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DEVELOPMENT AND VALIDATION OF UV SPECTROPHOTOMETRIC METHOD FOR SIMULTANEOUS ESTIMATION OF DOMPERIDONE AND PANTOPRAZOLE SODIUM IN BULK AND PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

A simple, rapid, precise and highly selective spectrophotometric method was developed for simultaneous estimation of Domperidone and Pantoprazole sodium in pure as well as tablet dosage form. The simultaneous equation method is based on measurement of absorbance at 288 nm and 291 nm as two wavelengths selected for quantification of Domperidone and Pantoprazole sodium using methanol as a solvent. The method was validated for specificity, linearity, accuracy, precision, robustness and ruggedness. A double-beam shimadzu UV-visible spectrophotometer, 1800 with a pair of 1 cm matched quartz cells was used to measure the absorbance of the solutions in developed method. The method was validated as per ICH guidelines. Linearity ranges from 5-25 µg/ml for Domperidone and 5-25 µg/ml for Pantoprazole of the drugs. % RSD calculated was less than equal to 2 which indicates accuracy and reproducibility of the method. Recovery study indicates that these drugs could be quantified simultaneously without interference of excipient present in formulation. The developed UV spectroscopic method is suitable for the analysis of DMP and PTZ in combined dosage form. The accuracy was found between 99-100% for DMP and 98-99% for PTZ respectively. The precision (% RSD) was found to be 0.308 for DMP and 0.123 for PTZ respectively. The LOD was found to be 0.045µg/ml for DMP and 0.01µg/ml for PTZ respectively. The LOQ was found to be 0.122µg/ml for DMP and 0.059µg/ml for PTZ respectively.

KEYWORDS

Domperidone, Pantoprazole sodium, Simultaneous Equation, Method Validation and UV Spectrophotometer.

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INTRODUCTION

Many fixed dose combinations are available in market and mixing of these two or more active pharmaceutical ingredients is important to develop these dosage forms. Domperidone and pantoprazole fixed dose combination is approved for the treatment of diabetic gastroparesis. Domperidone and Pantoprazole fixed combination is approved for

the treatment of diabetic gastroparesis. Gastroparesis is a chronic, symptomatic disorder of the stomach that is characterized by delayed gastric emptying in the absence of mechanical obstruction. Diabetic gastroparesis affect about 40% of patients with type 1 diabeties and up to 30% of patients with type 2 diabeties, especially those with long standing disease[1,2].

Both symptomatic and asymptomatic DGP seem to be associated with poor glycemic control by causing a mismatch between the action of insulin and the absorption of nutrients. Symptoms associated with DGP often include nausea, vomiting, early satiety, bloating, postprandial fullness, abdominal pain, and weight changes[2].

Domperidone is a potent dopamine antagonist used for treatment of nausea and vomiting. Domperidone does not cross the blood brain barrier and therefore has fewer adverse CNS effects than other dopamine antagonists. Domperidone has been determined in human plasma, human serum and human milk, and rat plasma has been evaluated in co-evaporates by HPLC, and has been determined, with cinnarizine, in tablets, by HPLC[1-3].

Pantoprazole is a selective and long acting proton-pump inhibitor used for treatment of acid- related gastrointestinal disorders[1]. Application is in the short- term treatment of erosion and ulceration of the esophagus[6].

Literature survey revealed that ALP has been estimated with other drugs using UV, HPLC, LCMS, Flourimetry and HPTLC. Similarly PRP has been determined along with other drugs by UV, HPLC, and HPTLC. The present study is to estimate DMP and PTZ using a simple, sensitive, accurate, precise and more economical UV spectroscopic method[1-8].

MATERIAL AND METHODS

Instruments

For weighing, a calibrated weighing balance (Shimadzu) of 1mg sensitivity was used. A Shimadzu UV-visible double beam spectrophotometer- 1800 was used. All the glass wares and were made of borosilicate and were calibrated.

Materials

Pure standards of DMP and PTZ were obtained as gift sample and their marketed combination (Domcid Tablets) was purchased from the market. Methanol of analytical grade was used as the solvent. A double-beam shimadzu UV- visible spectrophotometer, 1800 with a pair of 1 cm matched quartz cells were used to measure the absorbance of the solutions.

UV Spectroscopic Method

Solvent Selection

Domperidone and Pantoprazole sodium is soluble in methanol.

