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Original article

Highly Sensitive HPLC Method for the Determination of Some Impurities in Lansoprazole

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ABSTRACT:
Lansoprazole is a substituted benzimidazole and is chemically designated as 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulfinyl] benzimidazole. It inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_3N_3O_2S$ and molecular weight is 369.37.It is available worldwide under brand names like Prevacid, Helicid, Zoton, Inhibitol, Monolitum etc. Impurity is defined as any substance coexisting with the original drug. Determination of toxic impurities in drug substances is mandatory. These are to be determined as low as reasonably practicable and the development of such a highly sensitive method is a challenging one. Two toxic impurities namely 2,3-Dimethyl-4-nitropyridine N-oxide (DPN) and 2-Chloromethyl-3-methyl-4-(2,2,2-trifluoro ethoxy)pyridine hydrochloride (CTP) were found in Lansoprazole. These compounds are carried either from raw materials or intermediates. A highly sensitive High Performance Liquid Chromatography method was developed for the determination of these two toxic impurities using Inertsil ODS-3V (150 x 4.6 mm, 5 µm) column as stationary phase. A gradient mixture of Solution A (Buffer and Methanol in the ratio of 90:10 v/v) and Solution B (Acetonitrile and Methanol in the ratio of 90:10 v/v) was used as mobile phase. Buffer was prepared by dissolving 1.36 g of Potassium dihydrogen orthophosphate and 1.74 g Dipotassium hydrogen phosphate in 1000 ml water and the solution pH was adjusted to 7.4 with Triethyl amine. The eluted compounds were monitored at 210 nm. The limits of detection were found to be 1.0 ppm and 2.0 ppm respectively for DPN and CTP.
Keywords: lansoprazole, Impurity, DPN, CTP, Gradient.

1. INTRODUCTION

Lansoprazole is a proton-pump inhibitor (PPI) which prevents the stomach from producing gastric acid. It is chemically known as (RS)-2-([3-methyl-4-(2, 2, 2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl)-1H-benzo[d]imidazole. CAS number is 103577-45-3. Molecular formula is $C_{16}H_{14}F_3N_3O_2S$ with molecular weight is 369.36

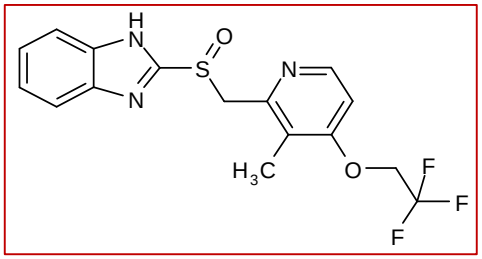

Fig 1: Structure of lansoprazole

Lansoprazole is manufactured by a number of companies worldwide under several brand names (Some brand names include: Prevacid, Helicid, Zoton, Inhibitol, Monolitum). It was first approved by the U.S. Food and Drug Administration (FDA) in 1995.Prevacid patent protection expired on November 10, 2009. As a result, prescription Lansoprazole is now available in the form of a generic drug.

An impurity in a drug substance as defined by the International Conference on Harmonization (ICH) Guidelines is any component of the drug substance that is not the chemical entity defined as the drug substance and affects the purity of active ingredient or drug substances [1-3].

The impurity profile of pharmaceuticals is of increasing importance as drug safety receives more and more attention from the public and from the media. Most of the Active Pharmaceutical Ingredients (APIs) are produced by organic chemical synthesis. Various components, including residual solvents, trace amounts of inorganic, and organic components can be generated during such a process. Those components remaining in the final API are considered as impurities [4, 5].

Impurity is defined as any substance coexisting with the original drug. Control of toxic impurities in drug substances has received more and more attention over the past years. These are to be determined based on the maximum daily dose. According to EMEA guidelines, a TTC value of 1.5 microgram/day intake of a toxic impurity is considered to be associated with an acceptable risk. The concentration limits in ppm of permitted toxic impurity in a drug substance is the ratio of TTC in microgram/day and daily dose in gram/day.

In lansoprazole (LPZ) drug substance, 2,3-Dimethyl-4-nitropyridine N-oxide (DPN) and 2-Chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine hydrochloride (CTP). These compounds are carried from raw materials. The maximum daily dose of lansoprazole is 90 mg /day. Hence, TTC is 16.66 ppm [6].

