ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

STABILITY INDICATING METHOD DEVELOPMENTAND VALIDATION FOR PANTOPRAZOLE USING RP-HPLC

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ABSTRACT

AIM: To develop and validate simple, accurate, sensitive, rapid and economical methods for simultaneous estimation of the drug from tablet dosage forms using RP-HPLC method

MATERIALS & METHODS: pH meter Eutech, Weighing balance Denver, Ultrasonicator UCA 701 Unichrome, HPLC LC Waters 2695- Empower software, Flow rate 1mL/min, Pump Isocratic model

REAGENTS AND CHEMICALS: Water HPLC**,** Acetonitrile HPLC, Formic acid HPLC, Tri fluoro acetic acid hplc, Pantoprazole was purchased from Indian market manufactured by USV, (Mumbai). Commercial pharmaceutical preparation of Pantoprazole tablets contain 100 mg was used in analysis

RESULTS: wavelength was selected at which the drugs showed maximum absorbance. The wavelength selected was 290 nm. X-Bridge phenyl (250mmx 4.6mm, 5µ). 0.1% formic acid: ACN (50:50v/v)used as mobile phase Retention time of Pantoprazole was about 3.746 The % assay should be within range of 98-102%, Linearity range 10-200 µg/ml Correlation coefficient0.999, LOD = 0.125 LOQ = 0.412,Method Precision 0.612. Assay **100.1**

CONCLUSION: Hence, the developed chromatographic method for Pantoprazole is said to be rapid, simple, precise, accurate, specific and cost effective that can be effectively applied for the routine analysis

INTRODUCTION

A characteristic feature of mammalian stomach is its ability to secrete acid as part of its involvement in digesting food. The acid secretory unit of the gastric mucosa is the parietal cell. Secretion of acid by gastric cells is regulated by the actions of various mediators at receptors, such as histamine agonism of H2-receptors, gastrin activity at G-receptors and acetylcholine at muscarinic M2-receptors[1] . Over the years, it became evident that gastric acid can lead to acid related disorders of stomach, esophagus and duodenum, such as gastritis, peptic ulcers and gastro-esophageal reflux disease. The first target in treatment of acid related diseases was the H2-receptors. The second medicinal target was the gastric acid pump, the gastric H+ ,K+ -ATPaze or proton pump[2]. Since the proton transport by the proton pump is the final step of gastric acid secretion, it was anticipated that drugs of this type would be more effective as inhibitors of acid secretion. So this group of drugs was called Proton pump inhibitors (PPIs)[3]. The first clinically useful PPI was omeprazole, after which lansoprazole, pantoprazole and rabeprazole were developed.

Pantoprazole sodium is chemically known as 6-(difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl) methylsulfinyl]-1*H*-benzimidazole[4]. Pantoprazole inhibits H+ K+ AT Pase pump function; thereby, healing the acid related conditions. Pantoprazole is chemically more stable than omeprazole and lansoprazole in neutral to mildly acidic conditions, but under strongly acidic medium, active species is formed[5].The molecular formula of Pantoprazole IS $C_{16}H_{15}F_2N_3O_4S$and it is freely soluble in water[6].

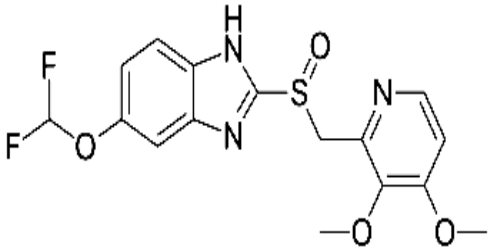


Fig 1: Structure of Pantoprazole

This paper deals with the development and validation of a sensitive method for the assay of Pantoprazole in pharmaceuticals, based on HPLC technique. The separation and determination were done on a reversed phase with X-Bridge phenyl (250mmx 4.6mm, 5µ). 0.1% formic acid: ACN (50:50v/v)used as mobile phase and flow rate of 1.0 ml/min. The detection was carried out at 290 nm and ambient column temperature was maintained.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

EXPERIMENTAL
MATERIALS
INSTRUMENTS USED

S.No	Name	Model	Manufacturer
1.	pH meter	-	Eutech
2.	Weighing balance	-	Denver
3.	Ultrasonicator	UCA 701	Unichrome
4.	HPLC	LC	Waters 2695- Empower software
5.	Flow rate	1mL/min	--
6.	Pump	Isocratic model	--

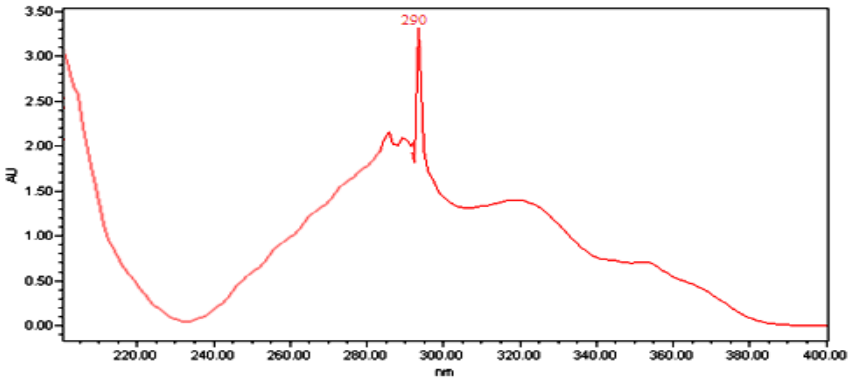
REAGENTS AND CHEMICALS:

S.No	Name	Grade	Manufacturer
1.	Water	HPLC	In house production
2.	Acetonitrile	HPLC	Merck
3.	Formic acid	HPLC	Merck
4.	Tri fluoro acetic acid	HPLC	Merck

