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ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF UV-SPECTROPHOTOMETRIC FOR ESTIMATION OF CINITAPRIDE HYDROGEN TARTRATE & PANTOPRAZOLE SODIUM IN COMBINED DOSAGE FORM

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ABSTRACT

Background: *The combination of Cinitapride Hydrogen Tartrate and Pantoprazole Sodium is prescribed for treatment of gastro-intestinal disorders in particular hyperacidity associated with gastro-intestinal dismotility.* ***Objective:*** *To develop a simple, rapid, precise and selective UV-spectrophotometric method for simultaneous estimation of Cinitapride Hydrogen Tartrate and Pantoprazole Sodium in combined capsule dosage form.* ***Materials and Methods:*** *The method was developed on Shimadzu UV–visible double beam spectrophotometer (model UV-1800). This method involves the measurement of absorbances of Cinitapride and Pantoprazole at the wavelengths of 262 nm (λ_{max} of Cinitapride) and 281 nm (λ_{max} of Pantoprazole) using methanol as solvent. The developed method was validated according to ICH Q2R1 guidelines.* ***Results and Discussion:*** *Linearity was observed in the concentration range of 4-30 µg/ml for both the drugs. The accuracy of the method was confirmed by recovery studies of capsule dosage form and was found to be 100.3% and 99.9% for Cinitapride and Pantoprazole respectively. The LOD of Cinitapride and Pantoprazole were found to be 0.259µg/ml and 0.367 µg/ml and LOQ of Cinitapride and Pantoprazole were found to be 0.865 µg/ml and 1.224- µg/ml respectively.* ***Conclusion:*** *Thus the proposed method was found to be rapid, precise, accurate and cost effective quality control tool for the routine analysis of Cinitapride and Pantoprazole in bulk and combined dosage form.*

KEYWORDS: *Cinitapride Hydrogen Tartrate, Pantoprazole Sodium, UV-Spectrophotometric method.*

INTRODUCTION

Cinitapride Hydrogen Tartrate [Figure 1] is gastroprokinetic agent and anti-ulcer agent of Benzamide class. It acts as an agonist of $5HT_1$ and $5HT_4$ receptors and as an antagonist of $5HT_2$ receptors. Cinitapride is indicated for gastro-intestinal disorders associated with motility disturbances such as gastro-esophageal reflux disease, non-ulcer dyspepsia and delayed gastric emptying. Pantoprazole Sodium [Figure 2] is a proton-pump inhibitor that inhibits gastric acid by blocking H^+/K^+ adenosine triphosphate enzyme system (proton pump) of gastric parietal cells. It is substituted benzimidazole indicated for stomach ulcers, intestinal ulcers, gastro esophageal reflux disease (GERD) by reducing amount of acid production in stomach. It is used to treat stomach ulcers caused due to medication with NSAIDs and by bacteria called H.Pylori [1-7].

Several analytical methods have been reported for the estimation of Cinitapride Hydrogen Tartrate and Pantoprazole sodium in individual dosage forms and in combination with other drugs which includes spectrophotometric methods, HPLC and RP-HPLC [10-20]. Hence there is a need for the development of newer, simple, sensitive, rapid, accurate and reproducible analytical method for the routine estimation of Cinitapride Hydrogen Tartrate and Pantoprazole Sodium in bulk and pharmaceutical dosage form.

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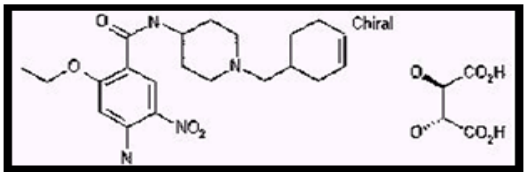

Fig. 1: Chemical structure of Cinitapride Hydrogen Tartrate

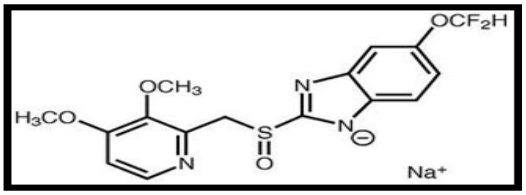

Fig. 2: Chemical structure of Pantoprazole Sodium

MATERIALS AND METHODS

Instrumentation:

The method was developed on Shimadzu UV–visible double beam spectrophotometer (model UV-1800). A Shimadzu Digital Electronic Balance (BL 220H) was used for weighing the materials.

