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DEVELOPMENT AND VALIDATION OF RP-HPLC METHOD FOR DISSOLUTION STUDY OF PANTOPRAZOLE SODIUM AND DOMPERIDONE IN CAPSULE DOSAGE FORM

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ABSTRACT

RP-HPLC method for dissolution study of Pantoprazole sodium and Domperidone in capsule dosage form was developed and validated. In RP-HPLC method for Pantoprazole sodium and Domperidone, chromatographic separation was carried out on Waters spherisorb®, 5µm, ODS (250 mm L × 4.6 mm Ø in size) column using mobile phase mixture comprising a Methanol:Acetonitrile (90:10 % v/v) and flow rate 1.0 ml/min at 288 nm. RP-HPLC method was developed with linearity range of 2 - 24 µg/ml and 1.5 - 18 µg/ml for Pantoprazol sodium and Domperidone respectively. The average retention times for Pantoprazole sodium and Domperidone were found to be 2.99 and 6.48 min respectively. Validation of developed method was performed according to ICH Q2 (R1) guideline. In vitro drug release studies of the sustained release capsule were conducted for a period of 24 hours by using an IP Type II (Basket) Dissolution apparatus (PLC Dissolution Rate Test Apparatus U.S.P/B.P/I.P. STD) at 37± 0.5°C temperature. The agitation speed was 100 rpm. The dissolution study was carried out in 900 ml of 0.1 N hydrochloric acid for first 2 hours, in 900 ml of 0.2 M phosphate buffer (pH 6.8) within 5 hours and then in 900 ml of 0.2 M phosphate buffer (pH 7.4) within 24 hours. Pantoprazole sodium and Domperidone sustained release capsules mean % cumulative release is 97.02 ± 1.7611 for Pantoprazole sodium within 7 hrs and 94.46 ± 1.9395 for Domperidone within 24 hrs. The result of the peak area obtained by the drug injected every hour upto 24 hrs was compared with the assay result obtained by performing the RP-HPLC method of

Pantoprazole sodium and Domperidone in the mobile phase of Methanol:Acetonitrile(90:10 %v/v).

KEY WORDS: RP-HPLC, In vitro Dissolution study, Pantoprazole sodium, Domperidone, Sustained release capsule.

INTRODUCTION

Pantoprazole sodium, chemically 5-[difluoromethoxy]-2-[[(3,4-dimethoxy-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole.[1] It is a newer H^+ K^+ ATPase inhibitor, similar in potency and clinical efficacy to omeprazole, but is more acid stable and has higher oral bioavailability. It has lower affinity for cytochrome P450 than omeprazole or lansoprazole: risk of drug interaction is minimal.[2] Proton pump inhibitors decrease secretion of gastric acid. They act by blocking the last enzyme in the system that actively transports acid from gastric parietal cells into the gastrointestinal lumen, hydrogen–potassium adenosine triphosphatase, also known as the proton pump. Pantoprazole sodium is used for short-term treatment of erosion and ulceration of the esophagus for adults and pediatric patients 5 years of age and older caused by gastroesophageal reflux disease. It can also be used for long-term treatment of Zollinger-Ellison syndrome.[3]

Domperidone, Chemically 5-chloro-1-[1-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazole-1-yl) propyl]-piperidin-4-yl]-1,3-dihydro-2H-benzimidazol-2-one is an antiemetic drug.[4] Domperidone is a peripherally selective dopamine D2 and D3 receptor antagonist. It has no clinically significant interaction with the D1 receptor, unlike metoclopramide.The drug provides relief from nausea by blocking receptors at the chemoreceptor trigger zone (a location in the nervous system that mediates nausea) at the floor of the fourth ventricle (a location near the brain).[5]

Literature survey revealed that, there are some methods available for estimation of Pantoprazole sodium and Domperidone in individual and in combined (with other drugs) dosage forms by UV Spectroscopic and HPLC. But, still there is not a single method existing for dissolution study of Pantoprazole sodium and Domperidone in capsule dosage form. Which contains Pantoprazole sodium enteric coated and Domperidone in sustained release form.

