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STABILITY INDICATING RP-HPLC METHOD FOR THE SIMULTANEOUS ESTIMATION OF PANTOPRAZOLE AND LEVOSULPIRIDE IN PHARMACEUTICAL DOSAGE FORM

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Keywords:

Stability indicating RP HPLC, Stress degradation, Levosulpiride, Pantoprazole

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ABSTRACT: Simple, sensitive, and rapid stability indicating RP-HPLC method for simultaneous estimation of Pantoprazole and Levosulpiride in pharmaceutical dosage form was developed and validated. The analysis was carried out on Hibar C_{18} column (250 × 4.6 mm, id, 5µ) and the mobile phase composition was 10 mM ammonium acetate (pH 4.0 adjusted using acetic acid): Acetonitrile in the ratio of 20:80% v/v with a flow rate of 1.0 mL/min at room temperature. The sample injection volume was 20 µL, and eluents of the isocratic elution mode were monitored at 241 nm. The retention time was 3.1 min and 5.2 min for Pantoprazole and Levosulpiride, respectively. The method was linear in the concentration range of 1-7 µg/ml for Pantoprazole sodium with an r^2 of 0.9973 and 4-10 µg/ml of Levosulpiride with an r^2 of 0. 9961. The LOD and LOQ were found to be 0.05 and 1.5 µg/ml for Pantoprazole and Levosulpiride. The drug stability was assessed under various stress degradation conditions at room temperature for 24 h. In photodegradation, the percentage of degradation of Levosulpiride and Pantoprazole when exposed to sunlight for 8 h was found to be 42.7% and 2.75%, respectively. Whereas under other stress conditions *viz* acidic, basic, and oxidative degradation studies carried out for 24 h, the % degradation of the active constituent was found to be 23.21%, 21.98%, and 22.98% for Levosulpiride & 100%, 100% and 66.78% for Pantoprazole respectively. The proposed method was validated as per ICH guidelines Q2B.

INTRODUCTION: Pantoprazole (PT), a derivative of substituted benzimidazole is a proton pump inhibitor and used in the short-term treatment of Gastroesophageal reflux disease (GERD). It suppresses the final step involved in gastric acid production by covalently binding to the (H^+, K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell.

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This effect leads to the inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus. The binding to the (H^+, K^+)-ATPase results in the anti-secretory effect that persists longer than 24 h for all the doses tested [1, 2]. Levosulpiride (LS) is the levorotatory enantiomer of the Sulpiride, a substantial benzamide derivative. It is a typical antipsychotic agent used in the treatment of anxiety disorders, depression, schizophrenia and peptic ulcers [3, 4]. Levosulpiride selectively blocks Dopaminergic D_2 receptors at the central level and at the submucosal and myenteric plexus peripheral level, which interact with the cholinergic, adrenergic, and peptidergic fibers to regulate the motility of the gastrointestinal tract (GIT) [5].

Combined administration of both the drugs had shown proven activity against Gastro-Esophageal Reflux Disease (GERD). GERD results in regurgitation of the gastric contents into the lower esophagus with following symptoms like heartburn, retrosternal pain, dysphagia, and belching [6].

A thorough review of the literature revealed a Spectrophotometric method for the quantification of Levosulpiride in bulk drug and formulation [7]. A UV method [8] for quantification in dissolution samples, HPTLC, and validated HPLC methods were reported for the simultaneous quantification of Levosulpiride with rabeprazole sodium [9-13]. Validated HPTLC methods were reported for the simultaneous quantification of Levosulpiride and esomeprazole in capsule dosage forms [14, 15]. A UPLC method with QbD approach for the simultaneous quantification of Levosulpiride and rabeprazole was also reported [16].

Patel and coworkers reported a validated RP-HPLC method for the analysis of levosulpiride and pantoprazole sodium. The separation was carried out in an isocratic mode using a C_{18} column with water: Acetonitrile: trimethylamine (60:40:0.25 v/v/v) as the mobile phase [17]. Kothapalli and coworkers reported stability indicating RP-HPLC method for the simultaneous quantification of pantoprazole and levosulpiride in combined dosage forms. The separation was carried out on a thermos BDS C_{18} column utilizing 0.02M potassium dihydrogen orthophosphate solution (pH 4): Acetonitrile (60: 40 v/v) at a flow rate of 1.0 ml/min. Forced degradation studies under various stress conditions were also carried out and reported [18].

SG Khanage and coworkers had reported an RP HPLC method for the simultaneous estimation of levosulpiride and pantoprazole sodium in a capsule dosage form. The quantification was carried out on a C_{18} column with methanol: 5mM ammonium acetate buffer (pH 4) at the ratio of 70:30 v/v [19]. Kaliselvi and coworkers reported an RP HPLC method for the simultaneous quantification of levosulpiride and pantoprazole in tablets [20].

From the literature survey it was evident that the methods reported for the simultaneous quantification of pantoprazole sodium and levosulpiride suffer from LC-MS incompatibility and longer retention times. Also, the analytical stability methods reported utilize phosphate buffers which are not LC-MS compatible and thus may not support method transfer during the characterization of the degradation products. Therefore, the objective of the present work is to develop and validate a stability-indicating RP HPLC method, which will be compatible with high-end analytical instruments for the simultaneous quantification of pantoprazole and levosulpiride. Stress degradation studies will also be carried out as per standard ICH guidelines [21, 22].

