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Research Article

Development of a UV visible spectrophotometric method for simultaneous estimation of Ranolazine and Metoprolol

Krupa Vyas*[1], Moinuddin Soniwala [2], Amit Vyas [2], Nirav Shah[3]

[1] *Assistant Professor, Khyati College of Pharmacy, Ahmedabad, Gujarat, India*

[2] *B. K. Modi Government Pharmacy College, Rajkot, Gujarat, India*

[3] *SAL Institute of Pharmacy, Ahmedabad, Gujarat, India*

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*Address for Correspondence:

Krupa Vyas, Assistant Professor, Khyati College of Pharmacy, Ahmedabad, Gujarat, India

Abstract

Ranolazine being Na+ channel blocker agent, decreases the chances of angina attacks. Metoprolol exerts specific β1 blocking effect which results into decreased cardiac contractility and heart Rate [(1)]. Ultimately reduces oxygen demand of heart. Metoprolol enhances the pharmacological activity of Ranolazine so the combination gives better therapeutic activity [(2)].

There is no UV visible method present for the simultaneous estimation of Ranolazine and Metoprolol. To formulate and evaluate such a formulation involving mentioned drugs this simultaneous equation method was developed using 0.1 N HCl as a solvent. Chosen wavelengths were 272 nm and 242 nm for Ranolazine and Metoprolol Succinate respectively. Linearity range was seen to be 7.5 to 40 ppm for Ranolazine and 1 to 5 ppm for Metoprolol. Recovery studies and Validation were successfully performed according to ICH guidelines. This method can be applied for any formulation consisting mentioned drugs without interference of other excipients.

Keywords: UV visible spectrophotometry, Simultaneous estimation, Ranolazine, Metoprolol succinate, Analytical Method development, Angina Pectoris

INTRODUCTION

Intervention-- Metoprolol enhances the pharmacological activity of Ranolazine so the combination gives better therapeutic effect. There was no UV-Visible method present for the simultaneous estimation of Ranolazine and Metoprolol.

Literature review-

1. A study shows that Ranolazine may have a therapeutic role for the treatment of systolic and diastolic heart failure in addition to its antianginal role. Ischemia and heart failure precipitates because of atrial fibrillation. There is promising experimental data providing evidence for the effectiveness of Ranolazine in atrial fibrillation. Also there are favorable effects of Ranolazine on glycaemia. Since common antianginal and ant ischemic agents such as ß-blockers and Ca channel blockers rather worsen glycemic control and Ranolazine has largely been tested for its safety, it would be of particular interest for the treatment of angina in individuals with diabetes mellitus [3]
2. A simple Rapid and reliable RP-HPLC method has been developed for the simultaneous estimation of Metoprolol and Ranolazine either alone and/ or in combination in formulation. The method has advantages such as rapid, simple sample preparation, no need of any special reagents and high sensitivity. It is suitable for analysis of these drugs in binary formulation in a single isocratic run. The method is suitable for routine analysis of the combination product in quality control laboratories. [4]
3. A study indicates that monotherapy with RAN prevents the progression of heart failure, as evidenced by the prevention of LV dysfunction and attenuation of LV remodeling. In addition, treatment with an ACE inhibitor or a beta blocker, combined with RAN, resulted in improvement in LV systolic and diastolic function and reversal of global and cellular LV remodeling that was greater than with RAN alone. [5]

Ranolazine- Ranolazine inhibits sodium influx through cell membranes, Blocks the sodium channels and slows the rate and amplitude of initial rapid depolarization, reduces cell excitability,and reduces conduction velocity.[6, 7]

Metoprolol- Metoprolol competes with adrenergic neurotransmitters such as catecholamine for binding at beta (1)-adrenergic receptors in the heart. Beta (1)-receptor blockade results in a decrease in heart rate, cardiac output, and blood pressure. [8, 9]

UV-Visible spectrophotometry is one of the most frequently employed technique in pharmaceutical analysis. It involves measuring the amount of ultraviolet or visible radiation absorbed by a substance in solution. Instrument which measure the ratio, or function of ratio, of the intensity of two beams of light in the UV-Visible region are called Ultraviolet-Visible spectrophotometers.

In qualitative analysis, organic compounds can be identified by use of spectrophotometer, if any recorded data is available, and quantitative spectrophotometric analysis is used to ascertain the quantity of molecular species absorbing the radiation. Spectrophotometric technique is simple, rapid, moderately specific and applicable to small quantities of compounds. The fundamental law that governs the quantitative spectrophotometric analysis is the Beer -Lambert law.