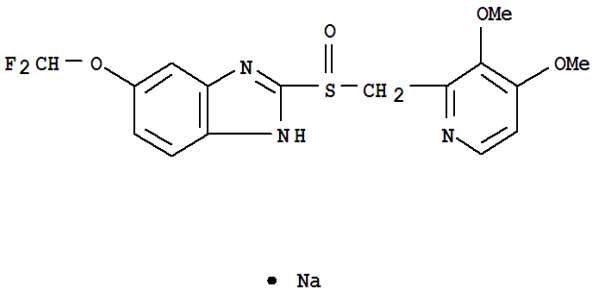

Fig 1: Pantoprazole sodium.[1]

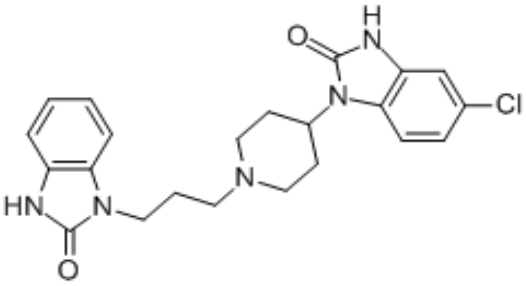

Fig 2: Domperidone.[4]

MATERIALS AND METHODS

Reference standard of Pantoprazole sodium was procured from Intas Pharmaceuticals ltd., Ahmedabad. Reference standard of Domperidone was procured from Mahrshee Laboratories Pvt. Ltd., Bharuch. Formulation of Pantoprazole sodium and Domperidone in market available as capsule and procured from local market of Rajkot. Reagent includes Methanol, Water and Acetonitrile HPLC grade (Merck Pvt. Ltd., Mumbai), HCl, NaOH, Phosphate buffer, Sartorius Filter Paper 0.20 µ, 47 mm Ø (Sartorius, Germany).

Instrumentation

Instruments used in the study were

For UV-visible spectrophotometer (Shimadzu 1800- Double beam spectrophotometer) with Quartz cuvette pair with 1 cm path length at 800 – 200 nm scanning range.

For RP-HPLC (Young - Linn Clarity 9100) arranged with a Quaternary pump YL – 9110, Vacuum degasser YL – 9101, Rhenodyne Injector with 20 µl loop, column was Waters spherisorb®, 5µm, ODS (250 mm L × 4.6 mm Ø) and PDA detector YL – 9160.

For Dissolution study (PLC Dissolution Rate Test Apparatus U.S.P/B.P/I.P. STD) IP apparatus Type II (Basket type), set Temperature 37 ±0.5^{0}C and Speed 100 rpm.

Experimental

RP-HPLC METHOD

Preparation of Mobile Phase

The HPLC grade Methanol and Acetonitrile were filtered through 0.2 µm membrane filter paper separately. Filtered solutions were ultrasonicated for 20 min. Solutions were allowed to come at room temperature if they were warmed due to sonication.

Preparation of working standard stock solution of Pantoprazole sodiun

Accurately weighed 10 mg of Pantoprazole sodium was transferred to 10 ml volumetric flask, dissolved and diluted up to mark with methanol to obtain final concentration of 1000 µg/ml Pantoprazole sodium. Solution was further diluted with methanol to obtain working standard solutions of 100 µg/ml of Pantoprazole sodium. This solution was filtered through 0.2 µm membrane filter paper and sonicated for 5 min.

Preparation of working standard stock solution Domperidone

Accurately weighed 10 mg of Domperidone was transferred to 10 ml volumetric flask, dissolved and diluted upto mark with methanol to obtain final concentration of 1000 µg/ml Domperidone. Solution was further diluted with methanol to obtain working standard solutions of 100 µg/ml of Domperidone. This solution was filtered through 0.2µm membrane filter paper and sonicated for 5 min.

Selection of suitable wavelength for analysis

Solution containing appropriate concentration of 10 µg/ml Pantoprazole sodium and 10 µg/ml Domperidone in methanol were scanned using UV spectrophotometer in spectrum mode in range of 400-200 nm and their spectra were overlaid from the overlaid spectra of both the drugs analytical wavelength was selected. Fig 1.