MATERIALS AND METHODS:

Chemicals, Reagents, and Solutions: HPLC grade Methanol and Acetonitrile, AR grade Hydrochloric Acid, Sodium Hydroxide, and Hydrogen Peroxide were procured from SD Fine Chem. Ltd., (Mumbai, India). Ammonium acetate AR Grade was procured from Rankem Laboratories (India). Millipore water from milli-Q RO system was used. Borosilicate glassware (Class A) was used for the preparation of solutions. Working standards of pantoprazole sodium were procured from Ranbaxy Laboratories, New Delhi, and levosulpiride from INC Chem Laboratories, Hyderabad. Pantocid-L capsule formulation marketed by Sun pharma was procured from the local pharmacy, The Nilgiris, Tamil Nadu.

Chromatographic Conditions: Chromatographic separations were performed on a Shimadzu gradient HPLC system equipped with LC-10 AT-VP solvent delivery system (pump), an Auto-sampling injector with 20 µl loop volume and SPD M-10A VP UV detector. CLASS VP software was used for data acquisition and handling. The analysis was carried out on a Hibar C_{18} column (250 × 4.6 mm, id, 5µm) in isocratic elution mode with the mobile phase composition of 10 mM ammonium acetate (pH 4.0 adjusted using acetic acid) and acetonitrile (20:80% v/v) at a flow rate of 1.0 ml/min at room temperature. The eluents were monitored at 241 nm. The pH measurements were carried out using a precalibrated Systronics pH meter 335 equipped with a glass electrode.

Assay of Marketed Formulation: About 10 capsules of the marketed formulation Pantocid were taken and weighed. A quantity of powder equivalent to label claim of pantoprazole and levosulpiride (40 mg pantoprazole and 70 mg

levosulpiride) was accurately weighed and transferred into a 50 ml volumetric flask, acetonitrile was added and sonicated for 15 min at room temperature, filtered and made up to the mark with acetonitrile. About 0.1 ml of the above solution was pipetted out into a 10 ml volumetric flask, diluted with mobile phase and was injected under the optimized chromatographic condition and the chromatogram was recorded. The percentage of purity was calculated based on the peak area and reported.

Stress Degradation Studies: The stress degradation studies were performed under different stress conditions specified as per ICH Q1 guidelines. The mixture of drug solutions was prepared at 1 mg/ml for all the stress studies. After the studies, the aliquots of the samples were neutralized and suitably diluted with mobile phase to obtain 10 µg/ml, and the samples were stored at -8°C until further analysis by the optimized chromatographic conditions. Blank solutions were also prepared at the same time as that of the stock solutions.

Preparation of Standard Stock Solutions: About 10 mg of working standards PT and LS were accurately weighed and transferred into a 10 ml volumetric flask and dissolved in HPLC grade Acetonitrile to obtain 1 mg/ml solution. The above stock solution was further diluted 10 times with HCl (0.1M), NaOH (0.1M), and Hydrogen Peroxide (6%) for acid hydrolysis, base hydrolysis, and oxidative degradation studies. For photolytic degradation studies, the solid drug sample was taken in a petri dish and exposed to sunlight for 3 days.

Acid Degradation:
Degradation Medium:
Hydrochloric Acid (0.1 M): 1ml of the stock solutions (Pantoprazole sodium & Levosulpiride) was taken in a 10 ml volumetric flask, and the solution was made up to the mark with 0.1M Hydrochloric acid. The solution was kept at room temperature for 24 h. The samples were withdrawn at 0, 2, 4, 6, 8, 12, and 24 h and stored in a refrigerator. 1.0 ml of the solutions withdrawn was further neutralized with 1ml of 0.1M Sodium hydroxide and made up to the mark with diluent (80:20 acetonitrile: 10mM ammonium acetate pH-4.0) in a 10 ml volumetric flask. They were analyzed under optimized chromatographic conditions, and the chromatograms were recorded.

Base Degradation:
Degradation Medium:
Sodium Hydroxide (0.1 M): 1 ml of the stock solutions (Pantoprazole sodium & Levosulpiride) was taken in a 10 ml volumetric flask, and the solution was made up to the mark with 0.1M sodium hydroxide. The solution was kept at room temperature for 24 h. The samples were withdrawn at 0, 2, 4, 6, 8, 12, and 24 h and stored in a refrigerator.

1.0 ml of the solutions withdrawn was further neutralized with 1ml of 0.1M Hydrochloric acid and made up to the mark with diluents (80:20 acetonitrile: 10mM ammonium acetate pH-4.0) in a 10 ml volumetric flask. They were analyzed under optimized chromatographic conditions, and the chromatograms were recorded.

Oxidative Degradation:
Degradation Medium:
Hydrogen Peroxide (6%): 1.0 ml of the stock solutions (Pantoprazole sodium & Levosulpiride) was taken in a 10ml volumetric flask and the solution was made up to the mark with 6% Hydrogen Peroxide. The solution was kept at room temperature for 24 h. The samples were withdrawn at 0, 2, 4, 6, 8, 12, and 24 h. 1.0ml of the solution withdrawn was further diluted with diluents (80:20, acetonitrile: 10mM ammonium acetate pH-4.0) in a 10 ml volumetric flask. They were analyzed under optimized chromatographic conditions, and the chromatograms were recorded.

