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DEVELOPMENT AND VALIDATION OF A SENSITIVE AND SPECIFIC HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC METHOD FOR ASSAY OF A BINARY MIXTURE OF PANTOPRAZOLE AND DOMPERIDONE IN ORAL SOLID DOSAGE FORMULATIONS

Arindam Basu [1] and Jui Chakraborty [*2]

Department of Chemistry [1], Jadavpur University, Kolkata - 700032, West Bengal, India.
Bioceramics and Coating Division [2], CSIR Central Glass and Ceramics Research Institute, 196, Raja S.C. Mullick Road, Jadavpur, Kolkata - 700032, West Bengal, India.

Keywords:

High-performance liquid chromatography, Pantoprazole, Domperidone, Simple and accurate assay, Reverse phase chromatography

Correspondence to Author:
Jui Chakraborty

Senior Scientist,
CSIR Central Glass and Ceramics Research Institute, 196, Raja S.C. Mullick Road, Jadavpur, Kolkata - 700032, West Bengal, India.

E-mail: jui@cgcri.res.in

ABSTRACT: A simple new rapid, accurate, robust, and specific HPLC method was developed for the assay of pantoprazole and domperidone from the oral solid dosage pharmaceutical formulations. The reverse-phase chromatographic method was developed on an RP C8 column (250 mm × 4.6 mm, 5 µm) using a mixture of 25 mM sodium dihydrogen phosphate solution of pH 6.8 and methanol in the ratio 40:60 v/v as mobile phase in an isocratic mode of elution at a flow rate of 1.0 ml/min at 35 ºC with a load of 20 µl. The detection was carried out at 286 nm. The method was validated concerning linearity, robustness, precision, accuracy, specificity & stability as per ICH guidelines. The method produced excellent separation with good linear correlation coefficients (≥ 0.999) for both the components. The proposed method could be successfully applied for the assay of pantoprazole and domperidone in the various oral solid dosages pharmaceutical formulations, namely tablets and capsules in the sustained release form.

INTRODUCTION: Chemically pantoprazole is sodium 5- (difluoromethoxy)-2- [(RS)- [3, 4, -di methoxy pyridine-2-yl) methyl]sulphinyl] benzimidazole-ide sesquihydrate and belongs to the class of substituted benzimidazole. It is widely used in the treatment of gastric-related diseases. It is a proton pump inhibitor with action similar to those of omeprazole, but it is more acid-stable and has higher oral bioavailability.

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It is usually administered orally with a dose of 20-40 mg once daily in the treatment of gastro-oesophageal reflux diseases and finds a useful application in peptic ulcer diseases along with for NSAID-associated ulceration. The drug can also be administered intravenously as sodium salts.

On the contrary, domperidone is 5-chloro-1-{1-[3-(2-oxo-2,3-dihydro-1H1,3-benzodiazol-1yl)propyl] piperidine-4-yl}-2, 3-dihydro-1H-1, 3-enzodiazol-2-one is a dopamine antagonist with action and uses similar to those of metoclopramide. Popularly, it is used as an antiemetic for the short term treatment of nausea and vomiting of various aetiologies [1-3]. The chemical structures of both drugs pantoprazole and domperidone are given in **Fig. 1** and **Fig. 2,** respectively.

A literature survey revealed that few UV methods are available either for estimation of pantoprazole alone or in combination with domperidone from the finished formulations [4-5]. RP-HPLC methods for only domperidone with itopride in pharmaceutical and human plasma [6], estimation of *in-vivo* and *in-vitro* application of pantoprazole or related substances in pantoprazole [7-8] are available. HPLC method for pantoprazole and domperidone combinations in bulk and pharmaceutical dosage form is also reported [9]. The proposed method uses reliable combination of UV transparent phosphate buffer and methanol as mobile phase, and working wavelength was chosen at the absorption maxima of domperidone (286 nm). The selection of wavelength has given more freedom to work at a lower concentration level for domperidone and also offered a very wide range of linearity for both components. One advantage of the proposed method is in terms of selection of working pH of the mobile phase which is well below pk_a values of the pantoprazole and domperidone that enables the elution more robust concerning the small change of pH of the mobile phase. The method was subsequently validated following ICH guidelines [10].

