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Research Article

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Use of perchloric acid for the development and validation of a non-aqueous titrimetric assay of lansoprazole in pharmaceutical capsules

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ABSTRACT

Lansoprazole (LAN) is an important proton pump inhibitor that suppresses gastric acid secretion. A simple and rapid titrimetric method has been developed for the determination of LAN in pure drug and in its capsule formulation. The method is based on the neutralization of basic amino group in LAN with perchloric acid as titrant in 1,4-dioxane medium. The end point was detected using methyl red as indicator with the color change from yellow to red. Method is applicable over 2 – 20 mg range and the calculations are based on the molar ratio of 1: 1 (LAN: $HClO_4$). The method was statistically evaluated by calculating percent relative error (%RE) for accuracy and percent relative standard deviation (% RSD) for precision, and were applied successfully to the determination of LAN in capsules. No interference was observed from common additives found in pharmaceutical capsules. The accuracy and reliability of the method were further ascertained by performing recovery tests via standard-addition technique.

Keywords: Lansoprazole, Non-aqueous Titrimetry, Perchloric Acid, Capsules.

INTRODUCTION

Lansoprazole (LAN), chemically known as 2-([3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl)sulphinyl benzimidazole, is used to treat ulcers, gastro-oesophageal reflux disease and peptic ulcer disease [1]. LAN is a weak base and breaks down rapidly in an acidic medium and thus must be administrated in the form of enteric-coated granules in capsules, to prevent gastric decomposition and improve their systematic bioavailability [2, 3]. This drug is official in the United States Pharmacopoeia (USP) [4] and in the British Pharmacopoeia (BP) [5]. USP describes a high performance liquid chromatographic method and BP recommends potentiometric titration.

Different analytical methods have been reported in the literature for the assay of LAN in pharmaceutical formulations and include high-performance liquid chromatography (HPLC) [6-19], ultra-performance liquid chromatography (UPLC) [20-23], high-performance thin layer chromatography (HPTLC) [24,25], liquid chromatography/tandem mass spectrometry (LC-MS) [26], capillary electrophoresis [27,28], polarography [29-31], voltammetry [32], UV spectrophotometry [33-40], flow-injection analysis (FIA) [14,41], fluorimetry [35], spectrofluorimetry [42,43] and visible spectrophotometry [6, 44-58]. The reported chromatographic techniques although sensitive, require expensive instrumental-set up. A large volume of solvents is required for these techniques, which are expensive, hazardous to health, and harmful to the environment. Polarography and

voltammetric methods involve rigid pH control. Most of the reported visible spectrophotometric methods suffer from one or the other disadvantage such as poor sensitivity [6,46,47], narrow range of determination [48-52], use of heating step [46,50], use of extraction step [54-57].

To the best of our knowledge, no titrimetric method has ever been reported for the determination of LAN in pharmaceuticals except the official BP method [5]. However, BP method requires fairly large quantities of LAN for each titration. The non-aqueous titrations have become of considerable importance in pharmaceutical analysis and have been accepted by the majority of modern pharmacopoeias as an official analytical method [59]. Therefore, the purpose of present work was to develop a simple, rapid and cost-effective titrimetric assay for the determination of LAN in pharmaceutical capsules. The proposed method employed basic property of the drug molecule and the drug solution in 1,4-dioxane was titrated directly with perchloric acid in 1,4-dioxane medium using methyl red as indicator. The proposed method was demonstrated to be simple, rapid, cost-effective and easily adoptable to determine the LAN content in milligram level in the quality control laboratories across the developing countries where modern and expensive instruments are not available.

EXPERIMENTAL SECTION

Materials and reagents

Pharmaceutical grade LAN reported to be 99.80 % pure was received from Cipla Ltd., Bangalore, India. The following pharmaceutical preparations were purchased from commercial sources in the local market and subjected to analysis: Lan-30 and Lan-15 from Intas Pharmaceuticals, Dehradun, India; Lanzol-30 from Cipla Ltd., Sikkim, India.