Chemicals and Reagents:

Pharmaceutical grade Pantoprazole and Cinitapride were received as gift samples from Comprime Labs pvt.ltd, Kukatpally, Hyderabad. CINTODAC capsules were purchased from local market.

Methanol (AR grade) was received from S.D.Fine Chemicals Ltd., Mumbai.

Preparation of Cinitapride standard stock solution:

Accurately weighed 10mg of Cinitapride drug was transferred into a clean, dry 10 ml volumetric flask and dissolved with sufficient volume of methanol. The volume was made up to 10 ml with methanol to get 1000 µg/ml.

Preparation of Pantoprazole standard stock solution:

Accurately weighed 10mg of Pantoprazole drug was transferred into a clean, dry 10 ml volumetric flask and dissolved with sufficient volume of methanol. The volume was made up to 10ml with methanol to get 1000 µg/ml.

Selection of media:

Solutions of Cinitapride and Pantoprazole were prepared in different solvents like methanol and ethanol. UV-spectrum of both were recorded by scanning between 200-400nm. Better absorbances were observed for the drugs when methanol was used as media. Hence methanol was selected as an analytical media.

Selection of analytical wavelength:

Standard solutions of Cinitapride (10µg/ml) and Pantoprazole (10µg/ml) were prepared by appropriate dilution of two standard stock solutions with methanol and were scanned separately in the wavelength range of 200 nm - 400 nm to determine wavelength having maximum absorbance for both the drugs. Cinitapride showed absorbance maxima at 262 nm and Pantoprazole at 281 nm from the overlain spectrum [figure 3].

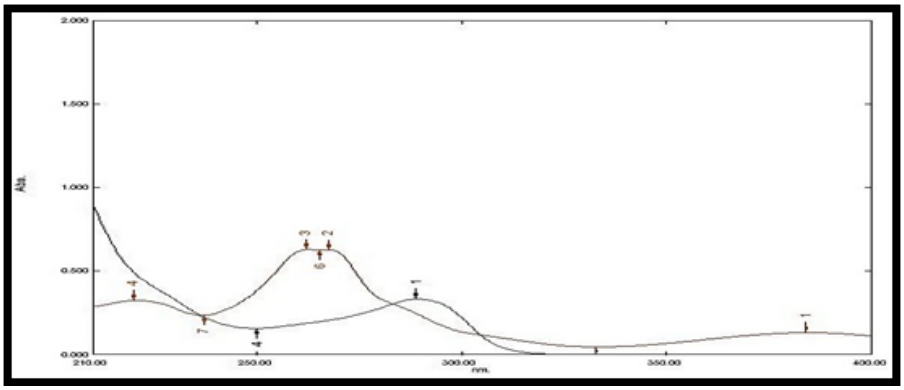

Fig. 3: Overlain spectra of Cinitapride and Pantoprazole in methanol

Validation of UV-Spectroscopic method:

The developed UV-Spectroscopic method was validated for linearity, accuracy, precision, Limit of detection (LOD), Limit of quantification (LOQ) as per ICH guidelines [8, 9].

Linearity:

The linearity was determined by plotting calibration graph of concentration against absorbance. Cinitapride and Pantoprazole showed linearity in the concentration range of 4-30 µg/ml with correlation coefficient (r^2) of the calibration curves as 0.998.

Precision:

The precision of the developed method was assessed in terms of repeatability (intra-day) and intermediate precision (inter-day).

Intraday precision study was carried out by preparing drug solution of same concentration (12 µg/ml and 14 µg/ml) and analyzing it at three different times in a day.

Interday precision study was carried out similarly for three different days. The results were reported as %RSD. The precision result showed a good reproducibility with percent relative standard deviation less than 2.

Accuracy:

Recovery studies were carried out by standard addition method according to ICH guidelines to check the accuracy.

To study the accuracy 20 capsules were weighed, emptied in a glass mortar and powdered. An amount of powder equivalent to 20mg of Pantoprazole and 18.5mg of Cinitapride was accurately weighed and added to 50ml volumetric flask so that sample contains 20mg equivalent of each drug. Then a known quantity of Cinitapride and Pantoprazole were added at 50% and 100% levels and contents were analyzed by proposed method. The %Recovery and %RSD were calculated and reported.

