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Development and Validation of a Stability Indicating HPLC Method for the Simultaneous Analysis of Esomeprazole and Itopride in Bulk and In Capsules

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ABSTRACT

A rapid, simple, selective, precise, and accurate stability indicating HPLC method has been developed and validated for the simultaneous analysis of esomeprazole and itopride in bulk and in capsule form. An isocratic separation was achieved using a Hypersil C4 (250 x 4.6 mm), 5 µm particle size column with a flow rate of 1 mL/min and photodiode array detector at 272 nm. The mobile phase consisted of 0.1M dipotassium hydrogen phosphate: acetonitrile (40:60 *v/v*). The method was validated for selectivity, specificity, linearity, precision, accuracy and robustness. The selectivity of the method was determined by assessing interference from the placebo, components of mobile phase and common excipients in pharmaceutical formulations. Whereas, specificity was established by stress degradation studies. The method was linear over the concentration range 40–120 µg/mL (R^2 = 0.9999) and 150-450 µg/mL (R^2 = 0.9999) for esomeprazole and itopride, respectively. Limit of detection is 0.207 and 0.724 µg/mL & Limit of quantitation is 0.691 and 2.415 µg/mL for esomeprazole and itopride, respectively. The precision and accuracy of the method was found to be acceptable. The method was found to be robust and suitable for the simultaneous analysis of esomeprazole and itopride in a capsule formulation. Degradation products resulting from the stress studies did not interfere with the detection and quantification of esomeprazole and itopride. The proposed HPLC method is thus stability-indicating.

INTRODUCTION

Esomeprazole (Evangelos and Einar, 2007; McKeage *et al.,* 2008), chemically known as (*S*)-5-Methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]-3*H*-benzoimidazole (Fig. 1), is a proton pump inhibitor. By inhibiting the H^+/K^+ ATPase in the parietal cells of the stomach, esomeprazole decreases the production of acid in the stomach. Esomeprazole is approved for the management of reflux oesophagitis, the symptomatic treatment of gastro-oesophageal reflux disease, the prevention and healing of non steroidal anti-inflammatory drugs-associated gastric ulcer disease, the treatment of duodenal ulcer disease caused by *Helicobacter pylori* infection and Zollinger-Ellison syndrome. Literature survey reveals that visible spectrophotometry (Akheel and Ayesha, 2007; Nafisur *et al.,* 2008; Patil *et al.,* 2009; Soujanya *et al.,* 2014), ultra violet spectrophotometry (Putta *et al.,* 2010; Magesh *et al.,* 2010), HPLC (Shetty *et al.,* 2005; ÖNal and ÖZtunÇ, 2006; Bellah *et al.,* 2012; Khalil et al 2012; Mahaparale and Deshpande, 2015), UPLC (Nalwade *et al.,* 2012) and liquid chromatography with tandem mass spectrometry (Hultman *et al.,* 2007; Sathiyaraj *et al.,* 2010; Ramakotaiah *et al.,* 2011) techniques have been reported for determination of esomeprazole in bulk, pharmaceutical dosage forms and biological samples.

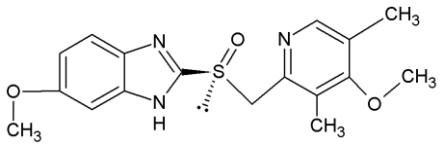

Fig. 1: Chemical structure of esomeprazole.

Itopride (Sun *et al.,* 2011; Huang *et al.,* 2012), chemically known as *N*-((4-(2-Dimethyl amino ethoxy) phenyl) methyl)-3,4-dimethoxybenzamide (Fig. 2), is an effective anti-nauseant and promotility drug. Itopride performs action by increasing acetylcholine at nerve junctions by inhibiting acetylcholine esterase. The increased acetylcholine in turn stimulates gastric motility. Itopride is used in the treatment of dyspepsia of a non-ulcer or dysmotility type, delayed gastric emptying, heartburn, anorexia, bloating, nausea and vomiting.

