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Stability-indicating HPLC method for the determination of related substances in lansoprazole sulphide

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Abstract

Symmetric peak shape was on a C18 stationary phase with the dimensions of 250 mm column length, 4.6 mm as internal diameter, 5 microns particles with an economical and straightforward mass-compatible mobile phase combination of formic acid and acetonitrile delivered in gradient mode at a flow rate of 1.0 mL/min at 260 nm. The resolution between Lansoprazole sulphide (LAN30) and its impurities (LAN30-I & LAN30-II) in the developed method was more than 2.0, indicating a significant separation. Regression analysis shows a correlation coefficient greater than 0.999 for Lansoprazole sulphide and its related substances. The detection limits of Lansoprazole sulphide and its impurities are 0.003%, 0.01%, and 0.01%; the quantitation limits are 0.01%, 0.03%, and 0.03% for LAN30, LAN30-I, and LAN30-II. This method indicates that the recovery at different levels is 95 to 105% accurate. The test solution was stable in the diluent for 48 h at refrigerator temperature and subjected to stress conditions. The mass balance was close to 99.5%.

Keywords: Lansoprazole Sulphide; High-Performance Liquid chromatograph (HPLC); Validation; Stress Study

1 Introduction

Lansoprazole sulphide (LAN30) is the key intermediate for the synthesis of lansoprazole drug substance. The purity of Lansoprazole sulphide determines the quality of lansoprazole drug substance with high yield in the synthetic process during the manufacturing [1-8]. Its molecular formula is $C_{16}H_{14}F_3N_3OS$. LAN30 is a white to light orange powder or crystals. It is highly sensitive to heat, light and prone to degrade through oxidation.

This study describes a simple, sensitive, and cost-effective mass-compatible mobile phase method for the quantitation of impurities of LAN30. The effort includes the method development and validation as per ICH guidelines [9]. Hitherto, there is no article for the quantification and determination of related substances of LAN30. This research study is a novel and sensitive method for the Lansoprazole sulphide using high-performance liquid chromatograph (HPLC) and applying this work, the packaging integrity could be defined.

2 Material and methods

2.1 Materials

TCI Chemicals supplied Lansoprazole sulphide and used it as a reference standard with the help of structural elucidation techniques. The impurities of Lansoprazole sulphide have been isolated, purified and characterized in the synthetic research and development laboratory. Merck delivered formic acid, HPLC grade acetonitrile and methanol from Darmstadt, Germany. Millipore water purification system generated the USP purified water.

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The HPLC system was an Agilent 1200 quaternary pump, an autosampler, and a diode array detector. The chromatographic output signal was monitored and processed by Empower software on an Intel Core i5 computer (Dell). Hydrolytic studies have been conducted in a water bath with controllers, Julabo, Seelbach, Germany. Stability studies were carried out in a humidity chamber (Thermo lab humidity chamber, India), and light-sensitive studies were conducted in a photostability chamber (Sanyo photostability chamber, Leicestershire, UK). Thermal stability studies were performed in a dry air oven (MACK Pharmatech, Hyderabad, India). The structure of the Lansoprazole sulphide and its impurities are given in Fig.1.

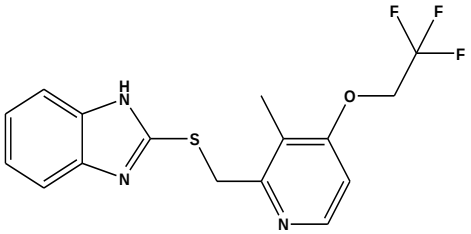
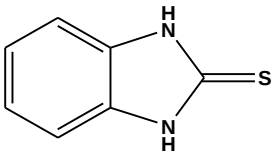
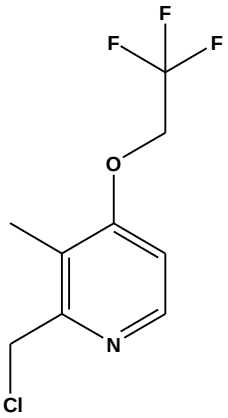
Compound Name	Structure	Chemical Name	Retention time (minutes)
LAN30		2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1h-benzimidazole	29.3
LAN30-I		2-Mercaptobenzimidazole (Process related impurity)	19.9
LAN30-II		2-chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine (Degradation impurity)	27.3