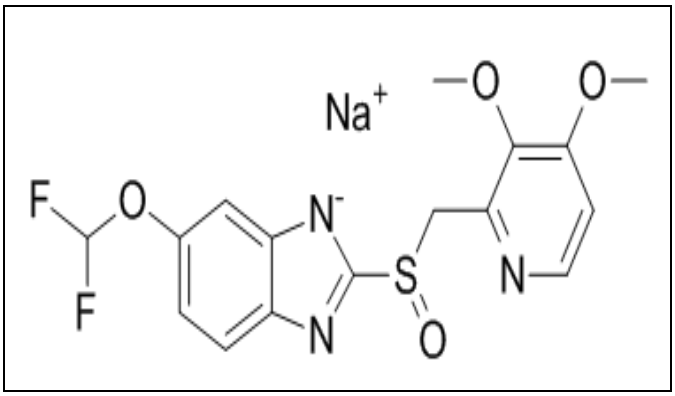

FIG. 1: CHEMICAL STRUCTURE OF PANTOPRAZOLE SODIUM

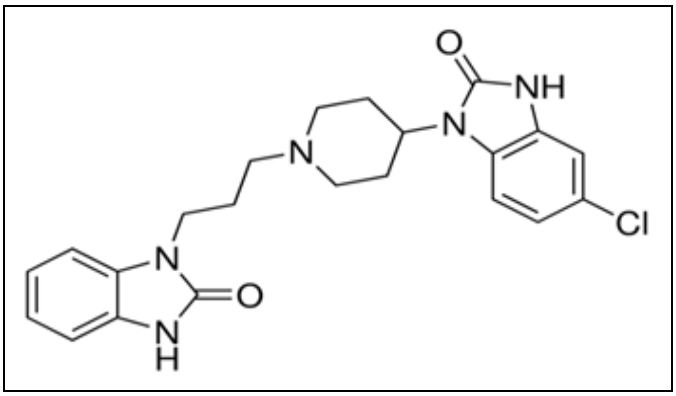

FIG. 2: CHEMICAL STRUCTURE OF DOMPERIDONE

MATERIALS AND METHODS: The pantoprazole and domperidone standards were obtained as a gift from Alkem Laboratories limited. The commercially available finished formulations of pantoprazole and domperidone used in the experiment namely Pantosec DSR, Pantocid DSR and Opan DSR containing 40 mg pantoprazole and 30 mg domperidone were procured from the market for the analysis purposes. The sodium dihydrogen phosphate and sodium hydroxide were of AR grade from Merck, HPLC grade methanol from Rankem was used in the experiment. Milli Q water was used for the preparation of buffer solution for the mobile phase. Glasswares used were of Borosil make. Millex Syringe filters of 0.45 µm, of Merck Millipore, were used to filter the sample solutions.

Instrumentation: The Lambda 45 UV visible spectrophotometer of Perkin Elmer make equipped with UV win Lab ES software version 6.0.4 was used for recording the UV spectrum. The Agilent 1200 series HPLC system with Quat Pump (Serial No G1311A), UV/VIS detector (1260 MWD VL G1365 D), EZchrome Elite software version (3.3.2 SP2), C8 column (Waters X Bridge 250mm x 4.6mm, 5 µm) and Ultrasound bath of PCI make were used in the experiment.

Chromatographic Condition: An isocratic mixture of 25 mM sodium dihydrogen phosphate solution of pH 6.8 and methanol in the ratio 40: 60 v/v was chosen as the mobile phase. The buffer solution was filtered through 0.45 µm Millex polyvinylidene difluoride membrane filter before the adjustment of pH. The pH of the buffer solution was adjusted to 6.8 with 10% NaOH solution and was mixed with methanol in the ratio buffer: methanol = 40:60. The mobile phase was ultrasonicated for 5 min to degas the mixture and then used. The separation was achieved on a C8 column (Waters X Bridge 250 mm × 4.6 mm × 5 µm) at a flow rate of 1.0 ml/min in an isocratic mode of elution. All determinations were performed at a constant column temperature of 35º C with a load of 20 µl of the mobile phase. The detection was carried out at 286 nm. The finalized chromatographic condition is given in **Table 1.**