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Several techniques were found in the literature for the assay of itopride in bulk, pharmaceutical dosage forms and biological samples. They include visible spectrophotometry (Hussainy *et al.*, 2006; Felice and Saradhi, 2008; Choudhary *et al.*, 2009a; Choudhary *et al.*, 2009b; Sneha *et al.*, 2015), ultraviolet spectrophotometry (Santosh *et al.*, 2010; Gupta *et al.*, 2010), spectrofluorimetry (Mohamed *et al.*, 2013), atomic emission spectrometry (Khalil, 2013), HPLC (Kaul *et al.*, 2005; Neeraj *et al.*, 2005; Singh *et al.*, 2005; Zhao, 2000; Thiruvengada *et al.*, 2010; Payal *et al.*, 2011), liquid chromatography with flourometric detection (Singh *et al.*, 2005; Pavel *et al.*, 2009; Ma *et al.*, 2009), HPTLC (Suganthi *et al.*, 2006; Vidya *et al.*, 2006; Dighe, 2007) and liquid chromatography with tandem mass spectrometry (Heon *et al.*, 2007; Payal *et al.*, 2011).

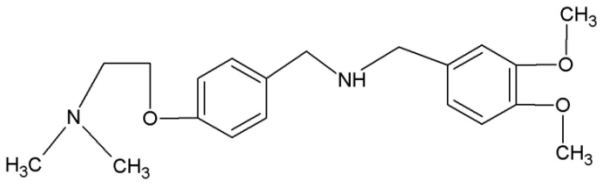

Fig. 2: Chemical structure of itopride.

Combination of esomeprazole and itopride is used for the treatment of gastric esophagus reflux disease (Peng and Li, 2009; Wang and Chen, 2012). The detailed survey of literature indicated that only two HPLC methods (Rajesh *et al.*, 2010; Kumar *et al.*, 2014) have been reported for the simultaneous estimation of esomeprazole and itopride in their combined dosage form. Rajesh *et al.*, (2010) have reported an HPLC method using a Phenomenex C18 column with a mobile phase consisting of ammonium acetate buffer (pH-5.5), water and methanol (25:15:60 *v/v*) at a flow rate of 1.5 mL/min. In the second HPLC method reported by Kumar *et al.*, (2014) the separation and assay of esomeprazole and itopride was carried out on Agilent Zorebax C18 column using a mixture of dipotassium hydrogen phosphate buffer (pH 7.29) and methanol (60:40, *v/v*) as mobile phase at a flow rate of 1.0 mL/min.

HPLC method reported by Rajesh *et al.*, (2010) for simultaneous estimation of esomeprazole and itopride in pharmaceutical dosage forms were found to have drawbacks such as narrow range of linearity, less accurate and have less correlation coefficient value. Use of more flow rate (1.5 mL/min) and triple solvent system increases the utilization of solvents, which inturn increases the cost of the analysis. Further more the method is not stability indicating. Though the Kumar *et al.*, (2014) method is stability indicating, accurate and precise but is less sensitive. The total run time is more (>6 min) in both the reported methods. Due to lengthy total run time, the time taken for the analysis of a single sample and utilization of solvent increases.

For this reason, in the present study an attempt was made to develop an economic and rapid stability indicating reverse-phase high performance liquid chromatographic method for the assay of esomeprazole and itopride, simultaneously, in capsule dosage form with short run time and low solvent consumption. The developed method was validated as per guidelines given by International Conference on Harmonization (International Conference on Harmonization, 2005).

MATERIALS AND METHODS

Mobile phase

The solvents and chemicals used in the preparation of mobile phase were of HPLC grade and analytical grade, respectively. The mobile phase used was 0.1M K_2HPO_4 and acetonitrile (Merck India Ltd., Mumbai) in the ratio of 40:60 *v/v*. To prepare 0.1M K_2HPO_4, 1.75 g of K_2HPO_4 (Sd. Fine Chemicals Ltd., Mumbai) was dissolved in 30 ml of double distilled water in a volumetric flask and made up to 100 ml with double distilled water. The pH of the mobile phase was adjusted to 5.4 with dilute orthophoshoric acid. Before use, the mobile phase was filtered through millipore membrane filter and degassed for 15 min by sonication.

Apparatus and chromatographic conditions

In the present study Waters 2695 alliance with binary HPLC pump equipped with Waters 2998 PDA detector and Waters Empower2 software was used. Hypersil C4 (250 x 4.6 mm; 5 µm particle size) analytical column was used for separation and simultaneous analysis of esomeprazole and itopride. The column temperature was maintained at 30 ± 1 ^oC. The separation was carried out under isocratic elution. The flow rate was maintained as 1.0 mL/min. The injection volume was 10 µL. The eluents were detected at 272 nm.

Standard solutions

Esomeprazole and itopride bulk samples were obtained from Lara drugs pvt Ltd., Hyderabad. The standard stock solution was prepared by dissolving 40 mg of esomeprazole and 150 mg of itopride in 100 mL mobile phase. Working standard solutions equivalent to 40, 60, 80, 100 & 120 µg/mL esomeprazole and 150, 225, 300, 375 & 450 µg/mL itopride was prepared from stock solution by appropriately diluting the stock standard solution with the mobile phase.

