Scientific Journal of Impact Factor (SJIF): 5.71

e-ISSN (O): 2348-4470
p-ISSN (P): 2348-6406

International Journal of Advance Engineering and Research Development

International Conference of Trends in Information, Management, Engineering and Sciences (ICTIMES)
Volume 5, Special Issue 02, Feb.-2018 (UGC Approved)

DETERMINATION OF PANTOPRAZOLE IN BULK AND PHARMACEUTICAL FORMULATIONS BY VALIDATED RP-HPLC METHOD

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ABSTRACT

A sensitive, highly specific validated, stability indicating RP-HPLC method for the determination of Pantoprazole in bulk and pharmaceutical dosage forms. The method was developed using Luna CN (250×4.6 mm,5µm) and a mixture of Water: Acetonitrile in the ratio of 30:70 v/v was used as mobile phase at a flow rate of 1.0 mL/min with UV detection at 215 nm for Pantoprazole. The retention time of the drug was 3.7 minutes. The developed method was validated for specificity, linearity, precision, accuracy and robustness as per ICH guidelines. Linearity was found in the range of 10-150 µg/ml. The mean recovery of the drug was 102.0 %. The proposed method could be used for routine analysis of Pantoprazole in their dosage forms and the method is accurate, precise, simple, sensitive and rapid and can be applied successfully for the estimation of Pantoprazole in bulk and in pharmaceutical formulations without interference and with good sensitivity.

Keywords: Liquid Chromatography, Pantoprazole, dosage forms, determination, Validation

INTRODUCTION

Drug Profile

Pantoprazole **[**6-(difloromethoxy)-2-[3,4-imethoxy pyridine-2-yl)mehylsulfinyl]-1H-benzimadazole. M W**:** 383.36 g/mol, $C_{16}H_{15}F_2N_3O_4S$ and Freely soluble in water.] is a proton pump inhibitor[1-5] (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H^+, K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus. The binding to the (H^+, K^+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested (20 mg to 120 mg).

Pantoprazole[6-13] is contraindicated in patients with known hypersensitivity to any component of the formulation or any substituted benzimidazole. Hypersensitivity reactions may includeanaphylaxis,
anaphylactic shock,angioedema,bronchospasm,acute interstitial nephritis,and urticaria.Short-term treatment (7 to 10 days) of patients with gastroesophageal reflux disease (GERD) who have a history of irritation of the esophagus. It may be used for conditions that cause your body to make too much stomach acid (eg, Zollinger-Ellison syndrome).

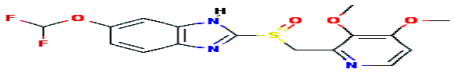


Fig 1: Pantoprazole Structure

Pantoprazole sodium For Delayed-Release Oral Suspension, 40 mg has been shown to be comparable to PROTONIX (pantoprazole sodium) Delayed-Release Tablets in suppressing pentagastrin-stimulated MAO in patients (n = 49) with GERD and a history of EE. In this multicenter, pharmacodynamic crossover study, a 40 mg oral dose of PROTONIX for delayed-release Oral Suspension administered in a teaspoonful of applesauce was compared with a 40 mg oral dose of PROTONIX Delayed-Release Tablets after administration of each formulation once daily for 7 days. Both medications were administered thirty minutes before breakfast. Pentagastrin-stimulated (MAO) was assessed from hour 23 to 24 at steady state.

Several analytical methods[14-28] have been reported for the determination of Methyl hydroxyl benzoate in pure drug, pharmaceutical dosage forms and in biological samples using spcetrophotometry, liquid chromatography, electro kinetic chromatography high performance thin layer chromatography either in single or in combined forms.

MATERIALS AND METHODS

Instrumentation:

Waters HPLC containing LC 20AT pump and variable wavelength programmable UV-Visible detector and Rheodyne injector was employed for investigation. The chromatographic analysis was performed on a Luna CN 5µm (4.6 x 250 mm) or equivalent. Degassing of the mobile phase was done using a Unichrome ultrasonic bath sonicator. A Ohaus Analytical balance was used for weighing the materials.