Preparation of calibration curve of Pantoprazole sodium and Domperidone

Accurately weighed quantity of 40 mg of Pantoprazole sodium and 30 mg of Domperidone were transferred into 50 ml volumetric flask, dissolved and diluted up to mark with methanol to obtained final concentration 800 µg/ml of Pantoprazole sodium and 600 µg/ml of Domperidone. Solution was further diluted with methanol to obtained working standard solution 40 µg/ml of Pantoprazole sodium and 30 µg/ml of Domperidone. By appropriate dilution using methanol, from working standard solutions of Pantoprazole sodium and Domperidone, standard mixture containing 2 + 1.5, 4 + 3, 8 + 6, 12 + 9, 16 + 12, 20 + 15 and

24 +18 µg/ml of Pantoprazole sodium and Domperidone were prepared. These solutions were filtered through 0.20 µm membrane filter paper and sonicated for 10min. Prepared solution was injected to system with stated chromatographic conditions as described above. The chromatogram was stopped after separation achieved completely. Peak areas were recorded using YL - Clarity software (Ver.3.0.04.444). Concentration of Pantoprazole sodium and Domperidone were computed by putting value of their peak areas in respective standard regression equation obtained from calibration curve. Fig 2, 3.

METHOD VALIDATION

The optimized chromatographic condition where validated by evaluating linearity, limit of detection (LOD), limit of quantification (LOQ), accuracy and precision as per ICH Guideline.[6,7]

Linearity and range

Linearity was determined by plotting the standard curve in the concentration range of Pantoprazole sodium 2-24 µg/ml and Domperidone 1.5-18 µg/ml. Fig 4. The linearity of the methods was evaluated by linear regression analysis. Table 1.

LOD and LOQ

The limit of detection (LOD) and limit of quantitation (LOQ) parameters were calculated using the following equations; LOD = 3.3 σ\S and LOQ = 10 σ\S, where σ is standard deviation of y-intercept of calibration curve (n=6) and S is slope of regression equation. Table 2.

Accuracy

These studies were performed for both Pantoprazole sodium and Domperidone at three different levels (50%, 100% and 150%), the mixture were analyzed by the proposed method. Standard deviation (SD) and Relative standard deviation (RSD) of both drugs was calculated Table 3.

Precision

The repeatability was evaluated by assaying 6 times of sample solution prepared for assay determination. The intraday and interday precision study of Pantoprazole sodium and Domperidone was carried out by estimating different concentrations of both drugs, 3 times on the same day and on 3 different days respectively. Table 4.

Specificity

Specificity of the method was evaluated by injecting the blank sample, standard sample separately into HPLC. The subjected drug peaks of Pantoprazole sodium and Domperidone were evaluated with PDA detector. Table 5.

Robustness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate change in method parameters and provides an indication of its reliability during normal usage. Robustness of the method was investigated under a variety of condition like change in flow rate by ±0.2ml/min and change in mobile phase composition. Table 6.

System suitability

The system suitability parameter with respect to theoretical plates, resolution peak and tailing factor were established. Table 7.

APPLICATION OF DEVELOPED RP-HPLC METHOD TO THE DISSOLUTION STUDY OF PANTOPRAZOLE SODIUM AND DOMPERIDONE

Preparation of Dissolution Medium

Preparation of Dissolution Medium 0.1N HCl

35.7 ml of 36 % pure concentrated HCl was added to distilled water to prepare 6 litres of 0.1N HCl.

Preparation of Dissolution Medium (Phosphate Buffer 6.8 pH)

1.5 litres of 0.2 M Potassium dihydrogen phosphate and 672 ml of 0.2 M NaOH were added to distilled water to prepare 6 litres of 0.2M phosphate buffer 6.8 pH.

Preparation of Dissolution Medium (Phosphate Buffer 7.4 pH)

1.5 litres of 0.2 M Potassium dihydrogen phosphate and 1.173 litres of 0.2 M NaOH were added to distilled water to prepare 6 litres of 0.2M phosphate buffer 7.4 pH.

Preparation of 1N NaOH

2g of Sodium Hydroxide was dissolved in sufficient amount of methanol to produce 50 ml of 1N NaOH.