Sample Solution

Sompraz IT (Torrent Labs (P) Ltd. Ahmedabad) capsules, labeled to contain esomeprazole 40 mg and itopride 150 mg, were purchased and used in the present study. Ten capsules were emptied and the powder was mixed well to obtain a homogenous mixture. The powder equivalent of 40 mg of esomeprazole and 150 mg of itopride was transferred to a 100 mL volumetric flask containing 20 mL of mobile phase, sonicated for 20 min and made up to mark with the same solvent. The resultant mixture was filtered through 0.45 µm filter. The filtrate was diluted appropriately with the mobile phase to get a final concentration 80 µg/mL and 300 µg/mL of esomeprazole and itopride, respectively.

Placebo solution

The placebo solution was prepared by dissolving 129 mg of placebo in 20 mL of mobile phase in a 100 mL volumetric flask. The contents of the flask was sonicated for 20 min and made up to mark with the same solvent. The resultant mixture was filtered through 0.45 µm filter. Five mL of the above solution was diluted to 25 mL with mobile phase in a 25 mL volumetric flask.

Stress degradation study

Stress degradation study was carried out by subjecting the capsule powder to degradations such as acid, alkaline, oxidative, thermal and photolytic conditions to assess the interference of degradants.

For acidic hydrolysis, powder equivalent of 40 mg of esomeprazole and 150 mg of itopride was mixed with 10 mL of 0.1N HCl in 100 mL volumetric flask. The resultant solution was sonicated for 30 min. After hydrolysis, the solution was neutralized with sufficient volume of 0.1 N NaOH and diluted with mobile phase up to the mark.

For alkaline hydrolysis, powder equivalent of 40 mg of esomeprazole and 150 mg of itopride was mixed with 10 mL of 0.1N NaOH in 100 mL volumetric flask and sonicated for 30 min. After hydrolysis, the solution was neutralized with sufficient volume of 0.1 N HCl and diluted with mobile phase up to the mark.

Oxidative degradation was carried out by mixing powder equivalent of 40 mg of esomeprazole and 150 mg of itopride with 10 mL of H_2O_2 (3% *v/v*) in a 100 mL volumetric flask and the resultant solution was sonicated for 30 min. After oxidation, the solution was diluted with mobile phase up to the mark.

Photo degradation studies were carried out by the exposure of sample powder containing esomeprazole 40 mg and itopride 150 mg to direct sunlight for 24 hrs. The photo degraded sample was transferred to a 100 mL volumetric flask containing 30 mL of mobile phase and mixed well. The volume of the flask was completed up to mark with mobile phase.

Dry heating was performed by keeping sample powder containing esomeprazole 40 mg and itopride 150 mg in oven at 105 °C for 30 min. The treated sample was dissolved in 30 mL of mobile phase in a 100 mL volumetric flask. The contents of the flask were mixed well and diluted up to the mark with mobile phase. All forced degradation studies were analyzed at 80 µg/mL esomeprazole and 300 µg/mL itopride concentration levels.

Assay of esomeprazole and itopride in bulk

The working standard solutions, in the concentration of 40, 60, 80, 100 & 120 µg/mL esomeprazole and 150, 225, 300, 375 & 450 µg/mL itopride, prepared from stock solution were injected into the column. The eluents were monitored at 272 nm. Peak area was recorded for each concentration of drugs.

The calibration curve was plotted as concentration *vs* peak area. The regression equation was derived. The concentration of unknown was determined either from the calibration curve or regression equation derived.

Assay of esomeprazole and itopride in combined capsule dosage forms

Ten µL of the sample solution prepared in the section "sample solution" was injected into the HPLC system five times. The peak areas were recorded and the content of esomeprazole and itopride in combined capsule dosage form was determined from the calibration curve or from the regression equation.

RESULTS AND DISCUSSION

Method development

The main objective of the present study was to develop a stability indicating HPLC method for the simultaneous estimation of esomeprazole and itopride simultaneously in bulk and capsule dosage form and to obtain well resolved peaks of esomeprazole, itopride and their stress degradation products.

During method development, chromatographic parameters such as mobile phase composition, flow rate of mobile phase, detection wavelength, analytical column and column temperature were optimized to get improved efficiency of the chromatographic system. Two HPLC analytical columns, Phenomenex C18 (150 mm x 4.6 mm; 5 µm particle size) and Hypersil C4 (250 mm x 4.6 mm; 5 µm particle size) were tested during method development.

