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Visible Spectrophotometric Determination of Lansoprazole in Pure and Pharmaceutical Formulations

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ABSTRACT

Four simple, accurate and highly sensitive spectrophotometric methods have been developed for the determination of Lansoprazole in both pure and in pharmaceutical preparations. The method A andB are based on the ion associationcomplex formation between Lansoprazole and Supracen Violet 3B (method A) or Tropaeolin OOO (method B) the third and fourth are indirect methods where the drug is oxidsed by a known excess of Chloramine T and determining the consumed Chloramine T with decrease in colour intensity of the dye Gallocyanine (method C) or oxidation with excess of N-Bromosuccunimide in acid medium. followed by the determination of unreacted N-Bromosuccunimide with the dye Celestin Blue - (method D) .Regreesion analysis of Beer's law plots showed good correlation in the concentration range of 5.0 - 40 µg ml^{-1}, 5.0 -25 µg ml^{-1} , 2.5 – 12.5 µg ml^{-1}, 1.0 – 6.0µg ml^{-1} for methods A, B ,C and D respectively, and the corresponding molar absorptivity values are 0.9232 x 10^4 , 1.0857 x 10^4 , 7.0997 x 10^4 and 2.3265 x 10^4 $1mol^{-1}cm^{-1}$. All variables have been optimized and the results were statistically compared with those of literature methods by employing the student's *t*-test and *F*-test. No interference was observed from excipients normally added to the tablets.

Keywords: Oxidation, Ion associationcomplex; Visible spectrophotometry; LANSAPRAZOLE; Pharmaceutical preparations

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INTRODUCTION

LANSAPRAZOLE (RS)-2-([3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl)-1H-benzo[d]imidazol is a substituted benzimidazole compound and it is a proton pump inhibitor[1,2], widely used as an antiulcer drug in the treatment and maintenance of healing of duodenal or gastric ulcers, erosive and reflux esophagitis. It is official in USP[3], The characteristic properties of LAN are due to its 2^0 , 3^0 amino groups and sulphoxide grouping.Literature mensions a few methods such as HPLC[4, 5, 6], HPTLC[7], LC-MS-MS[8,9] C13 NMR,Tirimetric[10,11,12-17],U.V spectrophotometry[,18,19]and visible spectrophotometry[, 20]relatively little attention was paid to the development of visible spectrophotometric methods for this drug. The chemical features of the drug molecule offers a lot of scope for the development of new methods with better sensitivity, specificity, precision and accuracy. The reported chromatographic techniques (HPLC or GC) require expensive experimental set-up and are not affordable in every laboratory for routine analysis.Although visible spectrophotometric methods are the instrumental methods of choice commonly used in industrial laboratories, for their simplicity, selectivity and sensitivity there is only e a single report so far for the determination of Lansaprazole. Therefore,the need for a fast, low cost and selective method is obvious, especially for routine quality control analysis of pharmaceutical products containing Lansaprazole This paper describes the development of sensitive and rapid spectrophotometric methods using SV3B (method A) or TPOOO (method B) or CAT-GC method C and NBS-CB :method D Which have been found to be satisfactory for the determination of Lansaprazole in pure and pharmaceutical formulations.

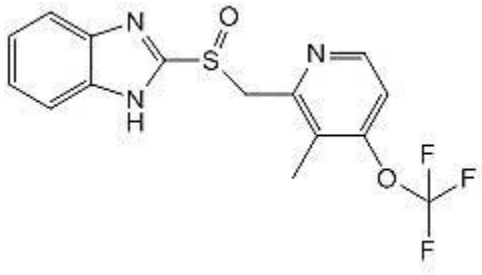


Figure 1 (Imidazole, 3^0 Amine,Sulphoxide groups)

MATERIALS AND METHODS

Apparatus

All absorbance measurements were performed using a Systronics Model 166 digital spectrophotometer provided with 1-cm matched quartz cells. An Elico 120 digital pH meter was used for pH measurements..

Reagents and standards

All chemicals and reagents used were of analytical reagent grade and distilled water was used throughout the investigation.