In literature, no method was reported for the determination of these two impurities. Hence, the present studies are aimed towards the determination of these two compounds in lansoprazole at the level of 16 ppm (lower end) by High Performance Liquid Chromatography.

2. MATERIAL AND METHODS

i. Instrument:

A water-alliance HPLC system (Alliance 2695) equipped with Photo Diode Array Detector (2996), UV-Visible detector (2487) and Empower2 software was used.

ii. Chemicals and Solvents:

Lansoprazole and the impurities were supplied by Hetero (R&D), Hyderabad. All the chemicals and solvents used were of analytical grade. Milli Q water was used throughout the experiment.

Preparation of Buffer:

Dissolved 1.36 g of Potassium dihydrogen orthophosphate and 1.74 g Dipotassium hydrogen phosphate in 1000 ml of water. Adjusted pH to 7.4 with Triethyl amine and mixed.

Preparation of Mobile Phase A:

Mixed Buffer and methanol in the ratio of 90:10 v/v. Filtered and degassed the mixture through 0.45 µm membrane filter paper.

Preparation of Mobile Phase B:

Mixed acetonitrile and Methanol in the ratio of 90:10 v/v. Filtered and degassed the mixture through 0.45 µm membrane filter paper.

Table 1: Gradient Programme

Time (Minutes)	Mobile Phase A (% v/v)	Mobile Phase (% v/v)
0.01	85	15
9.0	85	15
12.0	70	30
25.0	60	40
40.0	30	70
45.0	85	15
50.0	85	15

Preparation of DPN and CTP Individual Stock Solutions (100 ppm):

Weighed accurately about 10.0 mg of DPN or CTP into separate 100 ml volumetric flasks, dissolved and diluted to volume with diluent and mixed. Diluted 1 ml of each solution separately to 50 ml with diluent.

Preparation of LPZ Test Solution (20 mg/ml):

Weighed accurately about 200 mg of the LPZ test sample into a 10 ml volumetric flask, dissolved and diluted to the volume with diluent and mixed.

3. RESULTS AND DISCUSSION

HPLC Method Development:

The method development was targeted to develop a RP-HPLC method that can separate LPZ from DPN, CTP and three impurities listed in USP (RCA, Imp-B and Imp-C) (Figure 1). High Performance Liquid Chromatography method was developed for the determination of these two toxic impurities using Inertsil ODS-3V (150 x 4.6 mm, 5 µm) column as stationary phase. A gradient mixture of Solution A (Buffer and Methanol in the ratio of 90:10 v/v) and Solution B (Acetonitrile and Methanol in the ratio of 90:10 v/v) Auto sampler temperature: 5 ºC.

HPLC Method Validation:

I. Specificity:

Specificty was conducted by spiking DPN and CTP along with RCA, Imp-B and Imp-C. DPN and CTP were eluted at retention times of 6.3 and 30.1 min., respectively. There is no interference due to blank at the retention times of DPN and CTP. DPN and CTP resolved from each other and from known impurities and LPZ (Figure 2) [7].

II. Limit of Detection (LOD):

Limits of Detection for DPN and CTP have been established. LOD solution was prepared so as to obtain the S/N ratio is in between 3 to 5 for DPN and CTP the results are given below (Figure 3).

III. Limit of Quantitation (LOQ):

Limits of Quantitation for DPN and CTP have been established. Based on the concentration obtained from LOD, the LOQ solution was prepared (3 times to LOD concentration) so as to obtain the signal to noise ratios are in between 10 to 15 for DPN and CTP, and the results are given below (Figure 4) [8].

IV. Precision at Limit of Quantitation:

LOQ solution of DPN and CTP was injected six times and calculated % RSD. The results are summarized below.

V. Linearity:

Linearity study was conducted for DPN and CTP and the range from LOQ level to 150% to specification as per the procedure mentioned in the protocol. Linearity graphs were obtained for DPN and CTP in the range of LOQ to 150% of specification. The results are given below.

The %RSD values for 6 replicate injections of Level-1 and Level-6 are less than 2.0Correlation coefficient values of DPN and CTP are within the limit (Not less than 0.99) No

systematic trend was observed (not more than 5 consecutive points on single side) [9].