TABLE 1: CHROMATOGRAPHIC CONDITION

Parameters	Conditions
Column	C8 (4.6 × 250 mm, 5µm)
Mobile phase	25mM sodium dihydrogen phosphate pH 6.8 : methanol 40:60 v/v
Diluent	1st dilution in methanol and subsequent dilution in the mobile phase
Flow rate	1.0 ml/min
Temperature	35 °C
Detection wavelength	286 nm
Injection volume	20 µl
Retention time	Pantoprazole 3.4 min, Domperidone 8.2 min

Assay of Formulations: The working concentration of pantoprazole and domperidone were selected as 100 µg/ml and 75 µg/ml, respectively. To assay the drug formulations a mixed standard stock solution having a concentration of 400 µg/ml pantoprazole sodium equivalent to pantoprazole and 300 µg/ml domperidone was prepared in methanol. The 5 ml of such a mixed standard solution was further diluted to 20 ml in the mobile phase to obtain a working concentration of 100 µg/ml pantoprazole and 75 µg/ml domperidone. To assay formulations containing pantoprazole sodium equivalent to pantoprazole, 40 mg and domperidone 30 mg were taken. Sample powder equivalent to 50 mg pantoprazole and 37.5 mg domperidone was weighed in 100 ml volumetric flask. About 80 ml of methanol was added, and the solution was ultrasonicated for 20 min. The resulting solution was cooled to room temperature, and volume was made up to the mark with methanol. Next, 5 ml of the solution was further diluted to 25 ml with mobile phase in order to have a final concentration of 100µg/ml for pantoprazole and 75 µg/ml for domperidone.

Method Validations: The proposed method was validated as per the ICH guidelines Q2 for Linearity, LOD, and LOQ, accuracy, precision, specificity, and robustness.

Linearity and Range: The linearity of a method is the ability to elicit test results that are directly proportional to the concentration of the analyte in samples. To construct the calibration curve, a mixed standard solution of pantoprazole and domperidone was prepared in methanol with each having a concentration of 500 µg/ml. The stock solution was further diluted in the mobile phase to obtain solutions having a concentration of 10, 20, 50, 75, 100, 125, 150, and 200 µg/ml for each component. Each solution was injected in triplicate, and the calibration curves for pantoprazole and domperidone were constructed by plotting peak area versus concentration. The obtained data were subjected to linear regression analysis using the least square method.

LOD and LOQ: The limit of detection (LOD) and limit of quantitation (LOQ) were determined as per ICH guidelines using equations (1) and (2) from the standard deviation of y-intercepts of the regression line.

$$LOD = 3.3 \times \sigma/S \quad .....(1)$$

$$LOQ = 10 \times \sigma/S \quad .....(2)$$

Where σ = standard deviation of the response;
S = slope of the regression line.

Accuracy: The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as true conventional value or an accepted reference value and the value found or measured. This is sometimes termed trueness. Accuracy of the proposed method was determined using standard addition method or recovery study by spiking standard pantoprazole and domperidone at three different levels of sample concentration (at 80%, 100%, and 120%) to the pre-analyzed sample of pantoprazole- domperidone combination. Three different marketed formulations namely Pantocid DSR, Pantosec DSR and Opan DSR (with the claim of pantoprazole 40 mg and domperidone 30 mg) were taken as sample for accuracy. The target concentration for the method was 100 µg/ml for pantoprazole and 75 µg/ml for domperidone (100% level). For each of three brands sample powder equivalent to 13 mg of pantoprazole and 10 mg, domperidone was weighed in separate 50 ml volumetric flasks. To each of the flasks, the measured amount of pantoprazole and domperidone standards (at 80%, 100% and 120% level of pantoprazole and domperidone contributed from the sample) were added. Subsequently, each solution was diluted to five folds with mobile phase and injected in replicate.