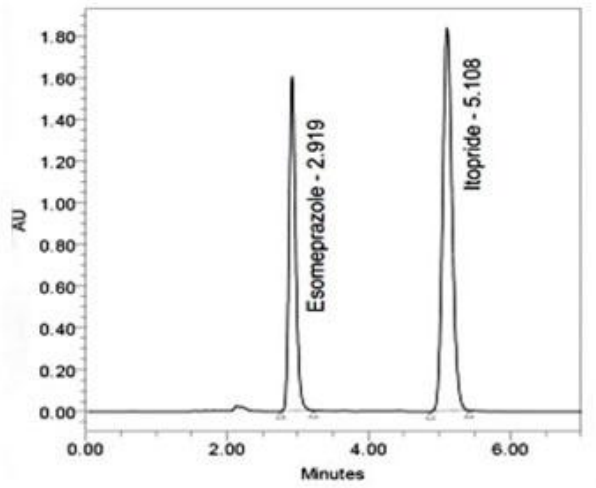

Fig. 3: Typical chromatogram of esomeprazole and itopride Method validation

The system suitability parameters like tailing factor, resolution, and plate count were considered. Based on the above said parameters Hypersil C4 column (250 mm x 4.6 mm; 5 µm particle size) was finalized. Different composition of mobile phases containing a mixture (*v/v*) of 0.1 M dipotassium hydrogen phosphate, 0.1 M potassium dihydrogen phosphate, 0.1% orthophosphoric acid in water and acetonitrile were evaluated so as to obtain appropriate composition of mobile phase. Finally the mixture of 0.1 M dipotassium hydrogen phosphate and acetonitrile in the ratio of 40:60 (*v/v*) was selected as optimal. At a flow rate of 1 mL/min and with column temperature of 30°C well defined and swell resolved peaks of esomeprazole and itopride are obtained. At the wavelength 272 nm, best detector response for

esomeprazole and itopride was obtained. Therefore, 272 nm was selected as the analytical wavelength for the detection and simultaneous quantification of esomeprazole and itopride. Under the optimized chromatographic conditions, the retention time for esomeprazole and itopride was found to be 2.919 min and 5.108 min, respectively. The developed method was validated for system suitability, selectivity, linearity, precision, accuracy, limit of detection (LOD), limit of quantification (LOQ), specificity and robustness as per International Conference on Harmonization (ICH) guidelines (International Conference on Harmonization, 2005).

System Suitability Studies

Mixed standard solution of esomeprazole (80 µg/mL) and itopride (300 µg/mL) solution was injected in five replicates in the HPLC system to determine system suitability. System suitability parameters established for the developed method include number of relative standard deviation of peak area, theoretical plates, resolution and tailing factor. The values obtained (Table 1) demonstrated the suitability of the system for the analysis of this drug combinations.

Selectivity

The selectivity of the developed HPLC method was investigated by non-interference of excipients in capsule dosage form and components of mobile phase. Selectivity of the proposed method was demonstrated by comparing the chromatograms of standard solution of esomeprazole (80 µg/mL) and itopride (300 µg/mL) with the chromatogram of sample solution (containing esomeprazole 80 µg/mL and itopride 300 µg/mL), blank mobile phase and placebo blank. The chromatograms are shown in Fig. 4. There were no difference in the chromatograms of standard solution and sample solution (Fig. 4A & 4B). There are no peaks in the chromatogram of blank mobile phase and placebo blank (Fig. 4C & 4D). The results indicated the selectivity of the proposed method.

Table 1: System suitability parameters.

Parameters	Esomeprazole	Itopride	Recommended limits
Retention time	2.919(%RSD – 0.148)	5.108(%RSD – 0.141)	-
Peak area	10242324 (%RSD – 0.109)	17047280 (%RSD – 0.226)	RSD ≤2
USP resolution	-	10.54(%RSD – 0.616)	> 1.5
USP plate count	5008(%RSD – 1.75)	7121(%RSD – 1.57)	> 2000
USP tailing factor	1.21(%RSD – 1.012)	1.13(%RSD – 1.083)	≤ 2

