Original Article

Formulation And Evaluation Of Stability Indicating Hplc For Simultaneous Estimation Of Drugs Pantoprazole And Thiethylperazine

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DOI: 10.47750/pnr.2023.14.03.313

Abstract

According to the US Food and Drug Administration and the International Conference on Harmonization (ICH), the quality of drug substances and drug products can be altered over time by a wide variety of environmental conditions. The findings of the stability test can be used to evaluate the impact of this factor. The molecular stability of a substance is an essential consideration for selecting an appropriate formulation and container, as well as when calculating the requisite storage conditions and shelf life for regulatory documentation. Analysis is a technique that is defined as the process of determining the precise concentrations of active ingredients in a formulation without interfering with the concentrations of degradation products, process pollutants, excipients, or any other possible impurities. This is accomplished by separating the active ingredients from the other components of the formulation. Impurities that are unique to new medication components need to be demonstrated as well in order to demonstrate that degradation products in the drug product, whether they are defined or unknown, do not interfere with new medication components or are kept separate from them.

Keywords: ICH, Pre formulation, Pantoprazole, Thiethylperazine,

Introduction

Since the efficacy and safety of a drug are directly related to its chemical stability, this is a critical issue to solve. Stability testing results should be used to determine how the impacts of external variables change over time on the quality of drug substances and drug products, as recommended by the USFDA and ICH. An item's molecular stability is crucial in determining its formulation and container, as well as in determining its required storage conditions and

shelf life for regulatory paperwork. The long-term stability of a medicine or chemical can be determined by studying its breakdown products when subjected to conditions beyond those required for its quick disintegration. In order to confirm the stability indicators that have been implemented and to identify likely degradation products that help assess the stability of the molecule, stress testing is recommended by the International Council for Harmonization (ICH). Researchers and government entities alike have an immediate need to learn more about the effects of experimentally caused deterioration ([1]). New pharmaceutical companies must now perform stability studies before submitting their registration dossiers. Experiments in which degradation is artificially caused may be useful in both short-term and long-term stability studies as a method for demonstrating stability. Titrimetry, spectroscopy, and chromatography were only some of the many analytical methods used to probe the materials' stability. Quality control of bulk pharmaceuticals and the pharmaceutical formulations used in them rely heavily on the results of pharmaceutical analysis [2]. The rapid growth of pharmaceutical firms and the production of pharmaceuticals in many parts of the world has boosted the need for cutting-edge analytical methods within the pharmaceutical industry. In response, researchers have created cutting-edge techniques for statistical analysis. [3] Medications and their breakdown products, contaminants and the degradation products of bulk drug materials, mixing products, and drug products are all possible components of biological samples collected for drug research. Compendial monographs have included analytical procedures ever since the dawn of regulated pharmaceutical analysis. Through the application of these analytical methods, the potency of therapeutic compounds in bulk form can be characterised. In recent years, electroanalytical techniques like titration, spectroscopy, chromatography, and capillary electrophoresis have been incorporated into the testing protocols for monographs. [2-3] The number of therapeutically useful new drugs is growing annually. These medicines, along with a plethora of others, are then introduced in a variety of novel dosage forms. That's why it's crucial to constantly develop new, precise techniques for identifying these drugs in large-scale samples and finished products. With so many new treatments and formulations on the market, stopping the spread of subpar or even fake versions of these products is crucial. The availability of safe and effective medication formulations for customers and the protection of the general public from the dangers of misunderstanding medicines necessitate stringent quality control and quality assurance of and formulations for pharmaceutical chemicals. The usage of medications and combination therapies is on the rise as the benefits of their combined mode of action become increasingly apparent in the face of a rising tide of lifestyle-related disorders and an accompanying rise in microbial resistance. At each and every point in the drug-making process, the active pharmaceutical ingredient (active ingredient) or drug composition must be identified. Every time a new analytical method is created for a specific use, it must comply with the standards established by the International Conference on Harmonization. Screening innovative pharmaceuticals for features that are susceptible to alteration during storage and are likely to compromise quality, safety, and efficacy is required by the ICH guideline Q1A and requires the use of established stability-indicating testing protocols. For innovative medications, these methods are required. Recently, high-performance liquid chromatography has become the gold standard for detecting drugs. It is a great approach for analysing a wide range of pharmacological and biological fluid dosages because to its simplicity, high sensitivity, and high specificity. The purpose of this research is to provide an analysis strategy that can handle the extensive complexity caused by the presence of several pharmaceutical compounds. [7] Since analytical processes are used to analyse the medicines in their formulation, the study's goal is to establish how reliable an indicator of stability can be. The fundamental purpose of this research is to artificially induce a degradation process in the therapeutic formulation so that the drug may be identified and quantified in the presence of the degradation product, assuming it is stable and robust in analytical solutions. Since SIAM is one of just a handful of simultaneous estimation methods, it was employed for the following medications in combination dose forms. Medications to prevent nausea and vomiting and antihistamines Thiethylperazine in addition to Pantoprazole.