Precision: The precision of an analytical procedure expresses the closeness of agreement (degree of

scattering) between a series of measurements under the prescribed conditions and is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements. To evaluate the precision and reproducibility of the proposed method, repeatability, inter-day, and interday analyses were carried out. For repeatability test, pre-analysed a sample of pantoprazole, and domperidone combination were subjected to assay at 3 different levels, *i.e.* 50%, 100% and 150% of the entire concentration range in triplicate. Assay was done against a mixed standard solution of 100 µg/ml pantoprazole and 75 µg/ml domperidone (100% concentration level). The interday and intraday precisions were also carried out on three different commercially available formulations at three different concentration levels.

Specificity: Specificity is the ability to assess the analyte unequivocally in the presence of components which may be expected to be present. To carry out specificity analysis, the pre-analyzed sample was taken, and the solution was prepared in methanol following the method as directed under assay of formulations. Separately 2 ml of such sample solution (494.6 µg/ml pantoprazole and 371 µg/ml domperidone) were subjected to various stress conditions like exposure to water, heat, and oxidative hydrolysis, UV light, acidic and alkaline hydrolysis for specified periods. A portion of the same sample solution was kept under the refrigerated condition and also at ambient condition for overnight. Finally, each of 2 ml of stress-induced solutions, as well as sample solutions kept under refrigerated and ambient conditions were diluted five-folds with mobile phase to have a final concentration of pantoprazole around 100 µg/ml and domperidone around 75 µg/ml. Each solution was assayed against a freshly prepared mixed standard of pantoprazole (101.6 µg/ml) and domperidone (74.3 µg/ml). The assay results were compared against the assay of freshly prepared solution of the same sample having a concentration of 99.44 µg/ml pantoprazole and 74.56 µg/ml domperidone.

Robustness: The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage. One consequence of the evaluation of robustness study should be that a series of system suitability parameters are established to ensure that the validity of the analytical procedure is maintained whenever used. A mixed standard solution containing 100 µg/ml of pantoprazole and 75 µg/ml of domperidone was prepared, and replicate injections were given. A pre-analyzed sample taken, and the solution was also prepared following method as directed under assay of formulations with an exact concentration of 99.44 µg/ml pantoprazole and 74.6 µg/ml domperidone. To evaluate the robustness study, some small deliberate variations in chromatographic parameters like change in flow rate (± 0.1 ml/min), detection wavelength (± 2 nm), column temperature (± 2 ºC), ratio of buffer to methanol in mobile phase and pH of buffer (± 0.1 unit) used in mobile phase were done. Under each varied condition, replicate injections of mixed standard and sample solutions were given to assay the sample and to see the effect of such deliberate variation on the assay value of the sample.

RESULTS AND DISCUSSION:

Method Development: The HPLC method was developed and optimized after a series of trials in terms of selection of mobile phase composition and its pH, detection wavelength, choice of the stationary phase of column, flow rate and column temperature. To select the detection wavelength, UV spectrum of pantoprazole (0.001% w/v), domperidone (0.001% w/v) and pantoprazole-domperidone mixed standard (containing 0.0005% w/v each) in methanol were recorded. The overlay UV spectrum is represented in **Fig. 3**.

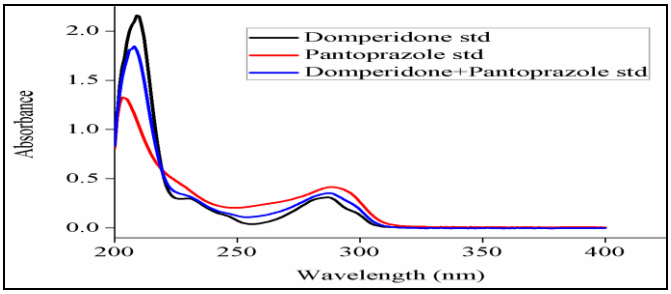

FIG. 3: OVERLAY UV SPECTRUM OF PANTOPRAZOLE, DOMPERIDONE STANDARDS INDIVIDUALLY AND PANTOPRAZOLE – DOMPERIDONE MIXED STANDARD

Pantoprazole showed absorption maxima at 288 nm while that for domperidone was found to be at 286 nm. However, keeping the view of the lower ratio of domperidone in the finished formulation of

pantoprazole-domperidone combination drugs, 286 nm was chosen as the working wavelength for the HPLC method. Several buffers at different pH were tried as a component of the mobile phase; however, considering the pKa values for pantoprazole (3.92 and 8.19) and domperidone (7.9) the pH of 25 mM NaH_2PO_4 buffer was kept at 6.8.