Photolytic Degradation:
Degradation Medium:
Sunlight: 25 mg of pantoprazole sodium & levosulpiride were taken individually on a watch glass and exposed to sunlight for 8 h/day for 3 days. 1 mg/ml solutions were prepared from the above-exposed samples. The solutions were further diluted to obtain a final concentration of 10 µg/ml with diluent (80:20% v/v acetonitrile: 10mM ammonium acetate pH-4.0). The samples of photolytic degradation were analyzed under optimized chromatographic conditions, and the chromatograms were recorded.

Thermal Degradation:

Degradation Medium:

Temperature 80 ºC: 25mg of pantoprazole sodium & levosulpiride were taken individually on a watch glass and kept in an oven at 80 ºC for 8 h. 1mg/ml solutions were prepared from the above solution with the diluent. The solutions were further diluted to obtain a final concentration of 10µg/ml with diluent (80:20 acetonitrile: 10mM ammonium acetate pH-4.0). The samples of thermal degradation were analyzed under optimized chromatographic conditions, and the chromatograms were recorded.

RESULTS AND DISCUSSION:

Optimization of Chromatographic Conditions: Optimization of the chromatographic conditions is intended to reach out various goals of the method development to weigh each goal (resolution, runtime, sensitivity, peak symmetry, *etc*.,) accurately according to the requirements of HPLC that can be used for the estimation of pantoprazole and levosulpiride in their degradation samples. A mobile phase composition of acetonitrile: 10mM ammonium acetate (pH 4.0 adjusted using acetic acid) as mobile phase in the ratio of 80:20% v/v at a flow rate of 1.0 ml/min was used for optimized separation of pantoprazole and levosulpiride on a C_{18} column (250 × 4.6mm. id, 5µm) as stationary phase. The separation was carried out at room temperature, and the eluents were monitored using a UV detector at 241 nm. The contents of the mobile phase and all the samples were filtered through a 0.45µ membrane filter and degassed before analysis. The chromatographic separation was carried out on a Shimadzu gradient HPLC system. The typical retention times of pantoprazole and levosulpiride were about 3.1 ± 0.2 min and 5.2 ± 0.2 min, respectively.

Validation of the Stability Indicating Analytical Method: The developed RP-HPLC method was validated according to ICH Q2 R1 guidelines concerning linearity, accuracy, precision, specificity, selectivity, the limit of quantification and limit of detection.

Accuracy: The accuracy of the method was demonstrated by performing recovery studies at 3 levels. The results in **Table 1** were found to be significant within the specification limits for pantoprazole and levosulpiride with percentage recovery of 98.38-99.7% and 98.7-100.16%, respectively (within the limits of 98-102%)**.**

TABLE 1: EVALUATION OF THE ACCURACY OF PANTOPRAZOLE AND LEVOSULPIRIDE

	Pantoprazole			Levosulpiride		
Amount spiked (µg/ml)	**2**	**4**	**6**	**5**	**7**	**9**
% Recovery ± % RSD	98.5 ± 0.02	98.38 ± 0.04	99.07 ± 0.02	98.7 ± 0.03	100.16 ± 0.02	98.87 ± 0.02

Precision: The precision studies were carried out at 3 different concentration level for pantoprazole (2, 4 & 6 µg/ml) and levosulpiride (5, 7 & 9 µg/ml). The % RSD values for inter-day and intra-day precision studies were less than 2% indicating that the method developed was highly precise. The intraday and inter-day precision were evaluated and reported in **Table 2**.

TABLE 2: PRECISION STUDIES OF PANTOPRAZOLE AND LEVOSULPIRIDE

Intraday precision studies						
Peak area	82309	149943	210933	262724	363979	472376
	83047	150126	221983	260695	366177	466177
	82890	149949	219567	262162	365481	467291
Mean	82749±388.77	150006±382.35	217494±5810.87	262162±1281.98	365212±1123.36	468615±388.77
%RSD	0.46	0.06	2.67	0.49	0.30	0.705
Inter-day precision studies						
Inter-day precision studies Day 1						
Peak area	78652	155471	216674	264824	378176	445392
	77638	157856	218975	259095	364632	456095
	78890	156789	220352	264767	369975	453897
Mean	78393±664.87	156705±1194.69	218667±1858.24	262895±3291.31	370928±6822.07	451795±5656.73
%RSD	0.848	0.762	0.849	1.252	1.839	1.25
Inter-day precision studies Day 2						
Peak area	82309	149942	210933	262724	363979	472376
	83047	150126	219567	262162	365481	467291

	82890	149949	219567	262162	365481	467291
Mean	82749±388.77	150006±382.35	217494±5810.87	262162±1281.98	365212±1123.36	468615±388.77
% RSD	0.46	0.06	2.67	0.49	0.30	0.705
Inter-day precision studies Day 3						
Peak area	79568	165471	227864	263884	387176	446438
	78638	165856	228753	262118	384632	454795
	79880	169877	225352	264787	380975	452869
Mean	79362±646.11	167068±2440.27	227323±1763.86	263597±1357.55	384261±3117.10	451367±4376.19
% RSD	0.814	1.406	0.776	0.515	0.811	0.969

Linearity: The linearity range for pantoprazole and levosulpiride was established from 1-7 µg/ml and 4-10µg/ml respectively **Table 3**. The correlation coefficient (r^2) was found to be 0.9973 and 0.9961 for pantoprazole and levosulpiride, indicating that the method was linear. The linearity plot of pantoprazole and levosulpiride are given in **Fig. 1** and **2**.