Figure 1 Structure of Lansoprazole sulphide and its impurities

2.2 Methods

2.2.1 Chromatographic Conditions

The wide bore column of YMC ODS-Aq with a length of 250 mm, an internal diameter of 4.6 mm, and a 5.0 µm particle size has been manufactured and supplied by YMC, India, was used to determine Lansoprazole sulphide and its impurities. The mobile phase A solution has prepared by adding 2.0 mL of formic acid in 1000 mL of water, and acetonitrile as mobile phase B solution. The method flow rate was 1.0 mL/min. The gradient composition for %B and time is 0.0/10, 10.0/10, 45.0/60, 50.0/65, 51.0/10, and 60.0/10. Monitored the column temperature throughout the analysis at 25°C and monitored the detection was at a wavelength of 260 nm. The injection volume was 15 µL. Mixed about 900 mL of methanol and 100 mL of methanol in a 1L bottle and considered as diluent.

2.2.2 Preparation of stock solutions, system suitability, and sample

Accurately weighed and transferred 5 mg each of LAN30, LAN30-I, and LAN30-II into a 500 mL volumetric flask. Dissolved in 200 mL of diluent and made upto the volume of 300 mL with diluent. Pipetted out 5.0 mL of this solution and transferred into a 50 mL volumetric flask, made upto the volume of 45 mL with diluent. This solution is considered as standard solution with the concentration of 1 µg/ mL for LAN30, LAN30-I, LAN30-II and used as system suitability for related substances determinations. The LAN30 sample solution was prepared by weighing 10 mg and transferred

into a 10 mL volumetric flask. Dissolve in and dilute to 10 mL with diluent. Prepare the sample solutions freshly prior to the injection for accurate results.

2.2.3 Analytical Method Development

Lansoprazole sulphide and its impurities had UV maxima at around 260 nm; monitored detection at 260 nm for the method development. The primary concern was obtaining the resolution between the analyte and its known and unknown impurities peak symmetry to develop a selective and sensitive method.

By modifying the column oven temperature to 25°C, the LAN30 and its impurities peak symmetry has significantly improved, which has impacted the USP Tailing factor to 1.2. The resolution between LAN30 and known peaks has been substantially enhanced by altering acetonitrile's composition. The results were satisfactory by using these chromatographic conditions. Buffer pH and % acetonitrile did not play a significant role in peak shape for Lansoprazole sulphide. This study has executed the analysis with different batches of bulk drug intermediate samples (n = 3). Results were within specification limits.

2.3 Statistical Method

Using the Minitab 17 software, executed the robustness study with four number factors viz., flow, column oven temperature, mobile phase organic ratio, and wavelength.

