Research Article

RP-HPLC Method for the Simultaneous Determination of Pantoprazole Sodium, Omeprazole, Rabeprazole Sodium, Lansoprazole, and Domperidone in Bulk and Pharmaceutical Dosage Form

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ABSTRACT

An RP-HPLC method for the simultaneous determination of Pantoprazole sodium, Omeprazole, Rabeprazole sodium, Lansoprazole, and Domperidone in tablets was developed and validated as per ICH and FDA guidelines. The separation was achieved with a 150 mm x 3.0 mm, 3.5 µm C18 column, by using a simple linear gradient. Mobile phase A was Buffer (1.0% Triethylamine containing 20mM KH2PO4; pH adjusted to 7.5 with Orthophosphoric acid) and Mobile Phase B was a mixture of Buffer and Solvent mixture in the ratio 20:80 v/v (Solvent mixture is mixture of Acetonitrile and Methanol in the ratio of 20:80 v/v) and with simple gradient program was delivered at a flow rate of 0.5 mL/min. The column temperature was kept at 30°C. The detector was set at the wavelength of 285 nm. Injection volume was kept 10 µL. The gradient separation was achieved within 25 minutes. The linearity of the proposed method was investigated in the range 0.018-0.057 mg/mL (r2= 1.000) for Pantoprazole sodium, 0.009-0.031 mg/mL (r2= 1.000) for Omeprazole, 0.009-0.027 mg/mL (r2= 1.000) for Rabeprazole sodium, 0.014-0.045 mg/mL (r2= 1.000) for Lansoprazole and 0.014-0.044 mg/mL (r2= 1.000) for Domperidone. The assay method is considered to be specific as there was no blank and placebo interference at retention time of Pantoprazole sodium, Omeprazole, Rabeprazole sodium, Lansoprazole, and Domperidone peaks. The developed method has an advantage that all the drugs can be quantified alone or in combination using a single mobile phase.

Keywords: RP-HPLC, ICH, Validation, Pantoprazole sodium, Rabeprazole sodium, Omeprazole, Lansoprazole and Domperidone.

INTRODUCTION

Pantoprazole sodium (PANTO), Omeprazole (OME), Rabeprazole Sodium (RABE), Lansoprazole (LANSO), and Domperidone (DOME) are members of benzimidazole class of drugs. They are important benzimidazole derivatives which are used in the treatment of anti-peptic disease such as gastric and duodenal ulcers, and reflux oesophageal ulceration.[1] A literature survey reveals that several methods have been used for determination of the above mentioned drugs in pharmaceutical dosage forms and biological fluids alone or in combination with other drugs including titrimetry[2,3] UV-spectrophotometry,[5] Colorimetry,[6] Spectrofluorimetric[7], high performance thin-layer chromatography[7-8], high performance liquid chromatography[12-14] and electrochemical methods[9,10].

Pantoprazole sodium is a proton pump inhibitor drug that inhibits gastric acid secretion. Lansoprazole is chemically known as 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl]-1H-benzimidazole. Omeprazole is substituted benzimidazole and chemically known as 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole. Rabeprazole sodium a substituted benzimidazole, inhibits gastric acid secretion and chemically it is known as 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl] methylsulfinyl]-1H-benzimidazole sodium salt. Domperidone is organic compounds containing a benzene ring fused to an imidazole ring. It is chemically known as 5-chloro-1-{1-[3-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-propyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one.

Literature survey revealed that there is only one method available for simultaneous determination of only four active ingredients (Pantoprazole, Lansoprazole, Rabeprazole and Domperidone) and the method is linear in the concentration range 0.5-10 µg per mL for these drugs.[14] However, none of the method available has been reported for the simultaneous determination of Rabeprazole sodium, Lansoprazole, Omeprazole, Domperidone and Pantoprazole sodium in pharmaceutical dosage form with great difference in label claim (Pantoprazole sodium 40 mg, Omeprazole 20 mg, Rabeprazole sodium 20 mg, Lansoprazole 30 mg, Domperidone 30 mg).

The method was validated as per the present ICH guideline on validation of analytical procedure Q2A (R1).[15] Quantitation was achieved with UV detection at 285 nm based on peak area with linear calibration curves at concentration ranges.