Material & Methods

Preliminary Studies and Spectral Studies of Pantoprazole and Thiethylperazine[12-13]

The FT-IR spectra for both the drugs were recorded by using FT–IR (Brukers Alpha) to Confirm the medication identity. The solubility of the two medications was assessed by the dissolution of the pharmaceuticals in different solvents that vary in polarity. UV drug spectra (10 µg/ml) have been acquired using the Shimadzu 2203 UV Visible spectrophotometer to measure the maximum absorbance (βmax). The wavelength for the current study was likewise captured in the overlay spectrum. Standard pharmaceuticals melting point was established by the open capillary method by means of a digital melting point instrument, the temperature of the heating bath was increased automatically at 100 ºC/min. The temperature at which the medicine began to dissolve was recorded. This has been done three times and the average value has been calculated.

Preparation of Mobile Phase and Diluent [17-19]

A buffer mixture (0.1% v/v OPA in water) with acetonitrile at a ratio of 65:35 (filtered and degassed). HPLC water grade: acetonitrile (65:35) has been manufactured and used for the whole investigation as a diluent.

Preparation of Standard Solutions [14]

When transferring 20 milligrammes of Pantoprazole and 20 milligrammes of Thiethylperazine, two volumetric flasks of 100 millilitres each were utilised. After adding 70 cc of the diluent, it was dissolved by sonicating the mixture. To facilitate the process of marking, the stock solution was diluted with ice before being brought to room temperature. The standard stock solutions of Pantoprazole and Thiethylperazine have been transferred into two bottles of 100 millilitres each, and the volume of each bottle has been indicated using diluents, as illustrated. In addition to that, the solution of using mixed standard stock has also been put into place.

Preparation of Sample Solution (Pantoprazole & Thiethylperazine 10 mg+30 mg)[15]

The materials were weighed and combined with 20 capsules (label claim 10 mg + 30 mg). An amount equal to 50 mg of Pantoprazole (150 mg Thiethylperazine) was dispensed from five capsules (3030.1 mg), to which 200 ml of diluit was added. The volumetric flask was then filled to the brim. An further 250 millilitres of diluent were added when the solution had cooled down and reached room temperature. This solution has been filtered with a syringe of 0,45µ Teflon filter and 3ml of that solution diluted and blended into 100 ml.

Optimization of Chromatographic Conditions and Method Development [19]

Several chromatographic cycles have been taken for individual medicines and their mix in various mobile phase combinations. Proper method selection depends on the type (ionic/ionizing/neutral, molecular and soluble) of the sample. Here, due to its simplicity, adaptability, robustness and its wider use, the reverse phase HPLC method was selected for first separation. Several mobile phases, including acetonitrile and water, acetonitrile and buffer (KH2PO4, OPA buffer), methanol buffers have been explored. Finally, the buffer (0.1 percent v/v OPA in water) and acetonitrile were selected as mobile for further chromatographic studies, with a ratio of 65:35.

Method Validation [20]

The validation study was designed to demonstrate that the approach is suitable for testing and stability studies of the capsule-dosage Pantoprazole Thiethylperazine. The technique validation was carried out in accordance with the ICH specificity, forced degradation, accuracy, linearity, precise analysis and stability standards (ICH 1996, Q2 (R1) ICH 2005)

System Suitability Study

20 µl of standard preparations in five duplicates have been injected (preparation of solutions. For Pantoprazole and Thiethylperazine, the chromatograms and the peak responses were measured. The method's system appropriateness was tested in terms of Rt, peak area, tail factor, resolution and theoretical plate.

i) Specificity

To be more specific, one needs to be able to analyse an analyte while also taking into account the existence of components that one would consider to be present under normal circumstances. It is probable that they will contain a wide variety of things, ranging from contaminants to products of degradation to matrix. Blank solutions, standard solutions, and a standard mixture consisting of Pantoprazole(6 µg/ml) and Thiethylperazine (18 µg/ml) were all injected into the HPLC system. The standard mixture was used to determine the concentration of the two individual components. By comparing the two sets of data about their peak purity, it was found that there should not be any interaction between Pantoprazoleand Thiethylperazine during primary peak retention.

ii) Assay of the Formulation

Sample solutions (20µl) in duplicates were injected and the peak responses were measured and % assay were calculated for Pantoprazole and Thiethylperazine.