All chemicals used were of analytical-reagent grade and the solutions were prepared as follow:
Perchloric acid (0.006 M): The commercially available 0.1 M perchloric acid (Merck, Mumbai, India) was appropriately diluted with 1,4-dioxane (Merck, Mumbai, India) to get 0.006 M perchloric acid and it was standardized against 0.006 M potassium dihydrogen phthalate [59].

Methyl red indicator: A 0.1 % methyl red (B. D. H. Laboratory Chemicals, Bangalore, India, 95% dye content) indicator was prepared in methanol.

Standard LAN solution: A standard solution 2 mg/ml LAN was prepared by dissolving accurately weighed 200 mg of pure drug in 1,4-dioxane and diluting with the same solvent to the mark in a 100 ml calibrated flask.

Assay procedure

Different volumes (1.0-10.0 ml) of standard solution containing 2.0 mg/ml LAN were taken in a 100 ml dry titration flask and the volume was made up to 10 ml with dioxane. Two drops of 0.1 % methyl red indicator were added and the solution was titrated with standard solution of 0.006 M perchloric acid to a red end point. A blank titration was performed in the same manner without drug, and the necessary corrections were made.

The amount of LAN in the measured aliquot was computed from the following formula:

$$Amount(mg) = \frac{V \times Mw \times S}{n}$$

Where V = ml of the perchloric acid reacted, Mw = relative molecular mass of LAN, S = molarity of perchloric acid and n = number of moles of perchloric acid reacting with each mole of LAN.

Assay procedure for capsules

The content of twenty capsules each containing 15 or 30 mg LAN were weighed. An accurately weighed quantity equivalent to 200 mg of LAN was transferred into a 100 ml calibrated flask and 30 ml of dioxane was added. The content was shaken thoroughly for 15-20 min to extract the drug into the liquid phase; the volume was finally diluted to the mark with the same solvent, mixed well and filtered using a Whatman No. 42 filter paper. An aliquot of the filtrate (2 mg/ml LAN) was subjected to analysis following the assay procedure described above.

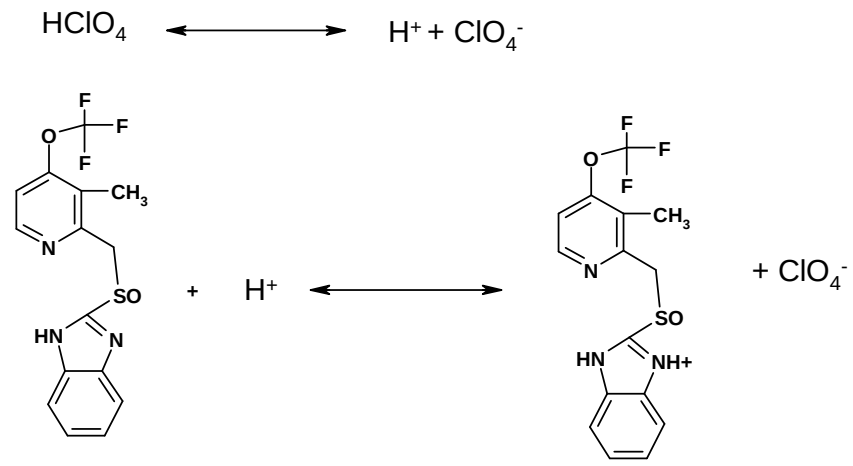
RESULTS AND DISCUSSION

Chemistry

LAN is a weak base containing amino group and the present method is based on the neutralization of LAN with perchloric acid as a titrant in dioxane medium. The proposed neutralization reaction follows Bronsted-Lowry theory. In this theory, any acid (HB) is considered to dissociate in solution to give a proton (H^+) and a conjugate base (B^-); whereas any base (B) will combine with a proton to produce a conjugate acid (HB^+):

$$HB \leftrightarrow H^+ + B^- \;\&\; B + H^+ \leftrightarrow HB^+$$

The same mechanism is followed in the present method where perchloric acid ($HClO_4$) undergoes dissociation into H^+ and ClO_4^-. LAN which is a base combined with H^+ to form a conjugate acid as shown below. The end point was detected using methyl red as indicator and the color change from yellow to red being taken as the end point. The reactions occurring are as follows:



