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[Research article]

Validated UV Method Development for the Simultaneous Estimation of Rabeprazole sodium and Cinitapride in Tablets

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ABSTRACT

Current research attempts to develop simple, cost effective, and time saving, validated UV spectrophotometric method for the simultaneous estimation of Rabeprazole (RPZ) and Cinitapride (CTP) in tablet formulations by simultaneous equation method. The sampling wavelengths for RPZ and CTP are 284.5 nm and 267 nm respectively. Assay results showed 10.008 mg of RPZ and 2.974 mg of CTP were found in the tablet dosage form. The method was validated as per ICH guidelines. Linearity was obtained in the concentration range of 3-8 µg/mL for RPZ and 2-7 µg/mL for CTP. The %RSD for intraday and interday variations of RPZ was found to be 0.183±0.002 and 0.317±0.001 respectively. An intraday and interday variation of CTP was found to be 0.194±0.002 and 0.298±0.001 respectively. In both cases values were within the acceptance limit of < 2%. The mean percent recovery for RPZ and CTP were found to be 98.57 % and 99.43 % respectively, within the acceptance limit of 98% to 102%. From the high recovery values (> 98%) it can be inferred that the method is free from the interference of excipients used in the formulation. Based on the results obtained the proposed method can be regarded as simple, accurate, precise, reliable and cost effective which can be employed for routine quality control of RPZ and CTP in combined tablet dosage forms.

Keywords: UV method development, Rabeprazole, Cinitapride, validated, ICH guidelines.

INTRODUCTION

Analytical method development being a vital part of preformulation-formulation research and development obviates the need to develop reliable, effective, ecofriendly and cost effective methodologies for routine analysis of active pharmaceutical ingredients for both small and large scale pharmaceutical industries worldwide.[1-6] Rapid, simple, sensitive, cost effective analytical method development is of imperative necessity since the design of the drug delivery system is related to it. Moreover drug analysis is also necessary in various steps of formulation design and dissolution studies.[1-6] Sophisticated chromatographic methods with HPLC, HPTLC which are being employed for analysis are relatively expensive; many methods necessitate analyte extraction from respective sample matrices thus necessitating complicated sample preparation steps, use of internal standards for analysis increases the time required and error in recovery.[7-21] UV-vis spectrophotometric method is one of the earliest, yet easy, sensitive, relatively cost effective method applied for drug estimations

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in both small and large scale pharmaceutical R&Ds.[22-29] Multi-component formulations have gained a lot of importance now a days due to the greater patient compliance and acceptability, increased potency, multiple action, fewer side effects and faster relief. However analytical complexities of these multi-drug component dosage forms put forward considerable challenges to the analytical chemist during the analytical procedure.[8-12,15] Gastroesophageal Reflux Disease (GERD) or no ulcer dyspepsia (NUD) is a form of recurrent chronic disease requiring long term medical therapy where proton pump inhibitors and gastrprokinetic agents are the first line drug of choice. Combination of Rabeprazole sodium (RPZ) and Cinitapride (CTP) is very effective therapy for the GERD.[22-29]

Rabeprazole Sodium (RPZ), chemically Benzimidazole derivative 2-[[[4-(3-methoxy propoxy)-3-methyl 2-pridinyl] methyl] sulfinyl]-1-benzimidazole sodium (**Fig.1**), is a proton pump inhibitor which inhibits the enzyme system of hydrogen/potassium adenosine triphosphatase (H^+/K^+ ATPase) at the secretory surface of gastric parietal cells thereby suppressing gastric acid secretion. The $–OCH_3$, pyridine, benzimidazole moieties largely attribute to the therapeutic actions of RPZ.[22-24] Cinitapride (CTP), chemically 4-amino-N-[3-(cyclohexan-1-yl-methyl)-4-piperidinyl] -2 -ethoxy-5-nitrobenzamide (**Fig.2**) is a substituted benzamide gastroenteric prokinetic agent acting via synergistic effects on serotonergic 5HT-2 (inhibition) and 5-HT4 (stimulation) receptor and dopaminergic D2 (inhibition) receptors in the neuronal synapses of the myenteric plexi. [27-29]

Marketed formulations containing 10 mg Rabeprazole sodium and 3 mg Cinitapride in a tablet dosage form was selected for UV method development. Literature reports various HPLC, LC-MS methods for the analytical estimation of Rabeprazole sodium alone or in combination. Similarly various UV-HPLC analytical methods were reported for the estimation of Cinitapride alone or in combination with other drugs. However, there is no validated UV method development for the simultaneous estimation of these two drugs in combination to the best of our knowledge.

The current research focuses on a UV method development for simultaneous analysis of RPZ and CTP. The prime requisite is to develop new methods to analyze the drugs simultaneously and without interference. The UV methodology becomes much more beneficial and acceptable if it can simultaneously estimate more than one drug at a time.