% Assay = AT AS × Std wt (mg) 100 × 3 100 × 250 Wt of sample taken × 100 3 × % Potency of std drug 100 × Average weight Labeled Claim × 100

iii) Precision

a) System Precision

Injected into the HPLC system six mixed standard solution replicates of 6 µg/ml Pantoprazole and 18 µg/ml Thiethylperazine were added. Prepared solutions have been analysed in accordance with the approach given. The average, SD and RSD percent were determined.[19]

Method Precision Six samples containing the known amount of Pantoprazole and Thiethylperazine were examined by test method and the percentage test and percent RSD were computed for both medicines.

b) Intraday and Interday Precision

The intraday precision of the Pantoprazole and Thiethylperazine test method has been assessed at three concentrations created from the stock solution of the samples (Pantoprazole3, 6, 9 µg/ml & Thiethylperazine 9, 18, 27 µg/ml) during a two-hour analysis for 12 hours. The interday precision investigation was also conducted for three separate days, i.e. day 1, day 2, and day three, at three levels of intraday concentration.

iv) Accuracy (Recovery Study)

The five pre-analyzed capsules carefully weighed and transferred with a volumetric flask of 500 ml (3028,3 mg) equal to 50 mg Pantoprazoleand 150 mg Thiethylperazine. Added 50 mg of Pantoprazole and 150 mg of Thiethylperazine standard to dissolve the substance for 30 minutes. 3.0 ml was transferred from this solution into 100 ml volumetric flask and diluted with diluents to 100 ml. The total recovery percent is expected to range from 98 to 102% and the overall RSD percentage should not exceed 2.0.

% Recovery = A B + C × 100

Where,

A = Total drug estimated (mg)

B = Wt. (mg) of drug contributed by tablet powder

C = Amount of pure drug added (mg)

v. Linearity and Range

The linearity of Pantoprazole and Thiethylperazine was established by generating the standard solutions for Thiethylperazine from stock solutions at 5 concentration in six duplicate levels in the 3-9 µg/ml range for Pantoprazole 9-27 µg/ml range. The HPLC system was injected with 20 µl each solution, and the maximum chromatogram area obtained was reported. The mean area was determined with its standard deviation and relative percentage standard deviation of the peak areas. Mean AUC was displayed for the calibration curve against the concentration. Regression equations, correlation coefficients from calibration curves have been calculated.

vi) Stability in Analytical Solution

The analysis of the sample (6 µg/ml and 18 µg/ml for Pantoprazole and Thiethylperazine) in six duplicates before and after 24 hours was performed by refrigeration (8 °C) and storage under room temperature. The percentage test has been determined from the Pantoprazole and Thiethylperazine peak regions.

vii) Limit of Detection (LOD) and Limit of Quantitation (LOQ)

Pitch and standard deviation of Pantoprazole and Thiethylperazine responses were used to calculate LOD and LOQ. The LOD and LOQ were determined.

$LOD = 3.3 \times \sigma\sigma\ SS$

$LOQ = 10 \times \sigma\sigma$

Where; $\sigma\sigma$ = Standard deviation of response, S = Slope of calibration curve

viii) Robustness

Pre-analyzed sample solution comprising Pantoprazole combination of 18 µg/ml Thiethylperazine has been created and analysed by adjusting the flow rate to 1.2 ml/min and 0.8 ml/min according to the proposed method. In each

scenario, system appropriateness parameters and peak regions (or percentage test) were examined and the findings compared with the results of method accuracy.

Result & Discussion

Preliminary Studies and Spectral Studies of Pantoprazole and Thiethylperazine [12-13]

The preliminary identifying of the FTIR (fig. 1 & 2) spectra for Pantoprazole and Thiethylperazine was carried out. The group frequencies observed are shown in Table 1. In water, Pantoprazole was virtually insoluble, and Thiethylperazine was found to be sparingly soluble in water. Both medicines were discovered in solvents such as methanol and acetonitrile to be easily soluble. The wavelength for chromatographic technique development was selected for the overlay spectrum of Pantoprazole and Thiethylperazine 215 nm (fig 3). The melting point of Pantoprazole was found to be 93.1°C – 95.2°C, and of Thiethylperazine 241.3°C – 243.5°C, confirming the identity of the medicinal substances.

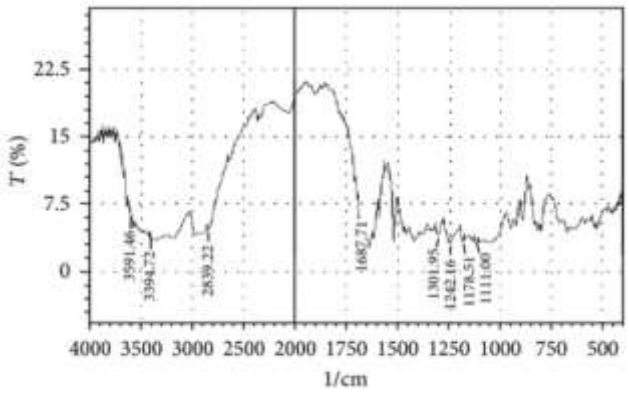


FIG 1: FTIR Spectrum Of Pantoprazole

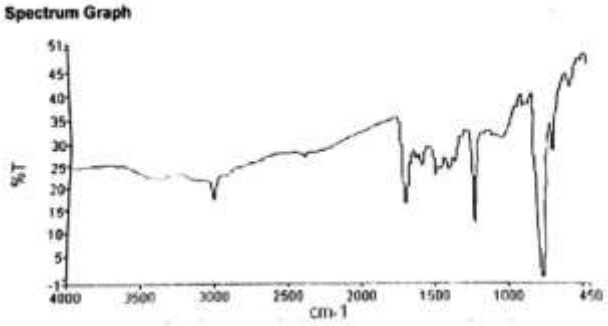


FIG 2: FTIR Spectrum Of Thiethylperazine

Table 1 FT-IR Frequencies Observed

Drug name	expected group	Frequency
Pantoprazole	N-h	3611 cm^{-1}
	C=o	1636 cm^{-1}
	S=o	1037 cm^{-1}
Thiethylperazine	N-h	3735 cm^{-1}
	C=o	1685 cm^{-1}

