pyridine ring nitrogen as possible site of interaction with chloranil, leading to an n-π complex through overlapping of the electron cloud of the pyridine ring with the electron deficient chloranil molecule which further dissociates due to high ionizing power of the polar solvent and leads to the formation of radical ions. The newly formed complex showed absorption maxima at 528 nm respectively against reagent blank prepared under the same conditions. Figure 3 represented the electronic absorption spectra of complex and the proposed reaction was illustrated in Scheme 2.



Scheme 2. The proposed reaction mechanism between LOR and chloranil

METHOD DEVELOPMENT

A number of preliminary experiments developed optimum conditions necessary to achieve complete quantitative reaction formation. Optimum conditions were fixed by varying one parameter at a time while keeping other parameters constant and observing its effect on the absorbance at 399 nm for method A and 528 nm for method B.

Effect of Reagent Concentration

Maximum absorption was obtained when 2.00ml of 0.1% iodine (method A) and 2.00 ml of 0.1% chloranil (method B) solutions were used in a total volume of 5 ml. Figure 5 and figure 6 showed the relationship between absorbance and concentration of iodine and chloranil at 26mM and 2 µg/ml LOR concentrations.

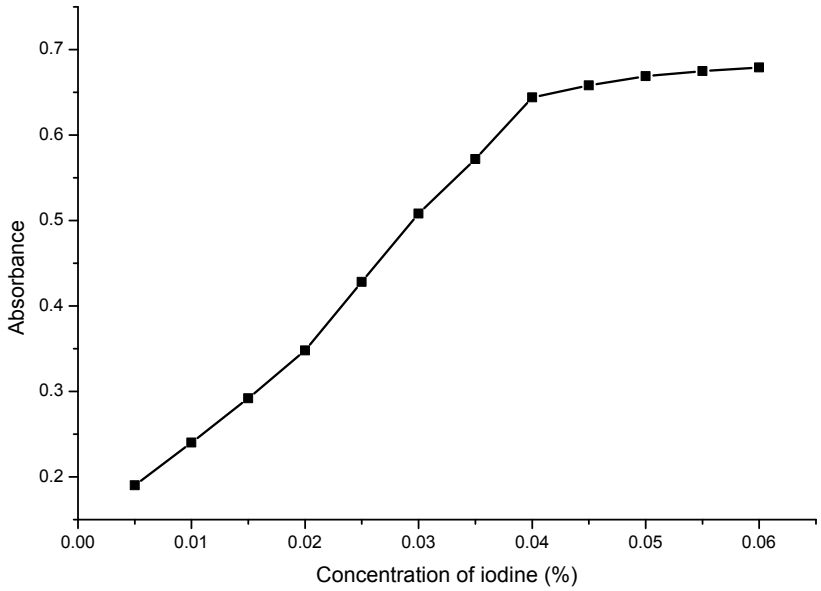


Figure 5. Effect of iodine on LOR-I_2 CT complex formation

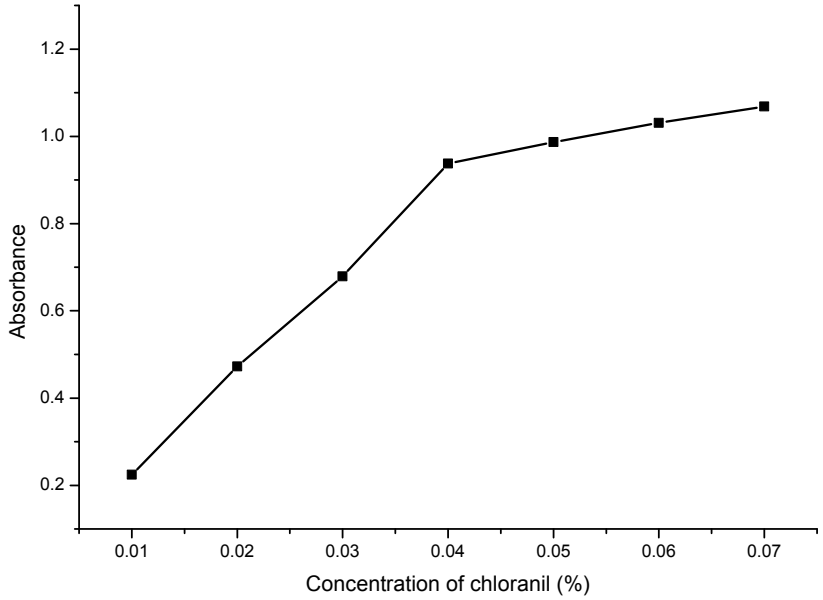


Figure 6. Effect of chloranil on LOR-chloranil CT complex formation

Selection of Solvent

Organic solvents, namely, chloroform, dichloromethane (DCM), 1,2-dichloroethane, DMSO and acetonitrile were tested for quantitative formation of CT complexes. Based on the results, chloroform for method A and DMSO for method B were selected as solvent due to its efficiency, the greater stability of the complex (>24 h), its high sensitivity, maximum absorbance of the measured complex and short time required for its formation.