Limit of Detection (LOD) AND Limit of Quantification (LOQ):

The limit of detection (LOD) and Limit of quantification (LOQ) were calculated from

$$\mathbf{LOD = 3.3\sigma/S; \qquad LOQ = 10\sigma/S}$$

Where σ is the standard deviation of the lowest standard concentration

S is the slope of the standard curve

Analysis of marketed formulation:

Twenty commercial capsules were weighed, emptied in a glass mortar and powdered. An amount of powdered equivalent to 40 mg of Pantoprazole and 37mg of Cinitapride was accurately weighed and added to 100 ml volumetric flask. About 20 ml of methanol was added to this flask and sonicated for 10 min and volume was made up to the mark with same solvent. The solution was filtered through Whatman filter paper No.41. Appropriate aliquot of this standard stock solution of commercial formulation was taken into a 10 ml volumetric flask and volume was made up to mark with methanol to obtain final solution containing 12 µg/ml of Cinitapride and 12 µg/ml of Pantoprazole and absorbance were measured at 262 and 281 nm. The concentrations of two drugs in sample were determined by using simultaneous equation.

RESULTS AND DISCUSSION

Estimation of Cinitapride Hydrogen Tartrate and Pantoprazole Sodium was achieved by simultaneous equation method using double beam UV-visible spectrophotometer. The normal spectra of both the drugs were recorded in methanol. The calibration curves were obtained for Cinitapride at 262 nm and Pantoprazole at 281 nm in the range of 4-30 µg/ml for both. The slope, intercept and correlation coefficient values were found to be 0.057, 0.010 and 0.998 for Cinitapride and 0.033, 0.006 and 0.998 for Pantoprazole. Precision studies were performed. Low % RSD values were obtained which indicate that the proposed method has good precision. In this method, accuracy was determined by recovery studies calculated at 50 and 100% levels by using standard addition method. The recovery values between prescribed limit of 98-102% shows that method is free from interference of excipients present in formulation. Hence the developed method was validated as per ICH guidelines

Table No. 1: Calibration data of Cinitapride at 262nm and Pantoprazole at 281nm

S. No	Concentration (µg/ml)	Cinitapride Absorbance (262nm)	Pantoprazole Absorbance (281nm)
1	4	0.244	0.143
2	6	0.357	0.202
3	8	0.460	0.268
4	10	0.588	0.345
5	12	0.693	0.405
6	14	0.829	0.482
7	16	0.927	0.547
8	18	1.029	0.609
9	20	1.121	0.661
10	22	1.285	0.727
11	24	1.362	0.784
12	26	1.532	0.886
13	28	1.586	0.930
14	30	1.747	1.021