DRUG SAMPLES:
Pantoprazole was purchased from Indian market manufactured by USV, (Mumbai). Commercial pharmaceutical preparation of Pantoprazole tablets contain 100 mg was used in analysis.
METHOD DEVELOPMENT:
Selection of the wavelength for Simultaneous Estimation
In setting up the conditions for development of the assay method, the choice of the detection wavelength was based on the scanned absorption spectrum for Pantoprazole.
Accurately Weigh 100mg of Pantoprazole working standard into a 100ml volumetric flask, add 70ml of diluents sonicate for 15min to dissolve the contents, diluted volume with diluent. Further diluted 5ml of above solution to 50ml volumetric flask make up with diluent.
The prepared solution was loaded into the auto sampler and the system was set in order to take the auto injection in HPLC with PDA detector. The Spectrum obtained is as follows

Fig- 2 Spectrum of Pantoprazole

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021



From the above spectra of drug, a wavelength was selected at which the drugs showed maximum absorbance. The wavelength selected was 290 nm.

Selection of chromatographic method

The choice of chromatographic method is based on the nature of sample, its molecular weight and solubility. As drugs are polar in nature, the reverse phase chromatographic technique was selected for the present work.

OPTIMIZED METHOD

Preparation of Mobile Phase:

1ml of formic acid dissolved in 1lt of water, and acetonitrile in the ratio of 50:50 v/v was prepared.

Column : X- bridge phenyl (250mmx 4.6mm, 5µ)
Injection Volume : 10 µl
Wavelength : 290 nm
Flow rate : 1.0 ml/ min
Temperature : Ambient
Diluent : Same as mobile phase

Retention time of Pantoprazole was about 3.746 respectively.

Preparation of standard solution:

Weigh accurately about100mg of pantoprazole working standard into a 100 mL volumetric flask. Add 70 mL of diluent, sonicate to dissolve and dilute to volume with diluent.
Further dilute 5mL of the above solution to 50 mL with the diluent.

Preparation of Sample solution:

Weigh 1 tablet and crush to powder then take equivalent weight of sample into a 100 mL volumetric flask. Add 70 mL of diluent, sonicate to dissolve and dilute to volume with diluent. Further dilute 5 mL to 50 mL with the diluent. Filter through 0.45µ Nylon syringe filter.

ASSAY CALCULATION:

% Assay of was carried out in tablet formulation with results were calculated by using the formula given below and reported

$$\text{Potency} = \frac{\text{Test area x STD weight x Test dilution x Avg. Weight x 100}}{\text{STD area x test weight x STD dilution x label claim x 100}}$$

Assay Results:

Acceptance Criteria:

Table-1 Assay observations of Pantoprazole

The % assay should be within range of 98-102%

Drug	Label Claim for sample taken (mg)	Sample weight (mg)	% of Assay
Pantoprazole	100	172	100.1

Observation: The % assay was found to be within the range.

METHOD VALIDATION

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

The validation of HPLC method for the determination of Pantoprazole as per the protocol and to demonstrate that the method is appropriate for its intended use was studied for the following parameters. All the validation parameters were carried out according to ICH.

RESULTS AND DISCUSSION

Initial conditions selection

The developed method for simultaneous estimation of Pantoprazole was carried out X- bridge phenyl (250mmx 4.6mm, 5µ) in an isocratic mode, using mobile phase composition of 0.1% formic acid and acetonitrile in the ratio (50:50 v/v) with a flow rate 1.0 ml/min. The effluents were monitored at 290 nm.

Method validation

System suitability:

System suitability test should be carried out to verify that the analytical system was working properly and can give accurate and precise results. A standard solution of Pantoprazole working standard was prepared as per the test procedure and was injected six times into the HPLC system. The system suitability parameters were evaluated form standard chromatograms obtained by calculating the retention times, tailing factor, theoretical plates and % RSD of peak areas from the six replicate injections. The results were shown in table.

Table-2 Results of System Suitability

Parameter	Pantoprazole
Retention Time	3.746
Theoretical Plates	5634
Tailing Factor	1.14
USP Resolution	---
%RSD of peak areas	0.16

1. Linearity and Range

The linearity method was demonstrated over the concentration range of 10-200 µg/ml for pantoprazole. Aliquots of the above solutions were prepared from stock solution and tabelled as solution 1, 2, 3, 4, 5, 6, 7, 8 respectively and the solutions ware injected into the HPLC system as per test procedure. Calibration curve for Pantoprazole was plotted accordingly by taking concentration Vs peak area. The chromatograms and results were shown below.

Acceptance criteria

Correlation Coefficient should be not less than 0.999.

Representative Linearity Chromatograms of Pantoprazole

Table-3 Linearity of Pantoprazole

S.NO	Conc. (µg/ml)	Peak Area
1	10	184880
2	25	459113
3	50	896209

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

4	75	1206347
5	100	1834505
6	125	2178517
7	150	2655617
8	200	3502114

Figure-12 Calibration curve of Pantoprazole

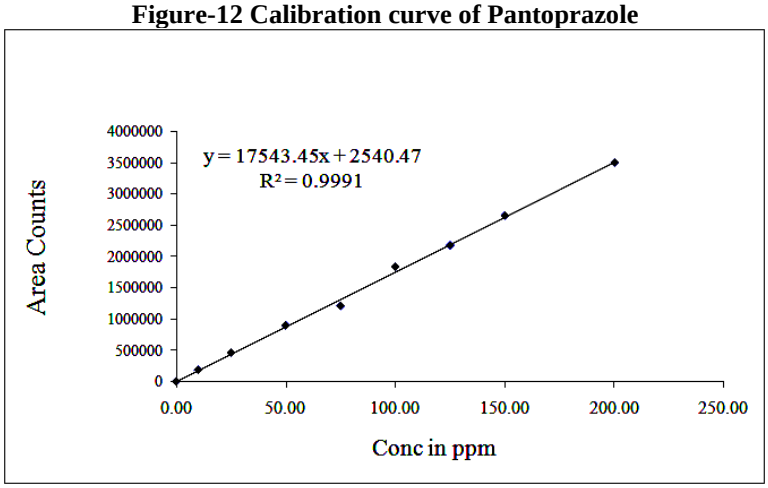


Table-4 Linearity Parameters for Pantoprazole

Parameters	Pantoprazole
Linearity range	10-200 µg/ml
Correlation coefficient	0.999

Observation:
The correlation coefficient values were found to be within the acceptance limits for the drugs.