Standard LAN solution

Pharmaceutical grade LAN was obtained from Ranbaxy India, as a gift sample. A stock standard solution equivalent to Working standard was prepared from the stock solution. One mg ml^{-1} stock solution of LAN in aqueous medium was prepared by dissolving 100 mg of LAN in 10 ml of 0.1M HCl followed by dilution to 100 ml with distilled water (method A, B, C and D).Working standard solution is prepared by further diluting the stock solutions suitably where ever necessary with distilled water.Pharmaceutical formulations of Lansec 30mg (Cipla), Lanzap 30mg (Dr.Reddy's) Levant 30mg (Ranbaxy) were purchased from local markets in India.

Standard SV3B Solution

SV 3B Solution (Croma,0.2%,4.63 x 10^{-3}M): Prepared by dissolving 200 mg of Supracen Violet 3B in 100 ml distilled Water.

TPOOO solution

TPOOO solution Fluka; 0.2%, 5.709 x 10^{-3}M:Prepared by dissolving 200 mg of Tropeolin OOO in 100 ml with distilled water

CAT solutions:

CATsolution Loba; 0.02%, 0.11xl0^{-3}M) : Prepared by dissolving 20 mg of CAT in 100 ml of distilled water and standardized

GC solution:

GC solution Croma; 0.01%, 0.2969 x $l0^{-3}$M :Prepared by dissolving 50 mg of GC in 500 ml of distilled water

NBS Solutions:

NBS Solution (Loba; 0.01%,0.5617 x10^{-3}M) : Prepared by dissolving 10 mg NBS in 100 ml of distilled water and standardized.

CB solution: CB

solution Croma; 0.02%,(0.2748 x 10^{-3}M) : Prepared by dissolving 20 mg of CB in 100 ml of distilled water.

Hydrochloric acid

(E. Merck) 0.25 M and (E. Merck; 0.25 M) : Prepared by diluting 21.5 ml of Conc.HCl to 1000 ml with distilled water.0.1 M: Prepared by diluting 8.6 ml of concentrated hydrochloric acid to 1000 ml with distilled water and Standardized

Buffer solution: (pH-1.3)

prepared by mixing of 226 ml of 0.1M glycine solution (7.507 g of glycine and 5.85 g of NaCl dissolved in one litre) and 774 ml of 0.1 M hydrochloride acid and the pH of the solution was adjusted to pH 1.3

Method A (SV 3B)

Aliquots of standard drug solution (1.0 - 5.0 ml; 50 µg/ ml) of LAN is placed into a series of 125 ml separating funnels. Then 4.0 ml of pH 1.3 buffer solution and 2.0 ml of (4.63×10^{-3}M SV 3B) solution were added to each funnel. The total volume of aqueous layer in each funnel was brought to 15 ml with distilled water. A 10.0 ml portion of chloroform was added to each and the contents were shaken for 2 min. The absorbance of the separated chloroform layer was measured after 5 min at 590 nm against a reagent blank (Fig 4). The amount of LAN were computed from its calibration graph (Fig 2).

Method B (TP OOO)

To each one ofa series of 125 ml separating funnels, aliquots of (1.0-5.0ml; 50 µg/ml) of LAN to each funnel 6.0 ml of 0.1M hydrochloric acid and 2.0 ml of 5.70×10^{-3}M TP 000 solution were added successively. The total volume of aqueous phase in each funnel wad brought to 15 ml with distilled water. Then 10.0 ml of chloroform was added to each and the contents were shaken for 2 min. Then the two phases were allowed to separate and the absorbance of the separated chloroform layer was measured after 5 min at 500 nm for LAN against a reagent blank (Fig. 5). The drug concentration was computed from its calibration graph (Fig.2)

Method C (CAT/GC):

Aliquots of standard drug solution (0.5- 2.5 ml, 50 µg/ ml) of LAN 0.5 ml of 0.25M HCl and 1.0 ml of CAT ($0.11 \times l0^{-3}$M, 200 µg /m1) were taken into a series of 10 ml calibrated tubes and the volume was made upto 7.5 ml with distilled water. After 15 min 2.5 ml of GC ($0.2969 \times l0^{-3}$M) was added and mixed thoroughly and the absorbance was measured after 5 min at 540 nm against distilled water(fig. 6). Blank was prepared appropriately. The decrease in absorbance corresponding to consumed CAT, which in turn to the drug quantity was obtained by subtracting the absorbance of the blank solution from that of the test solution. The calibration graph was drawn by plotting the decrease in the absorbance of the dye (GC) against amount of drug. The amount of drug in any sample was computed from its calibration graph (Fig. 3).