Objectives- Metoprolol enhances the pharmacological activity of Ranolazine so the combination gives better therapeutic effect. This method was developed for simultaneous estimation of mentioned drugs. The method was then used for Evaluation of gastro-retentive tablet of Ranolazine and Metoprolol. There was no UV-Visible method available for the simultaneous estimation of Ranolazine and Metoprolol. So as to evaluate the drug Release of the Tablet, this method was developed.

MATERIALS AND METHODS

Reagents and chemicals

- Drugs- Ranolazine and Metoprolol Succinate
- Dilution media- 0.1 N HCl
- Instruments- Spectrophotometer, A Shimadzu UV/vis 1800 double beam spectrophotometer, 1 cm matched quartz cells, UV probe 2.6, digital weighing balance and MS excel as analytical tool.

Method development

Preparation of 0.1 N HCl: To prepare 0.1 N HCl, 800 ml RO water was added to 8.5 ml Concentrated Hydrochloric acid and made it up to 1000 ml with RO water.

Preparation of stock: 10 mg of drug was dissolved in 100 ml 0.1 N HCl to make 100 ppm solution. Withdraw 0.2 ml stock and dilute it up to 10 ml with 0.1 N HCl, which results in 2 ppm solution.

Preparation of Calibration Curve of Ranolazine in 0.1 N HCl

Table 1 Preparation of Calibration curve of Ranolazine in 0.1 N HCL

Concentration(ppm)	Abs. 1	Abs. 2	Abs. 3	Mean Absorbance	Standard Deviation (+/-)
0	0	0	0	0	0
20	0.143	0.142	0.135	0.140	0.00436
40	0.268	0.27	0.365	0.301	0.05543
60	0.421	0.418	0.405	0.415	0.00850
80	0.55	0.549	0.55	0.550	0.00058
100	0.712	0.708	0.695	0.705	0.00889

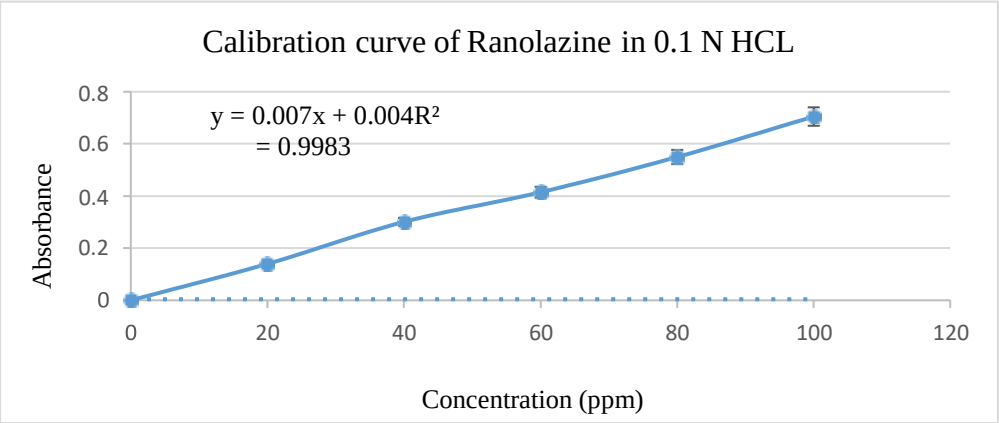

Figure 1 Calibration curve of Ranolazine 0.1 N HCl

Table 2 Preparation of Calibration curve of Metoprolol Succinate in 0.1 N HCl

Conc.	Abs. 1	Abs. 2	Abs. 3	Mean Absorbance	Standard Deviation (+/-)
0	0	0	0	0	0
5	0.151	0.152	0.151	0.1513	0.0006
10	0.258	0.258	0.257	0.2577	0.0006
15	0.404	0.404	0.403	0.4037	0.0006
20	0.55	0.58	0.56	0.5633	0.0153
25	0.668	0.667	0.666	0.6670	0.0010
30	0.757	0.758	0.754	0.7563	0.0021
35	0.928	0.929	0.926	0.9277	0.0015
40	1.032	1.031	1.035	1.0327	0.0021