2. Precision :

The precision of the analytical method was studied by analysis of multiple sampling of homogenous sample. The precision expressed as standard deviation or relative standard deviation. According to the ICH, precision should be performed at three different levels:

- System Precision (Repeatability)
- Method Precision (Reproducibility)

(a) System Precision (Repeatability)

For injection repeatability, six injections from the same standard preparations were made and the relative standard deviation for the replicate injections was calculated. The readings of system precision were given below.

Acceptance criteria
The % Relative standard deviation of peak areas of Pantoprazole from the six replicate injections should be not more than 2.0 %.

Figure – 13 Chromatogram for System Precision

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

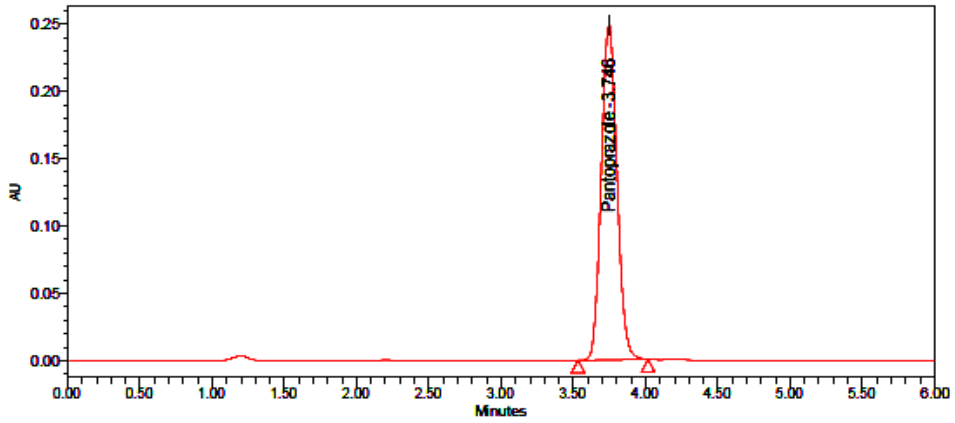


Table-5 System Precision values for Pantoprazole

S.No	RT	Area	USP Plate Count	USP Tailing
1	3.746	1891923	5634	1.14
2	3.752	1895508	6057	1.10
3	3.753	1887820	4801	1.08
4	3.744	1891040	5300	1.11
5	3.748	1888217	4641	1.09
6	3.750	1893460	5788	1.07
Mean		1891328		
%RSD		0.157		

Observation:

From the system precision studies it was observed that all the parameters like %RSD of peak areas are within limits.

(b) Method Precision (intraday)

Method Precision was carried out using six different sample preparations from same homogenous blend of marked sample. The chromatograms were recorded and mean, standard deviation and %RSD was calculated. The results and chromatograms were shown below.

Acceptance criteria

The % Relative standard deviation of peak areas of Pantoprazole from the six replicate injections should be not more than 2.0 %.

Figure – 14 Chromatogram for Method Precision:

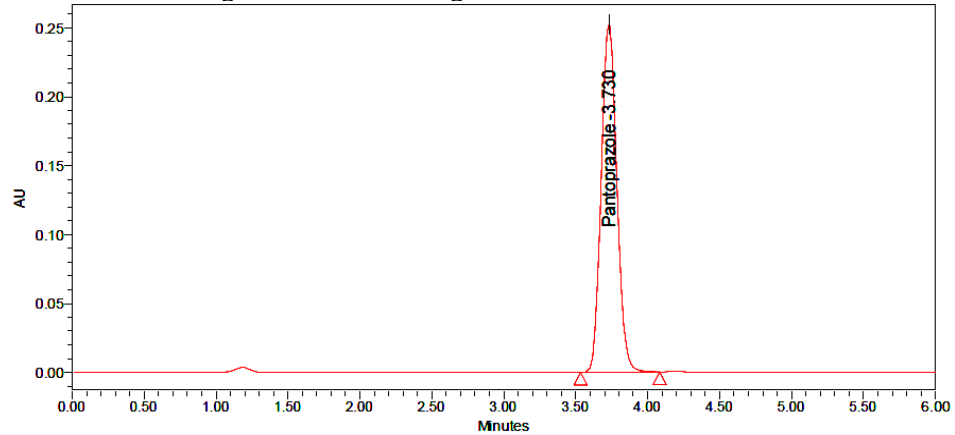


Table-6 Method Precision values for Pantoprazole

S.No	RT	Area
1	3.730	1900847
2	3.733	1897995

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

3	3.738	1903999
4	3.736	1907151
5	3.735	1903482
6	3.737	1902710
Mean		1902697
%RSD		0.162

Observation:
From the method precision studies, it was observed that all the parameters like %RSD of retention time and peak area were within the limits.

3. Accuracy :

A Study of Accuracy for Pantoprazole assay in triplicate (50%, 100% and 150%) as per test method with equivalent amount of drug containing Pantoprazole into each volumetric flask for each spike level to get the concentration of pantoprazole equivalent to 50%, 100% and 150% of the labeled amount as per the test method. The average % recovery was calculated.

Acceptance Criteria:
The mean % recovery of the Pantoprazole at each level should be not less than 98% and not more than 102%.