Preparation of Standard Stock Solution

The standard stock solution of Domperidone (DMP) and Pantoprazole sodium (PTZ) was prepared by transferring accurately weighed 10 mg of Domperidone and Pantoprazole sodium Separately into 10ml volumetric flask containing methanol, then volume was made up to the mark by using methanol to give a concentration of 1000µg / ml. From this, 1ml of the solution was transferred to a 10ml volumetric flask and make up the volume with methanol to give a concentration of each 100µg/ml, which is a standard stock solution and it is further diluted with methanol to get concentration range of 10µg/ml of each, Domperidone (DMP) and Pantoprazole sodium (PTZ).

Determination of absorption maxima:

The prepared standard solutions (10µg/ml) were scanned in the UV-VIS spectrophotometer in the wavelength range of 200-400 nm and an overlain spectrum was recorded. Using the overlain spectra, the wavelength maxima of both drugs, i.e. 288 nm (λ_1 for DMP) and 291 nm (λ_2 for PTZ), were selected as two sampling wavelengths for simultaneous equation method. The prepared stock solutions were then diluted to get the solution of 5-25 µg/ml and 5-25 µg/ml for Alprazolam and Proprazolam hydrochloride respectively. The absorbance of these solutions were measured at the selected wavelengths and absorptivities were determined (Table No.1).

Vierodt's Method of Simultaneous Equations

This method is based on absorption of drugs at the wavelength maximum of the other. The

concentrations of the drugs were calculated from the following equations:

$$C_x = \frac{A_2 ay_1 - A_1 ay_2}{ax_2 ay_1 - ax_1 ay_2} \quad \text{.....Eq. 1}$$

$$C_y = \frac{A_1 ax_2 - A_2 ax_1}{ax_2 ay_1 - ax_1 ay_2} \quad \text{.....Eq. 2}$$

Where, A_1 and A_2 are absorbance of mixture at 288 nm and 291 nm respectively, ax_1 and ax_2 are absorptivities of DMP at λ_1 and λ_2 respectively, ay_1 and ay_2 are absorptivities of PTZ at λ_1 and λ_2 respectively. C_x and C_y are the concentrations of DMP and PTZ respectively.

Quantitative Analysis of Tablet Dosage Form

20 Tablet of marketed formulation of Domperidone of 10 mg and pantoprazole sodium of 20mg (Domcid Tablet) respectively were weighed, their average weights determined. The correct amount of drug powder equivalent to label claim was weighed and transferred to 10 ml volumetric flask, dissolved in methanol and sonicated for 15 min. The volume was then made up to the mark using same solvent, from this 1 ml was taken and diluted to 10 ml with methanol which gives 100µg/ml of DMP and 200µg/ml of PTZ. From this 1ml was taken and diluted to 10ml with methanol which gives 10µg/ml of DMP and 20µg/ml of PTZ. Absorbance of these sample solutions was recorded at 288 nm and 291 nm and then concentration of both the drugs was calculated using Equation 1 and 2 and the results are given in Table No.2.

Method Validation

The developed method was validated as per ICH guidelines for the following parameters:

Linearity

From the each 'Std Stock DMP' (1000µg/ ml) 1ml and 'Std Stock PTZ' (1000µg/ml) 1 ml and made up to the volume 10 ml with methanol to make the conc. of DMP (10 µg/ml) and PTZ (100 µg/ml).

From this solution 0.5, 1, 1.5, 2, 2.5 ml for DMP and 0.5,1, 1.5, 2, 2.5 ml for PTZ were transferred in a series of 10 ml volumetric flasks. The volume was made up to the mark with methanol to obtain the concentration of 5, 10, 15, 20, 25 µg/ml and 5, 10, 15, 20, 25 µg/ml for DMP and PTZ respectively.

Calibration curves of DMP and PTZ was constructed by plotting the Absorbance of DMP v/s Conc. of DMP and Absorbance of PTZ v/s Conc. of PTZ. The correlation coefficient (r^2) of least square linear regression for DMP and PTZ was calculated.

Range

The Range of the analytical method was decided from the interval between upper and lower level of calibration curve by plotting curve.

Accuracy

Recovery study was carried out by the standard addition method by adding a known amount of DMP and PTZ to the pre-analyzed sample at three different concentration levels that is 80%, 100%, 120% of assay concentration and percent recovery were calculated. 1ml of tablet solution was transferred to 4 different 10 ml volumetric flasks (labeled as blank, 80%, 100%, 120%) separately and 0, 8, 10, 12µg/ml standard solution was added respectively and the volume was made up to the mark with methanol. Absorbance was noted for these samples. Standard deviation and % RSD was calculated. Accuracy is reported as % recovery, which was calculated from the expression as equation given below:

% Recovery = Observed value / True value ×100

Precision

The precision of an analytical procedure expresses the closeness of agreement (degree of scattering) between a series of measurements obtained from multiple sampling of the same sample under the prescribed conditions. The precision of the method was determined in terms of repeatability and intra-day and inter-day precisions. Intra-day and inter-day precision (Intermediate Precision) Intraday precision was determined by analyzing the drugs at concentration (10µg/ml) for both the drugs and each concentration for three times, on the same day. Inter-day precision was determined similarly, but the analysis being carried out daily, for two consecutive days.