The method was linear over wide concentration range of 0.018-0.057 mg/ml for Pantoprazole, 0.009-0.031 mg/ml for Omeprazole, 0.009-0.027 mg/ml for Rabeprazole, 0.014-0.045 mg/ml for Lansoprazole and 0.014-0.044 mg/ml for Domperidone.

The accuracy of the method was evaluated in triplicate at three concentration level i.e. 80%, 100% and 120% of target test concentration.

MATERIALS AND METHODS

Chemicals and Reagents

Rabeprazole sodium (RABE), Omeprazole (OME), Lansoprazole (LANSO), Domperidone (DOME) and Pantoprazole sodium (PANTO) were obtained from Bioleo Labs and K.P Labs, Hyderabad, India. Excipients for preparation of placebo were obtained from K.P. LABS, Hyderabad, India. Branded formulation of Lansoprazole, Pantoprazole sodium, Rabeprazole sodium, Omeprazole, and Domperidone were procured from local market.

HPLC grade, methanol and acetonitrile were obtained from Merck Chemicals (Mumbai, India). HPLC grade Orthophosphoric acid (88%) was from Merck (Mumbai, India). Triethylamine was obtained from Merck Chemicals (Mumbai, India), HPLC grade water was prepared using a Milli-Q system (Millipore). Nylon syringe filters (0.45 µm) were from Millipore (Mumbai, India). All the other used reagents were of analytical grade.

Selection of UV wavelength

10ppm solution of each Lansoprazole, Pantoprazole sodium, Omeprazole, Rabeprazole sodium and Domperidone was prepared separately in methanol. UV scan of the above solutions were carried out over a wavelength range of 200–400 nm by using the Shimadzu UV spectrophotometer, Model- UV-1800. The detection wavelength was set at 228 nm because all the components had higher responses. An overlaid UV absorption spectrum is shown in Figure-1.

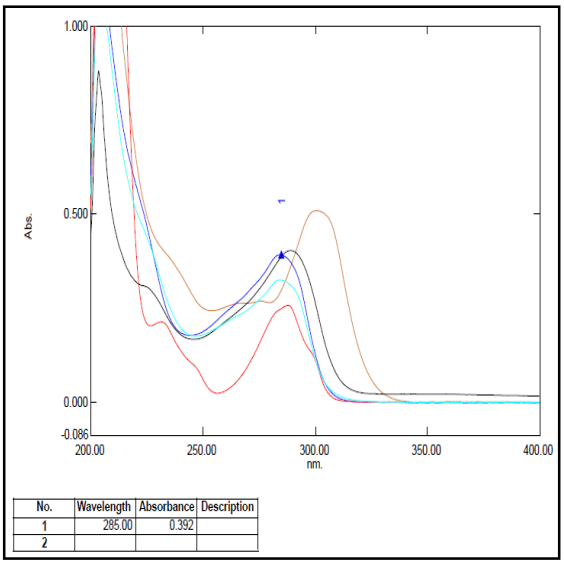

Figure 1: Overlaid UV absorption spectrum of Lansoprazole, Pantoprazole sodium, Omeprazole, Rabeprazole sodium and Domperidone.

HPLC instruments and analytical conditions

Chromatographic separation was achieved using HPLC System (Waters Alliance 2695 Separation Module) containing binary solvent manager, an autosampler and UV detector. The output signal was monitored and processed using Empower software.

An Waters X Bridge C18 column (150 mm X 3.0 mm id and 3.5 µm particle size) was used as the stationary phase.

Mobile phase A was Buffer pH-7.5 (1.0% Triethylamine containing 20mM KH2PO4; pH adjusted to 7.5 with Orthophosphoric acid) and Mobile Phase B was, Mixture of Buffer pH-7.5 and Solvent mixture in the ratio of 20:80 v/v (Solvent mixture is mixture of Acetonitrile and Methanol in the ratio of 20:80 v/v) with simple gradient program (0-3 min :: MP-A : 50-50; 3-7 min :: MP-A : 50-45; 7-20min :: MP-A : 45-10) ; 20-21 min :: MP-A : 10-50; 21-25 min :: MP-A : 50-50; was delivered at a flow rate of 0.5 mL/min.

The mobile phase was filtered through a 0.45 µ membrane filter and sonicated for 10 min. The column temperature was kept at 30°C. The detector was set at the wavelength of 285 nm. Injection volume was kept 10 µL.