Lansoprazole

Choice of the solvent

Non-aqueous acid-base titration is the most common titrimetric procedure used in pharmacopoeial assays. The ability of substances to act as acids or bases will very much depend on the choice of solvent system. Solution of $HClO_4$ in either glacial acetic acid or dioxane solution is frequently used for titration of weak bases [59]. The solution of perchloric acid (titrant) in glacial acetic acid functions as a strongly acidic solution. Unlike acetic acid, dioxane does not exert leveling effect on strong acids. Dioxane is a relatively neutral solvent and the sharp end point is obtained in this medium. Since, LAN was found to give red color in glacial acetic acid, use of glacial acetic acid as solvent in the present method was dropped. Dioxane was used to prepare the solutions of perchloric acid and LAN; and as the reaction medium in the proposed method.

Choice of the indicator

Crystal violet is the frequently used indicator in non-aqueous acid-base titration. However in the present titration, the end point was difficult to detect using crystal violet. The solution of LAN in dioxane was found to give pH of about 6. Among the indicators studied, crystal violet, bromophenol blue, bromocresol purple, neutral red, chlorophenol red and methyl red, only methyl red was found to give sharp end point because the pH range for color change of methyl red falls in the range of 4.2-6.3 (red-yellow). Although the approximate pH range for color change of chlorophenol red is 4.8-6.4 (yellow to orange), the detection of end point was difficult. Methyl red was found to dissolve easily in methanol, hence methyl red solution in methanol was used in the proposed titrimetric method.

Method validation

The validation of the method was done according to the present ICH guidelines [60].

Range and stoichiometry

The proposed procedure is applicable over the range of 2-20 mg of LAN. The reaction stoichiometry was found to be 1: 1 (LAN: $HClO_4$) inferring only one amine is involved in the titration. The nitrogen atom present in the benzimidazole ring is reported to be the most basic nitrogen in LAN [61] and based on this benzimidazole nitrogen undergoes protonation.

Accuracy

The accuracy of the proposed method was determined by performing replicate determinations. The intra-day and inter-day variation in the analysis of LAN was measured at three different levels. Accuracy was evaluated as percentage relative error (% RE) between the measured and taken amounts. The results of this study are compiled in Table 1 and speak of the excellent accuracy of the results.

Precision

The precision of the method was evaluated in terms of intermediate precision (intra-day and inter-day). Three different amounts of LAN within the range of determination were analyzed in seven replicates during the same day (intra-day precision) and five consecutive days (inter-day precision). The %RSD values of intra-day and inter-day studies for LAN showed that the precision of the method was good (Table 1).

Selectivity

The proposed method was tested for selectivity by placebo blank analysis which prepared of the composition: talc (40 mg), starch (30 mg), acacia (30 mg), methyl cellulose (40 mg), sodium citrate (30 mg), magnesium stearate (40 mg) and sodium alginate (35 mg). A convenient aliquot of placebo solution was subjected to analysis according to the recommended procedure. It was confirmed that the change in the titre value with respect to the dioxane blank was caused only by the analyte. The proposed method was tested for selectivity again by synthetic mixture analysis. To the placebo blank of the composition described above, 100 mg of LAN was added and homogenized, transferred to a 50 ml calibrated flask and the solution was prepared as described under "Assay procedure for capsules" and subjected to analysis. Five milliliters of the synthetic mixture solution (2 mg/ml) was assayed (n=5) which yielded % recovery with standard deviation in the range of (99.74 ± 0.92) to (101.5 ± 1.03) suggesting no interference by the excipients in the assay of LAN under the described conditions.