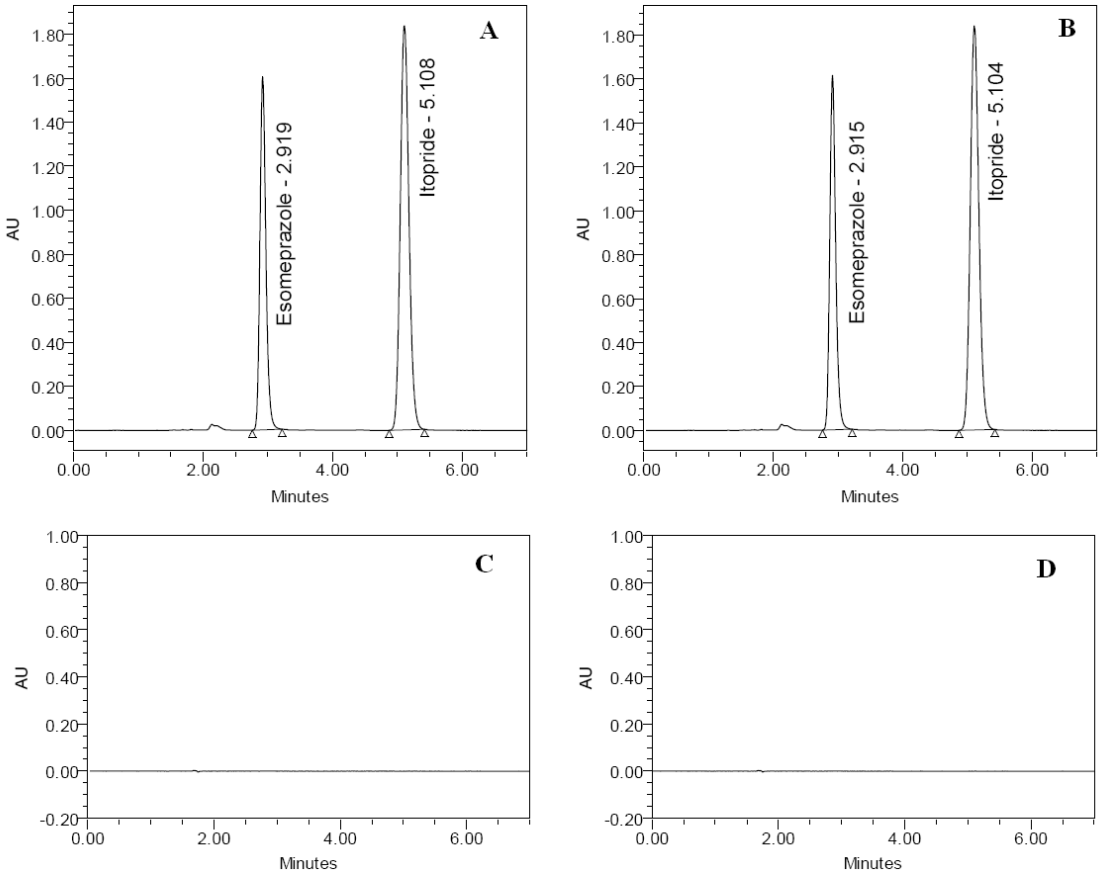

Fig. 4: Chromatogram of (A) standard drug solution (B) capsule dosage form (C) mobile phase blank (D) Placebo blank .