Procedure for Dissolution Study

900 ml of dissolution medium (0.1N HCl) was transferred in to each vessel of dissolution apparatus. The capsule was placed at each of the basket of vessels. The baskets were lowered up to the specified position. Then rpm was set to 100 and temperature to 37 ± 0.5ºC.

5 ml of sample was withdrawn from each of the vessel at 0, 0.5, 1, 2 hours from the zone midway between the surface of the dissolution medium and the top of vessel, not less than 100 mm from the wall of the vessel.

The medium withdrawn for analysis was replaced with equal volume of fresh medium.
Each Sample which was withdrawn from the 0.1 N HCl dissolution medium was neutralized with 1 N NaOH before it was measured by HPLC.

After 2 hour, capsule contents were transferred in 900ml of 0.2M Phosphate Buffer 6.8 pH within 10 minutes and dissolution conditions were set as it were set in 0.1 N HCl.

5 ml of sample was withdrawn from each of the vessel at 3, 4 and 5 hours from the zone midway between the surface of the dissolution medium and the top of vessels, not less than 100 mm from the wall of the vessel.

The medium withdrawn for analysis was replaced with equal volume of fresh medium.

After 5 hour, capsule contents were transferred in 900ml of 0.2M Phosphate Buffer 7.4 pH within 10 minutes and dissolution conditions were set as it were set in above.

5 ml of sample was withdrawn from each of the vessel at 6, 7, 8, 9, 10, 11, 12, 24 hours from the zone midway between the surface of the dissolution medium and the top of vessels, not less than 100 mm from the wall of the vessel.

The medium withdrawn for analysis was replaced with equal volume of fresh medium. Samples were measured by HPLC.

The result of the peak area obtained by the drug injected every hour upto 24 hrs was compared with the assay result obtained by performing the RP-HPLC method of Pantoprazole sodium and Domperidone in the mobile phase of Methanol:Acetonitrile (90:10 %v/v).

The compared data was used to calculated the % drug release of the formulation for 24 hrs. Data of dissolution profile are represented in the Table 8 and Fig.5 for Pantoprazole sodium and in the Table 9 and Fig.6 for Domperidone respectively. Mean % cumulative release of Pantoprazole sodium and Domperidone are shown in Table 10 and Fig.7.

TABLES AND FIGURES

Table 1: Result of Range and Linearity study by RP-HPLC method.

Parameter	Pantoprazole sodium	Domperidone
Range	2-24 µg/ml	1.5-18 µg/ml
Linearity equation	y = 66.62x + 136.4	y = 37.27x + 123.2
Regression coefficient	R^2 = 0.999	R^2 = 0.999

Table 2: Result of LOD and LOQ study by RP-HPLC method.

Parameter	Pantoprazole sodium	Domperidone
LOD	0.0794 µg/ml	0.2110 µg/ml
LOQ	0.2408 µg/ml	0.6387 µg/ml

Table 3: Result of accuracy by RP-HPLC method.

Sr. No.	Drugs	Amount of sample taken (µg/ml)	Recovery level (n=6)	Amount of std added (µg/ml)	Amount of drug found (µg/ml)	% recovery	SD (n=3)	% RSD
1	Pantoprazole sodium	3.6	50%	2.4	5.98	99.61	0.7518	0.7547
			100%	8.4	11.93	99.39	0.2957	0.2975
			150%	14.4	17.95	99.74	0.3365	0.3374
2	Domperidone	2.7	50%	1.8	4.47	99.60	0.1680	0.1687
			100%	6.3	8.91	99.37	0.3593	0.3616
			150%	10.8	13.44	99.56	0.3361	0.3376

Table 4: Result of precision by RP-HPLC method.

Sr. No.	Drugs	Conc. (µg/ml)	Repeatability(n=6) Mean AUC (mV.s) ± SD	Intraday (n=3) Mean AUC (mV.s) ± SD	Interday (n=3) Mean AUC(mV.s) ± SD	Repeatability %RSD	Intra day %RSD	Inter day %RSD
1	Pantoprazole sodium	8		673.832±11.5041	669.562±7.8089		1.7074	1.1685
		12	971.963±9.4642	956.331±7.5350	966.371±9.3376	0.9737	0.7819	0.9556
		16		1211.321±9.0840	1216.651±18.2272		0.7494	1.4732
2	Domperidone	6		355.421±5.0543	354.268±5.4174		1.4250	1.5566
		9	465.106±7.3848	466.913±7.1898	463.245±6.5219	1.5878	1.5613	1.3870
		12		562.432±4.2525	556.325±8.8117		0.7559	1.5983

Table 5: Result of Specificity Study by RP-HPLC Method.