Table-7 Accuracy Results for Pantoprazole

S.No.	Spike Level	Amount of Placebo added (µg/ml)	Amount of API added (µg/ml)	% Recovery	Statistical analysis
1	50%	36	50	98.9	**Mean 99.1** **SD 0.13** **% RSD 0.130**
		36	50	99.0	
		36	50	99.2	
2	100%	72	100	100.9	**Mean 100.8** **SD 0.27** **% RSD 0.270**
		72	100	100.5	
		72	100	101.0	
3	150%	108	150	100.7	**Mean 100.4** **SD 0.22** **% RSD 0.220**

Observation:
The recovery results indicating that the test method has an acceptable level of accuracy. The results were found to be within the limits.

4. SPECIFICITY

A. Pantoprazole Identification

Solutions of the standard and the sample were prepared as per test procedure and injected into the system.

Acceptance Criteria:
Chromatogram of standard and sample should be identical with near retention time.

Figure – 18 Chromatogram ofPantoprazole (Standard)

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

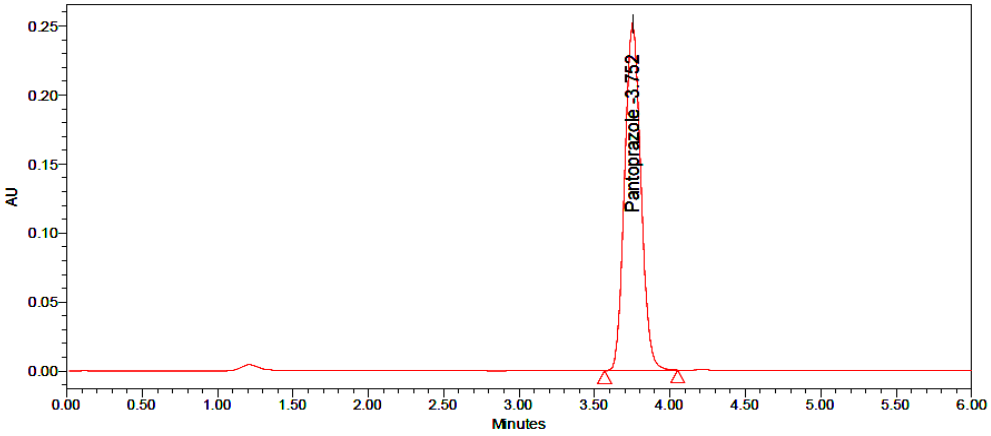
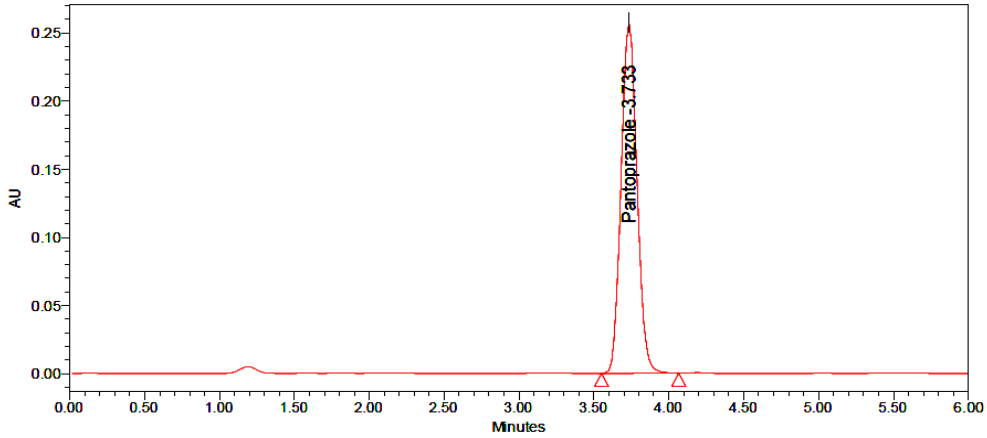


Fig - 19 Chromatogram ofPantoprazole (Sample)



Observation:

The chromatograms of the standard and sample were identical.

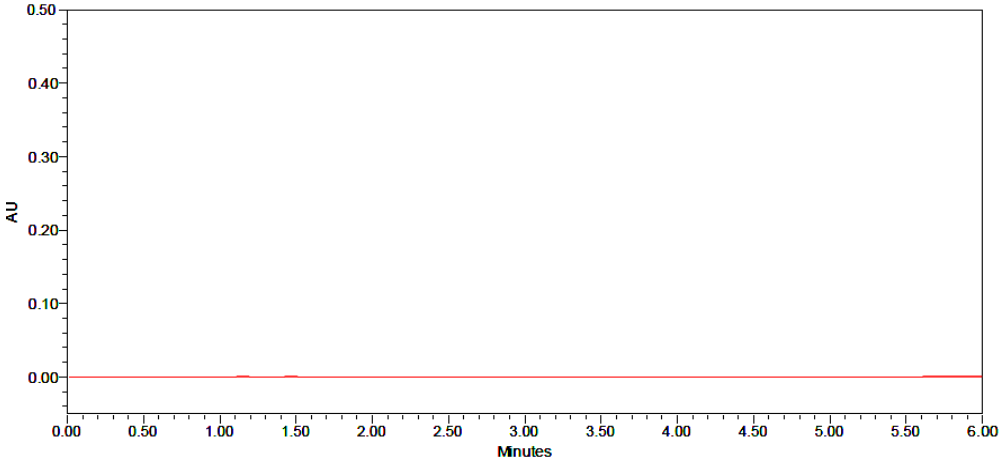
B. Blank Interference

A study to establish the interference of blank was conducted. Diluent was injected into HPLC system as per the test procedure.

Acceptance Criteria:

Chromatogram of blank should not show any peak at the retention time of the analyte peak.

Figure - 20 Chromatogram ofPantoprazole (Blank)



Observation:

There was no interference due to blank at the retention time of the analyte. Hence the method was specific.