Effect of Time, Sequence of Addition and Stability

The reactions between LOR and iodine/chloranil in chloroform/DMSO were instantaneous and the product remained stable for more than 24 h. Drug followed by iodine/chloranil addition gave maximum absorption than iodine followed by drug addition.

In order to make use of LOR-I_2 complex formation for the determination of LOR, two experimental conditions were necessary:

a) an iodine concentration suitable for quantitative complexation; this concentration should not be much higher than LOR concentration in order to avoid the formation of termolecular complexes with a consequent deviation from Beer's law; in this work 2 ml of 0.1% iodine solution was found suitable;
b) the absorbance should be measured in 10 min after the addition of the reactants in order to minimise changes in the absorbance with time.

Composition of LOR-I_2/LOR-chloranil Charge transfer Complex

This was determined by Job's method. A series of standard solutions of loratadine and iodine/chloranil in different proportions totally 5 ml were prepared in 5ml calibrated flasks. The solutions were heated to 50ºC for method B. After 10 min/1h, the absorbances were measured at 399nm and 528nm. The molar ratio of LOR-iodine/chloranil reactions showed that only nitrogen atom of pyridine moiety of LOR was involved in the reaction with iodine/chloranil (Figure 7 and 8). This may be explained on the basis that a univalent, partially positively charged nitrogen species may be formed initially during the charge-transfer process, which may not be easily engaged in additional complex formation. This suggestion was confirmed also by the finding that LOR gave a 1:1 molar ratio although it contains two possible sites of reaction. It is probable that the pyridine moiety contains nitrogen atom involved in the reaction as it is more basic than the other piperidine nitrogen atom[19] as confirmed by obtaining the same λmax (399 nm) when aniline[20] was treated similarly for method A.