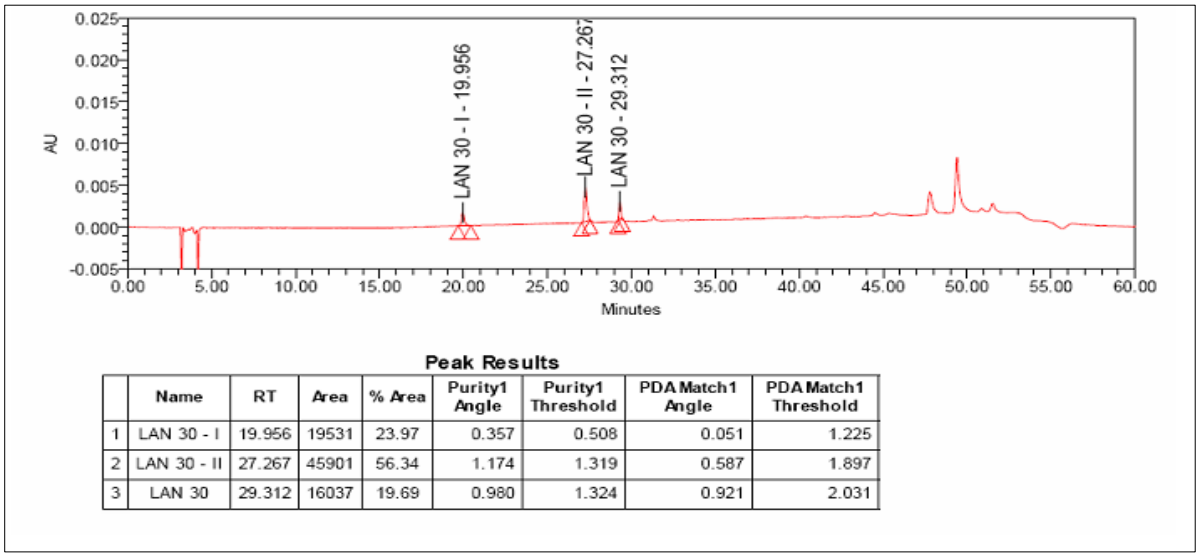
3 Results and discussion

3.1 Analytical Method Validation

The chromatographic method was developed and validated for specificity, forced degradation studies, linearity, range, precision, sensitivity, accuracy, robustness, and solution stability.

3.2 Specificity

All stress decomposition studies were at an initial drug concentration of 1000 µg/mL. Forced degradation studies were performed on LAN30 to indicate the stability-indicating property and specificity of the proposed method. The representation of the standard chromatogram is illustrated in Fig.2.



Peak Results

	Name	RT	Area	% Area	Purity1 Angle	Purity1 Threshold	PDA Match1 Angle	PDA Match1 Threshold
1	LAN 30 - I	19.956	19531	23.97	0.357	0.508	0.051	1.225
2	LAN 30 - II	27.267	45901	56.34	1.174	1.319	0.587	1.897
3	LAN 30	29.312	16037	19.69	0.980	1.324	0.921	2.031

Figure 2 Chromatogram of LAN30 and impurities standard

3.3 Results of Forced Degradation Studies

Stress studies were on LAN30 under different stress conditions. The research study exposed the LAN30 to acid, base hydrolysis, oxidation under reflux conditions. LAN30 showed significant degradation towards the acid/base hydrolysis treatment of 0.1 N NaOH (24 h reflux at 80°C) and 0.1 N HCl (24 h reflux at 80°C) and the oxidative stress of the compound has performed with 3% hydrogen peroxide at room temperature for 24 h. LAN30 showed highly sensitive

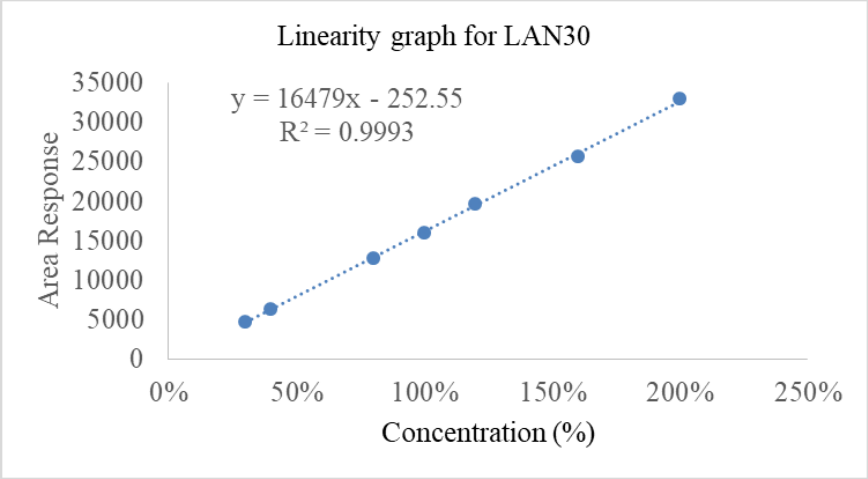
towards the treatment of hydrogen peroxide when compared to acid, and base. Complete degradation of LAN30 was observed when the LAN30 was exposed to 60°C for 7 days and 40°C/75% relative humidity for 7 days and found to be highly unstable toward the heat, and humidity. The LAN30 was highly sensitive to the effect of photolysis. Significant degradation was observed when the LAN30 powder was exposed to light for a total coverage of 1200000 lux hours and an integrated near ultraviolet energy of 200-Watt hours/square meter [10] in a photostability chamber. The drug intermediate was unstable to the effect of temperature. Peak purity results for stressed LAN30 samples, derived from the PDA detector (the purity angle within the purity threshold limit), confirm that the LAN30 peak was homogeneous and pure. No degradation product peaks were observed after 60 min in the extended run time of 120 min for all the LAN30 stressed samples. Assay studies were executed for stress samples against a qualified reference standard. The mass balance (% assay + % of impurities + % of degradation products) of stressed samples was close to 99.5%, confirming the stability-indicating power of the developed method.