Method D (NBS/CB) for LAN .

To the aliquots of standard drug solution (0.5- 3.0 ml 50 µg/ ml) taken into a series of 25 m1 calibrated tubes, 1.25 ml of 0.25M HCl, 2.0 ml of (0.5617×10^{-3}M) NBS were added and the volume was made upto 20 ml in each flask. After 15 min 5 ml of CB (0.2748×10^{-3}M) was

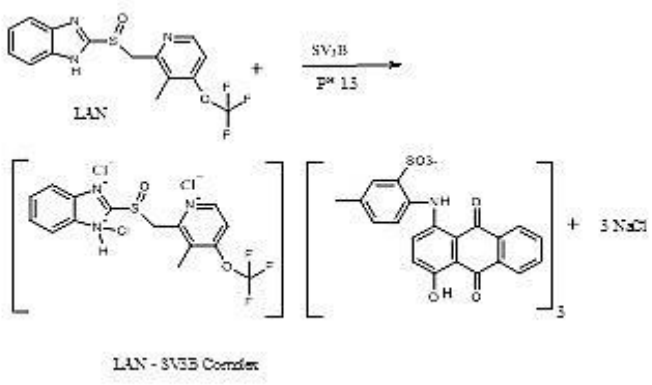
added and mixed thoroughly. After 5 min the absorbance was measured at 540 nm against distilled water(Fig.7). The blank (omitting drug) and dye (omitting drug and oxidant) solutions were prepared in a similar manner and their absorbances corresponding to consumed NBS, and in turn to drug concentration, were obtained by subtracting the decrease in absorbance of test solution (dye-test) from that of blank solution(dye-blank). The calibration graph was drawn by plotting the decrease in the absorbance of the dye (CB) against the amount of drug. The drug concentration in the sample was read out from the calibration graph (Fig.3).

Procedure for tablets

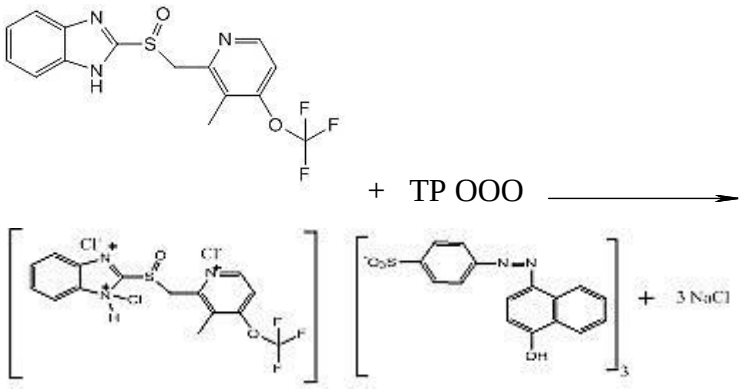
Twenty Capsules were weighed accurately and ground into fine powder. A quantity of the powder equivalent to 100 mg of LAN was weighed accurately into a 100 ml calibrated flask and 10 ml 0.1M HClwas added , the volume was diluted to the mark with water and mixed well and filtered using a Whatman No.41 filter paper. An appropriate dilute solution was subjected to analysis by the procedures described above.

Results and discussion

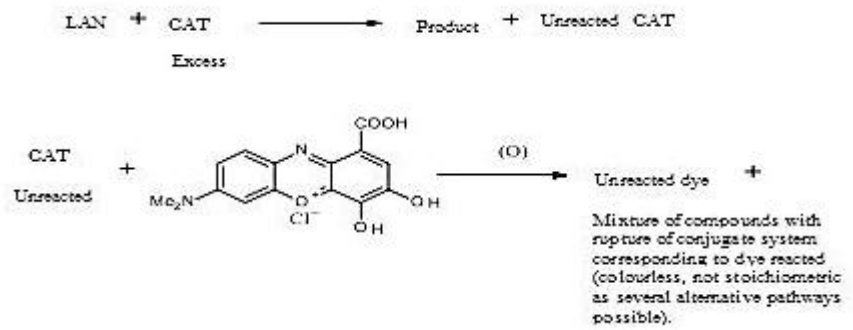
The absorption spectra of the coloured ion-pair complex of the dye and LAN in chloroform, the blank (omitting drug) and an aqueous solution of the dye maintaining the pH suitable for ion-pair complex formation in procedures for method A(LAN- Reaction with SV 3B) is represented in Scheme 1, method B (Lansoprazole with TP OOO)is represented in Scheme2. In method C, CAT undergoes hydrolysis in an aqueous acid medium to yield sodium hypochlorite followed by hypochlorous acid. This reacts with LAN to form the relevant oxidation products (probably a mixture), which appear to be reproducible under the specified experimental conditions. The remaining hypochlorous acid may be responsible for the bleaching of the color GC through destruction of the extended chromophoric system in the scheme 3.