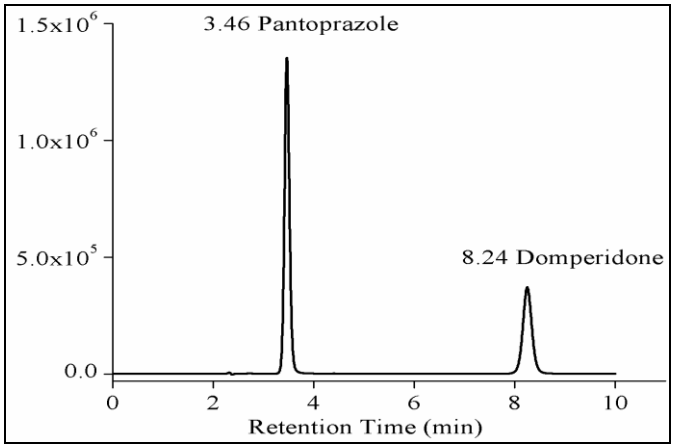

FIG. 4: REPRESENTATIVE CHROMATOGRAM OF PANTOPRAZOLE – DOMPERIDONE MIXED STANDARD SOLUTION

Method Validation: The optimum ratio for methanol to buffer was finalized at 60:40 at a flow rate of 1.0 ml/min. The separation was achieved on a C8 column maintained at 35 ºC. 20 µl injections were given for both the sample and standard solutions. Mean retention time was found to be 3.46 min and 8.24 min for pantoprazole and domperidone, respectively. A representative chromatogram of mixed standard for pantoprazole and domperidone is shown in **Fig. 4.**

Linearity, Range and LOD-LOQ: The regression equations for pantoprazole and domperidone were found to be y = 94215x-55223 and y = 68350x-48594, respectively. The calibration curves were found to be linear within the concentration range of 10-200 µg/m with a correlation coefficient value 0.999 for both components. The calibration curves for pantoprazole and domperidone are given in **Fig 5** and **Fig. 6,** respectively. The limit of detection (LOD) for pantoprazole and domperidone were found to be 1.893 µg/ml and 0.18 µg/ml respectively while the limit of quantitation (LOQ) was found to be 5.736 µg/ml for pantoprazole and 0.547 µg/ml for domperidone respectively. The results are reported in **Table 2**.

TABLE 2: LINEAR REGRESSION DATA FOR PANTOPRAZOLE AND DOMPERIDONE

Parameter	Pantoprazole	Domperidone
Regression equation	Y = 94215x - 55223	Y = 68350x-48594
Concentration range (µg/ml)	10-200	10-200
Slope	94215	68350
Intercept	-55223	- 48594
R^2	0.999	0.999