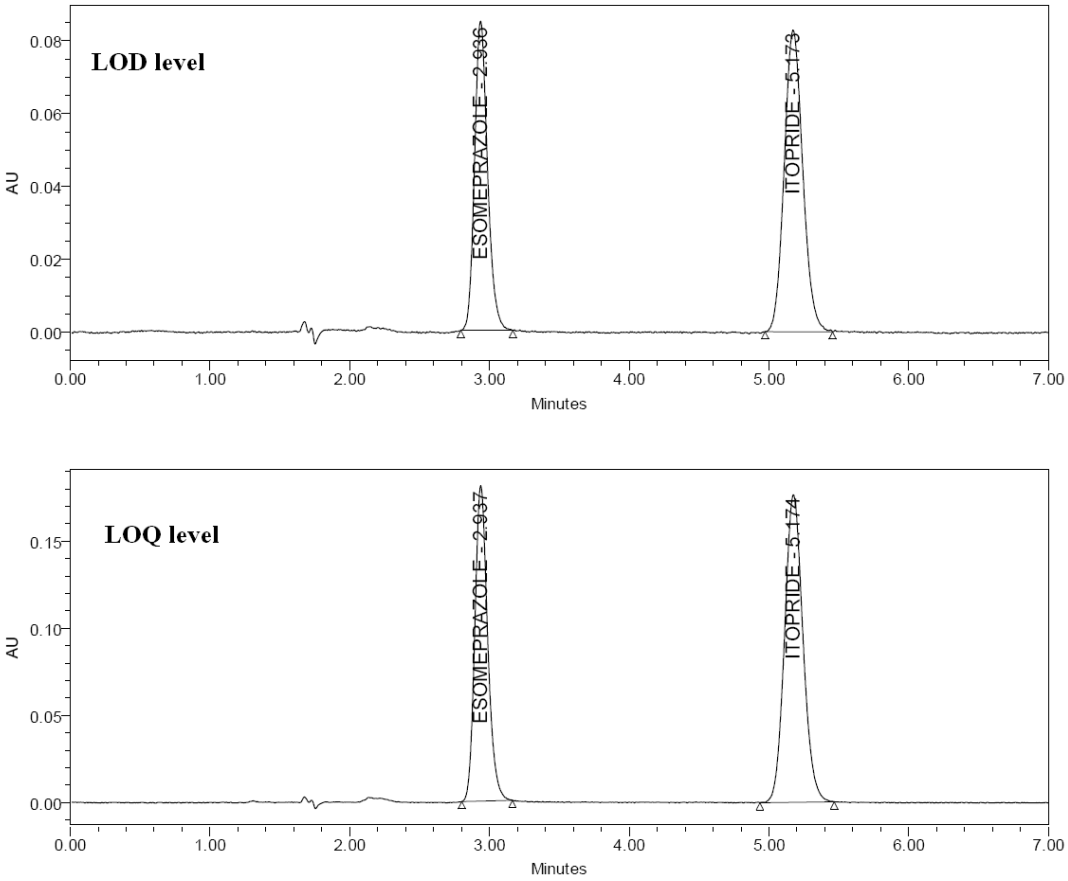

Fig. 5: Chromatograms of esomeprazole and itopride at LOD and LOQ levels.

Linearity and range

The linearity for the proposed method was established by least squares regression analysis of the calibration curve. Calibration curves were linear over the concentration range of 40-120 µg/mL for esomeprazole and 150-450 µg/mL for itopride with a regression coefficient (R^2) of 0.9999 for both the drugs. The results shows a good correlation exists between peak area and concentration of drugs within concentration range indicated above. The results for calibration data are shown in Table 2.

Table 2: Linearity for esomeprazole and itopride by proposed method.

Linearity for esomeprazole		Linearity for itopride	
Concentration (µg/mL)	**Peak area**	**Concentration (µg/mL)**	**Peak area**
40	5175501	150	8576751
60	7697342	225	12873107
80	10305838	300	17184024
100	12943487	375	21591549
120	15484880	450	25907883
Regression equation: y = 129149x - 8768.4 R^2 = 0.9999		**Regression equation:** y = 57602x - 44864 R^2 = 0.9999	

Limit of detection (LOD), limit of quantification (LOQ)

The Limit of quantification and detection determines the sensitivity of the method. The LOD and LOQ were calculated using the following formulas (1) and (2).

(1) LOQ = 10 sd / S

(2) LOD = 3.3 sd / S

Where, sd = standard deviation of response,
S = slope of the calibration curve.

The LOD of esomeprazole and itopride was found to be 0.207 and 0.724 µg/mL and the LOQ of esomeprazole and itopride was 0.691 and 2.415 µg/mL, respectively. The chromatograms of esomeprazole and itopride at LOD and LOQ levels are shown in Fig. 5. The results indicate that the developed method possess adequate sensitivity for the simultaneous determination of esomeprazole and itopride.

Precision

The precision of the proposed method was established by analyzing five standard solutions (esomeprazole-80 µg/mL; itopride-300 µg/mL). The peak area of esomeprazole and itopride and their percentage RSD were calculated. The results of are presented in Table 3. The results were within the acceptable limit and indicated that the method is precise.

Table 3: Precision of the method.

S. No.	Esomeprazole			Itopride		
	Concentration (µg/mL)	Peak Area	%RSD	Concentration (µg/mL)	Peak Area	%RSD
1	80	10329341		300	17027206	
2	80	10375535		300	17103866	
3	80	10296899	0.38	300	17052015	0.27
4	80	10288066		300	17047562	
5	80	10372197		300	17109716	

Table 4: Accuracy of the method.