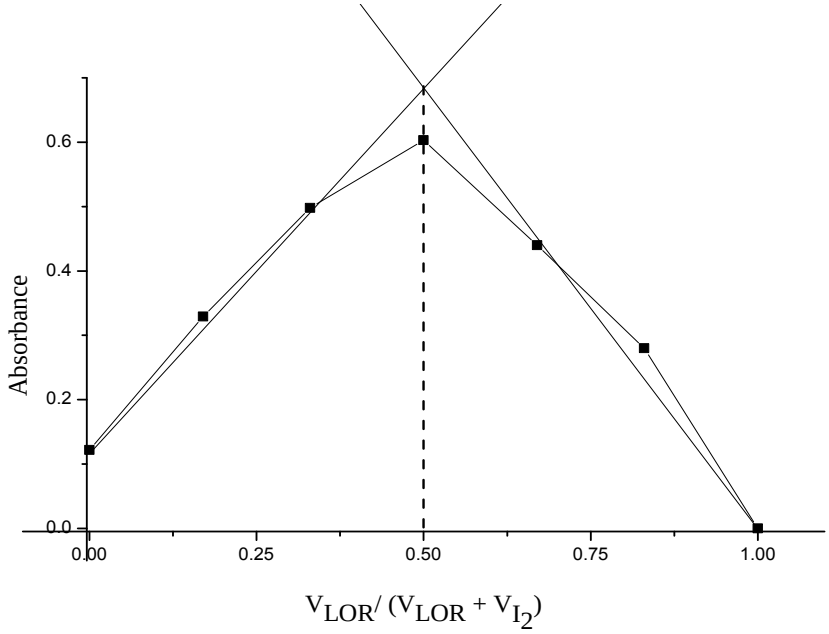


Figure 7. Job's continuous variation plot for LOR-I_2 CT complex

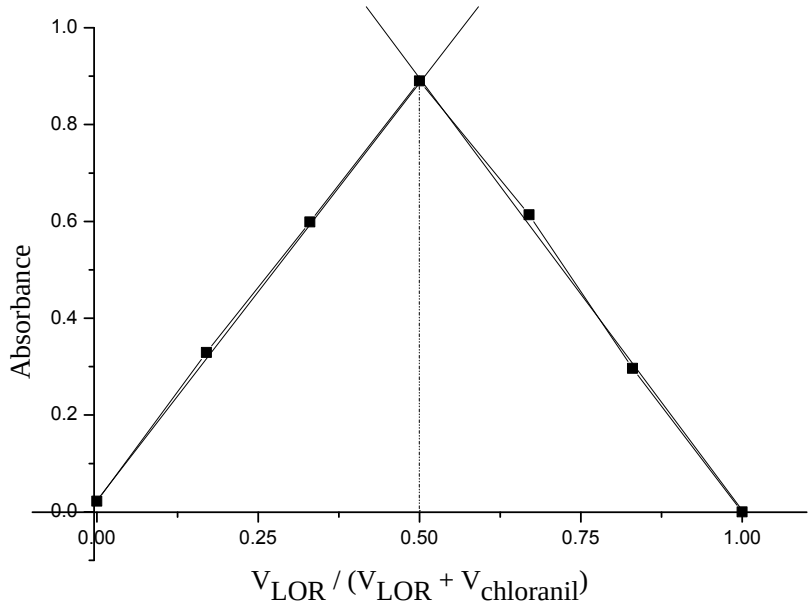


Figure 8. Job's continuous variation plot for LOR-chloranil CT complex

METHOD VALIDATION

The proposed methods were validated according to the current ICH guidelines.[21]

Analytical parameters

Under optimum experimental conditions for LOR determination, the standard calibration curve was studied by plotting the absorbance versus concentration. The linear regression equation was obtained by the method of least squares and Beer's law was obeyed over the

concentration ranges stated in table 1. Many parameters such as intercept (b), slope (m), molar absorptivity, Sandell's sensitivity, correlation coefficient (r), standard deviation of Y-values, standard deviation of slope (S_m), limits of detection and quantification for the proposed method were summarized in table 1. The linearity of calibration graphs was proved by the high values of the correlation coefficient (r) and the small values of the Y-intercept of the regression equation.

Sandell's sensitivity was calculated by using the equation: $S= 0.001/\varepsilon_s$

where ε_s – specific absorptivity(ml/g/cm) which was caluculated by $\varepsilon_s = \varepsilon \times 1000/$Molecular weight of LOR

Table 1. Analytical and regression parameters

Parameter	Method A	Method B
λ_{max}, nm	399	528
Beer's law limit	6.5-78 mM	0.2-6 µg/ml
Concentration of reagent	0.1% in $CHCl_3$	0.1% in DMSO
Molar absorptivity (L/mol/cm)	1.25×10^4	6.1×10^4
Sandell's sensitivity* (µg/cm^2)	3.06×10^{-8}	6.27×10^{-9}
Limit of detection	5 mM	0.35 µg/ml
Limit of quantification	15 mM	1.07 µg/ml
Regression equation, Y**		
Intercept (b)	0.1217	0.1256
Slope (m)	0.2847	0.2797
Correlation coefficient (r)	0.9999	0.9993
Standard deviation of Y-values	0.9254	0.0110
Standard deviation of slope (S_m)	0.3067	0.0042

**Limit of determination as the weight in µg/ml of solution which corresponds to an absorbance of A = 0.001 measured in a cuvette of cross-sectional area 1 cm^2 and l = 1 cm*