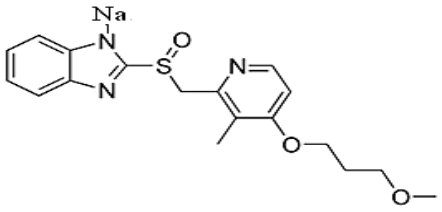

Fig. 1: Rabeprazole Sodium

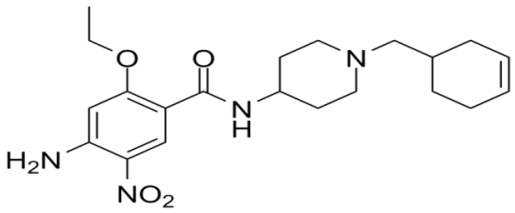

Fig.2: Cinitapride

MATERIALS AND METHODS

Instruments used

Electronic analytical balance (Shimadzu); Single beam UV-Vis spectrophotometer (Thermo Scientific Aquamate plus); Ultrasonic bath sonicator (Biotechnics) were used in the study.

Reagents and chemicals

Analytical pure drugs of RPZ and CTP were obtained as kind gift samples from Hetero Drugs, Hyderabad, India. The combined tablet formulations with a labeled claim of RPZ 10 mg and CTP 3 mg respectively, were obtained from local drug store. Reagents of analytical grade were purchased from Merck, Mumbai.

Selection of solvent

According to solubility profile and literature review, RPZ is freely soluble in water, methanol and chloroform. CTP was soluble in methanol and water. So, distilled water was chosen as the solvent for the proposed UV method development.

Preparation of standard stock solutions

10 mg each of pure RPZ and CTP were weighed separately, into two 10 mL volumetric flasks.

Then small amount of distilled water was added to dissolve the drugs and then the volume was made up to 10 mL to get a concentration of 1 mg/mL.

Selection of wavelength

From the above standard stock solutions, 0.1 mL aliquots were taken separately into two 10 mL volumetric flasks and diluted up to the mark with distilled water. These solutions were scanned in the UV region of 200-400 nm. Maximum absorbance was seen at the wavelength of 284.5 nm for RPZ and 267 nm for CTP. Hence all absorbance measurements were made at 284.5 nm for RPZ and 267 nm for CTP.

Calibration curve

A series of dilutions were prepared from the standard stock solutions of RPZ and CTP to obtain the concentration of 3-8 µg/mL of RPZ and 2-7 µg/mL of CTP. Absorbances of the above solutions were measured at 284.5 nm and 267 nm for RPZ and CTP respectively and a calibration curve of absorbance against concentration was plotted and the regression coefficient (R^2) was also determined.

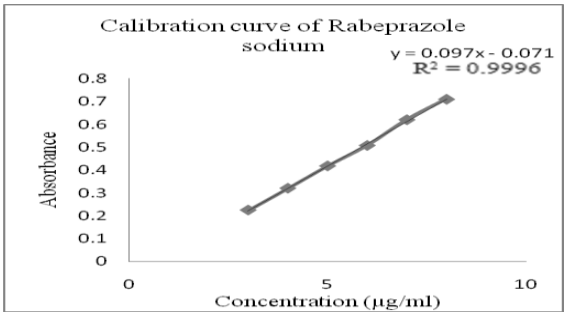

Fig.3: Standard Calibration curve of Rabeprazole Sodium

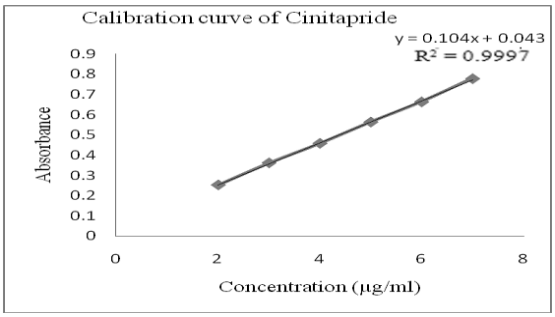

Fig.4: Standard Calibration curve of Cinitapride

Determination of absorptivity coefficients

The absorptivity coefficients of both drugs (RPZ and CTP) were determined at selected wavelengths by using the formula: **$A=A\ (^{1\%}_{1cm})\ b\ c$**. where, c = concentration of the absorbing species, in g/100mL and b = path length in cm

The absorptivity values are then substituted in the following equations (1) and (2):

A1= ax1Cx + ay1Cy…….(1)
A2= ax2Cx + ay2Cy……..(2)

Where,

A1 and A2 are absorbances of sample at 284.5 nm and 267 nm, respectively.

a_{X1} and a_{X2} are absorptivities of RPZ at 284.5 nm and 267 nm respectively.

a_{Y1} and a_{Y2} are absorptivities of CTP at 284.5 nm and 267 nm respectively.