5. Robustness

For demonstrating the robustness of the developed method, experimental conditions were purposely altered and evaluated. The method must be robust enough to withstand such slight changes and allow routine analysis of the sample.

Following optimized conditions were slightly varied

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

a. Effect of variation of flow rate :

A standard solution was prepared and injected into the HPLC by keeping flow rates (±0.2 ml/min) i.e., 1.2 ml/min and 0.8 ml/min, the effect is evaluated. The observation of variation of flow rate was given below.

Acceptance Criteria:

- The tailing factor (T) for the Pantoprazole should not be more than 2.0 for variation in flow.
- The system suitability parameters should pass as per the test method at variable conditions.

Figure - 21 Chromatogram for robustness (flow rate - 0.8ml/min)

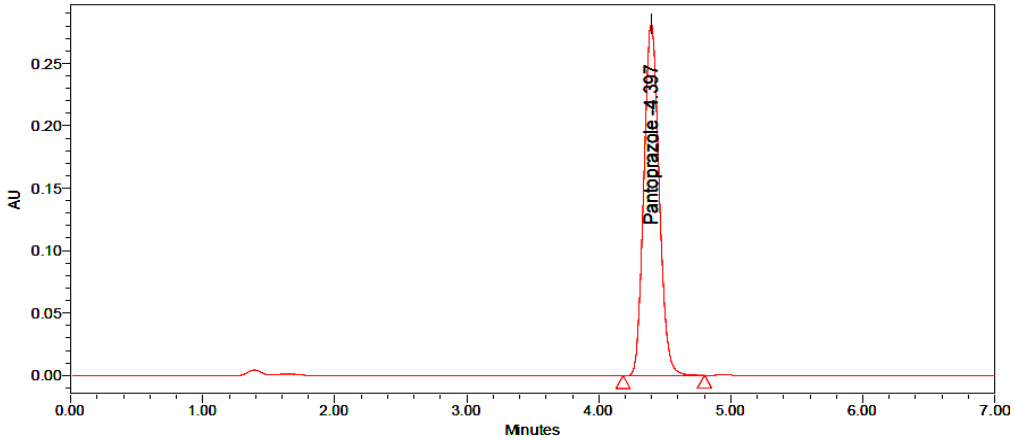


Fig-22 Chromatogram for robustness (flow rate - 1.2 ml/min)

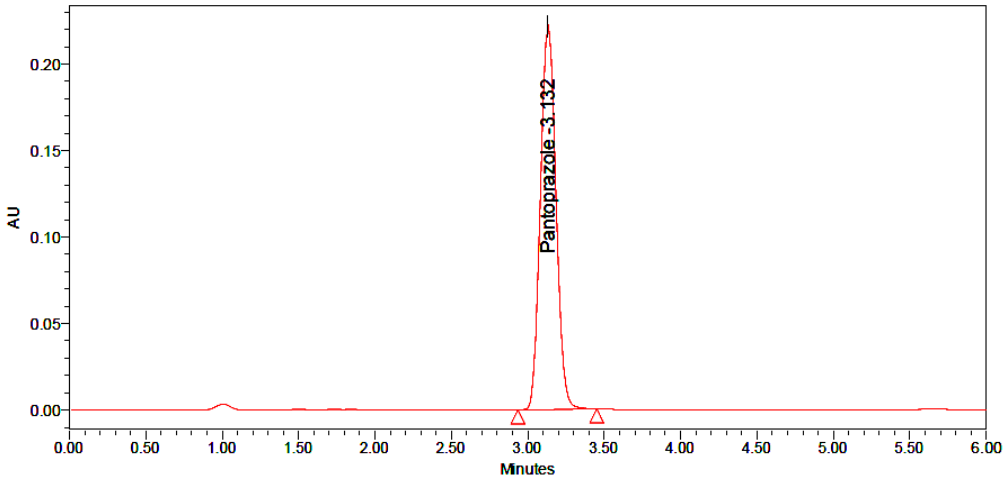


Table-8 Robustness data of Pantoprazole (Effect of variation of flow rate)

S.No.	Flow rate (ml/min)	Retention time (min)	Peak area
1	0.8	4.397	2270105
2	0.8	4.396	2274649
3	0.8	4.399	2277997
% RSD			**0.17**
2	1.2	3.132	1562279
3	1.2	3.119	1554826

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

3	1.2	3.128	1553007
% RSD			**0.31**

Observation:

It was observed that the system suitability parameters were within limits at all variable conditions.

Effect of variation of Organic Composition:

A study was conducted to determine the effect of variation in the mobile phase composition by changing the ratio of mobile phase i.e. Buffer: Acetonitrile from 50:50 v/v to 55:45 v/v and 45:55 v/v. Standard was prepared and injected into the HPLC system and the chromatograms were recorded.

Acceptance Criteria:

- The tailing factor (T) for the Pantoprazole should not be more than 2.0 for variation in composition of mobile phase.
- The system suitability parameters should pass as per the test method at variable conditions.

Figure-23 Chromatogram for Robustness (Organic Plus)