Solutions and sample preparation

For the system suitability test, the solution contains Rabeprazole (0.02 mg/mL), Lansoprazole (0.03 mg/mL), Omeprazole (0.02 mg/mL), Pantoprazole (0.04 mg/mL) and Domperidone (0.03 mg/mL).

For the linearity studies, variable weight of compounds was weighed and diluted with the solvent to yield solutions at different concentration.

For test sample solution, 5 tablets were weighed and transferred to 500 mL volumetric flask. Added 100 mL of methanol to this mixture sonicated the solution for approximately 10 minutes and vortex for about 10 minutes. Cooled to room temperature and diluted to the volume with diluent.

Further 5 mL aliquot of this sample stock solution was transferred to 100 mL volumetric flask and diluted to the mark with diluent to obtain a test solution of Rabeprazole (0.02 mg/mL), Lansoprazole (0.03 mg/mL), Omeprazole (0.02 mg/mL), Pantoprazole (0.04 mg/mL) and Domperidone (0.03 mg/mL). The solution was filtered through Nylon 0.45 µm membrane filter.

10 µL of these solutions were injected into the HPLC system and the peak area was recorded from the respective chromatogram.

Calculation

All active ingredients were quantified with the following calculation:

$$\%\ Assay\ = \frac{Sample\ Area \times Standard\ dilution\ factor}{Standard\ Area \times Sample\ dilution\ factor} \times 100$$

RESULTS AND DISCUSION

Literature survey revealed that, no method is available in the official compendia using HPLC for analyzing Lansoprazole, Pantoprazole sodium, Omeprazole, Rabeprazole sodium and Domperidone in dosage forms. The present proposed method was compared with the reported method in the literature and comparison is

shown in Table-1. The complete separation of the analytes was accomplished in less than 25 min and the method can be successfully applicable to perform routine analysis of Lansoprazole, Pantoprazole sodium, Omeprazole, Rabeprazole sodium and Domperidone in bulk and in commercially available dosage forms.

Table 1 Comparison of the performance characteristics of the present method with the published methods

S.No.	Method	Reagents	Detection Wavelength/ Runtime	Linearity (mg/mL)	Remark	Reference
1	HPLC	Dipotassium hydrogen phosphate, Acetonitrile, Methanol, Orthophosphoric acid	280 nm / 10 min	0.001 to 0.01 mg/mL for both pantoprazole and Rabeprazole, 0.00075 to 0.0075mg/ml for Lansoprazole and 0.0005 to 0.005 mg/m for Domperidone	Omeprazole was not analysed and method development and forced degradation study was performed only n individual component	[14]
2	HPLC	Potassium dihydrogen orthophosphate, Triethylamine, Acetonitrile, Methanol, Orthophosphoric acid	285 nm / 25 min	0.018-0.057 mg/ml for Pantoprazole, 0.009-0.031 mg/ml for Omeprazole, 0.009- 0.027 mg/ml for Rabeprazole, 0.014-0.045 mg/ml for Lansoprazole and 0.014-0.044 mg/ml for Domperidone.	Wide linearity range and also study was performed in combined form.	Present work

Table 2: System suitability

Reference solution Peak Area, for n=6					
	Pantoprazole sodium	**Omeprazole**	**Rabeprazole sodium**	**Lansoprazole sodium**	**Domperidone**
%RSD	0.65	0.16	0.68	0.12	0.15
Acceptance Criteria	Not more than 2.0%				
Reference solution Peak resolution, for n=6					
Resolution	-	3.48	2.61	8.34	17.92
Acceptance Criteria	Not less than 2.0				
Reference solution Peak Symmetry factor, for n=6					
Symmetry Factor	1.12	1.08	1.12	1.08	1.12
Acceptance Criteria	Should be between 0.8 – 1.2				
Reference solution Peak Theoretical plates, for n=6					
Theoretical plates	5391	7651	9436	20190	56811
Acceptance Criteria	Not less than 2000				

Results: It was observed that limits for percentage standard deviation for peak area's symmetry factor and theoretical plates for all individual analytes were within the limit, which shows that the method has good system suitability.