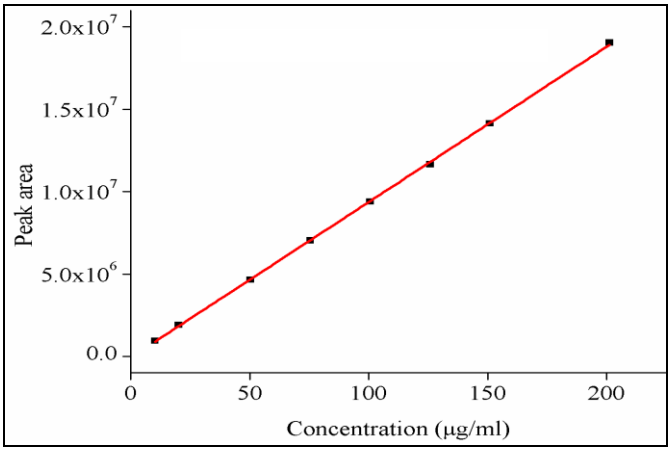

FIG. 5: CALIBRATION CURVE OF PANTOPRAZOLE STANDARD

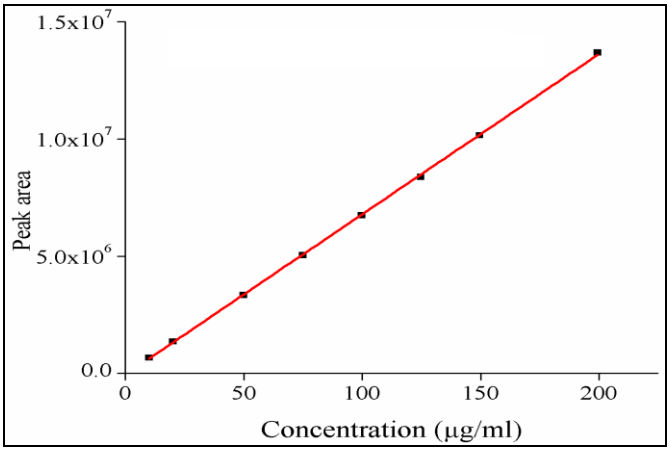

FIG. 6: CALIBRATION CURVE OF DOMPERIDONE STANDARD

Accuracy: The amount of drug recovered was calculated in each case. The percentage of recovery was calculated by using the following formula = (Amount of drug recovered in mg/ Amount of drug added) in mg × 100 and the result for all the nine determinations is presented in **Table 3** for pantoprazole and domperidone. The method was proved to be very accurate as the recovery for pantoprazole was 97.8%-100.68% while that for domperidone was 97.02-101.87% for all the three levels, *i.e.* 80%, 100%, and 120%.

TABLE 3: ACCURACY RESULTS FOR PANTOPRAZOLE AND DOMPERIDONE

% of standard spiked	Sets	Pantoprazole standard			Domperidone standard		
		Added (mg)	Recovered (mg)	Recovery (%)	Added (mg)	Recovered (mg)	Recovery (%)
80%	Rec. 1	11.6	11.55	98.57	7.7	7.55	98.05
	Rec. 2	11.7	11.49	98.21	7.7	7.56	98.18
	Rec. 3	11.7	11.78	100.68	7.5	7.64	101.87
100%	Rec. 1	14.4	14.25	98.96	9.4	9.12	97.02
	Rec. 2	14.7	14.65	99.66	9.6	9.47	98.65
	Rec. 3	14.6	14.31	98.01	9.4	9.23	98.19
120%	Rec. 1	17.3	17.16	99.19	11.7	11.39	97.35
	Rec. 2	17.4	17.2	98.85	11.3	11.06	97.88
	Rec. 3	17.3	16.92	97.8	11.6	11.41	98.36

Precision: The results of five replicate injections of mixed standard solutions showed very low %RSD for retention time, area of both components, and also for system suitability parameters. For all nine determinations, the assay of pantoprazole showed confidence interval (in %) 99.24 ± 0.76, while domperidone showed 99.92 ± 0.87. The % RSDs for nine determinations were found to be 1.17% for pantoprazole, and 1.33% for domperidone, and results are reported in **Table 4**. The interday and intraday precisions results for assay were found to be very precise with low % RSD for both components of all three brands, and results were summarised in **Table 5**.

TABLE 4: REPEATABILITY SUMMARY

Sets	Pantoprazole			Domperidone		
	µg/ml	Area	Assay (%)	µg/ml	Area	Assay (%)
Set 1	50.3	4731199	98.9	37.7	2466733	101.97
Set 2	50.1	4692863	98.48	37.6	2386227	98.9
Set 3	50.2	4699795	98.43	37.7	2462854	101.8
Set 1	101.3	9435544	97.93	76	4823265	98.9
Set 2	98.2	9291630	99.48	73.6	4732036	100.2
Set 3	100.2	9354556	98.15	75.1	4737362	98.3
Set 1	150.5	14396437	100.58	112.9	7190368	99.23
Set 2	151.4	14584153	101.28	113.5	7338827	100.77
Set 3	151	14348160	99.9	113.2	7207535	99.23
Mean			99.24			99.92
SD			1.156			1.332
% RSD			1.17			1.33
Confidence Interval			99.24 ± 0.76			99.92 ± 0.87