Scheme 1. LAN- Reaction with SV 3B



Scheme -2 Lansoprazole with TP OOO.

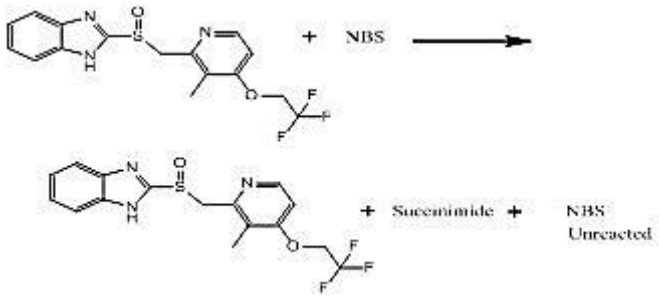


Scheme -3 CAT–GC–LAN

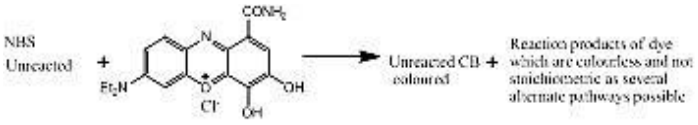
The method D is based on the oxidation of LAN by NBS to form oxidation products (probably mixtures, but reproducible under proposed experimental conditions) besides unreacted NBS, followedby the estimation of unreacted NBS using CB are shown in Scheme. 4

Probable reaction schemes**.**

Step 1.



Step 2.



Scheme -4 NBS- CB – LAN

The optimum conditions for the development of methods A (Scheme1), B(Scheme 2), C Scheme 3 and D (Scheme 4) were established by varying parameters one at a time and observing the effect produced on the absorbance of the colored species.

Optimum conditions for Method A :

In order to establish the optimum pH range, the LAN was allowed to react with SV 3B in aqueous solution buffered to pH 1.0-1.5 and the complex formed was extracted into chloroform for measurement. Constant absorbances were obtained over the pH range 1.1-1.5 in glycine-HC1 buffer. Hence a pH of 1.3 was used. A 2.0-ml portion of SV 3B solution was found to be optimal. Constant absorbance was obtained for shaking periods of 1-3 MINUTES: 2 min was selected for use. Chloroform was preferred over dichloromethane, carbon tetrachloride, chlorobenzene, and n-butanol for its selective extraction of the ion-pair from the aqueous phase. A 3:2 ratio of aqueous to chloroform phases was required for efficient extraction of the coloured species.

Optimum conditions for Method B :

The drug was allowed to react with TP 000 in 0.05-1.5 M HC1 and the complex was extracted into the chloroform layer. Constant absorbances were obtained with 0.08-0.12 M HCI: 0.1 M HC1 was used henceforth. 2.0ml of TP 000 solution was found to be optimal. Shaking times of 1-4 min produced constant absorbance: 2 min was chosen for use. A 3: 2 ratio of aqueous to organic phases was required for efficient extraction of the coloured species.

Optimum conditions for Method C :

Method C involved the oxidation of LAN with an excess of CAT (the first step) and estimating the unreacted CAT with GC (the second step). The effect of reagent concentration (acidity, CAT, and GC) and time in each step were studied by means of controlled experiments, varying one parameter at a time. Studies of the variation in acid concentration indicated that constant absorbance was obtained with 1.0–1.5 mL of 5 M HCl, 0.5–1.0 mL of 5 M H 2 SO 4 , or 1.5–2.5 mL of 5 M AcOH when 3.0 mL of CAT was used. Since the difference in absorbance between the sample and blank was found to be highest with the addition of HCl, subsequent studies were performed with 1.25 mL of 5 M HCl. In order to ascertain the linear relationship between the volume of added CAT and the decrease in absorbance of GC, experiments were performed in 1.25 mL of 5 M HCl with varying volumes of CAT. The decrease in absorbance was found to be linear up to 2.0 mL of CAT with 5.0 mL of GC. Hence, fixed amounts of HCl (1.25 mL,5 M), CAT (2.0 mL, 7.10×10–4 M), and GC (5.0 mL, 2.9 × 10 –4 M) were adopted for further investigation. A time span of 5 to 15 min for the reaction between LAN and CAT in the first step