Table 3: Precision and Intermediate Precision results

	Pantoprazole sodium	**Omeprazole**	**Rabeprazole sodium**	**Lansoprazole**	**Domperidone**
Precision (Day 1) –Assay %					
Average Assay (%)	99.9	100.4	99.6	99.8	99.4
%RSD	**0.28**	**0.26**	**0.33**	**0.36**	**0.41**
Intermediate Precision (Day 2) – Assay %					
Average	100.0	100.4	100.2	100.0	100.0
%RSD	**0.40**	**0.26**	**0.31**	**0.40**	**0.31**
Average for Precision and Intermediate Precision	100.0	100.4	99.9	100.0	99.8
% RSD for Precision and Intermediate Precision	**0.1**	**0.0**	**0.6**	**0.2**	**0.6**
Acceptance Criteria	**%RSD should not be more than 2.0% for day-1 and day-2.**				

Results: Percentage Relative standard deviation (%RSD) obtained was found to be less than 2% for day – 1 and day -2

Table 4: Accuracy (Recovery)

Active Ingredient Name	Concentration (%)	Amount Added (mg/mL)	Amount found (mg/mL)*	Mean Recovery (%)**	Average Recovery (%)
Pantoprazole sodium	80	0.003031	0.003027	99.88	99.90
	100	0.003797	0.003786	99.89	
	120	0.004539	0.004536	99.95	
Omeprazole	80	0.001599	0.001598	99.99	100.02
	100	0.002001	0.002004	100.15	
	120	0.002398	0.002396	99.93	
Rabeprazole sodium	80	0.001500	0.001507	100.42	100.50
	100	0.001894	0.001908	100.62	
	120	0.002293	0.002303	100.45	
Lansoprazole	80	0.002506	0.002519	100.52	100.28
	100	0.003011	0.003020	100.25	
	120	0.003586	0.003589	100.08	
Domperidone	80	0.002391	0.002401	100.42	100.30
	100	0.002976	0.002977	100.05	
	120	0.003588	0.003603	100.42	
Acceptance criteria	The mean and individual recoveries should be within 98.0 – 102.0%				

* mean of 3 readings for individual level

** Average recovery for all levels

Results: Accuracy results obtained shows that the mean and individual recoveries were in range of 98.0–102.0%

Table 5: Robustness results

Summary of system suitability Parameters															
Variations	Resolution					Symmetry Factor					Theoretical plates				
	PANTOPRAZOLE	RABEPRAZOLE	OMEPRAZOLE	LANSOPRAZOLE	DOMEPERIDONE	PANTOPRAZOLE	RABEPRAZOLE	OMEPRAZOLE	LANSOPRAZOLE	DOMEPERIDONE	PANTOPRAZOLE	RABEPRAZOLE	OMEPRAZOLE	LANSOPRAZOLE	DOMEPERIDONE
0.5 mL/min 30°C	-	3.49	2.61	8.30	17.98	1.12	1.08	1.12	1.08	1.12	5342	7547	9265	19854	56720
0.4 mL/min	-	3.70	2.87	9.29	19.61	1.00	1.01	0.96	0.95	1.01	6425	8952	10971	26213	74238
0.6 mL/min	-	3.92	2.91	8.62	20.78	1.07	1.06	0.99	0.95	1.01	5147	6684	8422	16394	72130
25°C	-	3.23	2.35	7.31	16.33	1.26	1.20	1.17	1.14	1.16	3755	5902	7539	17329	51014
35°C	-	3.28	2.42	7.29	20.64	1.20	1.15	1.13	1.09	1.10	3287	4577	5703	10739	49756
Buffer pH=7.3	-	3.30	2.11	6.72	21.85	1.16	1.07	1.13	1.01	1.00	3764	5040	5541	7922	36354
Buffer pH=7.7	-	3.45	2.18	7.00	21.45	1.16	1.07	1.08	1.02	1.02	4014	5293	5775	8684	38652
Acceptance Criteria	Not less than 2.0					Should be between 0.8 – 1.5					Not less than 2000				

Results: From variation in Temperature, flow rate and Buffer pH variation, it was observed that there were no marked changes in the chromatograms, which demonstrated that the method developed is robust. Resolution, symmetry factor and Theoretical plate limits for flow rate variation and temperature variation are within the acceptance criteria, which show that the method exhibit good system suitability under given set of conditions.