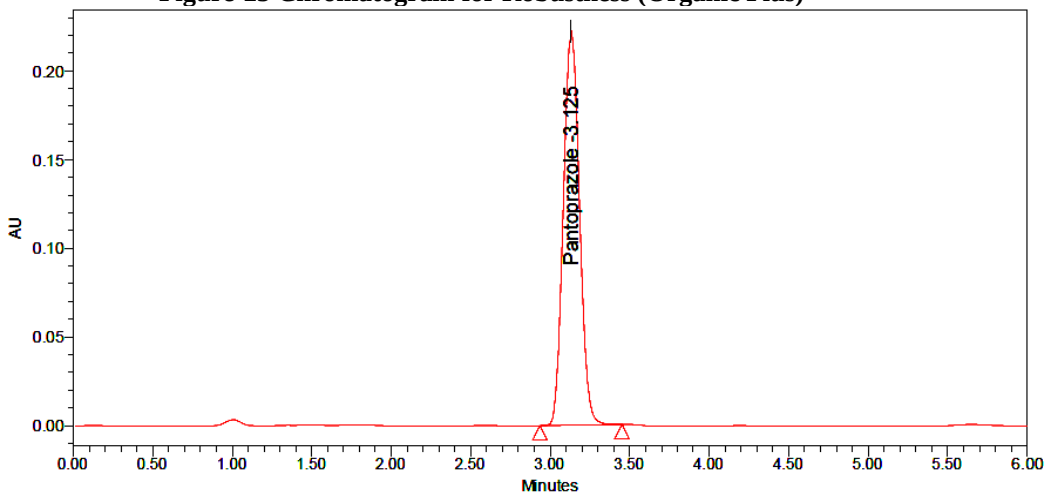


Figure -24 Chromatogram for Robustness (Organic Minus)

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

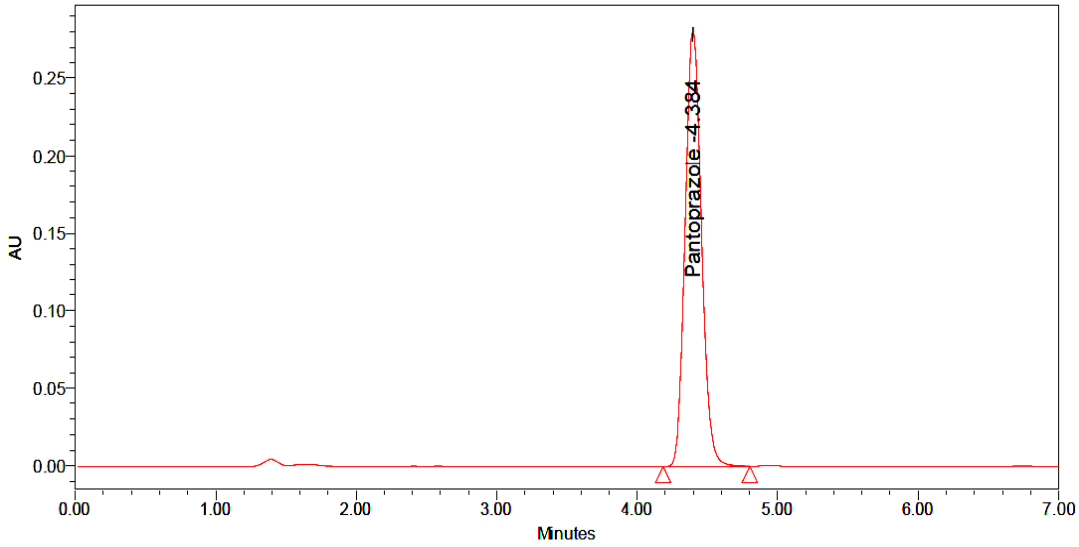


Table-9 Robustness data of Pantoprazole
(Effect of variation in mobile phase composition)

S.No.	Composition	Retention time (min)	Peak area
1	Organic Plus	3.125	1433129
2	Organic Plus	3.128	1412307
3	Organic Plus	3.124	1451989
% RSD			**1.38**
1	Organic Minus	4.384	1939870
2	Organic Minus	4.381	1940360
3	Organic Minus	4.383	1943200
% RSD			**0.12**

Observation:

It was observed that the system suitability parameters were within limits at all variable conditions.

6. RUGGEDNESS OF TEST METHOD

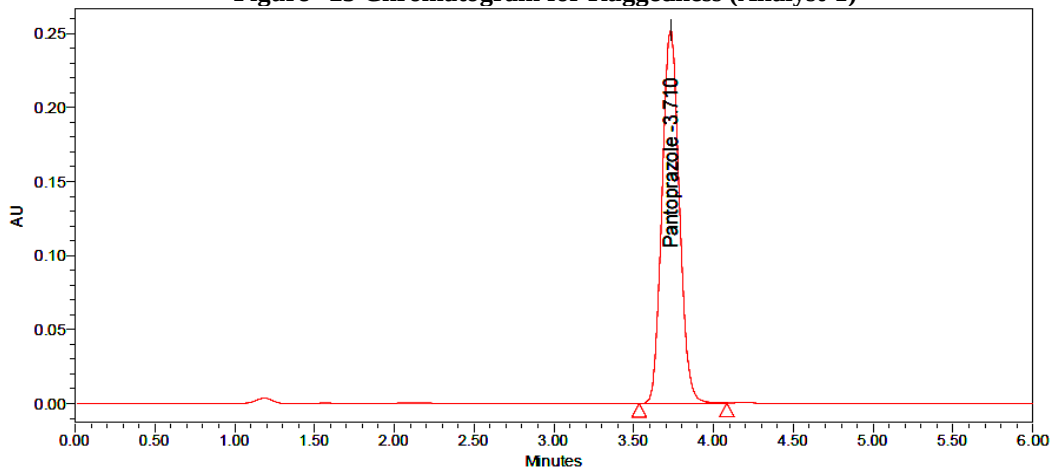
7. Analyst to Analyst variability

Analyst to Analyst variability study was conducted by different analysts under similar conditions at different times. Two samples were prepared and each was analyzed as per the test method. The data was shown in below table and chromatograms were shown below.