TABLE 5: INTERDAY AND INTRADAY PRECISION

Brand	Days	Sets	Pantoprazole		Domperidone	
			Assay (mg)	Assay (%)	Assay (mg)	Assay (%)
Brand 1		Set 1	39.39	98.48	29.49	98.3
	Day 1	Set 2	39.29	98.23	29.42	98.07
		Set 3	39.67	98.18	29.5	98.33
	Day 2	Set 1	39.06	97.65	29.45	98.17
		Set 2	38.88	97.2	28.84	96.13
		Set 3	39.03	97.58	29.43	98.1
Mean ± SD			39.22 ± 0.288	98.05 ± 0.721	29.36 ± 0.254	97.85 ± 0.849
Confidence interval			39.22 ± 0.23	98.05 ± 0.58	29.36 ± 0.2	97.86 ± 0.849
Brand 2		Set 1	39.4	98.5	29.56	98.53
	Day 1	Set 2	39.64	99.1	29.65	98.83
		Set 3	39.62	99.05	29.43	98.1
	Day 2	Set 1	39.65	99.13	29.33	97.77
		Set 2	39.6	99	29.54	98.47
		Set 3	39.43	98.58	29.59	98.63
Mean± SD			39.56 ± 0.111	98.89 ± 0.278	29.52 ± 0.117	98.39 ± 0.386
Confidence interval			39.56 ± 0.09	98.89 ± 0.22	29.52 ± 0.09	98.39 ± 0.31
Brand 3		Set 1	38.65	96.63	29.37	97.9
	Day 1	Set 2	38.8	97	29.87	99.57

		Set 3	38.78	96.95	29.53	98.43
	Day 2	Set 1	38.41	96.03	29.48	98.27
		Set 2	38.06	95.15	29.64	98.8
		Set 3	38.3	95.75	29.64	98.8
Mean± SD			38.5 ± 0.294	96.25 ± 0.736	29.59 ± 0.172	98.63 ± 0.573
Confidence interval			38.5 ± 0.24	96.25 ± 0.59	29.59 ± 0.14	98.63 ± 0.46

Specificity: Pantoprazole was found to be degraded somewhat under ambient storage (assay 92.73%), by heat (assay 82.28%), H_2O_2 (assay 85.45%) and UV light (assay 77.8%) and it was almost totally degraded by 0.1N HCl solution. Acid degradation produced about 11 degradation products in the sample. However, domperidone was found to be quite stable under ambient storage for 24 h and also under all stressed conditions showing assay values between 94%-99.9%. The chromatogram for forced degradation by UV light and 0.1 N HCl is represented in **Fig. 7** & **Fig. 8,** respectively.