Chemicals and Solvents:

The reference sample of Pantoprazole(API) was obtained from Sun Pharma Pvt Ltd. The Formulation Pantoprazole was procured from the local market. Acetonitrile used was of HPLC grade and purchased from Merck Specialties Private Limited, Mumbai, India.

The Mobile Phase:

A mixture of Water : Acetonitrile in the ratio of 30:70 v/v was prepared and used as mobile phase.

Preparation of Standard solution

100 µg/ml of Pantoprazole is prepared by diluting with mobile phase. This solution is used for recording chromatogram.

Preparation of Sample Solution

20 tablets (each tablet contains Pantoprazole 40 mg) were weighed and taken into a mortar and crushed to fine powder and uniformly mixed. Tablet stock solutions of Pantoprazole (µg/ml) were prepared by dissolving weight equivalent to 5 mg of Pantoprazole dissolved in sufficient mobile phase. After that the solution is filtered using 0.45-micron syringe filter and sonicated for 5 min and dilute to 50ml with mobile phase. Further dilutions are prepared in 5 replicates of 100 µg/ml of Pantoprazole.

METHOD DEVELOPMENT

For developing the method [37-43], a systematic study of the effect of various factors was undertaken by varying one parameter at a time and keeping all other conditions constant. Method development consists of selecting the appropriate wave length and choice of stationary and mobile phases. The following studies were conducted for this purpose.

Detection wavelength:

The spectrum of Pantoprazole solution was recorded separately on UV spectrophotometer. The peak maximum of absorbance wavelength was observed. The spectra of Pantoprazole were showed maximum absorbance at 215nm [Fig-2].

Choice of stationary phase and Mobile Phase:

Finally the expected separation and peak shapes were obtained on Luna CN 5µm (4.6cmX250 mm) column. A mixture of Water : Acetonitrilein the ratio of 30:70 v/v was proved to be the most suitable for all the combinations since the chromatographic peak obtained was better defined and resolved and almost free from tailing.

Flow rate:

Flow rates of the mobile phase were changed from 0.5 – 1.5 mL/min for optimum separation. It was found from the experiments that 1.0 mL/min flow rate was ideal for the successful elution of the analyte.

Optimized chromatographic conditions

Chromatographic conditions as optimized above were shown in Table 1. These optimized conditions were followed for the determination of Pantoprazole in bulk samples and in its formulations. The chromatograms for Standard Drug and Placebo are identified. Among all these for the Placebo no significant peaks are detected.

VALIDATION OF PROPOSED METHOD AND REQUIREMENTS:

The proposed method [29-36]was validated as per ICH guidelines. The parameters studied for validation were specificity, linearity, precision, accuracy, robustness, system suitability, limit of detection, limit of quantification, and stability.

SPECIFICITY

Blank interference

Specificity studies included application of the proposed method for blank, placebo solution, sample solution (control sample), standard solution. A study to establish the interference of blank was conducted. Diluent was injected into the chromatograph in the above defined chromatographic conditions and the blank chromatogram was recorded. Chromatogram of Blank solution **(**Fig. no.-4**)** showed no peaks at the retention time of Pantoprazole peak. This indicates that the diluent solution used in sample preparation do not interfere in estimation of Pantoprazole in Protonix tablets. Similarly typical representative chromatogram of standard and sample were also shown in figure -5 & 6.

Forced Degradation

The specificity studies also include deliberate degradation of the tablet sample by exposure to stress conditions. Forced Degradation study was carried out by treating the sample under the acidic, alkaline, thermal and photo conditions. Weighed ten tablets of pantoprazole and powdered uniformly in a mortar. An accurately weighed portion powder equivalent to 50 mg was transferred into 100 mL volumetric flask. The contents of the flask were sonicated for about 15 min for complete solubility of the drug and the volume was made up to 50 mL with mobile phase. Then the mixture was filtered through a 0.45µ membrane filter. The results pertaining to these degradation conditions were given in table – 2 and chromatograms were as shown in figures 26 – 28.