and 10 to 20 min between CAT and GC in the second step yielded the constant and maximum differences in the absorbance of the test and bulk solutions. Reaction periods of 10 and 15 min were therefore maintained in subsequent studies of the first and second step respectively.

Optimum conditions for Method D :

In method C, the effect of reagent concentration (acidity, NBS and CB), reaction period in each step were studied by means of controlled experiments varying one parameter at a time. Studies of the variation of acid concentration indicated that a constant absorbance was obtained with 0.15-0.35 M HC1, 0.1-0.25 M H_2SO_4 or 0.3-0.5 M CH_3COOH with an NBS concentration of 200 µg ml^{-1}. Since the difference in absorbance between the sample and the blank was found to be highest for the addition of HCl, subsequent studies were performed in 0.25 M HClIn order to ascertain the linear relationship between the Concentration of added NBS and the corresponding decrease in the absorbance of CB, experiments were carried out in 0.25M HCl medium with varying amounts of NBS. As the decrease in absorbance was found to be linear upto an amount of 200 µg (2.0 ml of 100 µg/ ml) of NBS subsequent studies were carried out with1000 µg (5.0 ml , 200 µg ml) of CB and 200 µg of NBS in 0.25M HCl medium.

The oxidation of LAN by SV 3B , TP OOO ,CAT-GC and NBS-CB was studied. Of the various acids (sulfuric and hydrochloric) studied, Hydrochloric acid was found to be the best acid for the system. Constant absorbance readings were obtained in the 0.1–1.5 ml range of 0.1 M Hydrochloric acid [pH-1.0–1.5] at a temperature 30 °C for 5 min for method A 6.0 ml of pH 0.1 M Hydrochloric acid at 30 °C for 2.0 min for method B and 0.25 M Hydrochloric acid at 30°C for 10 min for method C and D.