Sr. No.	Concentration (µg/ml)	Mean Peak purity (Pantoprazole sodium)	Concentration (µg/ml)	Mean Peak purity (Domperidone)
1	12	992	9	992.83

Table 6: Result of Robustness by RP-HPLC method.

Variation and level		Conc. (µg/ml)	AUC (mV.s)	Mean (n=3)	SD	RSD
Pantoprazole sodium						
Change in flow rate	0.8 ml/min	12	969.312	952.449	15.4054	1.6175
	1.0 ml/min	12	948.921			
	1.2 ml/min	12	939.113			
Change in mobile phase composition (% v/v)	M:A : 88:12	12	975.231	968.677	6.2089	0.6410
	M:A : 90:10	12	967.918			
	M:A : 92:08	12	962.883			
Domperidone						
Change in flow rate	0.8 ml/min	9	476.982	469.691	7.3832	1.5719
	1.0 ml/min	9	469.872			
	1.2 ml/min	9	462.219			
Change in mobile phase composition (% v/v)	M:A : 88:12	9	478.791	469.048	8.8699	1.8910
	M:A : 90:10	9	466.913			
	M:A: 92:08	9	461.441			

Table 7: Result of System suitability parameters by RP- HPLC method.

Sr.No.	Parameters	Value Obtained		Standard Value
		Pantoprazole sodium	Domperidone	
1	**Retention Time (R_t)**	2.99 min	6.48 min	-
2	**Theoretical plates (N) or Column Efficiency**	5470	2545	Should be >2000
3	**Resolution (R_s)**	8.1162		> 2
4	**Tailing factor (A_s) or Symmetry factor**	1.177	1.145	< 2

Table 8: Dissolution profile data of Pantoprazole sodium.

Time (hr)	% Cumulative Drug Release							
	T-1	T-2	T-3	T-4	T-5	T-6	Mean (n=6)	SD (n=6)
0	0	0	0	0	0	0	0	0
0.5	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
3	28.44	38.05	25.98	27.01	32.56	27.88	30.87	4.5471
4	68.23	62.86	52.12	49.92	58.45	47.95	56.35	7.9672

5	96.62	94.98	83.09	85.82	90.64	87.92	95.74	5.2618
6	97.05	95.86	92.68	94.09	96.65	96.81	97.02	1.7611
7	-	-	-	-	-	-	-	-
8	-	-	-	-	-	-	-	-
9	-	-	-	-	-	-	-	-
10	-	-	-	-	-	-	-	-
11	-	-	-	-	-	-	-	-
12	-	-	-	-	-	-	-	-
24	-	-	-	-	-	-	-	-

Table 9: Dissolution profile data of Domperidone.

Time (hr)	% Cumulative Drug Release							
	T-1	T-2	T-3	T-4	T-5	T-6	Mean (n=6)	SD (n=6)
0	0	0	0	0	0	0	0	0
0.5	7.26	5.89	6.08	4.82	7.16	5.64	6.14	0.9330
1	15.95	12.16	13.06	9.52	14.96	10.19	12.64	2.5488
2	29.46	23.91	25.52	21.42	28.23	22.69	25.21	3.1522
3	36.23	31.3	33.85	29.06	37.43	30.05	32.99	3.4028
4	42.65	39.55	40.86	38.92	43.75	39.56	40.88	1.9351
5	50.89	47.52	49.55	46.91	52.26	46.85	48.99	2.2664
6	54.02	50.92	53.65	49.71	58.09	48.85	52.54	3.4197
7	57.92	56.52	57.84	53.22	61.95	51.06	56.42	3.8425
8	62.55	59.54	60.66	58.94	63.13	57.07	60.32	2.2829
9	66.45	63.03	64.15	61.99	66.13	60.17	63.65	2.4286
10	70.04	65.35	68.51	64.75	71.58	66.42	67.78	2.7208
11	73.18	68.85	73.06	69.76	73.95	70.06	71.48	2.1623
12	77.62	72.95	76.25	76.31	77.52	73.26	75.65	2.0579
24	94.56	96.09	94.42	93.65	96.75	91.26	94.46	1.9395

Table 10: Mean % Cumulative release of Pantoprazole sodium and Domperidone.