SYSTEM SUITABILITY

System suitability is a measure of the performance and chromatographic quality of the total analytical system – i.e. instrument and procedure. Six replicate injections of API working standard solution were injected according to the method of analysis. The percentage relative standard deviations (% RSD) for the peak responses were determined. The % RSD of the peak responses due to Pantoprazole for six injections must be less than or equal to 5.0 %. The analytical system complies with the requirements specified by the system suitability. The Results are tabulated in the Table 3

Linearity and range

In the concentration range of 10.0 – 150.0 µg/ml for Pantoprazole standard curve was obtained. A statistical method known as linear regression analysis was used to evaluate the linearity of the curve. To assess the linearity of the proposed method slope, intercept and correlation coefficient [r^2] of standard curve was calculated and was given in Figure-5. The results were given in the Table- 4 & 5. From the data obtained (For Pantoprazole), the method was found to be linear within the proposed range. The linearity chromatograms were given in figure- 7 -12

Accuracy

Accuracy is defined as the closeness of results obtained by that method to the true value for the sample. Accuracy is expressed in terms of percentage recovery. Recovery % is determined by the standard addition method. In the present study recovery studies were carried out at 50%, 100% and 150% spiked levels. The results of Recovery % were given in Table - 6 and the chromatograms were given in Figures 13-21.

Precision

The closeness of replicate results obtained from analysis of the same homogeneous sample is known as precision of the method. The precision of the method was assessed by six replicate injections of 100% test concentration. The precision was expressed in terms of standard deviation and %RSD. The results were given in Table 7. The system precision was also analyzed and the results were given in the same table. Precision chromatograms were given figures 22 & 23.

Ruggedness

Degree of reproducibility of test results obtained by analyzing the same sample under variety of normal test conditions such as different analysts, instruments, days, reagents, column etc. The Ruggedness of the method was verified by analyzing the six samples of same batch for method precision as per test method on two different days. The analysis was carried out for six sample of the same batch on two different day's .Calculated %RSD on two different days in six samples for ruggedness results with the method precision. The results of ruggedness were given in Table 8

Robustness

The ability of the developed method to remain unaffected by the small changes in the parameters is known as Robustness. Robustness was assessed by varying the parameters such as percent organic content, pH of the mobile phase, buffer concentration, temperature, injection volume and flow rate. In the present investigation, a variation of ± 0.1 mL/min in the flow rate, change in organic content of mobile phase were adopted to study Robustness. The results were tabulated in Table -9 and the chromatograms were given in figures 24 & 25.

RESULTS AND DISCUSSION

To optimize the HPLC parameters, several mobile phase compositions were tried. A satisfactory separation and good peak symmetry was found in a mixture of Water : Acetonitrie in the ratio of 30:70 v/v and 1.0 mL/min flow rate proved to be better than the other mixtures in terms of resolution and peak shape. The optimum wavelength for detection was set at 215nm at which much better detector responses for drug was obtained as shown in Fig 2. The retention time was 3.7 min for Pantoprazole. Good number of theoretical plates were found, which indicates efficient performance of the column. A system suitability test was applied to representative chromatograms for various parameters. The results obtained were within acceptable limits and are represented in Table 3. Thus, the system meets suitable criteria.

The calibration curve was obtained for a series of concentration in the range of 10-150µg/ml and it was found to be linear. Seven points graphs was constructed covering a concentration range 10-150 µg/ml. The standard deviation of the slope and intercept were low. The data of regression analysis of the calibration curves are shown in Table 5.

Mean percentage recovery is found to be 102. The proposed method has been applied for the assay of the commercial tablets containing Pantoprazole. Sample was analyzed for five times after extracting the drug as mentioned in assay sample preparation of the experimental section. The results presented good agreement with the labeled content. Low values of standard deviation denoted very good repeatability of the measurement. Thus it was showing that the equipment used for the study was correctly calibrated and hence the developed analytical method is highly repetitive. For the intermediate precision analysis was carried out by different analysts working on the same day indicated a RSD of 0.1. This indicates good method precision.