Cx and Cy are concentrations of RPZ and CTP respectively.

Preparation of Sample solutions

Average weight of twenty tablets containing 10 mg of RPZ and 3mg of CTP (labeled claim) was calculated. The tablets were powdered well in glass mortar and pestle. Tablet powder weight equivalent to 10 mg of RPZ and 3 mg of Cinitapride was weighed accurately and transferred to a 25 mL volumetric flask. Then small quantity of distilled water was added and sonicated for 30 min

to dissolve the drugs completely and then the volume was made up to the mark with distilled water and filtered through 0.45 µm membrane filter. From this, 0.25 mL was taken and diluted to 10 mL with distilled water. The absorbance of this solution was measured at 284.5 nm and 267 nm against distilled water as a blank. The assay was performed in triplicate.

Analysis of tablet dosage form

Aliquot portion of the above sample stock solution was diluted with distilled water and the absorbance was measured at appropriate wavelengths and the concentrations of the two drugs were determined using equations (3) and (4). Analysis was done in triplicate.

$$\mathbf{Cx} = \frac{\mathbf{A2ay1 \ - \ A1ay2}}{\mathbf{Ax2\ ay1 \ - \ ax1\ ay2}} \ldots\ldots (\mathbf{3})$$

$$\mathbf{Cy} = \frac{\mathbf{A1ax2 \ - \ A2ax1}}{\mathbf{ax2\ ay1 \ - \ ax1\ ay2}} \ldots\ldots (\mathbf{4})$$

METHOD VALIDATION

The proposed method was validated as per ICH guidelines in terms of linearity, precision, accuracy.[30]

Linearity

A Series of solutions were prepared using RPZ and CTP standard stock solution at concentration levels from 3-8 µg/mL and 2-7 µg/mL respectively. The absorbances of the solutions were measured at 284.5 and 267 nm against distill water as blank. The calibration curves were constructed by plotting concentrations on x-axis and absorbance on y-axis. R^2 value not less than 0.99 was regarded as acceptance criterion.[30]

Accuracy

The accuracy of the developed method was determined by recovery studies at three different levels. The preanalyzed samples were spiked with 50, 100 and 150% of mixed standard solution. The mixtures were analyzed and the recoveries were determined. The study was carried out in triplicate. The mean % recovery of the RPZ and CTP at each level should be not less than 98.0% and not more than 102.0% was considered as the acceptance criterion.[30]

Precision

Precision was studied to find out intra and inter-day variations in the test method of RPZ and CTP. Intra-day assay precision was found by analysis of standard drug thrice on the same day. Inter-day assay precision was carried out at three different days and percentage relative standard deviation (%RSD) was calculated. The %RSD should not be more than 2.0%.[30]

Results

The standard calibration curves and linearity range of RPZ and CTP are presented in **Table 1-2** and **Fig.3-4**. The absorptivity values and assay results of RPZ and CTP are presented in **Table 3-4**. In method validation, the results of accuracy studies of RPZ and CTP are depicted in **Table 5-6** and precision of inter and intraday variations in **Table 7**. The summary of all validation parameters are presented in **Table 8**.

Discussion

The current research aims to develop a UV spectrophotometric method for the simultaneous estimation of RPZ and CTP in a commercially available tablet dosage.

From the solubility profile of both the drugs, distill was selected as the common solvent. From the overlain spectra, 284.5nm and 267nm were selected as sampling wavelengths for RPZ and CTP. The simplicity and reliability of the method requires knowledge very accurate molar absorptivities of the components and the measurement of absorbances at 284.5nm and 267nm. The calculations being very simple, can be done manually. The above said two wavelengths were selected to frame the simultaneous equation. [1-6]

From the assay results (**Table 3**), the amounts of RPZ and CTP in the tablet dosage form were found to be 10.008mg for RPZ and 2.974mg for CTP which are satisfactory.

The method was validated as per ICH guidelines.[30] Linearity was obtained in the concentration range of 3-8 µg/mL for RPZ and 2-7µg/mL for CTP (**Table 1-2**). The %RSD for intraday and interday variations of RPZ was found to be 0.183±0.002 and 0.317±0.001 respectively. An intraday and interday variation of CTP was found to be 0.194±0.002 and 0.298±0.001 respectively (**Table 7**). In both cases the results are

within the acceptance limit of <2% which indicates that the UV method developed has good precision.
While validating the accuracy of the method (**Table 5-6**), it was found that the mean percent recovery for RPZ and CTP were found to be 98.57 % and 99.43 % respectively, which are within the acceptance limit of 98%-102% indicating the significant accuracy of the method. From the high recovery values (< 98 %) it can be inferred that the method is free from the interference of excipients used in the formulation. Based on the results obtained the proposed method can be regarded as simple, accurate, precise, and reliable which can be employed for routine quality control of RPZ and CTP in bulk and combined tablet dosage forms.