TABLE 3: LINEARITY STUDIES

Pantoprazole		Levosulpiride	
Concentration (µg/ml)	**Peak area* (*n = 3)**	**Concentration (µg/ml)**	**Peak area* (*n = 3)**
1	46729	4	207102
2	78652	5	264811
3	118214	6	305908
4	155471	7	378176
5	185902	8	409925
6	216674	9	445392
7	253748	10	520217

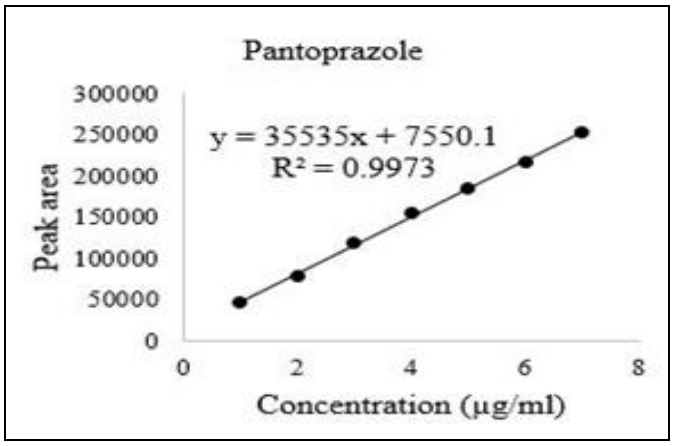

FIG. 1: LINEARITY OF PANTOPRAZOLE

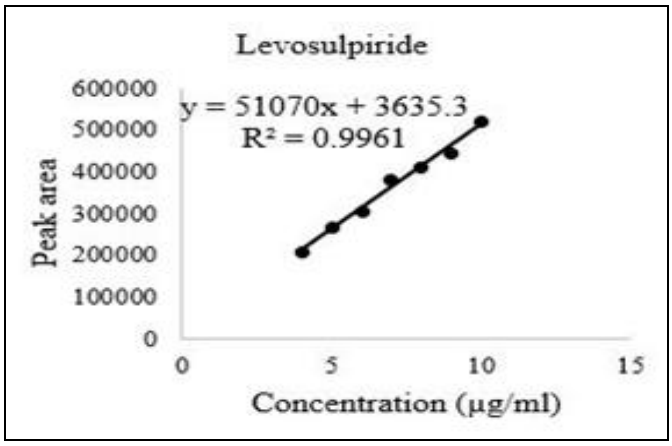

FIG. 2: LINEARITY OF LEVOSULPIRIDE

Limit of Detection & Limit of Quantification: The limit of detection (LOD) and limit of quantification (LOQ) for pantoprazole and levo-sulpiride was 0.05 µg/ml and 1.5 µg/ml **Table 4**.

TABLE 4: SYSTEM SUITABILITY

Parameters	Pantoprazole	Levosulpiride
Linearity and Range	1-7 µg/ml	4-10 µg/ml
Regression equation	y=35535x+7550.1	y=51070x+3635.3
Correlation coefficient (r^2)	0.9973	0.9961
Theoretical plates	42711	24144
Asymmetric factor	1.0	1.0
Tailing factor	1.16	1.0
Limit of Detection (LOD)	0.05 µg/ml	0.05 µg/ml
Limit of Quantification (LOQ)	0.15 µg/ml	0.15 µg/ml

Robustness: The robustness of the method was determined by analyzing the samples under a variety of conditions with slight changes in flow rate (± 0.1 ml/min), pH (± 0.2 units), mobile phase ratio (± 2%) and wavelength (±2nm). The % RSD for the robustness studies was less than 2% indicating that the method is robust.

Specificity: The specificity of the method was reasonable, and it was proven by analyzing the degraded samples. The resolution between the pantoprazole and levosulpiride and their degradation products were more than two indicating the specificity of the methods.

DISCUSSION: In the preliminary expected run for the separation of pantoprazole and levosulpiride, a C_{18} column was used, and the trials were carried out using a mobile phase consisting of water and methanol at different ratios. Pantoprazole was not retained. Methanol was replaced by acetonitrile to modify the peak shape, but there was no improvement in the retention time of pantoprazole.

Thus, the aqueous phase was replaced with a buffer solution. The optimized conditions used for the estimation provided a distinct separation between degradation products produced during stress degradation studies. Validation for the method has been performed as per ICH guidelines, and results were documented.