VI. Sample analysis:

Three Lansoprazole Samples were analyzed (in duplicate injections). The results are given below. The limit of detection value for DPN and CTP are 1.0 ppm and 2.0 ppm (Figure 5 and Figure 6).

VII. Accuracy at Limit of Quantitation:

Sample-1 was analyzed three times (from three individual preparations) for accuracy studies by spiking DPN and CTP at LOQ level to it and evaluated the % recoveries of DPN and CTP at LOQ solution in Lansoprazole. Results of accuracy at LOQ are given below [10].

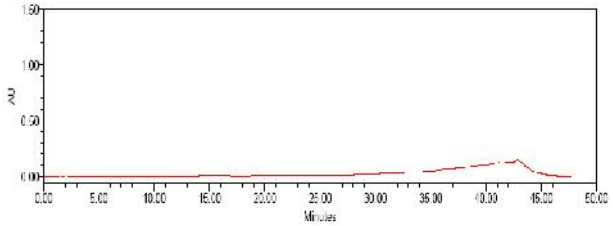

Fig 1: Blank Chromatogram

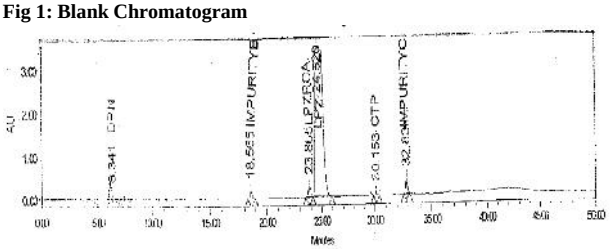

Fig 2: Specificity Chromatogram

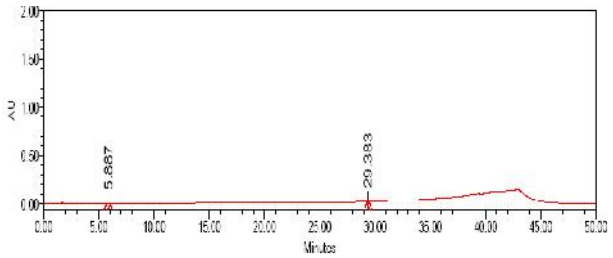

Fig 3: LOD Chromatogram

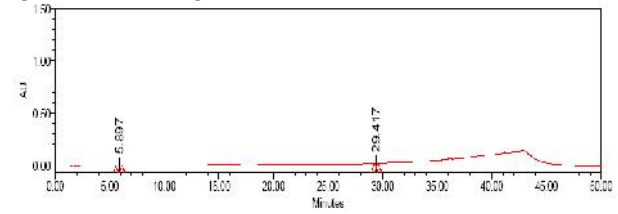

Fig 4: LOQ Chromatogram

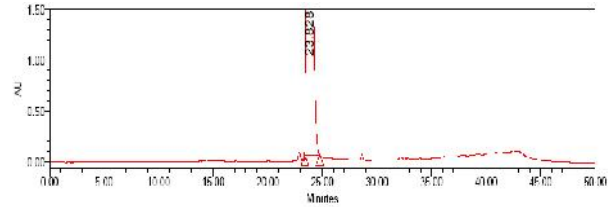

Fig 5: Sample Chromatogram

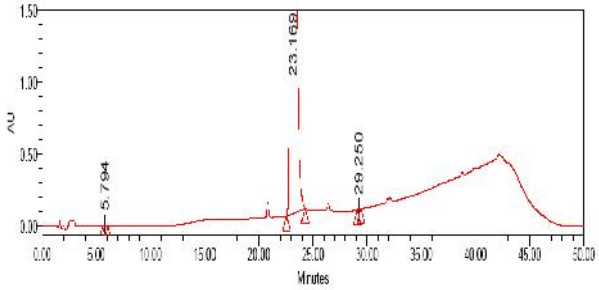

Fig 6: Recovery Chromatogram

4. CONCLUSIONS

Observations from the present study indicate that the HPLC method meets the acceptance criteria for all the parameters selected for quantitation study. Hence, the method is suitable for the determination of 2,3-Dimethyl-4-nitropyridine N-oxide (DPN) and 2-Chloromethyl-3-methyl-4-(2,2,2-trifluoroethoxy)pyridine hydrochloride (CTP) in Lansoprazole. Aanalysis of Lansoprazole (LPZ) samples demonstrates the absence of DPN and CTP.

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