***y = mx + b, where y is the absorbance and x is the concentration in µg/ml*

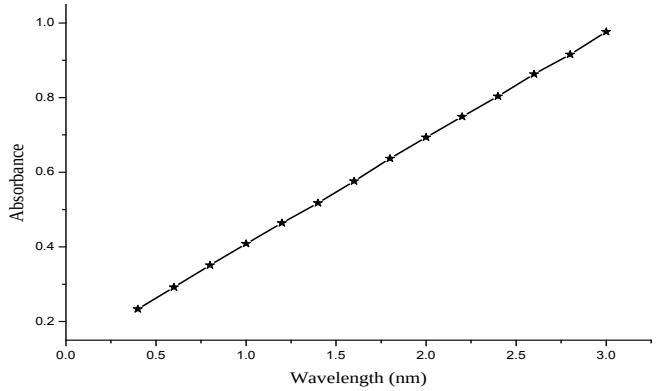


Figure 9. Calibration plot for method A

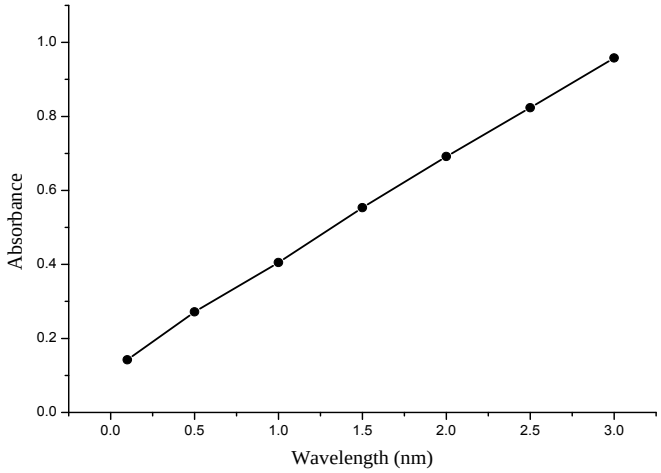


Figure 10. Calibration plot for method B

Precision and Accuracy

The precision of the proposed methods were calculated in terms of intermediate precision (intra-day and inter-day). Three different concentrations of LOR were analyzed in seven replicates (repeatability) during the same day (intra-day precision) and five consecutive days (inter-day precision). From the results shown in table 2, the percentage relative standard deviation (% RSD) values were ≤ 1.07% (intra-day) and ≤ 1.23% (inter-day) for method A and ≤ 2.01% (intra-day) and ≤ 1.54% (inter-day) for method B indicating high precision of the proposed methods. Also, the accuracy of the proposed methods was evaluated as percentage relative error (%RE) and from the results shown in table 2, it is found that the accuracy is good (RE ≤0.60%) for method A and (RE ≤1.67%) for method B.

Table 2. Intra-day and inter-day precision and accuracy studies

Method	LOR taken	Intra-day (n=7)			Inter-day (n=5)		
		LOR found[a]	%RSD[b]	%RE[c]	LOR found[a]	%RSD[b]	%RE[c]
Method A (mM)	35.0	35.21	0.82	0.60	35.10	1.14	0.29
	45.0	45.06	0.79	0.13	45.24	1.23	0.53
	55.0	54.97	1.07	0.06	55.23	0.99	0.42
Method B (µg/ml)	2.0	1.98	2.01	1.00	2.02	1.38	1.00
	3.0	3.05	1.92	1.67	2.99	1.54	0.30
	4.0	3.94	1.50	1.50	4.02	1.24	0.50

[a]Mean value of n determinations; [b]Relative standard deviation (%); [c]Relative error (%)

Selectivity

The selectivity of the proposed methods for the analysis of LOR was analysed by placebo blank and synthetic mixture analysis. From the placebo blank analysis, the change in the absorbance with respect to the reagent blank was caused only by loratadine. Non-

interference from placebo was further confirmed by carrying out recovery study from synthetic mixture by using 26mM of LOR for method A and 2 µg/ml of LOR for method B and the percent recoveries of LOR were 99.86 ± 1.08 and 101.02 ± 0.86.

Robustness and Ruggedness

The estimation of the method robustness was done by interchanging some parameters namely, strength of iodine and chloranil as 0.08% and 0.12% and the reaction time under the optimized experimental conditions. The effects of these changes on the absorbance reading were found to be negligible confirming the robustness of the proposed methods. Ruggedness was expressed as %RSD of the same procedures applied by three analysts and also by a single analyst performing analysis on three different instruments. The results given in table 3 showed that no statistical differences between different analysts and instruments suggesting that the proposed methods were rugged.