Table 1: Table for calibration curve of RPZ and CTP

Conc of RPZ (µg/mL)	Absorbance (nm)	Conc of CTP (µg/mL)	Absorbance (nm)
3	0.224	2	0.252
4	0.32	3	0.361
5	0.418	4	0.458
6	0.508	5	0.564
7	0.621	6	0.664
8	0.711	7	0.779
R^2 = 0.99		**R^2 = 0.99**	

Table 2: Linearity of Rabeprazole Sodium and Cinitapride

Parameters	RPZ	CTP
95% confidence intervals		
Slope	0.09794 ± 0.001298	0.1012 to 0.1074
Y-intercept	-0.07169 ± 0.007475	0.02886 to 0.05857
X-intercept	0.7319	-0.5778 to -0.2692
Goodness of Fit		
R^2	0.99	0.99
P value	< 0.0001	< 0.0001
Equation	Y = 0.09794X - 0.07169	Y = 0.1043X + 0.04371
Best fit values		
Slope	0.09434 - 0.1015	0.1043 ± 0.001112
Y-intercept	-0.09244 to -0.05093	0.04371 ± 0.005353
X-intercept	0.5389 - 0.9120	-0.4192

Table 3: Absorptivity values of Rabeprazole Sodium and Cinitapride

Absorptivity values of Rabeprazole HCL		Absorptivity values of Cinitapride	
284.5 (nm) –ax_1	846.67	284.5 (nm) –ay_1	516.67
267 (nm)- ax_2	663.33	267 (nm)- ay_2	1106.67

Table 4: Assay results of Rabeprazole Sodium and Cinitapride

Drug	Labeled amount(mg)	Amount present (mg)	% Assay
RPZ	10	10.008	100.07
CTP	3	2.974	99.14

Table 5: **Accuracy studies of Rabeprazole Sodium**

Sample No.	Spike Level (%)	Amount (µg / mL) added	Amount (µg / mL) Found	% Recovery	Statistical analysis	
1	50	1.5	1.473	98.21	Mean	98.51
	50	1.5	1.473	98.21	SD	0.515
	50	1.5	1.487	99.11	%RSD	0.523
2	100	3	2.973	99.11	Mean	99.70
	100	3	3.027	100.90	SD	1.030
	100	3	2.973	99.11	%RSD	1.034
3	150	4.5	4.473	99.40	Mean	100.50
	150	4.5	4.567	101.49	SD	1.045
	150	4.5	4.527	100.59	%RSD	1.040

Table 6: Accuracy studies of Cinitapride

Sample No.	Spike Level (%)	Amount (µg / mL) added	Amount (µg / mL) Found	% Recovery	Statistical analysis	
1	50	1	1.013	101.30	Mean	100.14
	50	1	0.996	99.57	SD	0.999
	50	1	0.996	99.57	%RSD	0.998
2	100	2	1.991	99.57	Mean	98.84
	100	2	1.974	98.70	SD	0.661
	100	2	1.965	98.27	%RSD	0.669
3	150	3	2.970	98.99	Mean	99.27
	150	3	2.978	99.28	SD	0.289
	150	3	2.987	99.57	%RSD	0.290

Table 7: Results of precision studies of Rabeprazole Sodium and Cinitapride

S.No.	Rabeprazole Sodium Concentration	Intra day (%RSD)	Inter day (%RSD)	Cinitapride Concentration	Intra day (%RSD)	Inter day (%RSD)
1	5	0.276	0.478	5	0.205	0.572
2	6	0.114	0.228	6	0.230	0.174
3	7	0.161	0.246	7	0.148	0.148

Table 8: Summary of the validation parameters of the proposed method

S.No.	Parameters	Rabeprazole sodium	Cinitapride
1	Linearity (µg/mL)	3-8	2-7
2	Correlation Coefficient	0.9996	0.9997
3	Precision(%RSD)		
	(i)IntradayPrecision	0.183	0.194
	(ii)Interday Precision	0.318	0.298
4	Accuracy (%recovery)	99.57	99.43
5	Tablet Assay (%)	100.08	99.14

CONCLUSION

Properly validated simple, cost effective, time saving UV method development are of immense benefit for the pharmaceutical R&Ds for routine drug estimations and in various phases of preformulation-formulation studies. The methodology becomes more acceptable when more than one drug can be simultaneously estimated by the same method with very less interference from the excipients added to the formulations. The current properly validated UV methodology is found to be successful for the simultaneous estimation of RPZ and CTP in combined tablet dosage form and expected to be beneficial for the routine estimations of the same.

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