	C-h aromatic	1486 cm^{-1}
	c-o	1048 cm^{-1}

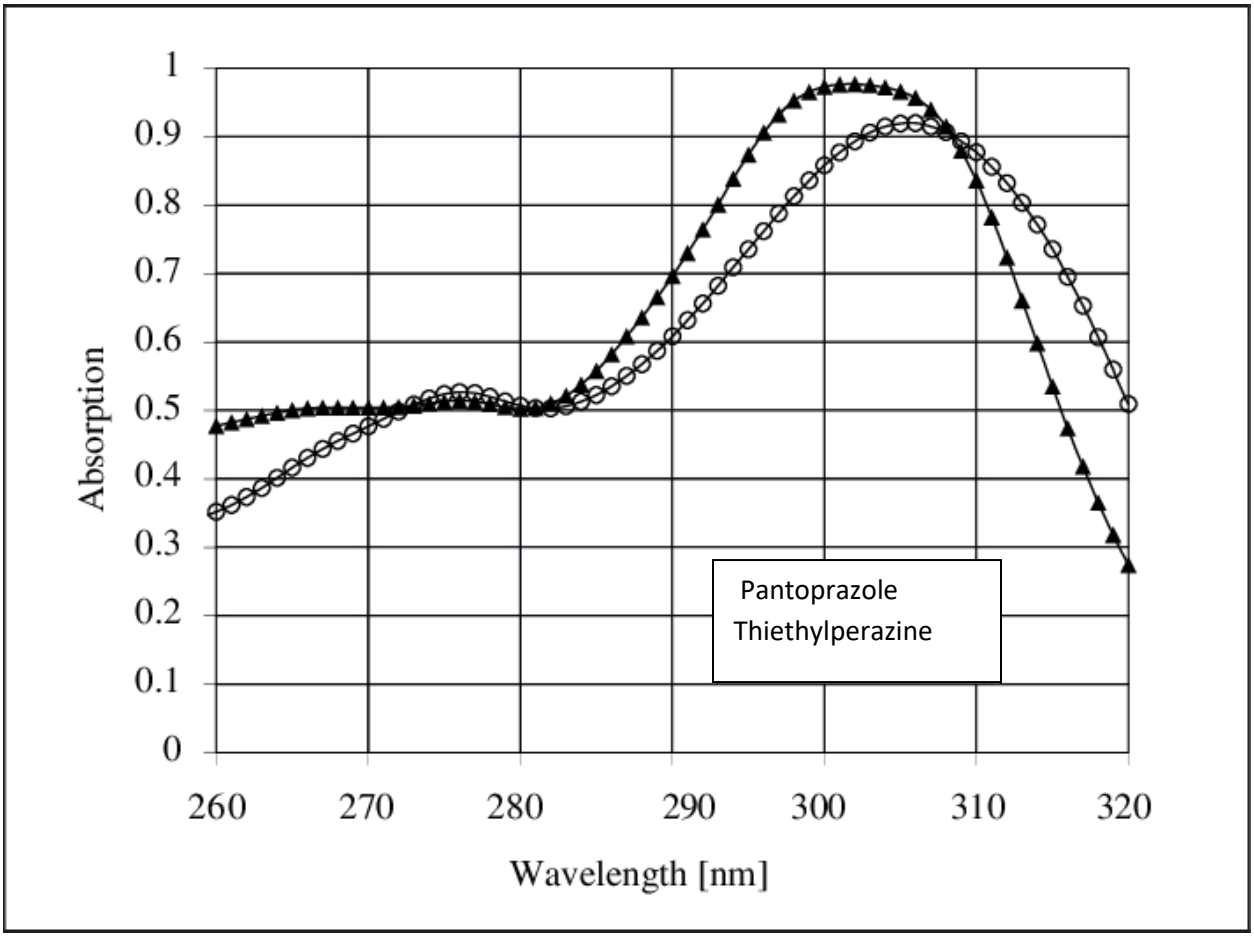


Fig 3 UV Spectrum Of Pantoprazole And Thiethylperazine

Optimization of Chromatographic Conditions and Method Development [14]

A single or two parameters have been adjusted for each test in order to produce optimal chromatographic conditions for separation and quantification of Pantoprazole and Thiethylperazine and chromatograms have been recorded under all specified chromatographic settings. The optimum chromatographic conditions were finalised in Fig 4. Few are referred to in Table 2. Low resolution, poor peak shapes, baseline disruptions were the few reasons why the experiments were rejected.