Table 1 Optimized chromatographic conditions for estimation Pantoprazole

S.NO	PARAMETERS	CHROMATOGRAPHIC CONDITIONS
1.	Mobile phase	Water : ACN 30:70
2.	Column	LUNA CN, 250×4.6mm ID, 5µm Particle size
3.	Flow rate	1.0 ml/min
4.	Column temperature	Room temperature(20-25^{o}C)
5.	Sample temperature	Room temperature(20-25^{o}C)
6.	Wavelength	215 nm
7.	Injection volume	10 µl
8.	Run time	6 min
9.	Retention time	2.7 min Pantoprazole

The system suitability parameter like capacity factor, asymmetry factor, tailing factor and number of theoretical plates were also calculated. It was observed that all the values are within the limits. The statistical evaluation of the proposed method revealed good linearity, reproducibility and its validation for different parameters and can be concluded that it could be used for the rapid and reliable determination of Pantoprazole in tablet formulation.

Table No 2: Forced Degradation Studies

S.no	Degradation Parameters	Time	Peak Area	%Recovery	%Degradation
1.	Acid	10min	2779976	78.22	21.6
2.	Base	10min	2745314	75.42	20.8
3.	Peroxide	10min	2700219	76.25	24.74
4.	Thermal	10min	2779976	75.22	26.78
5.	Humidity	10min	2780814	76.46	22.75
6.	Heat	10min	2773748	78.37	21.52
7.	Photolytic	10min	2741099	75.36	23.56
8.	Reduction	10min	2776007	78.64	24.33
9.	Hydrolysis	10min	2724933	79.22	21.7

Table No 3: System Suitability results

Injection	Retention time (min)	Peak area	Theoretical plates (TP)	Tailing factor (TF)
1	3.772	3428156	5825	1.11
2	3.721	3415872	5821	1.04
3	3.746	3428793	5863	1.01
4	3.735	3457893	5842	1.02
5	3.731	3432579	5827	1.06
6	3.708	3475632	5856	1.08
Mean	3.745	3415963	--	--
SD	0.1258	1852.14	--	--
%RSD	0.12	0.5304	--	--

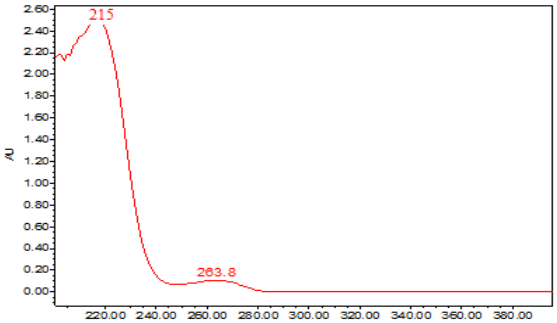


Table No 4: Linearity of Detector Response for Pantoprazole

S.No	Conc.(µg/ml) of Pantoprazole	Area Pantoprazole	Acceptance criteria
1	10 µg/ml	341712	Squared correlation coefficient should be not less than0.999.
2	25 µg/ml	853955	
3	50 µg/ml	1707911	
4	100 µg/ml	3415823	
5	125 µg/ml	4269778	
6	150 µg/ml	5123734	

Linearity graph of Pantoprazole:

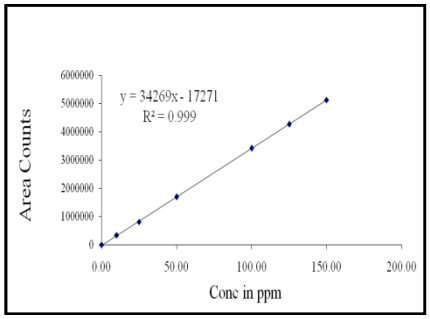


Table No 5: linearity Summary for Pantoprazole

S.No	Linearity Parameters	Pantoprazole
1.	Linearity range	10-150 µg/ml
2.	Correlation coefficient	0.999
3.	Y intercept	34269x -17271