Acidic Degradation: In acidic degradation studies, it was observed that the percentage degradation of pantoprazole sodium and levosulpiride at the end of 24 h at room temperature with 0.1 M Hydrochloric acid was found to be 100 and 23.21% respectively. The percentage of degradation of drugs at various time intervals was recorded and represented in **Table 5**. The degradation products were observed in the following retention time 1.3, 2.60, 2.90, 3.73 and 4.38 min, respectively and are depicted in **Fig. 3** and **4.**

TABLE 5: DEGRADATION STUDIES

Degradation medium	Sample withdrawal interval (hour)	Conc. of drugs taken (µg/ml)	Degradants		% of degradation	
			No. of degradants	Rt of degradants (min)	Pantoprazole	Levosulpiride
0.1M Hydrochloric Acid (Room temperature)	24	10	5	1.3, 2.60, 2.90, 3.73, 4.38	100	23.21
0.1M Sodium hydroxide (Room temperature)	24	10	5	2.49, 2.77, 3.62, 4.05, 18.19	100	21.975
30% Hydrogen peroxide (Room temperature)	24	10	3.322	7.702	66.78	22.98
Sunlight	8	10	2	1.82, 2.45	2.756	42.7
Heat 80° C	8	10	1	8.52	8.52	0

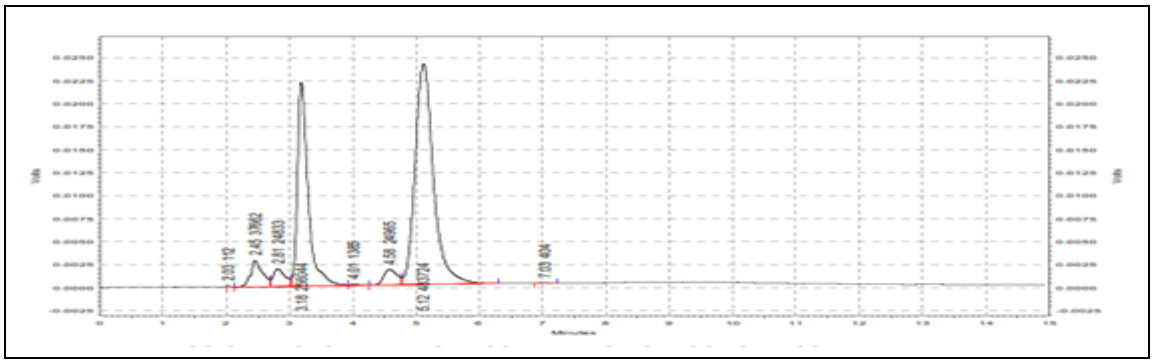

FIG. 3: ACID DEGRADATION SAMPLE WITH 0.1M HYDROCHLORIC ACID AT ROOM TEMPERATURE WITHDRAWN AT 0 h

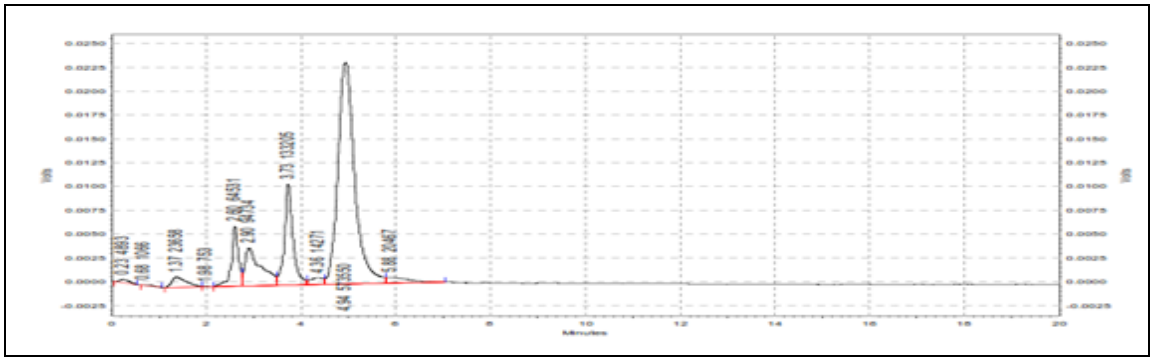

FIG. 4: ACID DEGRADATION SAMPLE WITH 0.1M HYDROCHLORIC ACID AT ROOM TEMPERATURE WITHDRAWN AT 24 h

Basic Degradation: In basic degradation studies, it was observed that the percentage degradation of pantoprazole sodium and levosulpiride at the end of 24 h at room temperature with 0.1 M sodium hydroxide was found to be 100 and 21.975% respectively. The percentage of degradation of drugs at various time intervals was recorded and represented in **Table 5**. The degradation products were observed in the following retention time 2.49, 2.77, 3.62, 4.05 and 18.19 min. respectively and depicted in **Fig. 5** and **6**.