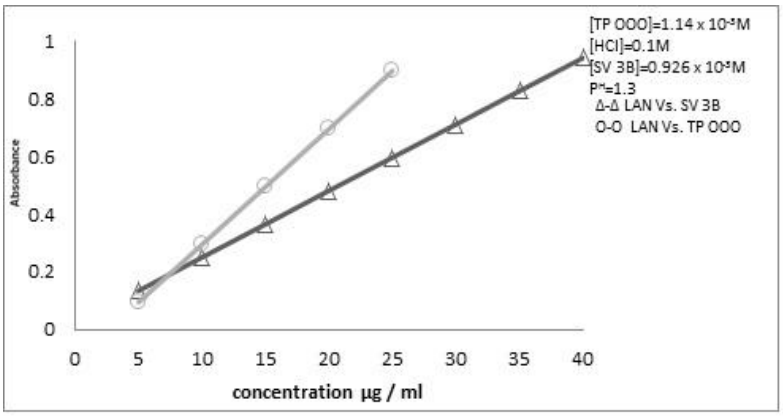


Figure .2 Beer's Law plots for Methods A&B

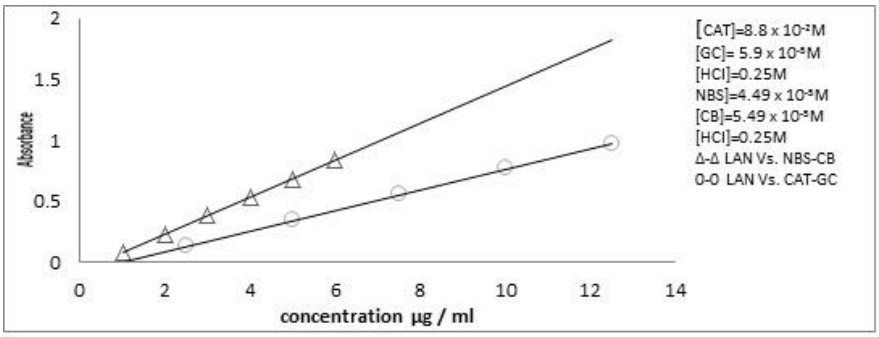


Figure .3 Beer's Law plots for Methods C & D

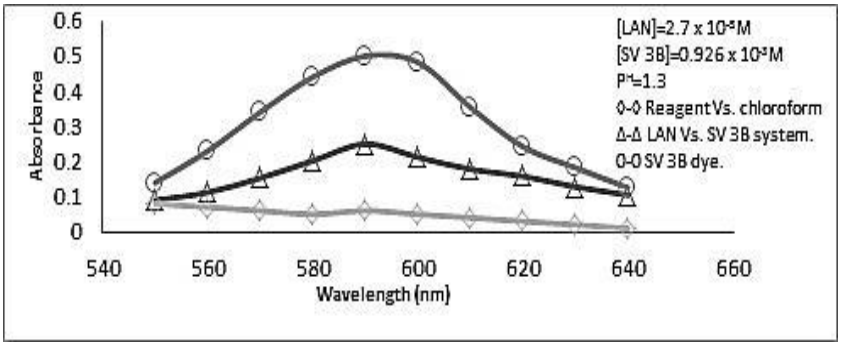


Figure .4 Absorption spectra of LAN-SV3B Method A

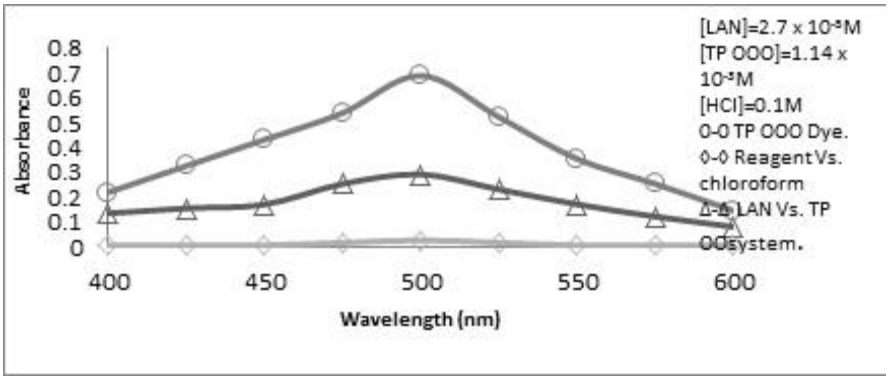


Figure 5. Absorption spectra of LAN -TPOOO Method B

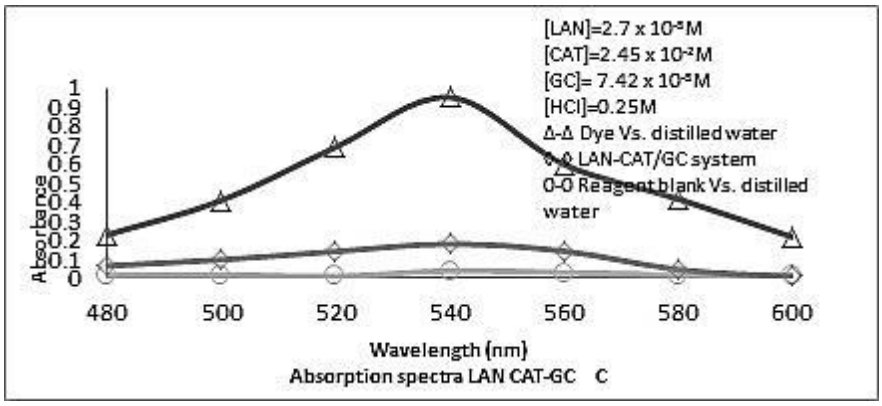


Figure 6. Absorption spectra LAN CAT-GC Method C

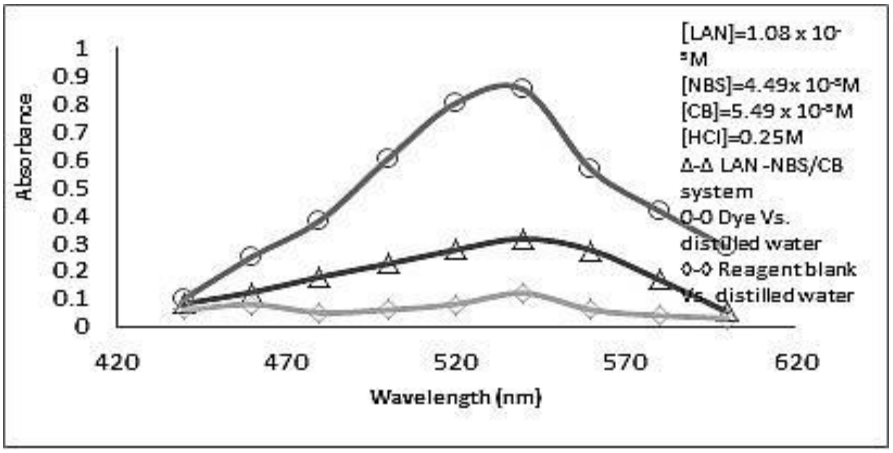


Figure 7. Figure 7.Absrption spectra of LAN NBS-CB Method D

Method validation

The proposed methods have been validated for linearity, sensitivity, precision, accuracy, selectivity and recovery.

Linearity and sensitivity

Under optimum conditions, a linear relation was obtained between the absorbance and concentration of LANin the range 0–2.5 μg ml^{-1}. The calibration graph is described by the equation: $Y = a + bx$, where$Y$ = absorbance, a = intercept, b = slope and x = concentration, obtained by the method of least squares. The correlation coefficient (r), intercept (a) and slope (b) for the calibration data and sensitivity parameters, such as apparent molar absorptivity and Sandell sensitivity values ,the limits of detection and quantification are compiled in Table 1

Table 1. Optical characteristic and statistical data of the regression equation.

Parameter(LAN)	SV 3B	TP OOO	CAT-GC	NBS-CB
λ max(nm)	590	500	540	540
beer's law limit μg/ml	5.0 -40	5.0- 25	2.5 – 12.5	1.0 -6.0
Sandle sensitivity	0.04	0.034	0.013	0.01869
Molar absorptivity € max	0.9232×10^4	1.0857×10^4	7.0997×10^4	2.3265×10^4
Regretionequation Y=a+bC				
Intercept (a)	0.01875	-0.1076	-0.0724	-0.0663
Slope (b)	0.0231	0.0402	0.08416	0.01507
Correlation coefficient (r)	0.9997	0.9999	0.9998	0.9999
Standard deviation on intercept (S_a)	4.143×10^{-4}	6.632×10^{-3}	1.624×10^{-3}	9.2×10^{-4}