Table 6: Solution Stability results

Test Solution - Solution stability										
Time (Hours)	% Assay of PANTO	% Change w.r.t. Initial	% Assay of OME	% Change w.r.t. Initial	% Assay of RABE	% Change w.r.t. Initial	% Assay of LANSO	% Change w.r.t. Initial	% Assay of DOME	% Change w.r.t. Initial
Initial	98.83	N/A	99.08	N/A	99.41	N/A	99.64	N/A	99.64	N/A
8	99.30	0.47	99.71	0.63	99.84	0.43	99.78	0.14	99.83	0.19
12	99.77	0.95	99.44	0.36	99.43	0.60	99.93	0.29	100.02	0.37
24	99.56	0.73	98.64	0.44	99.38	0.55	100.07	0.43	100.20	0.56
Acceptance Criteria :	% Change w.r.t. initial for Test solution should NMT 1.0% of initial assay results.									
Reference Solution - Solution stability										
Time (Hours)	Area of PANTO	% Change w.r.t. Initial	Area of OME	% Change w.r.t. Initial	Area of RABE	% Change w.r.t. Initial	Area of LANSO	% Change w.r.t. Initial	Area of DOME	% Change w.r.t. Initial
Initial	1396684	N/A	645957	N/A	754881	N/A	1324885	N/A	943987	N/A
8	1391991	0.34	648313	0.36	758246	0.45	1326638	0.13	947233	0.34
12	1403048	0.46	651342	0.83	759041	0.55	1326756	0.14	948152	0.44
24	1406384	0.69	650120	0.64	760453	0.74	1326993	0.16	948661	0.50
Acceptance Criteria :	% Change w.r.t. initial for reference solution should NMT 1.0% of initial.									

Results: Both Test and reference solution was found to be stable upto 24hours, at 25 °C (laboratory temperature).

Method Validation

The developed RP-HPLC method was validated as per International Conference on Harmonization (ICH) guideline, VALIDATION OF ANALYTICAL PROCEDURES: Q2 (R1)[15], for the parameters like system suitability, linearity and range, precision (repeatability), intermediate precision (ruggedness), specificity, accuracy and robustness.

System suitability

The system suitability test performed according to USP37. The standard solution was injected six times and results were recorded to find the adequate peak separation (resolution), percentage relative standard deviation for area and retention time, peak asymmetry and theoretical plates. The results obtained were compiled in Table-2.

Specificity

Specificity was performed to detect the presence of interference peak (blank and placebo peaks) at the retention time of the analyte peak. The specificity of the method was checked by comparison of chromatograms obtained from test sample solution and the corresponding placebo. The interference of placebo was detected by preparing placebo solution equivalent to about the weight in proportion of tablet preparation as per the test method and was injected into the HPLC system. The interference of blank was detected by injecting diluent as per the test method.

The representative chromatogram obtained for Lansoprazole, Pantoprazole sodium, Omeprazole, Rabeprazole sodium and Domperidone is shown in Figure-2.

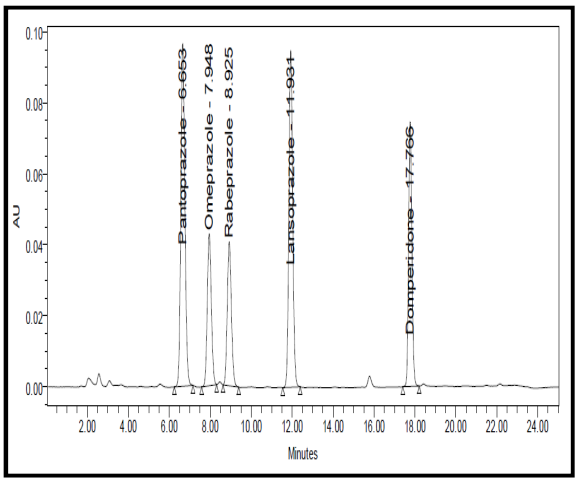

Figure 2: Typical Chromatograms of Standard Solution containing Pantoprazole sodium, Omeprazole, Rabeprazole sodium, Lansoprazole and Domperidone

Results: No interference from diluent, excipients or any other peak was found at the retention time of Pantoprazole sodium, Omeprazole, Rabeprazole sodium, Lansoprazole and Domperidone.

Precision and Ruggedness (Intermediate precision)

Method precision was evaluated by carrying out six different test sample solution preparation. Different analyst from the different laboratory evaluated the intermediate precision of the method.

The assay of these samples was determined. Precision and intermediate precision of the method was evaluated by calculating the %RSD. The values were given in Table-3.