Table No 6: - Accuracy data of Pantoprazole

Recovery level	Accuracy Pantoprazole					%RSD
	Amount taken (mcg/ml)	Area	Average area	Amount recovered (mcg/ml)	%Recovery	
50%	50	1741363	1741006	100.55	100.5	0.18
	50	1741916				
	50	1741739				
100%	100	3483786	3482827	100.26	100.2	0.26
	100	3483414				
	100	3483280				
150%	125	5125949	5123834	100.58	100.5	0.52
	125	5124797				
	125	5125755				

Table No 7: - Method precision data for 100mg

Pantoprazole		
S.No.	Rt	Area
1	3.715	3430293
2	3.721	3465113
3	3.712	3432722
4	3.727	3446699
5	3.720	3414899
6	3.721	3425974
Avg	3.720	3402617
St dev	0.148	2826.84
%RSD	0.46	1.082

Table No 8: Intermediate precision data of Pantoprazole

S.No	Analyst-1		Analyst-2	
	Peak area	% assay	Peak area	%assay
1.	3439641	100.8	3423786	100.2
2	3422962	100.6	3496414	*100.4*
3	3454852	100.5	3414755	100.1
4	3448131	100.4	3480335	100.2
5	3458903	100.7	3465113	100.7
6	3444468	100.1	3476505	100.2
Mean	3448160	100.6	3442818	100.1
%RSD	0.41	0.22	0.85	1.21

Table No 9: Flow rate and Organic Phase variations

Parameters	Pantoprazole		%RSD
Flow rate	Retention time	Tailing actor	
0.8ml/min	3.711	1.19	1.46
1.0ml/min	3.432	1.20	0.16
1.2ml/min	2.863	1.17	1.64
Organic phase			
65:35	3.823	1.17	1.67
70:30	3.421	1.20	0.16
75:25	3.628	1.19	1.37

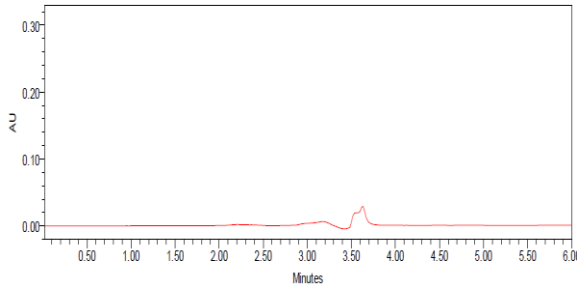


Fig 4: Blank chromatogram

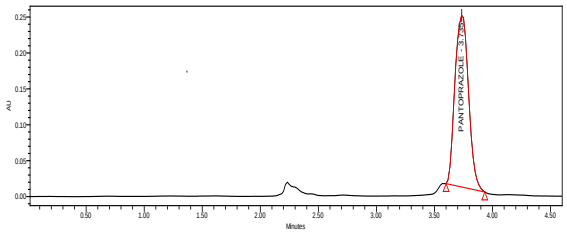


Fig 5: - Typical chromatogram of sample

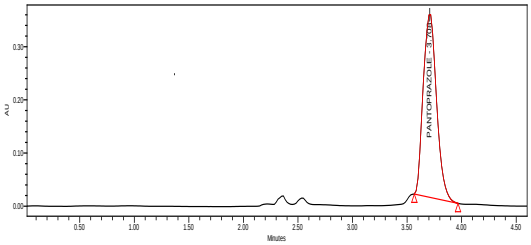


Fig 6: Typical Chromatogram of Standard

Chromatograms of linearity:

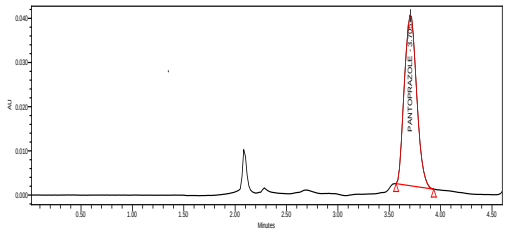


Fig 7: -Typical chromatogram of linearity 10 µg/ml

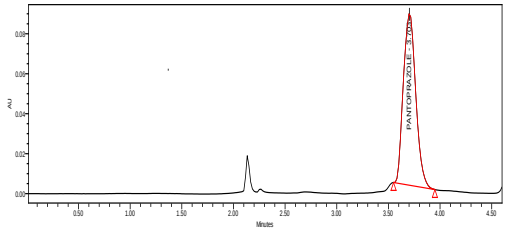


Fig 8: - Typical chromatogram of linearity 25 µg/ml

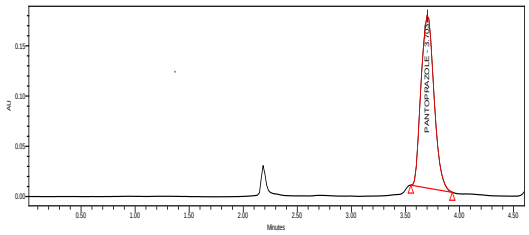


Fig 9: - Typical chromatogram of linearity 50 µg/ml

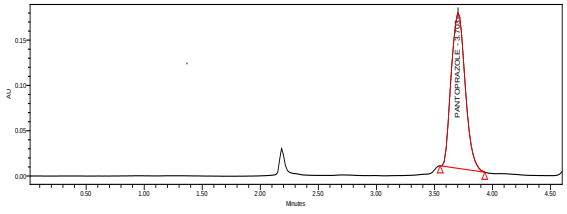


Fig 10: - Typical chromatogram of linearity 100 µg/ml

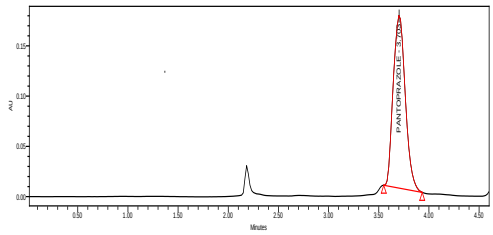


Fig 11: - Typical chromatogram of linearity 125 µg/ml

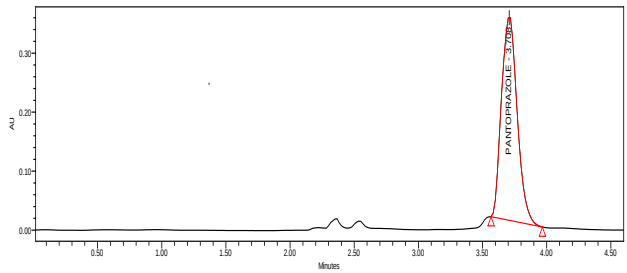


Fig 12: - Typical chromatogram of linearity 150 µg/ml

Chromatograms of accuracy:

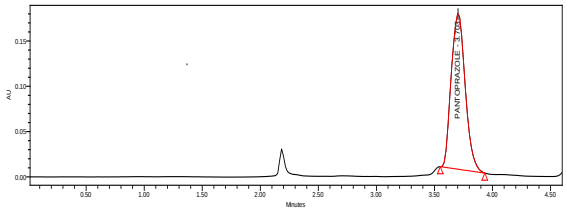


Fig 13: - Typical chromatogram of accuracy 50%-1

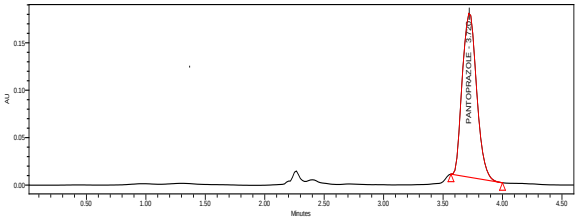


Fig 14: - Typical chromatogram of accuracy 50%-2

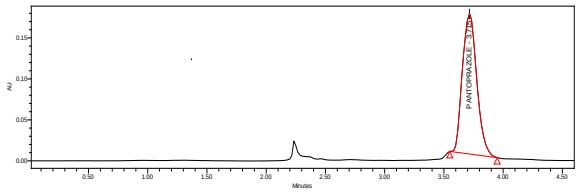


Fig 15: - Typical chromatogram of accuracy 50%-3

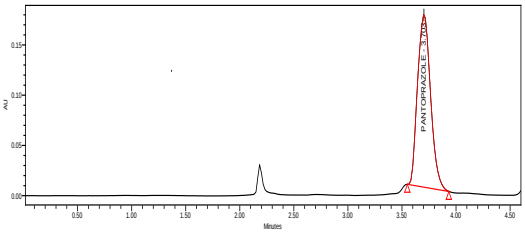


Fig 16: - Typical chromatogram of accuracy

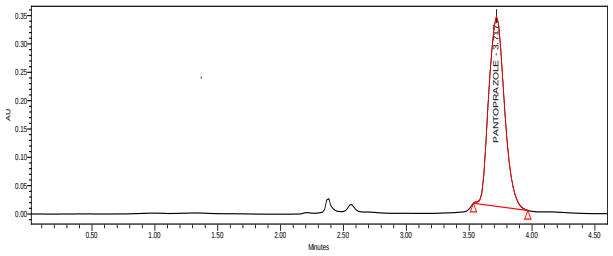


Fig 17: - Typical chromatogram of accuracy 100%-2

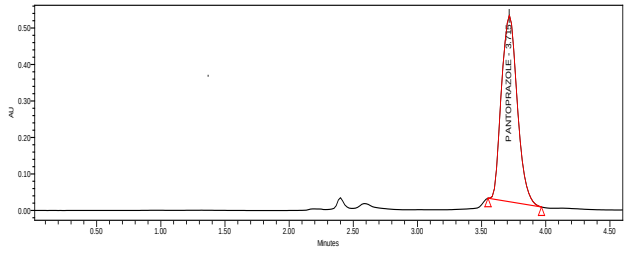


Fig 18: - Typical chromatogram of accuracy 100%-3

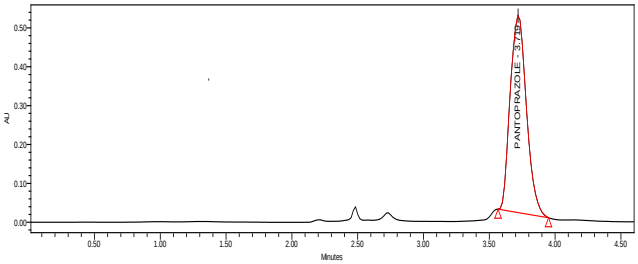


Fig 19: - Typical chromatogram of accuracy 150%-1

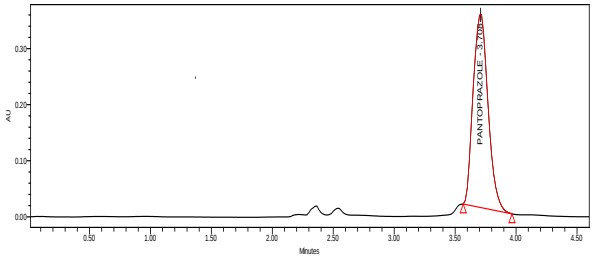


Fig 20: - Typical chromatogram of accuracy 150%-2

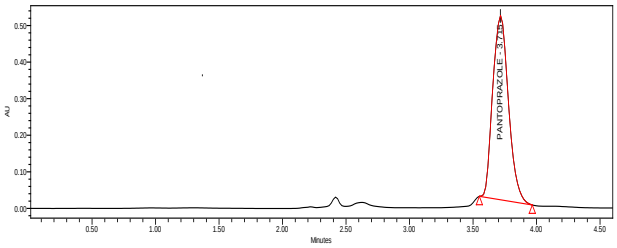


Fig 21: - Typical chromatogram of accuracy 150%-3

Precision chromatograms of Pantoprazole.