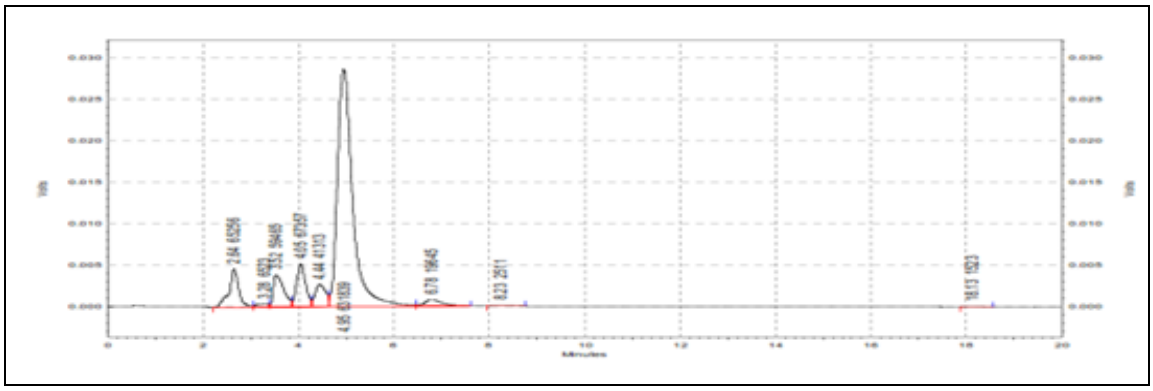

FIG. 5: BASE DEGRADATION SAMPLE WITH 0.1 M SODIUM HYDROXIDE AT ROOM TEMPERATURE WITHDRAWN AT 0 h

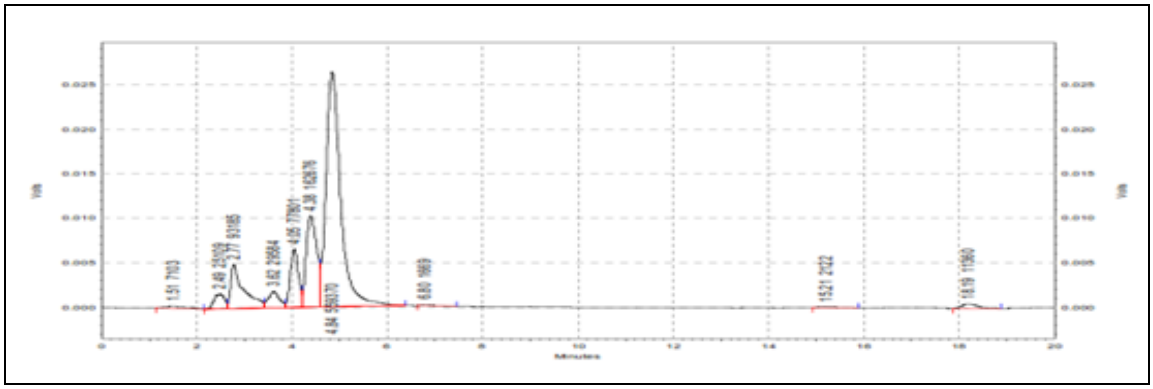

FIG. 6: BASE DEGRADATION SAMPLE WITH 0.1 M SODIUM HYDROXIDE AT ROOM TEMPERATURE WITHDRAWN AT 24 h

Oxidative Degradation: In oxidative degradation, it was observed that the percentage degradation of pantoprazole sodium and levosulpiride at the end of 24 h at room temperature with 30% hydrogen peroxide was found to be 66.78 and 22.98% respectively. The percentage of degradation of drugs at various time intervals was recorded and represented in **Table 5**. The chromatograms were recorded and depicted in **Fig. 7** to **10**.