Standard deviation on slope (S_b)	0.164×10^{-4}	0.000399	0.001624	2.3624×10^{-4}
LOQ(μg ml^{-1})	0.8329	0.3689	0.1952	0.7566
LOD(μg m^{-1})	0.2748	0.1217	0.0644	0.2496

$Y = a + bx$, where c is the concentration of LAN in μg ml^{-1} and Y is the absorbance at the respective λ_{max}, S_a is the standard deviation of the intercept, S_b is the standard deviation of the slope.

The limits of detection (LOD) and quantification (LOQ) were calculated according to the same guidelines using the formulas: LOD = $3.3\sigma/s$ and LOQ = $10\sigma/s$ where σ is the standard deviation (n = 5) of reagent blank determinations and s is the slope of calibration curve.

Accuracy and precision

To evaluate the accuracy and precision of the methods, pure drug solution at three different levels (within the working limits) was analyzed, each determination being repeated five times. The relative error (%) and relative standard deviation (%) were less than 2.0 and indicate the high accuracy and precision of the methods (Table 2).

Table 2. Evaluation of accuracy and precision.

Method	LAN taken (μg ml^{-1})	Lanfound[a] (μg ml^{-1})	RE%	S.D	SEM	RSD%	ROE [b]
Method A	0.5	0.49	1.21	0.008	0.002	0.873	±0.872
	1	1.02	-1.68	0.008	0.003	0.814	±0.813
	2	2.01	-0.28	0.016	0.006	0.776	±0.776
Method B	0.5	0.5	-0.58	0.006	0.002	1.103	±1.102
	1	0.99	-0.57	0.002	0.001	0.224	±0.224
	2	2.01	-0.26	0.005	0.002	0.271	±0.271
Method C	0.5	0.5	-0.94	0.004	0.002	0.789	±0.788
	1	1.02	-0.214	0.007	0.003	0.657	±0.657
	2	2	0.21	0.01	0.004	0.486	±0.486
Method D	0.5	0.49	1.21	0.008	0.002	0.873	±0.872
	1	1.02	-1.68	0.008	0.003	0.814	±0.813
	2	2.01	-0.26	0.005	0.002	0.271	±0.271

RE: relative error; SD: standard deviation; SEM: standard error of mean; RSD: relative standard deviation; ROE: range of error.[a]Mean value of five determinations [b] At the 95% confidence level for 4 degrees of freedom.