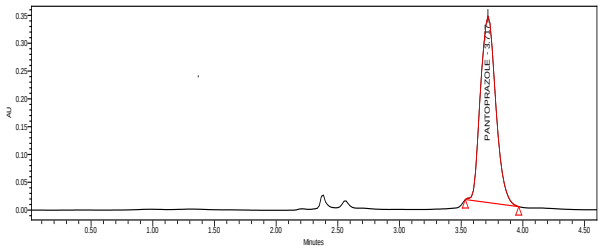


Fig 22: - Typical chromatogram of precision (injection-1)

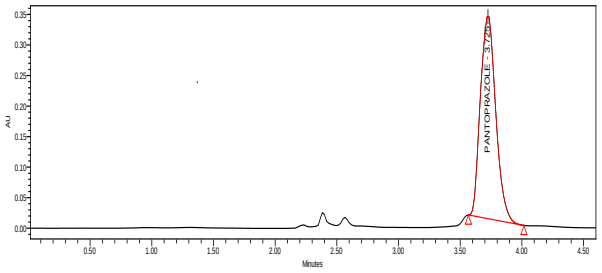
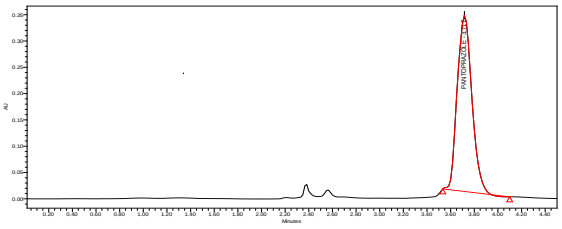


Fig 23: - Typical chromatogram of precision (injection-2)



Robustness Chromatograms.

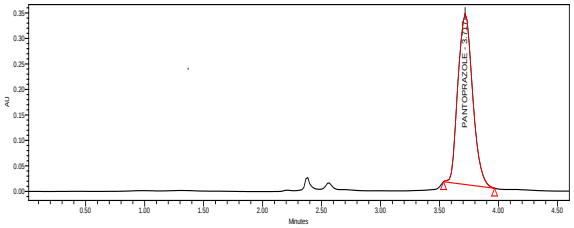
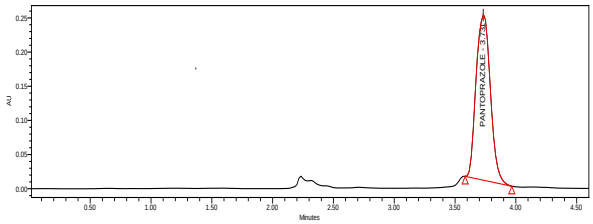


Fig 24: Chromatogram of robustness (flow rate 0.8ml/min)



[Fig 25: Chromatogram of robustness(Flow rate 1.2ml/min)

Forced Degradation Studies:

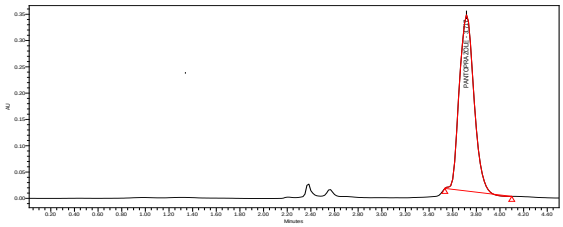


Fig 26: - Acidic degradation study

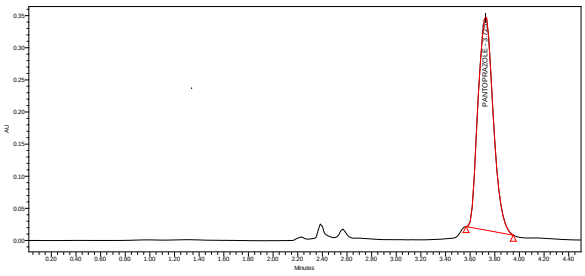


Fig 27:-Base degradation study

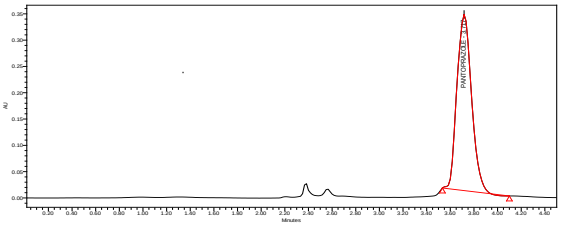


Fig 28:-Peroxide degradation

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