Table 2: Optimization Of Chromatographic Condition

Trial no.	Hplc system	Chromatographic condition	Observation	Remarks
1	Hplc (water 2996 with pda detector)	mobile phase- water stationary phase- zodiac c_{18} flow rate-1ml/min injection: 10 µl Run time-20min	Peak not clearly separated. Base line is not clear.	Rejected

		Wavelength- 215nm		
2	Hplc (water 2996 with pda detector)	Mobile phase: buffer stationary phase- zodaic c_{18} flow rate-1ml/min injection: 10 µl run time-20min wavelength- 215nm	Peak shape were good, with good resolution and intensity.	Accepted

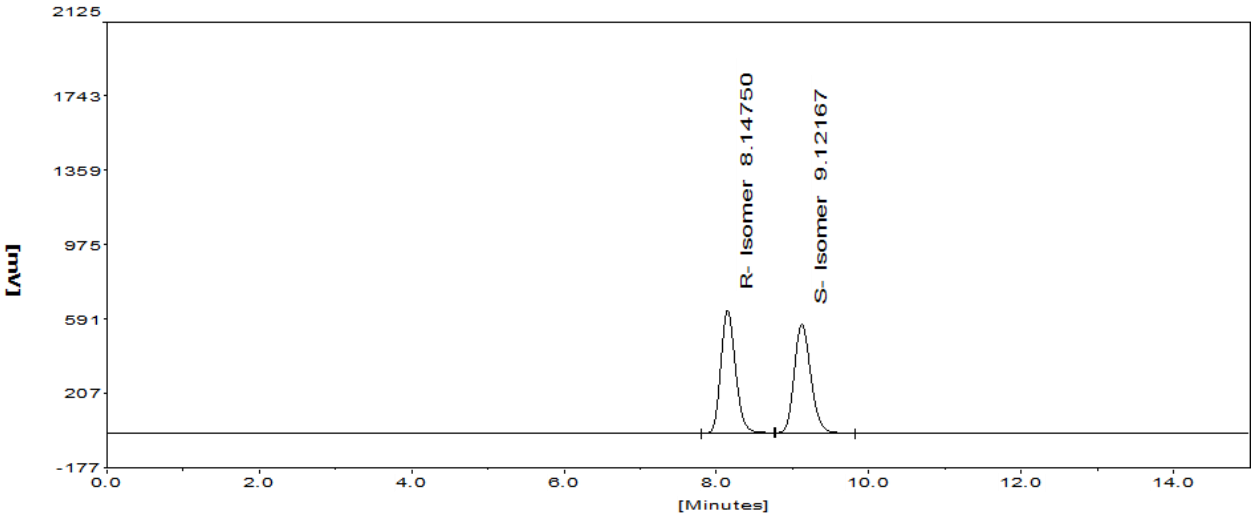


Fig 4: Trial of Chromatogram Development

Finalized Chromatographic Conditions

Based upon system suitability parameters the finalized chromatographic conditions was as follows: Column : ZODIAC C18 250 x 4.6 mm, 5µm
Wave length : 215 nm
Column Temp : Amibent
Injection Volume : 20 µl
Run Time : 10 min
Flow Rate : 1.0 ml / min
Pump Mode : Isocratic
Retention time : About 4.0 to 6.0 minutes (For Pantoprazole) About 8.0.to 10.0 minutes (For Thiethylperazine)

Method Validation [15]

i) System Suitability Study

The HPLC method was devised to determine the Pantoprazole and Thiethylperazine percentage test in their capsule forms. All conventional drug chromatograms and their mixing are illustrated in figures 5. The retention time was determined to be 4.9 and 8.3 min for Pantoprazole and Thiethylperazine and other parameters, such as resolution, tailoring factor and theory plates, within acceptable limits (table 3).

Table 3: Parameters Of System Suitability

S.No.	Drug	Retention Time	Area Cover	USP Resolution	USP Tailing	USP Plate Count
1	Pantoprazole	4.920505	312362.4		1.368	11602.34
2	Thiethylperazine	8.320712	2395881	14.53827	1.4277215	15283.45