Repeatability

Repeatability of the method was determined by analyzing six samples of same concentrations of the drug (10µg/ml) for both the drugs. Absorbance of each was measured.

Robustness

The robustness of the developed method is its capacity to remain unaffected by small changes in altered conditions. To determine the robustness of the method, the wavelength of analysis was deliberate and the assay was evaluated. The effect of detection wavelength was studied at ±5 nm.

Ruggedness

Ruggedness was determined by carrying out analysis by two different analysts and the respective absorbance was noted and the results were indicated as % RSD.

Limit of Detection

Detection limit was determined based on the standard deviation of absorbance of same concentration that is a standard solution of DMP (10µg/ml) and PTZ (10µg/ml) and LOD calculated by LOD = 3.3 (SD/S) Where, SD - standard deviation; S= slope of the curve.

Limit of Quantification

Quantification limit was determined based on the standard deviation of peak area of same concentration that is standard solution DMP (10µg/ml) PTZ (10µg/ml) prepared six times and LOQ calculated by LOD = 10(SD/S) Where, SD= standard deviation; S= slope of Curve.

RESULTS

Linearity

The linearity of this method was determined at ranges from 5-25µg/ml and 5-25µg/ml for DMP and PTZ respectively. The regression equation was found to be.

Accuracy

The accuracy of the analytical method for DMP and PTZ was determined at 80%, 100% and 120% levels of standard solution. Absorbance was measured at 288 nm and 291 nm results were expressed in terms of % recoveries.

Precision

The precision (measurement of intra-day, inter-day, repeatability) results showed good reproducibility with the relative standard deviation (% RSD) below 2.0 %. This indicated that method was highly precise.

DISCUSSION

Preliminary Analysis of Domperidone and Pantoprazole sodium

Preliminary analysis of Domperidone and Pantoprazole sodium such as description, solubility was performed.

Assay of Tablet formulation

Amount of drug present in tablet formulation was calculated using simultaneous equation at 288 nm and 291 nm for DMP and PTZ Respectively, and $y = 0.042x + 0.097$and $y = 0.221x + 0.079$ for DMP and PTZ respectively. Amount of Domperidone and Pantoprazole sodium were found to be 99.06% and 98.95% of label claim respectively. This method can be employed for routine analysis of both the drugs.

Summary and conclusion

Summary of UV Spectrophotometric Method for Domperidone and Pantoprazole sodium.

Table No.1: Absorptivity of DMP and PTZ at 288 nm and 291 nm respectively

S.No	Components (10µg/ml)	Absorptivity at 288 nm	Absorptivity at 291 nm
1	DMP	0.419	0.246
2	PTZ	0.414	0.523

Table No.2: Result analysis of the tablet Mixture

S.No	Drug	Label Claim (mg / tab.)	Amount found (mg)	% Drug found
1	DMP	10	9.96	99.6
2	PTZ	20	19.79	98.95

Table No.2: Linearity of Domperidone and Pantoprazole sodium

S.No	Domperidone (DMP)		Pantoprazole sodium (PTZ)	
	Concentration (µg/ml)	Absorbance	Concentration (µg/ml)	Absorbance
1	5	0.257	5	0.306
2	10	0.419	10	0.523
3	15	0.560	15	0.743
4	20	0.714	20	0.953
5	25	0.852	25	1.156
6	Regression equation: y = 0.029x + 0.114		Regression equation: y = 0.221x + 0.079	
7	R^2= 0.999		R^2=0.999	

Table No.3: Table for accuracy

S.No	Drug	Amount present (µg/ml)	Amount of standard drug added (µg/ml)	Amount found (µg/ml)	% Recovery
1	DMP	10	80% (8µg/ml)	17.89	99.38
		10	100% (10µg/ml)	19.80	99.00
		10	120% (12µg/ml)	21.95	99.77
2	PTZ	10	80% (8µg/ml)	17.80	98.88
		10	100% (10µg/ml)	19.85	99.25
		10	120% (12µg/ml)	21.80	99.09