Linearity and range

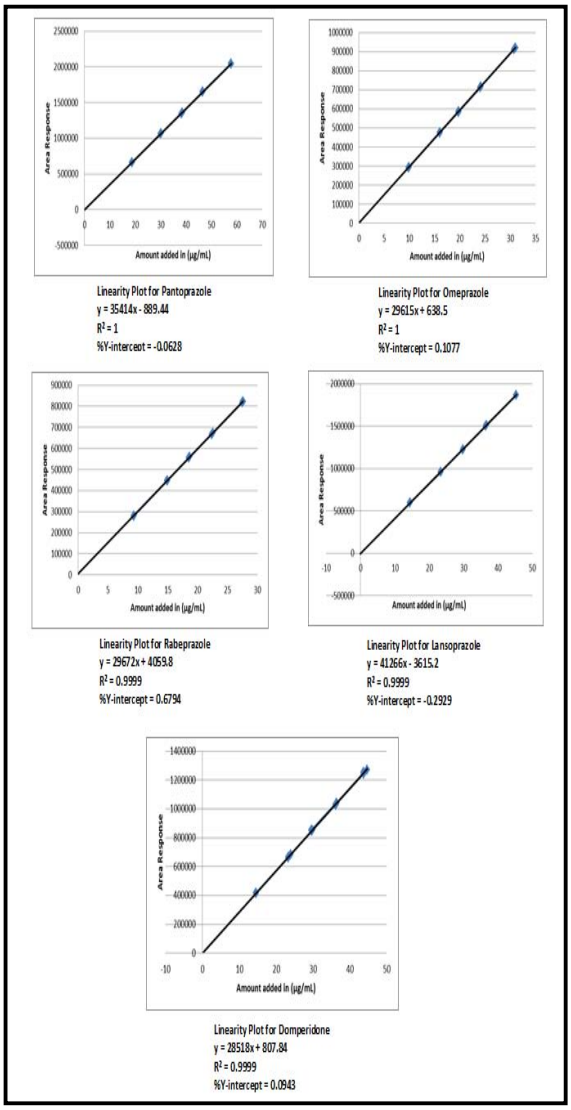

Figure 3: Calibration curves of Pantoprazole sodium, Omeprazole, Rabeprazole sodium, Lansoprazole and Domperidone showing linearity

The linearity of detector response was determined by preparing a series of solution of the working standards (mixture of all active ingredients) over the range of 80% to 120% of targeted concentration. These solutions were injected into the chromatographic system and response area was recorded.

Calibration curve was constructed by plotting area against concentration and regression equation was computed. The linearity plots with values were shown in Figure-3.

Results: The correlation coefficient values were within the limit 0.998 and Y-intercept values were within ± 2 %.

Accuracy (Recovery)

To study the accuracy of the method recovery experiments were carried out. The accuracy of the test method was determined by varying weights of crushed test sample at the level of 80%, 100% and 120% of targeted concentration. The recovery samples were prepared in triplicate at each level. The contents were determined from the respective chromatograms. The samples at different levels were chromatographed and the percentage recovery for the amount added was calculated. The values were given in Table-4.

Robustness - Effect of variation in Temperature and variation in flow rate

To study robustness of the test method, small, deliberate changes were made to the chromatographic condition. A study was performed by changing the temperature and flow rate. Standard solution prepared as per the test method and was injected into the HPLC system at 25°C temperature. Flow rate change was done by varying flow rate at from 0.5 mL/min to 0.4 mL/min and 0.6 mL/min.

The system suitability parameters were evaluated. The values were given in Table-5.

Solution Stability

To assess the solution stability, reference standard and test solutions were kept at 25 °C (laboratory temperature) for 24 hours, and injected in HPLC system at predetermined time interval.

The percentage change with respect to initial of test and reference standard solutions were evaluated. The values were given in Table-6.

CONCLUSION

A gradient RP-HPLC method has been developed and validated for the analysis of Lansoprazole, Pantoprazole sodium, Omeprazole, Rabeprazole sodium and Domperidone by RP-HPLC in tablet dosage forms. The results of the method validation revealed that the assay method is specific, selective, linear, accurate and robust. The validation performed further gives documented evidence, that the analytical method for the simultaneous estimation of Lansoprazole, Pantoprazole sodium, Omeprazole, Rabeprazole sodium and Domperidone by RP-HPLC in tablet dosage forms will consistently analyze these drugs quantitatively in combination and single dosage form and can be used for routine analysis in quality control and R&D laboratory.

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