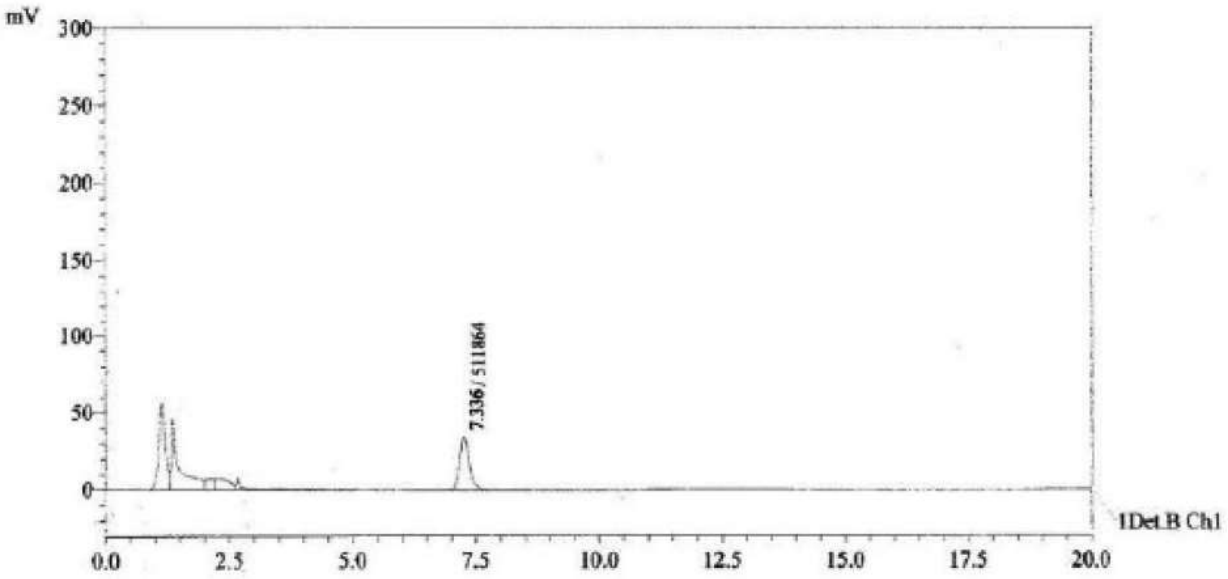
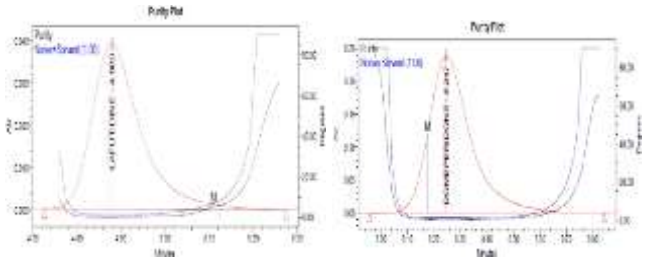


Fig 5: Standard Mixture Of Chromatogram Of Pantoprazole And Thiethylperazine

ii) Specificity

The lack of extra peaks in the chromatogram suggests that excipients are not interfering. At retention time of analyte peaks, there was no interference from the blank. The highest sample solution purety values were compared with the standard solution. The picture is displayed in fig6 (A-D), revealing the homogeneous peaks.



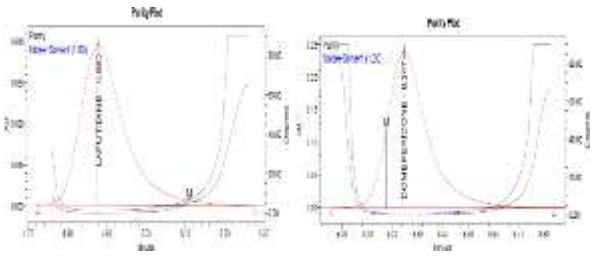


Fig 6: (A-D) Peak Purity Of Standard Sample

Table: 4 Assay Of Marketed Formulation

Marketed Formulation	Retention Time For Pantoprazole	Area	% Assay Pantoprazole	Retention Time For Thiethylperazine	Area	% Assay Thiethylperazine
Pantoprazole 10mg + Thiethylperazine 30mg	4.883 min	348545	100.6%	8.242 min	2565024	102.1%
		356092			2571951	
		352325				
Mean					2570003	
Pantoprazole 10mg + Thiethylperazine 30mg	4.902 min	344332	99.2%	8.272 min	2596697	101%
		3343381			2625678	
		339356.5			3611256	
Mean						

iii) Precision

a) System Precision

System precision was achieved by measuring the peak response in six replicates for standard medication solutions. For Pantoprazole & Thiethylperazine, peak response, mean, standard deviation and relative percent standard deviation was 1.75 and 0.228 percent. Table 5 shows the results and they were found according to the accepted criteria.

Table 5 Precision Data System

Sr.No.	Peak Area Of Pantoprazole	Peak Area Of Thiethylperazine
1.	358990	2659578
2.	344512	2665691
3.	343578	2440345
4.	344417	2670612
5.	343412	2670451
6.	347837	2667905
Mean	346663	2664215
SD	6158.37	6047.5
RSD%	1.756	0.228

b) Method Precision

The procedure accuracy was carried out in six replicates by measuring the peak response for sample solutions. The percentage test for Pantoprazole & Thiethylperazine was calculated in six samples. Table 6 shows the results of percent test and percent RSD.