Application to analysis of commercial samples

To check the validity of the proposed methods, LAN was determined in some commercial formulations. The result obtained from the determination is in close agreement between the results obtained by the proposed methods and the label claim. Statistical analysis of the results using Student's t-test for accuracy and F-test for precision revealed no significant difference between the proposed methods and the literature method[21] at the 95% confidence level with respect to accuracy and precision (Table 3). The calculated t- and F-values (Table 3) did not exceed the tabulated values (t = 2.57 and F = 5.05)

Table 3. Results of determination of LAN inCAPSULES and statistical comparison with the reference method.

Formulation[a]	Labelled amount (mg)	Found by reference method	Amount found (mg) using proposed methods[b]			
			A TP OOO	B SV 3B	C CAT-GC	D NBS-CB
TAB 1	30	30±0.59	30±0.56 F=1.11 t=1.94	30±0.69 F=1.36 t=0.37	30±0.72 F=1.48 t=0.32	30±0.64 F1.17= t=0.58
TAB 2	30	30±0.42	30±0.41 F=1.04 t=1.98	30±0.43 F=1.04 t=1.98	30±0.62 F=2.17 t=0.74	30±0.43 F=1.04 t=1.98

A = Difference batches of CAPSULES from four different pharmaceutical companies.

B = Average ± standard deviation of six determinations, the t- and F- test values refer to comparison of the proposed method with the reference method.

Theoritical values at 95% confidence limit, F= 5.05 , t= 2.57

C = Recovery of 10 mg added to the preanalysed pharmaceutical formulations (average of three determinations).

Recovery study

The accuracy and precision of the proposed methods were further ascertained by performing recovery studies. Pre-analyzed capsule powder was spiked with pure drug at three different concentrations and the total was found by the proposed methods. Each determination was repeated three times. The recovery of the pure drug added was quantitative and revealed that co-formulated substances such as talc, dextrose, alginate, acacia, etc. did not interfere in the determination. The results of recovery study are given in Table 4.

Table 4. Results of recovery experiments via the standard addition technique.

Tablet brand name	LAN tablet (µg ml−1)	Method A			Method B		
		Pure LAN added µg ml−1)	Total found (µg ml −1)	Pure LAN recovered[a] (% ± SD)	Pure LAN added µg ml−1)	Total found (µg ml−1)	Pure LAN recovered[a] (% ± SD)
Tablet 1	1	0.5	1.5	100.11±0.21	0.5	1.52	99.87±0.18
	1	1	1.99	99.12±0.14	1	2.01	100.06±0.25
	1	1.5	2.52	99.04±0.28	1.5	2.51	99.14±0.16

Method C			Method D		
Pure LAN added µg ml−1)	Total found (µg ml−1)	Pure LAN recovered[a] (% ± SD)	Pure LAN added µg ml−1)	Total found (µg ml−1)	Pure LAN recovered[a] (% ± SD)
0.5	1.506	100.22±0.25	0.5	1.499	99.78±0.12
1	2.008	99.86±0.11	1	1.99	100.12±0.22
1.5	2.489	100.12±0.18	1.5	2.5	100.18±0.21

[a] Mean value of three measurements.

CONCLUSIONS

A significant advantage of visible spectrophotometric method is that it can be applied to the determination of individual compounds in a multicomponent mixture. The instrument is simple and is not of high cost. The importance lies in the chemical reactions upon which the procedures are based rather than upon the sophistication of the instrument. In the present study, Lansaprazole was determined (Method A–D) successfully as pure compound as well as component in representative pharmaceutical formulations by exploiting different functional groups present. The ingredients usually present in the pharmaceutical formulations of Lansaprazole did not interfere in the proposed methods. Thus the proposed methods are simple, rapid and sensitive (C < D < B < A) and can be used in the routine determination of pharmaceutical formulations depending upon the need of specific situation.

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