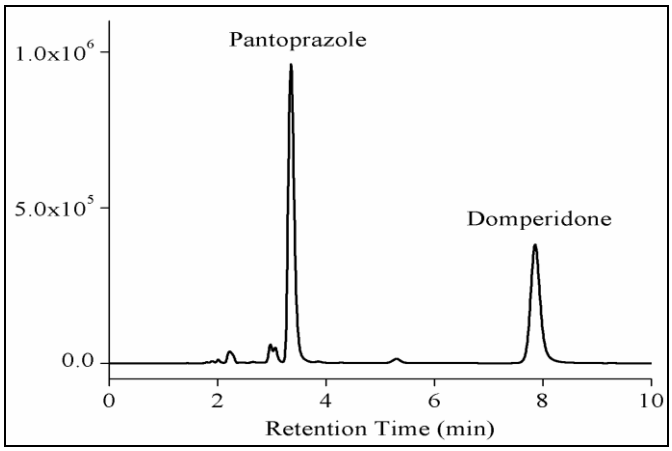

FIG. 7: FORCED DEGRADATION BY UV LIGHT

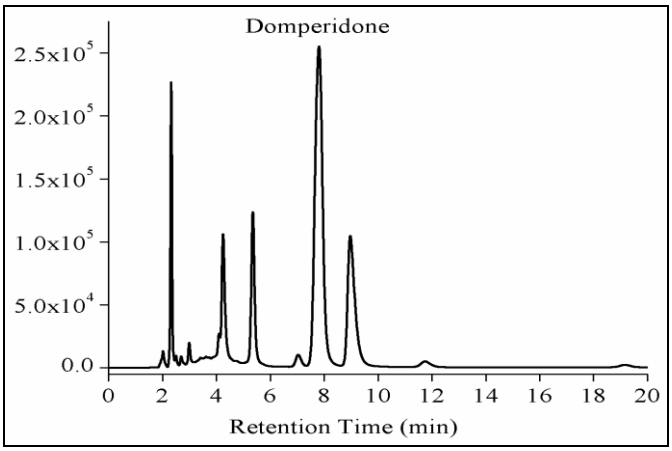

FIG. 8: FORCED DEGRADATION BY 0.1 N HCl

Robustness: The method was found to be very robust as deliberate variations did not lead to an appreciable change in peak shape, system suitability parameters like tailing factor, plate count, and resolution. The summary of the assay of the sample under deliberately varied conditions is given in **Table 6**.

TABLE 6: ROBUSTNESS DATA FOR ASSAY UNDER VARIED CONDITIONS

Parameters	Experimental conditions	Pantoprazole		Domperidone	
		Assay (mg)	Assay (%)	Assay (mg)	Assay (%)
Wavelength	284	40.03	100.08	30.76	102.53
	286	39.91	99.78	30.75	102.50
	288	40.04	100.1	30.73	102.43
Flow rate	0.9	39.65	99.13	30.60	102.00
	1.0	39.91	99.78	30.75	102.50
	1.1	40.8	102.0	31.05	103.50
Temperature	33ºC	39.98	99.95	30.73	102.43
	35ºC	39.91	99.78	30.75	102.50
	37ºC	39.15	97.88	30.10	100.33
CH_3OH :buffer	58:42	39.61	99.03	30.46	101.53
	60:40	39.91	99.78	30.75	102.50
	62:38	38.45	96.13	29.99	99.97
pH	6.7	38.48	96.20	29.81	99.37
	6.8	39.91	99.78	30.75	102.50
	6.9	38.83	97.08	28.90	96.33
Mean ± SD		39.64 ± 0.643	99.10 ± 1.608	30.46 ± 0.55	101.53 ± 1.83
% RSD		1.62	1.62	1.81	1.8
Confidence interval		39.64 ± 0.33	99.10 ± 0.81	30.46 ± 0.28	101.53 ± 0.93

System Suitability Testing: System suitability is an integral part of the method validation study. System suitability testing is used to verify that the reproducibility of the system is adequate for the analysis to be performed. System suitability was assessed from the replicate injections of mixed standards solution of pantoprazole and domperidone under optimized chromatographic conditions. Parameters such as theoretical plates, tailing factor, capacity factor were determined. The system suitability parameters for the method are listed below in **Table 7.**

TABLE 7: SYSTEM SUITABILITY PARAMETERS

Parameters	Pantoprazole	Domperidone
Concentration range (µg/ml)	10-200	10-200
Retention time (min)	3.46	8.24
Theoretical plate	5400	9300
Tailing factor	1.16	1.05
Capacity factor (*k'*)	3.9	10.7
Resolution	-	18.2
LOD (µg/ml)	1.893	0.18
LOQ (µg/ml)	5.736	0.547

CONCLUSION: The proposed method is supported by full validation parameters and proved to be very specific as all degradants produced during forced degradation study are found to be well separated from the peak of interests. The robustness is established from precise assay results (low % RSD) obtained under varied chromatographic conditions. The method offers simplicity in terms of short analysis time, isocratic mode of elution, easy sample preparation technique and wide concentration range, low LOD-LOQ values for both components, an effective resolution with reproducible system suitability parameters. The method has produced good accurate results for finished product formulations without any interference from the excipients or any degradation products. So, these advantages make this method reliable for the intended purpose.

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