Ruggedness

Method ruggedness was expressed as % RSD and performed by four different analysts as well as using three different burettes. The inter-analysts %RSD were ≤ 1.05 whereas the inter-burettes %RSD for the same LAN concentrations ranged from 2.14 - 2.54 suggesting that the developed method was rugged (Table 2).

Table 1: **Evaluation of Intra-day and Inter-day Accuracy and Precision**

LAN taken, mg	Intra-day accuracy and precision (n=7)			Inter-day accuracy and precision (n=5)		
	LAN found[a], mg	% RE	% RSD	LAN found[a], mg	% RE	% RSD
5	5.09	1.8	1.02	4.89	2.2	1.9
10	10.13	1.3	1.15	10.26	2.6	1.51
15	15.21	1.4	1.07	15.36	2.4	2.01

[a] *Mean value of n determinations, RE: Relative error and RSD: Relative standard deviation.*

Table 2: Ruggedness Expressed as Intermediate Precision (%RSD)

LAN taken, mg	Method ruggedness	
	Inter-analysts' RSD%, (n=4)	Inter-burettes' RSD%, (n=3)
5	0.98	2.26
10	1.05	2.14
15	1.01	2.54

Application to capsules analysis

The proposed method was successfully applied to the determination of LAN in commercial capsules. The results obtained by the proposed method were statistically compared to those of the reference method [5] by applying

Student's *t*-test for accuracy and *F*-test for precision at the 95% confidence level. The reference method involved the potentiometric titration in which LAN in 4:1 (ethanol: water) mixture was titrated against 0.1 M NaOH. The results appeared in Table 3 show that the Student's *t*- and *F*-values at 95 % confidence level are less than the theoretical values, which confirmed that there is a good agreement between the results obtained by the proposed method and the reference method with respect to accuracy and precision.

Recovery study

To further ascertain the accuracy and reliability of the method, recovery experiment was performed *via* standard-addition procedure. Pre-analyzed capsule powder was spiked with pure LAN at three different levels and the total was found by the proposed method. Each determination was repeated three times and the results of this study presented in Table 4 indicated that the various excipients present in the capsules did not interfere in the assay.

Table 3: Comparison of Assay Results of Proposed and Reference Methods

Capsule brand name	Label claim, mg/capsule	Found (Percent of label claim ± SD)[a]	
		Reference method	Proposed method
Lan-15	15	101.2 ± 0.64	102.4 ± 0.81 t = 2.62 F = 1.60
Lan-30	30	100.5 ± 0.87	101.6 ± 0.95 t = 1.91 F = 1.19
Lanzol-30	30	101.8 ± 0.92	103.1 ± 1.01 t = 2.13 F = 1.21
[a]Mean value of five determinations. *Tabulated t-value at the 95% confidence level is 2.78.* *Tabulated F-value at the 95% confidence level is 6.39.*			

Table 4: Results of Recovery Study using the Standard-addition Method

Capsule studied	LAN in capsule, mg	Pure LAN added, mg	Total found, mg	Pure LAN recovered[a] (Percent ± SD)
Lan-30	5.08	2.5	7.72	105.6 ± 1.11
	5.08	5	10.29	104.2 ± 1.17
	5.08	7.5	12.95	104.9 ± 1.09
[a] Mean value of three measurements.				

CONCLUSION

The proposed visual titrimetric assay is the first ever report for LAN and is applicable over wide linear dynamic ranges (2.0-20.0 mg of LAN). The proposed method is selective as the drug contains amino group, which preferentially gets neutralized by acid. In particular, titrimetry is much simpler in technique, more rapid than all the previous reported methods so far for the assay of LAN. The method shows no interference from the common excipients and additives. The statistical parameters and the recovery data reveal good accuracy and precision of the proposed method. Therefore, it is concluded that the method is simple, relatively specific, accurate and precise. These merits coupled with the use of simple and inexpensive instrument recommend the use of this method in routine quality control Laboratories.

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