Time (hr)	% Release ± SD of Drugs	
	Pantoprazole sodium	Domperidone
0.0	0.0	0.0
0.5	0.0	6.14±0.9330
1	0.0	12.64±2.5488
2	0.0	25.21±3.1522
3	30.37±4.5471	32.99±3.4028
4	56.35±7.9672	40.88±1.9351
5	95.72±5.2618	48.99±2.2664
6	97.02±1.7611	52.54±3.4197
7	-	56.42±3.8425
8	-	60.32±2.2829
9	-	63.65±2.4286
10	-	67.78±2.7208
11	-	71.48±2.1623
12	-	75.65±2.0579
24	-	94.46±1.9395

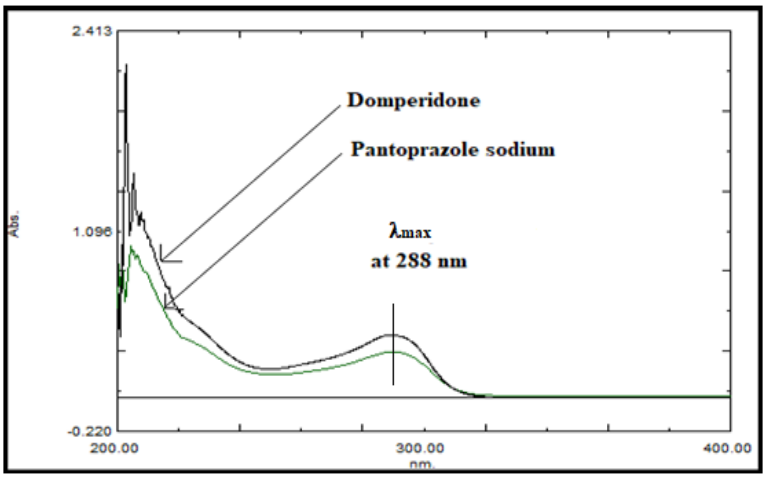

Fig. 1: Overlaid spectra of Pantoprazole sodium (10 µg/ml) and Domperidone (10 µg/ml) in methanol for selection of wavelength by RP-HPLC method.

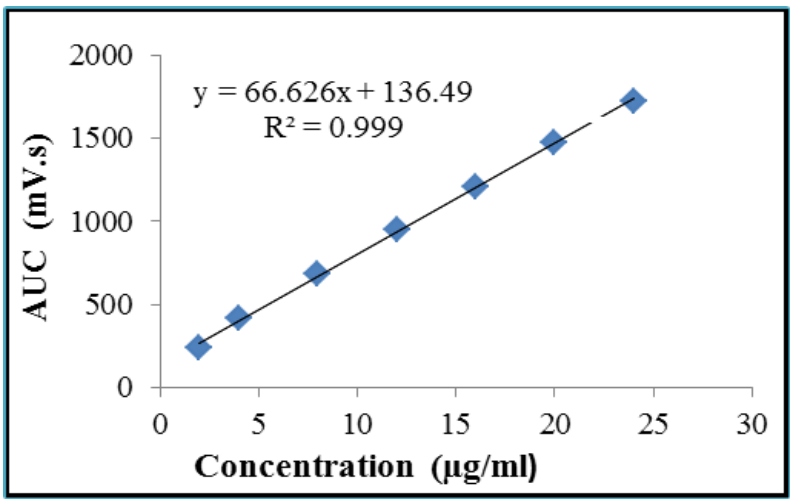

Fig. 2: Calibration curve of Pantoprazole sodium by RP-HPLC method.