Table 6 Method For Precision Data

S. No	% Assay Of Pantoprazole	% Assay Of Thiethylperazine
1.	99.1	100.2
2.	98.6	100.4
3.	99	99.2
4.	98	98.5
5.	100	99.6
6.	99.5	100.1
Mean	99.5	99.6
SD	0.452	0.456
RSD%	0.49	0.49

c) Intraday and Interday Precision

The percentage of RSD intraday accuracy for Pantoprazole (3, 6, 9 mg/ml) was determined to be 0.412, 1.38, 1.36 per cent and 0.645, 1.56, and 0.204 per cent for Thiethylperazine (9, 18, 27 µg/ml), respectively. In inter-day precision the percent RSDs were determined to be 0412, 1.38, 1.36% for Pantoprazole (3, 6, 9 µg/ml) and 0.68, 1,58, and 0.18% for Thiethylperazine (9, 18, 27 µg/ml). Percent RSD was well found within acceptable ranges in intraday and interday trials. The results are shown in Tables 7 & 8.

Table 7 Precision Intraday

	Pantoprazole						Thiethylperazine			
Sr.No	Conc (µg/ml)	Area	Mean	SDA	% RSD	Conc (µg/ml)	Area	Mean	SDA	% RSD
1	3	166879 166136 167539	166835	698.50	0.412	9	133275 1321259 1324545	1327752	8571.5	0.68
2	6	335960 326724 331258	331312	4613.5	1.38	18	2677369 2698789 2698768	2664792	41708.8	1.58
3	9	504209 495828 509358	503162	6770.4	1.36	27	3995893 3998345 3998814	3992718	8159.0	0.18

IV) Accuracy (Recovery Study)

The accuracy of the test method has been assessed triplicately using the standard addition procedure at the level of 100% of the labelled claim and the percentage recovery calculated. The average recovery percentage for Pantoprazole and Thiethylperazine was 99.47 and 99.71 percent respectively. Table 9 shows the outcomes of the recovery trial.

Table 8 Interday Precision

		Pantoprazole						Thiethylperazine			
Sr.No	Day	Conc (µg/m)	Area	Mean	SDA	% RSD	Conc (µg/ml)	Area	Mean	SDA	% RSD
1	Day 1	3	166879	166835	698.50	0.412	9	133275	1327752	8571.5	0.68
	Day 2		166136					1321259			
	Day 3		167539					1324545			
2	Day 1	6	335960	331312	4613.5	1.38	18	2677369	2664792	41708.8	1.58
	Day 2		326724					2698789			
	Day 3		331258					2698768			
3	Day1	9	504209	503162	6770.4	1.36	27	3995893	3992718	8159.0	0.18
	Day2		495828					3998345			
	Day3		509358					3998814			

Table 9 Recovery Study For Pantoprazole And Thiethylperazine

Weight Of Capsule (Mg)	Amount Of Pantoprazole (Mg)	Peak Of Area Sample Pantoprazole	Peak Area Of Standard Pantoprazole	Peak Area Of Sample + Standard	% Recovery
3025.3	45.1	157836	150235	312075	101.2987
3028.4	50.3	158078	151348	304258	98.31687
3072.5	50.3	156473	153658	306845	98.75687
SD (±)					1.602778
% RSD					1.611687

Weight Of Capsule (Mg)	Amount Of Thiethylperazine (Mg)	Peak Of Area Sample Thiethylperazine	Peak Area Of Standard Thiethylperazine	Peak Area Of Sample + Standard	% Recovery
3025.3	150.3	1332313	1322567	2668924	100.54
3028.4	151.6	1342378	1334531	2670417	99.47
3072.5	150.2	1329247	1319347	2640935	99.71
SD (±)					0.459178
% RSD					0.4597

vi) Linearity and Range

Linearity of Pantoprazole and Thiethylperazine in the range of between 3-9µg/ml and 9-27µg/ml with a correlation coefficient (r2) of 0.999 corresponding ly for both medications has been established.

Table 10 Linearity And Range

CON^C µg/ml Pantoprazole	Average Peak Area	CON^C µg/ml Thiethylperazine	Average Peak Area
3.00	166835	9.00	1337465
3.60	211000	10.70	1602447
4.80	261638	14.35	2082834
6.00	335945	18.00	2677372
7.20	404362	21.50	3208864
9.00	504211	27.00	3995898
SLOPE	56754	SLOPE	14853
CC	0.999	CC	0.999