Accuracy level	(µg/mL) added	(µg/mL) found	% Recovery	% Mean
Esomeprazole				
50%	40.000	40.14	100.35	100.12
	40.000	40.05	100.12	
	40.000	39.96	99.90	
100%	80.000	80.15	100.18	99.72
	80.000	79.23	99.04	
	80.000	79.96	99.95	
150%	120.000	119.73	99.77	99.96
	120.000	120.36	100.30	
	120.000	119.80	99.83	
Itopride				
50%	150.000	150.49	100.33	10.10
	150.000	149.28	99.52	
	150.000	150.68	100.45	
100%	300.000	300.38	100.12	100.03
	300.000	298.59	99.53	
	300.000	301.34	100.44	
150%	450.000	450.64	100.14	100.01
	450.000	448.64	99.69	
	450.000	450.90	100.20	

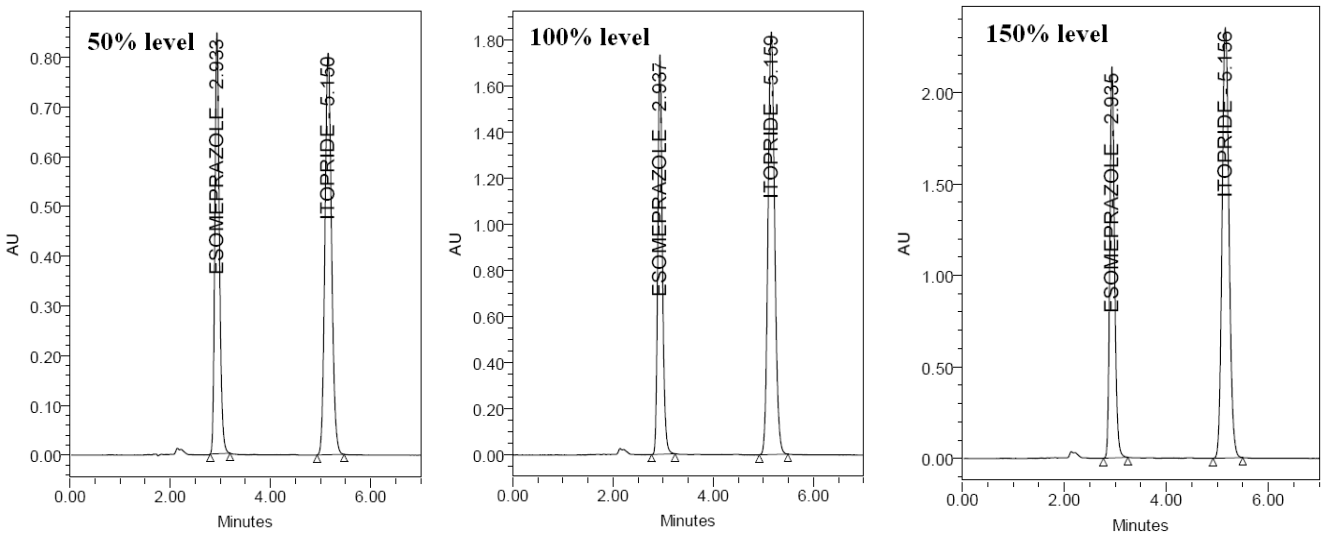

Fig. 6: Chromatograms of esomeprazole and itopride at three different levels.

Accuracy

Recovery experiments were performed to determine the accuracy of the method. The accuracy of the proposed method was established by preparing samples spiked with 50%, 100%, and 150% of the test concentration of esomeprazole and itopride. Each concentration level was analyzed.

Mean percent recovery was calculated for each concentration. Percent recovery was well within the acceptable limit. Results are presented in Table 4. From the data, added recoveries of standard drugs were found to be accurate. The chromatograms of three different levels are shown in Fig. 6.

Robustness

The robustness test was carried out by making deliberate changes in optimized chromatographic conditions. Retention time, tailing factor, resolution and plate count were measured to demonstrate the robustness of the method. The results are shown in Table 5. In all the deliberate varied chromatographic conditions, the parameters like tailing factor, peak area and theoretical plates were not much affected, which shows that the method is robust.

Table 5: Robustness of the method.

Parameter varied	Retention time	Peak area	USP plate count	USP Tailing	USP resolution
Esomeprazole					
Column temperature - 29 °C	2.942	10302901	4998	1.18	-
Column temperature - 31 °C	2.944	10380968	5008	1.17	-
Flow rate – 0.9 mL/min	2.940	10352026	4954	1.19	-
Flow rate – 1.1 mL/min	2.943	10318635	5035	1.18	-
Itopride					
Column temperature - 29 °C	5.183	17111327	7360	1.10	10.75
Column temperature - 31 °C	5.175	16952513	7420	1.14	10.75
Flow rate – 0.9 mL/min	5.177	17008673	7206	1.11	10.69
Flow rate – 1.1 mL/min	5.179	17005273	7262	1.13	10.71

Table 6: Stress degradation studies and spectral homogeneity data.