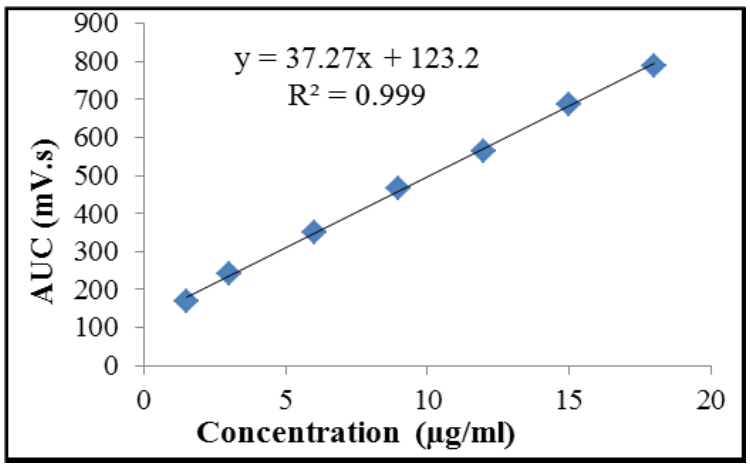

Fig. 3: Calibration curve of Domperidone by RP-HPLC method.

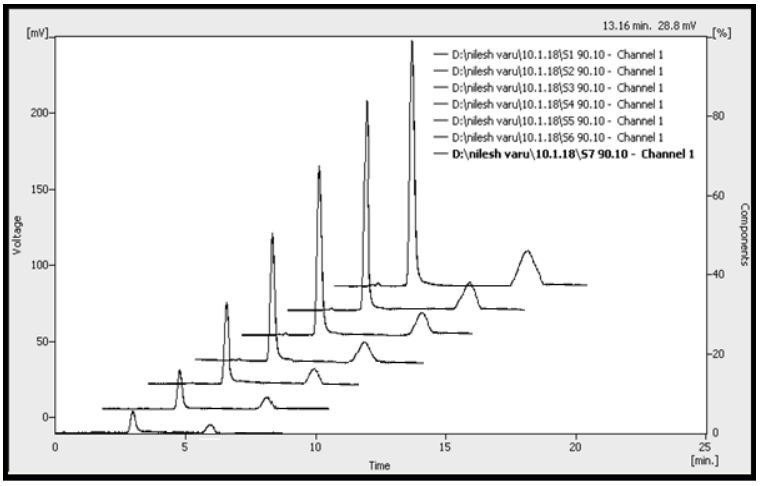

Fig. 4: Overlaid chromatogram in 3D view (2-24 µg/ml Pantoprazole sodium at R_t 2.99 min and 1.5-18 µg/ml Domperidone at R_t 6.48 min).

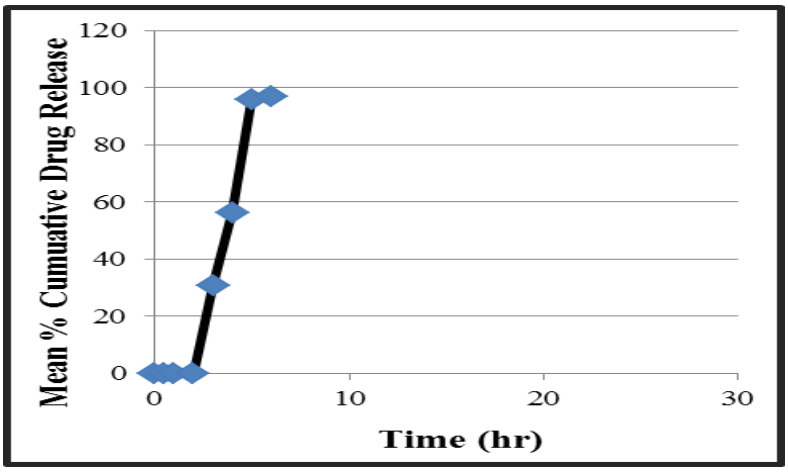

Fig. 5: Cumulative % Drug Release of Pantoprazole sodium vs. Time (hr).