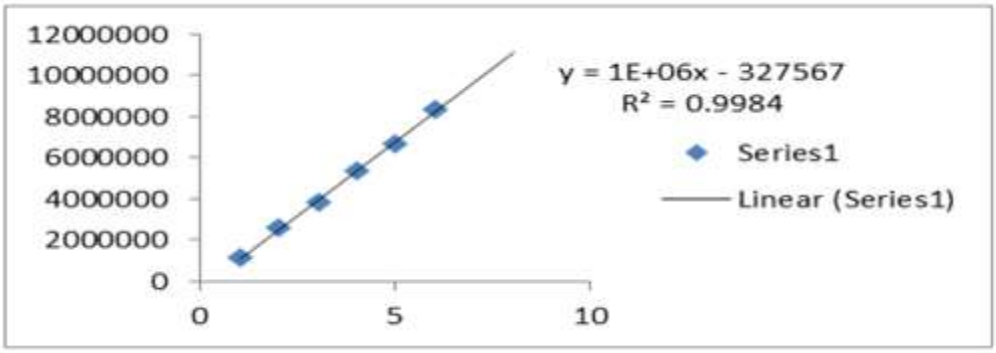


Fig 7 Linearity Plot For Pantoprazole

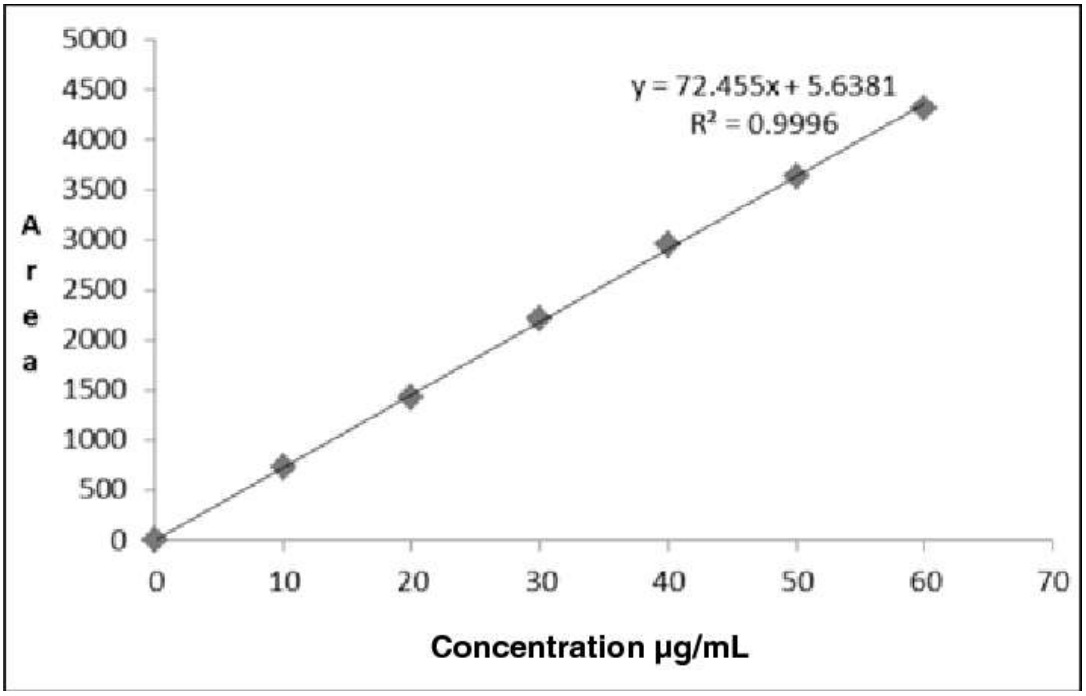


Fig 8 Linearity Plot For Thiethylperazine

i) Limit of Detection (LOD) and Limit of Quantitation (LOQ)

The LOD and LOQ were reported for Pantoprazole to be 0.151 µg/ml and 0.458 µg/ml respectively. The LOD and LOQ for Thiethylperazine were 0.661 µg/ml and 2.01 µg/ml. These figures show that the procedure is appropriate to determine the lower concentration and confirm that the method proposed is sensitive to determination.

ii) Robustness [16]

In each scenario the system suitability parameters and peak zones were examined and the findings were compared to the results of the technique precision. Less than 2 were found in percent RSD in each condition. This shows the method's robustness. Table 7.12 shows the results.

Table 11: Flow Rate Of Robustness Effect

Flow Rate	Pantoprazole				Thiethylperazine			
0.8 ml / min	R1	Area	Theoretical plates	Tailing factor	R1	Area	Theoretical plates	Tailing factor
Average	4.89	308545	10076.98	1.494	8.22	247879	14335.78	1.478
S.D	0.11	1659.04	67.066	0.0074	0.025	10429.4	133.7	0.00147
% RSD	0.240	0.542	0.6654	0.5147	0.317	0.405	0.9789	0.3124
1.2 ml/min	R2				R2			

Average	4.74	308789	160.93	0.0087	8.147	2540978	1424.49	1.347
S.D	0.035	17721	1.601	0.7894	0.045	1345789	72.48	0.00103
% RSD	0.841	0.558	1.601	0.614	0.457	0.254	0.5087	0.789

Conclusion

The easy, precise and resilient stability indicating test techniques were designed to estimate all the combinations specified in their formulations. All these newly established stability methods that indicate combinations of multiple medicines can be employed in research institutions, small industry quality control laboratories, industry quality control departments, raw materials analyses, intermediate and completed product products. The same technology can be used to extend the analyses of medicines and their biological fluid metabolites. In future it will give us an insight into the process of metabolism and degradation if products of degradation are isolated and their structure eluciated by advance techniques

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