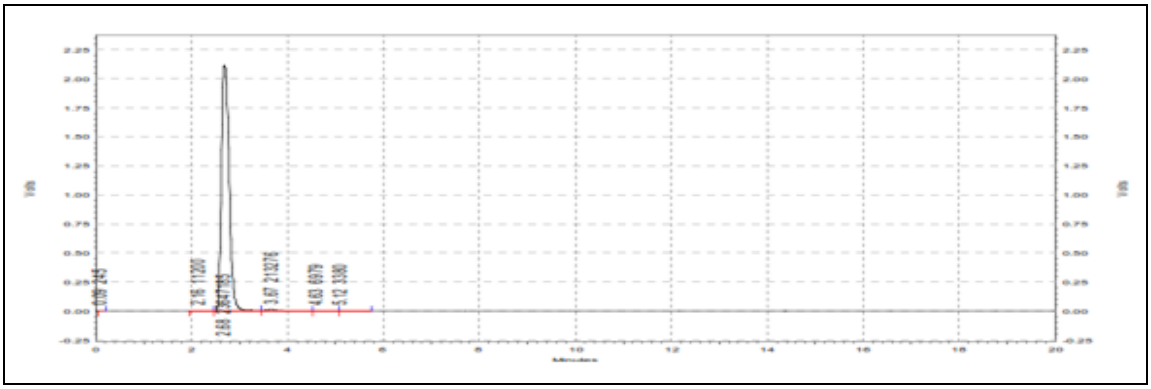

FIG. 7: OXIDATIVE DEGRADATION SAMPLE WITH 6% HYDROGEN PEROXIDE AT ROOM TEMPERATURE WITHDRAWN AT 0 h

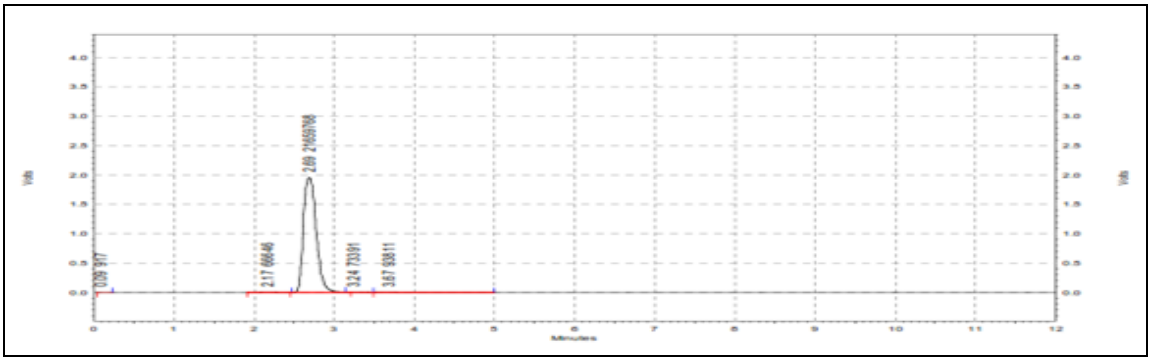

FIG. 8: OXIDATIVE DEGRADATION SAMPLE OF PANTOPRAZOLE WITH 6% HYDROGEN PEROXIDE AT ROOM TEMPERATURE WITHDRAWN AT 24 h

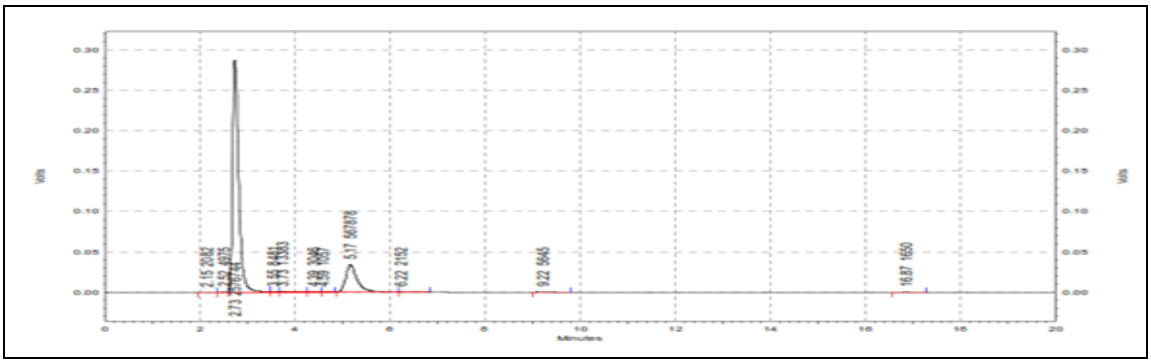

FIG. 9: OXIDATIVE DEGRADATION SAMPLE OF LEVOSULPIRIDE WITH 6% HYDROGEN PEROXIDE AT ROOM TEMPERATURE WITHDRAWN AT 0 h

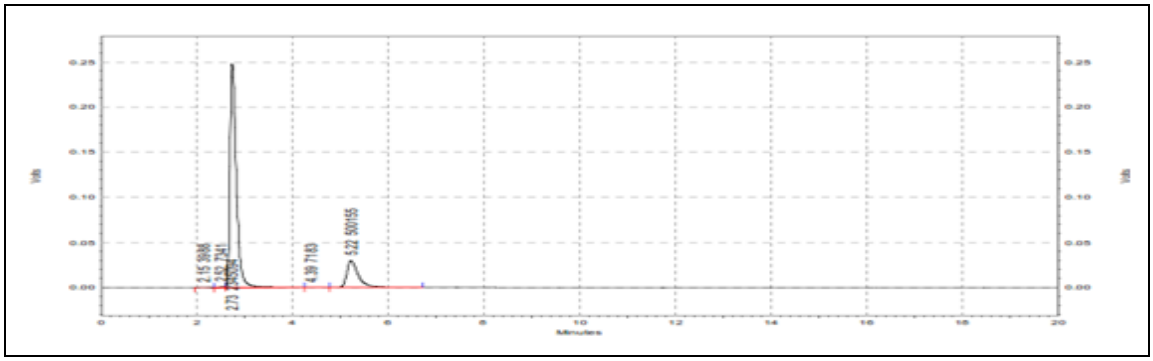

FIG. 10: OXIDATIVE DEGRADATION SAMPLE OF LEVOSULPIRIDE WITH 30% HYDROGEN PEROXIDE AT ROOM TEMPERATURE WITHDRAWN AT 0 h

Photodegradation: In photodegradation, the percentage of degradation of pantoprazole sodium and levosulpiride at the end of 8 h when exposed to sunlight in solid form was found to be 2.756 and 42.7% respectively.