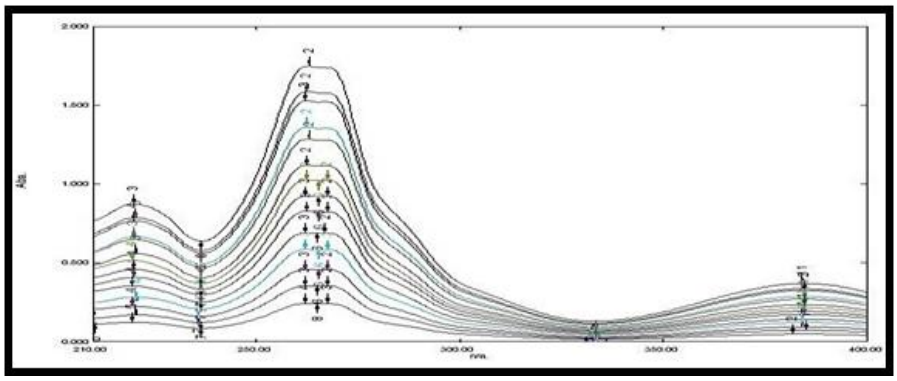

Fig. 4: Overlay spectra of Cinitapride

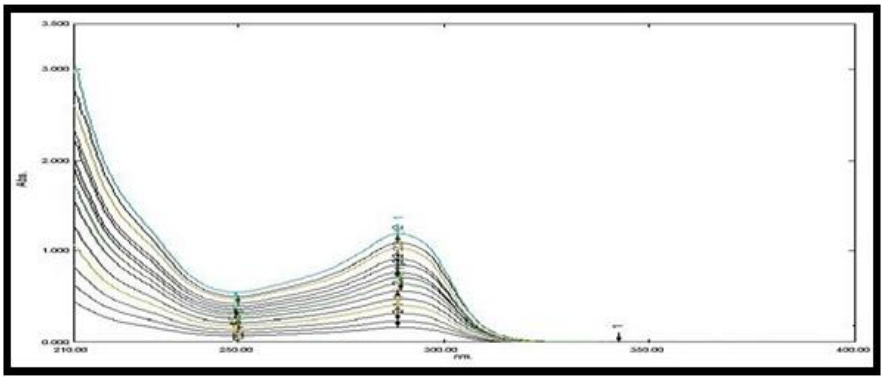

Fig. 5: Overlay spectra of Pantoprazole

Table No. 2: Intraday precision

Concentration (µg/ml)		Absorbance		% RSD	
CIN	**PAN**	**CIN**	**PAN**	**CIN**	**PAN**
		262nm	**281 nm**	**262nm**	**281 nm**
12	**12**	0.720	0.409	0.320	0.564
		0.720	0.405		
		0.724	0.409		
14	**14**	0.849	0.466	0.339	1.572
		0.844	0.463		
		0.849	0.477		

Table No. 3: Interday precision

Concentration (µg/ml)		Absorbance		% RSD	
CIN	**PAN**	**CIN**	**PAN**	**CIN**	**PAN**
		262nm	**281 nm**	**262nm**	**281 nm**
12	**12**	0.731	0.417	0.677	0.974
		0.732	0.417		
		0.723	0.410		
14	**14**	0.867	0.474	0.580	0.999
		0.862	0.476		
		0.857	0.467		

Table No. 4: Accuracy studies

Drugs	Initial amount	Amount added (%)	% Recovery	% RSD (n=3)
Cinitapride	20mg	50%	100.3%	0.49
	20mg	100%	100.5%	0.56
Pantoprazole	20mg	50%	99.9%	1.1
	20mg	100%	102%	0.95

Table No. 5: Linear data for calibration curves regression

PARAMETERS	Cinitapride	Pantoprazole
Linearity range(µg/ml)	4-30	4-30
Regression equation	y = 0.057x + 0.01	y = 0.033x + 0.007
Correlation coefficient(r^2)	0.998	0.998
LOD(µg/ml)	0.259	0.367
LOQ(µg/ml)	0.865	1.224

Table No. 6: Analysis of marketed formulation

Drugs	Label claim	Amount determined	% Label claim	% RSD
Cinitapride	3mg	3.15mg	102%	0.67
Pantoprazole	40mg	40.6mg	101.5%	0.44

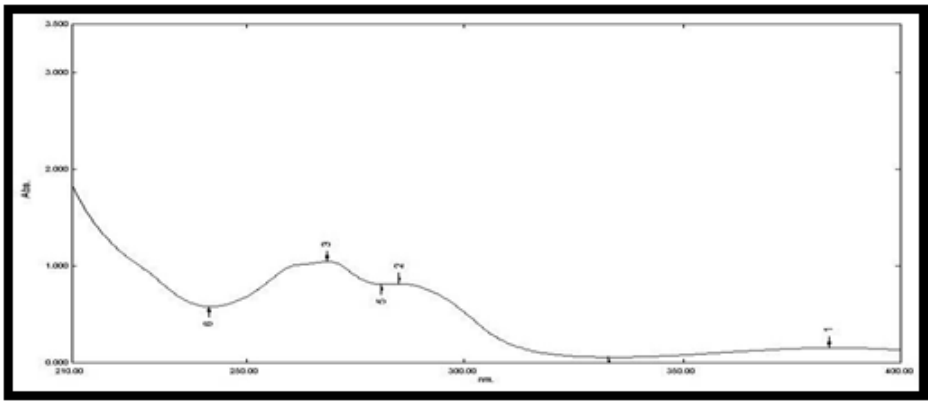

Fig. 6: UV spectra of marketed formulation

CONCLUSION

For the simultaneous estimation of Cinitapride Hydrogen Tartrate and Pantoprazole Sodium, the UV spectroscopic method was developed and validated according to ICH guidelines. The proposed method was proved to be superior to most of the reported methods. The sample recovery in the formulation was in good agreement with their respective label claims and they suggested noninterference of formulation in the estimation of both drugs.

Hence the proposed UV spectrophotometric method was found to be simple, precise, economic and less time consuming. It can be concluded that proposed method was suitable for routine quality control analysis of both the drugs in formulation.

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