Acceptance Criteria:

The relative standard deviations of peak area should not be more than 2.0%

Figure –25 Chromatogram for Ruggedness (Analyst-1)



ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Figure – 26 Chromatogram for Ruggedness (Analyst-2)

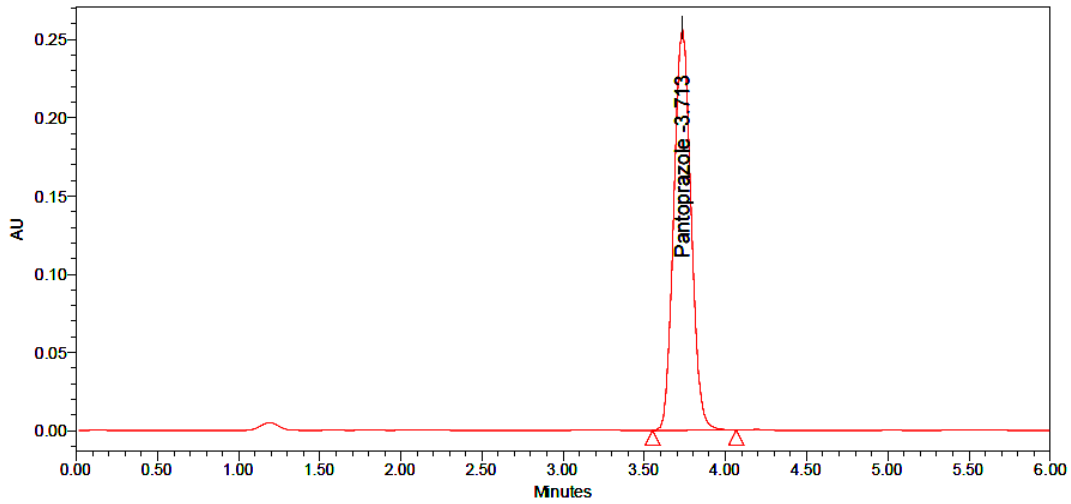


Table-10 Ruggedness data (Effect of changes in the analyst)

Analyst	Retention time of Pantoprazole (min)	Peak area of Pantoprazole
Analyst 1	3.710	1900654
Analyst 2	3.713	1903547
Mean	-	1902100
SD	-	2045.65
%RSD	-	0.107

Observation:

The %RSD was found to be within limits.

8. LOD AND LOQ

LOD and LOQ were calculated by the method based on the standard deviation (Σ) and slope of the calibration curve, using the formula

LOD = 3.3 σ / S

LOQ = 10 σ / S

Where,

σ = the standard deviation of the response

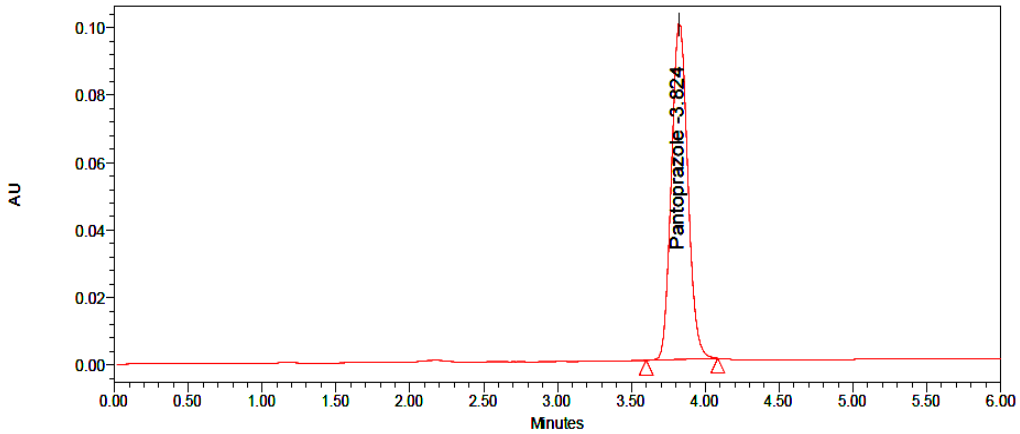
S = the slope of the calibration curve

The LOD and LOQ were calculated as per formula and were shown in the below table.

Table-11 Limit of Detection and Limit of Quantification

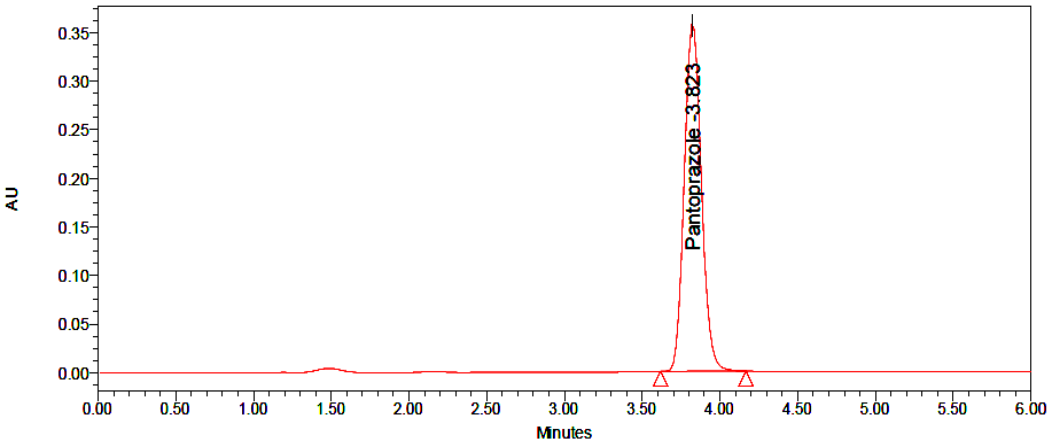
Sample	LOD	LOQ
Pantoprazole	0.125	0.412

Figure –27 Chromatogram for LOD



ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Figure –28 Chromatogram for LOQ



1. Forced Degradation Studies :

The specificity of the method was demonstrated through forced degradation studies conducted on the sample using acid, alkaline, oxidative, reductive, thermal and photolytic degradation. The sample was exposed to these conditions and the main peak was studied for the peak purity, thus indicating that the method effectively separated the degradation products from the pure active ingredient. Regulatory guidance in ICH Q2A, Q2B, Q3B and FDA 21 CFR section 211 requires the development and validation of stability-indicating potency assays.