Intra-day Precision

Table No.4: Intra-day precision

S.No	DMP		PTZ	
	Concentration (µg/ml)	Absorbance	Concentration (µg/ml)	Absorbance
1	10	0.419	10	0.523
2	10	0.418	10	0.524
3	10	0.419	10	0.523
4	10	0.418	10	0.525
5	10	0.420	10	0.522
6	10	0.418	10	0.525
7	% RSD	0.200	%RSD	0.231

Inter-day Precision

Table No.5: Inter-day precision

S.No	DMP		PTZ	
	Concentration (µg/ml)	Absorbance	Concentration (µg/ml)	Absorbance
1	10	0.419	10	0.522
2	10	0.421	10	0.523
3	10	0.419	10	0.522
4	10	0.419	10	0.523
5	10	0.419	10	0.523
6	10	0.419	10	0.523
	% RSD	0.123	%RSD	0.1

Repeatability

Table No.6: Repeatability study

S.No	DMP		PTZ	
	Concentration (µg/ml)	Absorbance	Concentration (µg/ml)	Absorbance
1	10	0.420	10	0.523
2	10	0.419	10	0.520
3	10	0.419	10	0.521
4	10	0.419	10	0.521
5	10	0.420	10	0.523
6	10	0.419	10	0.523
	% RSD	0.308	%RSD	0.123

Limit of Detection

Table No.7: For Limit of Detection

S.No	LOD (µg/ml)	Con.
1	DMP	0.045µg/ml
2	PTZ	0.01µg/ml

Limit of Quantification

Table No.8: For Limit of Quantification

S.No	LOQ (µg/ml)	Con.
1	DMP	0.122µg/ml
2	PTZ	0.059µg/ml

Robustness

Table No.9: Result for Robustness

S.No	Wavelength	Absorbance	
		DMP(10 µg/ml)	PTZ(10 µg/ml)
1	Wavelength 1	0.422	0.520
2	Wavelength 2	0.422	0.521
3	Wavelength 3	0.421	0.522
4	%RSD	0.13%	0.191%

Ruggedness

Table No.10: Results for Ruggedness

S.No	Analyst	Absorbance	
		DMP(10 µg/ml)	PTZ(10 µg/ml)
1	Analyst 1	0.420	0.122
2	Analyst2	0.421	0.521
3	Analyst3	0.420	0.522
4	%RSD	0.137%	0.1%

Table No.11: For Summary

S.No	Parameters	Values	
		DMP	PTZ
1	Beer's Law limit (µg/ml)	5-25	5-25
2	Absorption maxima (nm)	288	291
3	Standard regression equation	*y = 0.042x +0.097*	*y = 0.221x + 0.079*
4	Correlation coefficient (R^2)	0.999	0.999
5	Accuracy	99-100%	98-99%
6	Precision (% RSD) Repeatability	0.308	0.123
7	LOD (µg/ml)	0.045	0.01
8	LOQ (µg/ml)	0.122	0.059
9	Robustness (%RSD)	0.13	0.191
10	Ruggedness (%RSD)	0.137	0.1
11	Assay (%)	99.06	98.95