3.4 Linearity and Range

The linearity study has evaluated by determining seven concentration levels from LOQ to 200% of LAN30 and its impurities. The correlation coefficient obtained for LAN30-I, LAN30-II and LAN30 were 0.9999, and tabulated linearity results are in Table 1. The LAN30 and its impurities linearity graph demonstrated in Fig. 3.

Table 1 Compilation of concentrations and area responses for LAN30 and its impurities

Concentration	Area Response		
	LAN30	LAN30-I	LAN30-II
30%	4801	5870	13804
40%	6430	7890	18960
80%	12880	15660	36821
100%	16037	19531	46901
120%	19644	23490	55081
160%	25659	31256	73442
200%	33074	39000	91802
Slope	16479	19481	45691
Intercept	-252.55	69.388	466.53
R^2 (RSQ)	0.9993	1.0000	0.9998



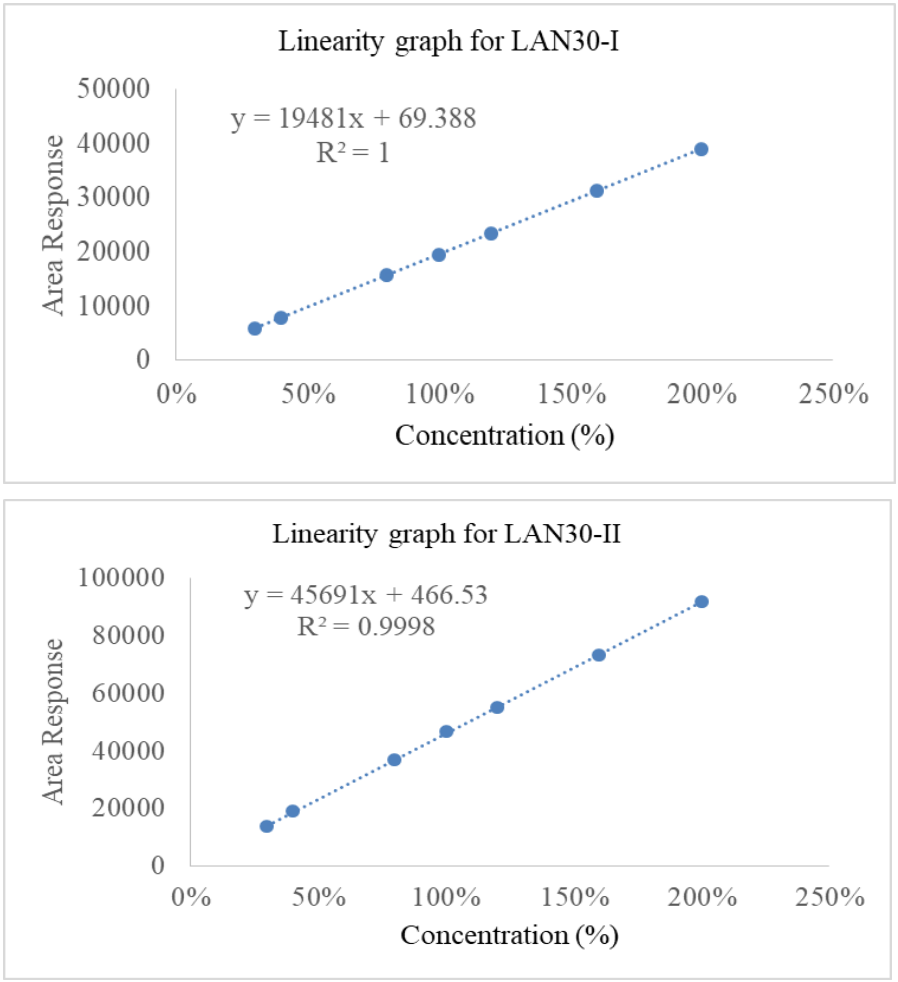


Figure 3 Linearity graph for LAN30, LAN30-I and LAN30-II

3.4.1 Precision

The precision was checked by injecting six individual preparations of (1 µg/mL) LAN30 and its impurities. The % RSD for the percentage of LAN30 and its impurities were below 0.4%. The % RSD was within 1.8% in the intermediate precision. The different analysts and columns evaluated the intermediate precision of the method, and by using another instrument, % RSDs were within 1.8%, confirming the ruggedness of the method.

3.4.2 Sensitivity

Determined the sensitivity by establishing the LOD (3:1) and LOQ (10:1) for LAN30 and its impurities estimated by dividing the height of the peak and baseline noise by injecting a series of dilute solutions with known concentrations. The limit of detection for LAN30 and its impurities were 0.003%, 0.01%, and 0.01%, and quantification for LAN30 and its impurities were 0.01%, 0.03%, and 0.03%, respectively. The precision study at the LOQ level with six replicate injections of LOQ solution and the % RSD for the area was within 1.1% and found that the method was susceptible.

3.4.3 Accuracy

In the method validation study, the recovery parameter is essential to determine the method capability and performed in triplicate preparations at 50, 100, and 150% of the LAN30 impurities specification limits (0.5%). The percentage of recovery for LAN30 and its impurities was between 95-105%, indicating that the method was suitable for determining LAN30 and its impurities.

3.4.4 Robustness