Preparation of working standard solution:

About 100 mg of Pantoprazole pure drug was accurately weighed and transferred to 100 ml volumetric flask and made up to the mark with the diluents.

DEGRADATION STUDIES

1. Acid Degradation:

From the working standard solution 5ml was taken in 50ml volumetric flask, add 3 ml of 5N HCl was added, contents are mixed well kept aside for 1 hour. Then followed by neutralization with 3 ml of 5N NaOH and made up to volume with mobile phase. The solution was injected in HPLC system to obtain chromatograms.

Base Degradation:

From the working standard solution 5 ml was taken in 50ml volumetric flask, add 5 ml of 5N NaOH was added, contents are mixed well kept aside for 1 hour. Then followed by neutralization with 3 ml of 5N HCl and made up to volume with mobile phase. The solution was injected in HPLC system to obtain chromatograms.

3. Oxidation:

From the working standard solution 5 ml was taken in 50 ml volumetric flask, add 1 ml of 30% v/v H_2O_2 was added, contents are mixed well kept aside for 1 hour. Then make up to volume with mobile phase. The solution was injected in HPLC system to obtain chromatograms.

4. Temperature Stress Studies:

From the working standard solution 5 ml was taken in 50 ml volumetric flask. The solution was heated at 45º C and cooled to room temperature. Then the solution is injected in HPLC system to obtain chromatograms.

6. Hydrolysis Degradation:

From the working standard solution 5 ml was taken in 50 ml volumetric flask, add 10ml of diluent added 20 ml of water to disperse and dissolve and heated at 70°C for 3 hours on a water bath. Remove the flask from the water bath, and allow the flask to cool at room temperature and diluted to volume with diluent and mixed. Then the solution is injected in HPLC system to obtain chromatograms.

Acceptance criteria for Forced degradation:

Purity angle should be less than purity threshold. Pantoprazole and its degraded substances should not have any flag in purity results table.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

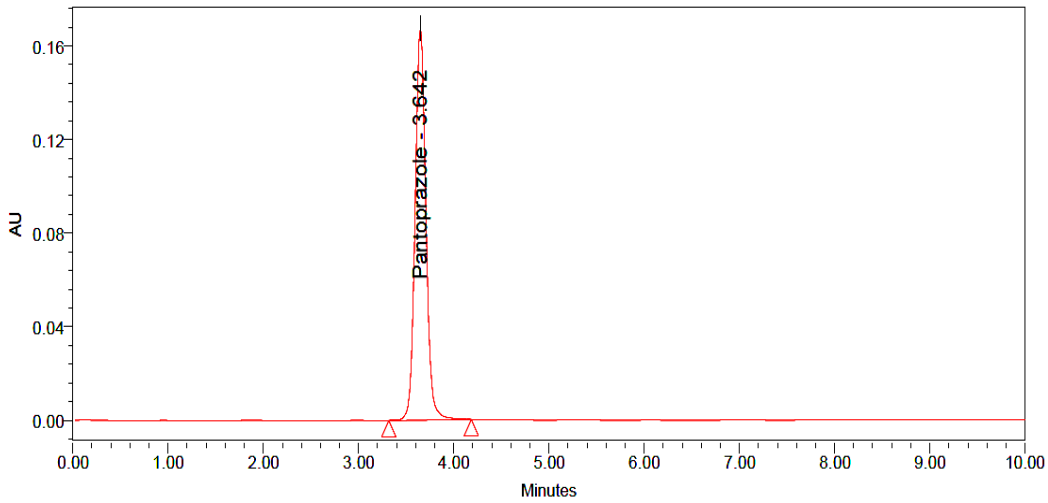


Table-12 Results of Forced Degradation study for Pantoprazole (6 Hrs)

		Pantoprazole				Peak Purity		
	Sample Weight in mg	Area Counts / Injections	Mean Area Count	% Label Claim	%Degradation	Purity Angle	Purity Thresold	Pass/Fail
Control	172	1883286	1883286	99.6	0.4	0.131	1.181	Pass
Acid	172	1801953	1801953	95.3	4.3	0.133	1.184	Pass
Alkali	172	1805472	1805472	95.5	4.5	0.142	1.187	Pass
Peroxide	172	1823592	1823592	96.4	3.6	5.354	35.517	Pass
Thermal	172	1795421	1795421	95	5	0.144	1.188	Pass
Hydrolysis	172	1807521	1807521	95.6	4.4	0.145	1.183	Pass

Observation: Purity angle is found to be less than threshold angle in all forced degradation studies without having signs of purity flags.

Table-13 Validation parameters for Pantoprazole

S.no	Parameters	Pantoprazole
1	**Linearity (µg/ml)**	10-200
	Correlation Coefficient	0.9991
2	**Precision**	
	(i) Method Precision	0.162
	(ii) Intermediate Precision	0.145

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

	(iii) System Precision		0.157
3	**LOD**		0.125
	LOQ		0.412
4	**Accuracy (% of recovery)**	**50%**	0.13
		100%	0.27
		150%	0.22
5	**Assay (%)**		100.1
6	**Robustness RSD NMT 2%in modified condition**		Complies
	Flow Plus		0.31
	Flow Minus		0.17
	Org Plus		1.38
	Org Minus		1.20

CONCLUSION

The proposed RP-HPLC method was suitable methods for the determination of Pantoprazole in dosage forms. All the parameters of the developed methods met the criteria of ICH guidelines for method validation.

The developed HPLC method has the following advantages:

- No tedious extraction procedures were involved.
- These methods are also having an advantage than reported method of good resolution and with retention time.
- The developed method has good recovery and sensitivity.
- The run time required for recording chromatogram was below 10.0mins.

Suitable for the analysis of raw materials and formulations.

Hence, the developed chromatographic method for Pantoprazole is said to be rapid, simple, precise, accurate, specific and cost effective that can be effectively applied for the routine analysis.

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