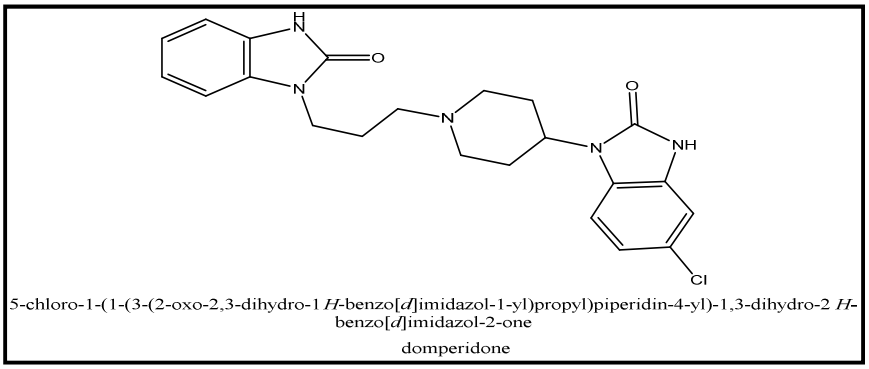

Figure No.1: Structure of Domperidone

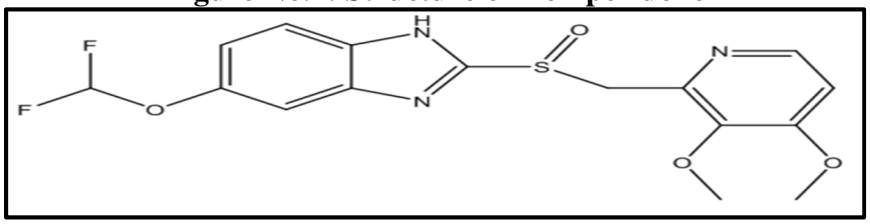

Figure No.2: Structure of Pantoprazole

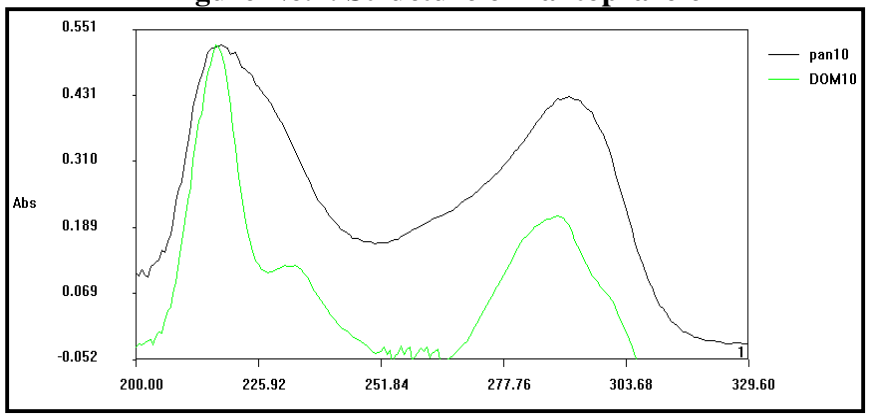

Figure No.3: Overlain spectra showing absorption maxima of DMP at 288 nm and PTZ at 291 nm

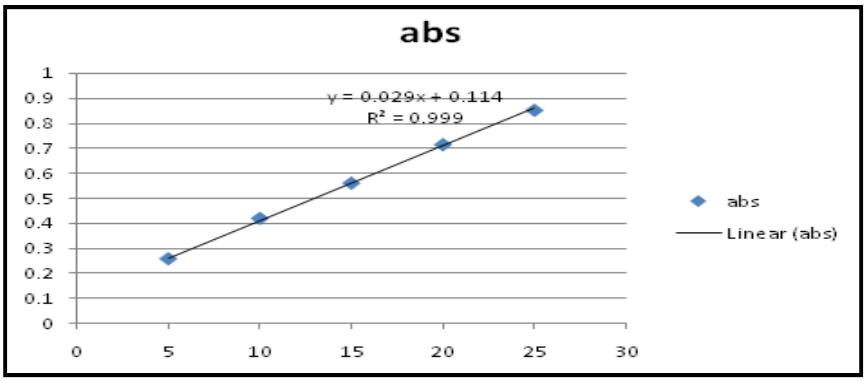

Figure No.4: Linearity of DMP

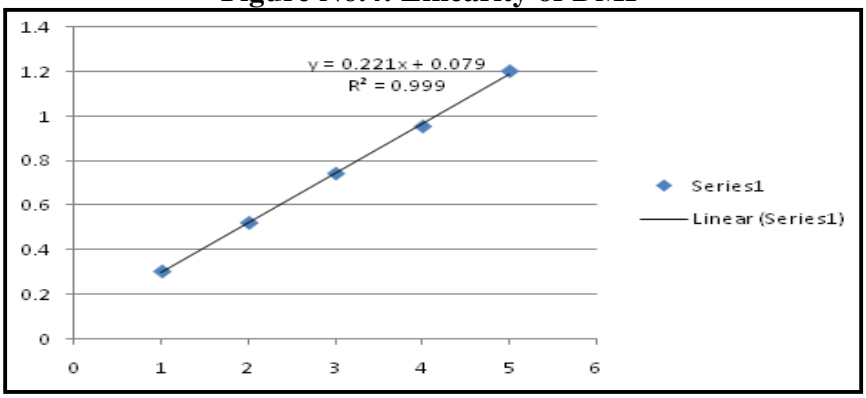

Figure No.5: Linearity of PTZ

CONCLUSION

The UV-Spectrophotometric method was developed and it is found to be simple, accurate, precise, highly sensitive, reproducible and inexpensive. The proposed method was found suitable for determination of Domperidone and Pantoprazole sodium in API and its dosage form without any interference from the excipients. This method can be effectively applied for the routine analysis of Domperidone and Pantoprazole sodium in API. Its advantages are the low cost of reagents, speed and simplicity of sample treatment, satisfactory precision and accuracy.

ABBREVIATIONS

UV-Ultra Violet
API- Active Pharmaceutical Ingredient
DMP- Domperidone
PTZ- Pantoprazole sodium
LOD- Limit of Detection
LOQ- Limit of Quantification

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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