The robustness study was performed using the Minitab 17 software using the four number factors: flow, column oven temperature, mobile phase organic ratio, and wavelength. The resolution between the LAN30 and its impurities peaks by changing experimental conditions is in Table 2. The developed and validated method has a flow rate of 1.0 mL/min. To study the consequence of flow rate on the resolution, 0.1 units changed it from 1.1 to 0.9 mL/min. The result of column temperature on the resolution was studied at 20°C and 30°C instead of 25 °C. To check the effect of an organic ratio of 10:90 (%v/v), it was transformed from 9 to 11 (%v/v). The impact of the detection wavelength, 260 nm, changed it from 258 nm to 262 nm. In all the deliberate varied chromatographic conditions (flow rate, column oven temperature, and detection wavelength), the resolution between LAN30 and its impurities was more significant than 1.5, illustrating the method's robustness.

Table 2 Design of experiments for robustness study

Experiment	Flow (mL/min)	Column oven temperature (°C)	Acetonitrile (% v/v)	Wavelength (nm)
1	0.9	30	9	258
2	1.1	30	11	262
3	1.1	30	11	262
4	0.9	20	11	262
5	1.1	20	11	262
6	1.1	20	11	258
7	1.1	30	9	258
8	0.9	30	11	258
9	0.9	30	11	258
10	1.1	20	11	258
11	0.9	20	11	262
12	0.9	20	9	258
13	0.9	20	9	258
14	0.9	30	9	262
15	0.9	20	11	262
16	1.1	30	11	258

3.4.5 Solution Stability

The solution stability of LAN30 and its impurities were carried out by leaving the sample solution, which was prepared in a volumetric flask and kept at room temperature and refrigerator for 48 hours. The mobile phase stability was performed using freshly prepared sample solutions against reference standard solutions at 48 hours. The %RSD of LAN30 and its impurities during solution stability at refrigerator and mobile phase stability experiments was 1.1%. There was significant change observed in the content of LAN30 and its impurities during solution stability at room temperature experiment. The data confirms that standard and sample solutions were stable for up to 48 hours at refrigerator temperature.

4 Conclusion

A new, sensitive, and stability-indicating HPLC method was successfully developed to quantify LAN30 and its impurities in bulk intermediates. The technique was accurate and precise, with excellent and consistent recoveries. The validated method may be used for the routine analysis of the determination of LAN30 and its impurities from the bulk drug, pharmaceutical preparation, and other quality control samples of product development.

Compliance with ethical standards

Funding

The study did not receive any funding.

Disclosure of conflict of interest

The authors declare no conflicts of interest.

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