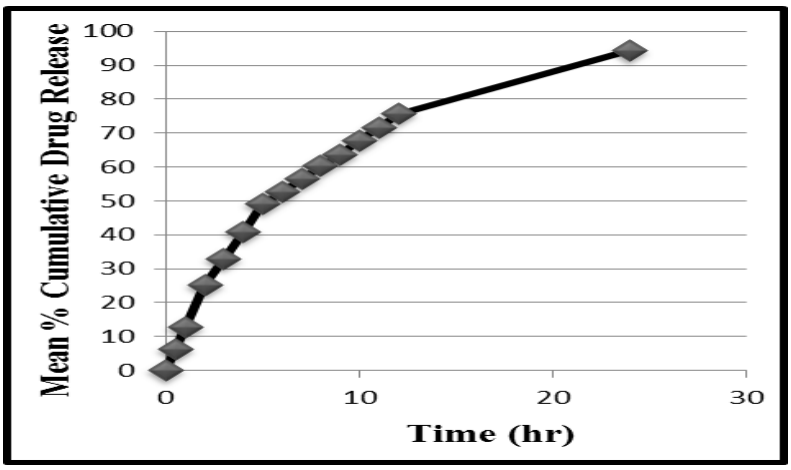

Fig. 6: Cumulative % Drug Release of Domperidone vs. Time (hr).

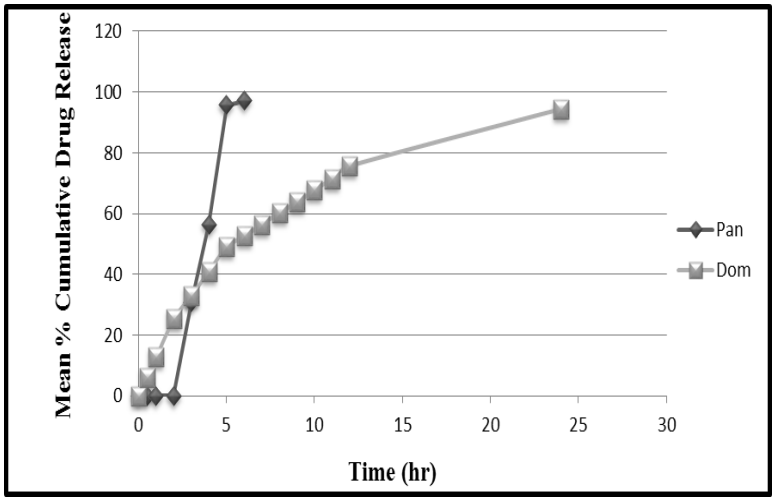

Figure 7: Mean % Cumulative release of Pantoprazole sodium and Domperidone vs. Time(hr).

RESULT AND DISCUSSION

RP-HPLC method

RP-HPLC method was developed with linearity range of 2 - 24 µg/ml and 1.5 - 18 µg/ml for Pantoprazole sodium and Domperidone respectively. Correlation coefficient was found to be 0.999 for both Pantoprazole sodium and Domperidone.

From the results it was found that the mean percentage recovery values were found to be 99.39 – 99.74 % for Pantoprazole sodium and 99.37 – 99.60 % for Domperidone. The % RSD values of Pantoprazole sodium for Repeatability, Intraday and Interday precision was found to be 0.9737, 1.0795 and 1.1991 respectively. The % RSD values of Domperidone for Repeatability, Intraday and Interday precision was found to be 1.5878, 1.2474 and 1.5140 respectively.

LOD, LOQ, specificity and robustness were determined by statistical methods and found to be in standard acceptance criteria according to ICH Q2(R1) guideline.

PANTOCID-DSR (Pantoprasole sodium enteric coated and Domperidone Sustained release capsules) show mean % cumulative release of 97.02 ± 1.7611 and 94.46 ± 1.9395 of labelled amount of Pantoprazole sodium and Domperidone Sustained release capsules within 24 hours respectively.

Pantoprazole sodium and Domperidone sustained release capsules mean % cumulative release is 97.02 ± 1.7611 for Pantoprazole sodium within 7 hrs and 94.46 ± 1.9395 for Domperidone within 24 hrs.

CONCLUSION

After successful completion of work, not only simple and rapid but also economical and validated method for estimation of Pantoprazole sodium and Domperidone in their capsule dosage form was developed. The proposed method could be used as Quality Control tool for routine dissolution study in industry without any prior separation. Developed method also could be specific, accurate and precise.

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