Type of stress	Peak area	% Assay	% Degradation	Purity Angle	Purity Threshold	Purity flag
Esomeprazole						
Undegraded	10251788	100	-	-	-	-
Acid	9819341	95	5	0.627	0.887	No
Base	9885535	96	4	0.655	0.872	No
Peroxide	9840689	95	5	0.643	0.941	No
Heat	9800106	95	5	0.699	0.909	No
Sunlight	9897219	96	4	0.616	0.861	No
Itopride						
Undegraded	17032285	100	-	-	-	-
Acid	16027206	94	6	6.507	33.764	No
Base	16303866	95	5	6.709	29.258	No
Peroxide	16052015	94	6	6.786	33.740	No
Heat	16447562	96	4	6.497	31.034	No
Sunlight	16349716	96	4	6.959	33.546	No

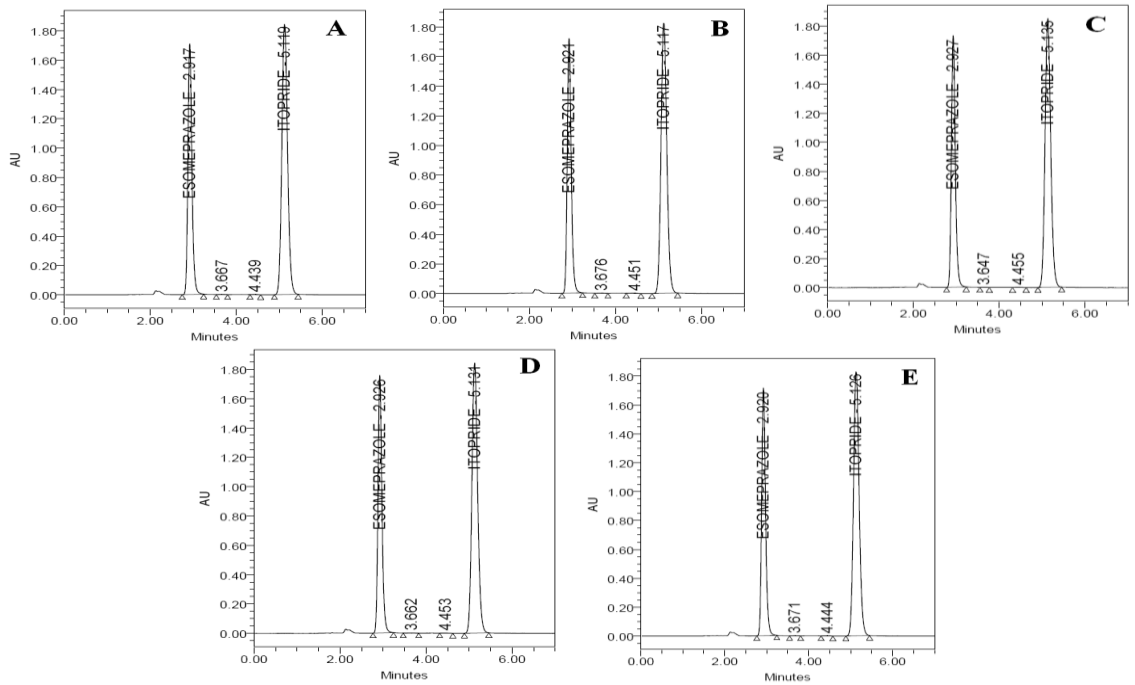

Fig. 7: Chromatograms of esomeprazole and itopride after stress degradation (A) Acid (B) Base (C) Hydrogen peroxide (D) Dry heat (E) Photolytic.

Stress degradation study

The stress degradation study was done to make sure that the proposed method was able to separate esomeprazole and itopride from the degradation products generated during the stress degradation study. The results of degradation study are summarized in Table 6. The chromatograms of degraded samples are shown in Fig. 7. The degradation products produced due to stress did not interfere with the detection of esomeprazole and itopride, and the proposed method can thus be regarded as stability-indicating.

For all stress degradation samples, the purity angle was less than the threshold angle and there was no purity flag for esomeprazole and itopride. The confirmation of peak purity indicates that there is no interference from stress degradants, facilitating quantification of esomeprazole and itopride without error.

CONCLUSION

The proposed stability indicating HPLC method was found to be rapid, simple, precise, accurate, selective and sensitive for the simultaneous estimation of esomeprazole and itopride in capsules. Therefore, this method can easily and conveniently take up for routine quality control analysis of esomeprazole and itopride in bulk and in capsules.

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