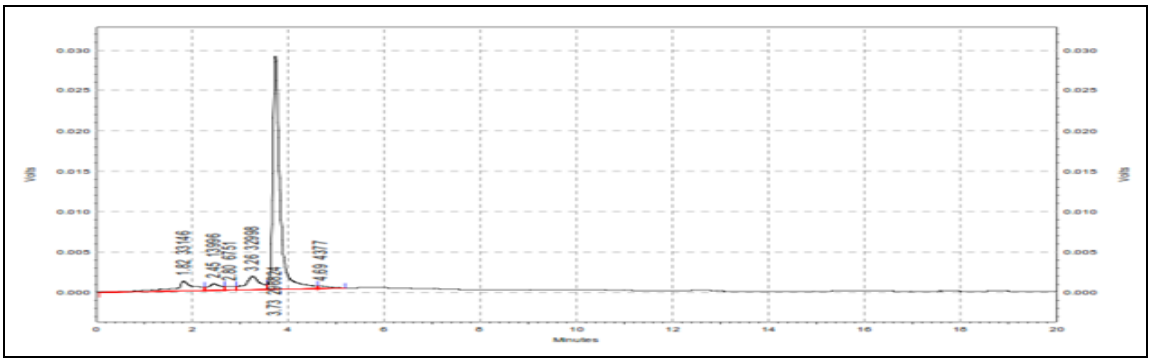

FIG. 11: PHOTOLYTIC DEGRADATION SAMPLE IN SUNLIGHT AFTER 8 h

The percentage of degradation of drugs at the end of 8 h was recorded and represented in **Table 5**. The degradation product was observed in the retention time 1.82 &, 2.45 min, and depicted in **Fig. 11**.

Thermal Degradation: In thermal degradation, the percentage degradation of pantoprazole sodium and levosulpiride at the end 8 h when exposed to heat at 80 °C in solid form was found to be 8.52 and 0% respectively.

The percentage of degradation of drugs at the end of 8 h was recorded and represented in **Table 5**. The chromatograms were recorded and depicted in **Fig. 12** and **13**.

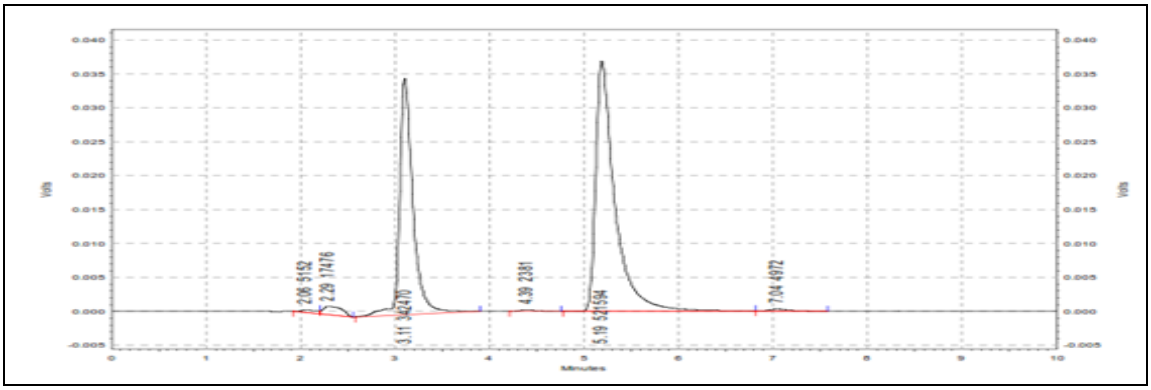

FIG. 12: THERMAL DEGRADATION SAMPLE AT 80 °C HEAT AT 0 h

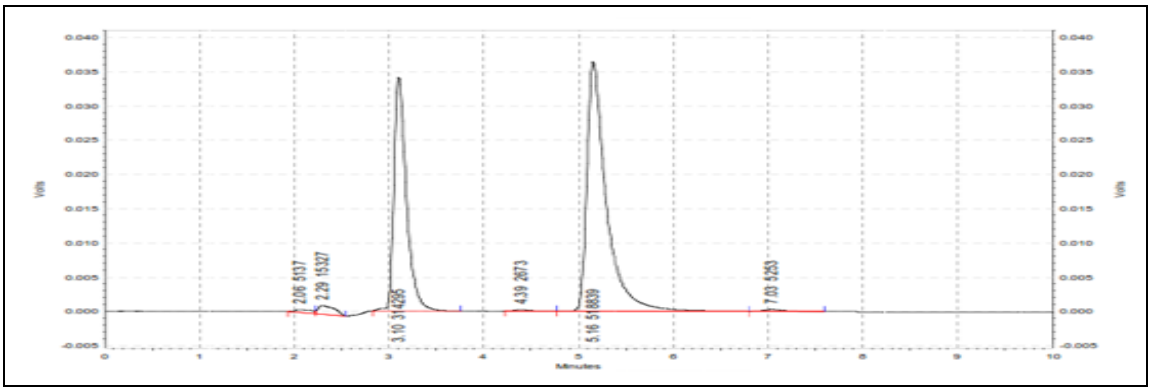

FIG. 13: THERMAL DEGRADATION SAMPLE AT 80 °C HEAT AFTER 8 h

CONCLUSION: A simple, specific, accurate and stability-indicating RP-HPLC method was developed for the simultaneous estimation of pantoprazole and levosulpiridein the presence of their degradation products and validated according to ICH guidelines. The method was found to be specific, accurate and robust for the routine assay. The developed method can be further applied for routine analysis in different quality control and research laboratories for analysis in a formulation.

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