Table 3. Results of robustness and ruggedness

Method	LOR taken	Robustness (%RSD)		Ruggedness (%RSD)	
		Parameters interchanged		Inter analysts (n=3)	Inter instruments (n=3)
		Volume of I_2/chloranil[a] (ml)	Reaction time[b] (min)		
A	45mM	1.84	1.06	1.23	1.72
B	3 µg/ml	2.01	0.65	0.94	1.51

[a]*In methods A and B, volumes of iodine/chloranil were 1.8, 2.0 and 2.2 ml for 0.1% solution and concentration of iodine/chloranil also changed as 0.08% and 0.12%*

[b]*In method A, the reaction times were 8, 10 and 12 min; in method B, they were 0.75, 1 and 1.15 h*

Applications to Analysis of Pharmaceutical Formulations

The proposed methods were successfully applied to the determination of LOR in two representative tablets Lorinol-10 and Lorfast Meltab. The results obtained are shown in table 4, were compared with reference method[22] by means of Student's t-test for accuracy and F-tests for precision at 95% confidence level. As can be seen from the table 4, the calculated t- and F-values at 95% confidence level did not exceed the tabulated values of 2.57 and 5.05, respectively, indicating that there were no significant differences between the proposed methods and the reference method in which 39mM LOR for method A and 3 µg/ml LOR for method B were used. To ascertain the accuracy and validity of the proposed methods, recovery experiment was performed via the standard addition procedure. To a fixed and

known amount of LOR in tablets powder (pre-analyzed), pure drug (API) was added at three levels of the quantity present in the tablets powder and the total was measured by the proposed methods A and B. The determination with each concentration was repeated three times and the results of this study presented in table 5 indicated that the various excipients present in the formulations did not interfere in the assay.

Table 4. Comparison of assay results of reference and proposed methods

Tablet brand name	Nominal amount, mg	Found % (of nominal amount ± SD)*		
		Reference Method	Proposed methods	
			Method A	Method B
Lorinol[a]	10	99.83 ± 1.02	99.96 ± 0.69 t = 1.59 F = 2.83	100.24 ± 0.54 t = 1.84 F = 2.36
Lorfast Meltab[b]	10	100.17 ± 0.82	99.89 ± 1.48 t = 1.63 F = 2.08	99.75 ± 1.33 t = 0.99 F = 2.87

**Mean value of five determinations*

[a]Manufactured by Micro labs Ltd., South Sikkim, India

[b]Manufactured by Cadila Pharmaceuticals Ltd., India

Tabulated t-value at the 95% confidence level is 2.57

Tabulated F-value at the 95% confidence level is 5.05

Table 5. Results of recovery study by standard addition method

Formulation studied	Method A (mM)				Method B (µg/ml)			
	LOR taken in tablet	Pure LOR added	LOR total found	Pure LOR recovered[a] (percent ± SD)	LOR taken	Pure LOR added	LOR total found	Pure LOR recovered[a] (percent ± SD)
Lorinol (10 mg)	13.0	35.0	48.13	100.37 ± 0.56	1.0	2.0	3.02	101.00 ± 0.53
	13.0	45.0	58.05	100.11 ± 0.63	1.0	3.0	4.05	101.67 ± 0.34
	13.0	55.0	67.95	99.91 ± 1.96	1.0	4.0	4.98	99.50 ± 1.79
Lorfast Meltab (10 mg)	13.0	35.0	47.92	99.77 ± 2.02	1.0	2.0	2.98	99.00 ± 1.62
	13.0	45.0	58.14	100.31 ± 1.05	1.0	3.0	4.03	101.00 ± 0.66
	13.0	55.0	68.08	100.15 ± 0.64	1.0	4.0	4.94	98.5 ± 2.03

[a]Mean value of three determinations

CONCLUSION

Compared with the other methods cited in the literature, the proposed methods have the following advantages:

1. The determination of LOR is direct, rapid and simple
2. The enhanced sensitivity of the methods permits the determination of LOR with high accuracy.

3. The low standard deviation proved the good reproducibility of the method.
4. The complex formed is stable for more than 24 h. The methods make use of cheaper and readily available analytical reagents.
5. The procedures do not involve any critical reaction conditions and no pH-adjustment is required.
6. From the Student's t-test and F-test values, it is clear that the results obtained by the proposed methods are in a good agreement with reference method and indicate a high accuracy and precision
7. Thus, the methods are useful for the quality control and routine analysis of LOR in pharmaceutical preparations since there is no interference was observed from the common excipients that might be found in commercial formulations.

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