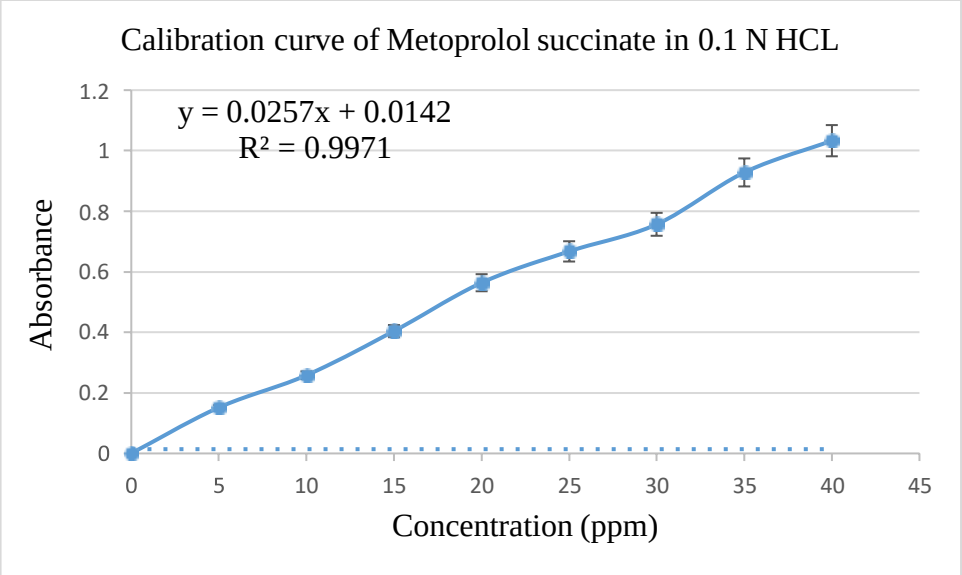

Figure 2 Calibration curve of Metoprolol succinate in 0.1 N HCL

Design-

Preparation of stock solution-

- 10 mg of Ranolazine is dissolved in 0.1 N Hydrochloric acid and made up to 100 ml with 0.1 N Hydrochloric acid to make 100 ppm. From the stock solution 3 ml was withdrawn and made upto 10 ml using 0.1 N HCl. Absorbance was taken within the wavelength range 200 nm to 400 nm. Maximum absorbance was found to be at 272 nm.

Method development and validation

- First derivative spectrophotometric method was developed for simultaneous estimation of Ranolazine and Metoprolol succinate. All the validation parameters were in acceptance limits given by ICH (Q2R1) guidelines.

- The overlay of both drugs suggests that Ranolazine possesses maximum absorbance at 212 nm in first order derivative and metoprolol succinate possesses 203 nm so both the wavelengths wereselected for estimation of both drugs.

- Linearity was determined for Ranolazine and metoprolol succinate by plotting calibration curves of D1 absorbance versus concentration at the range 7.5 to 45 ppm and 1 to 5 ppm respectively.

1. Linearity study

Linearity was determined for Ranolazine and metoprolol succinate by plotting calibration curves of D1 absorbance versus concentration at the range 7.5 to 45 ppm and 1 to 5 ppm respectively.

Overlay spectra of both drugs

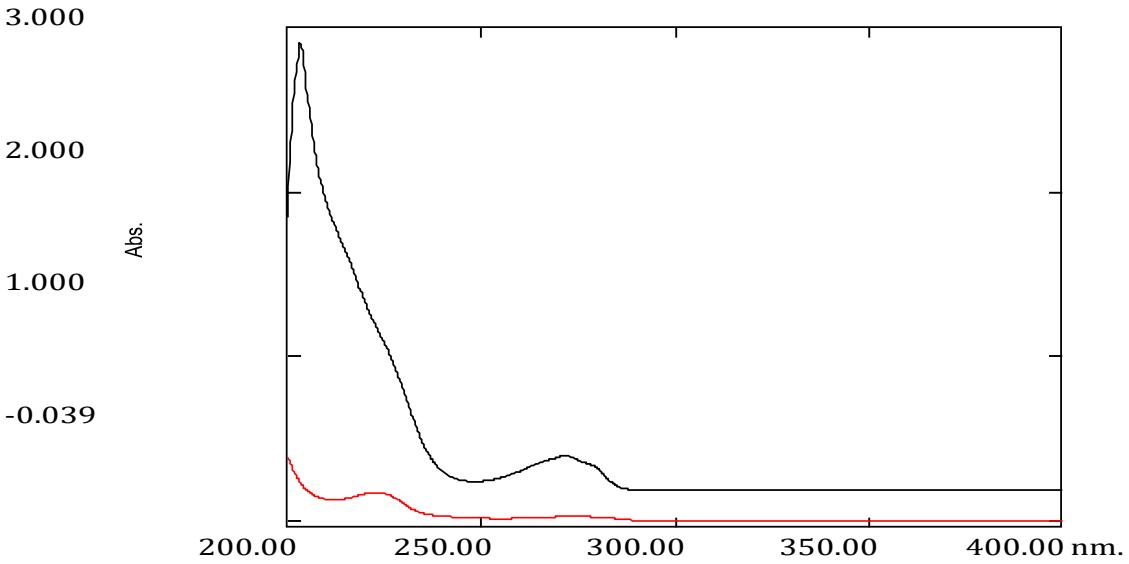

Figure 3. Overlay spectra of RAN and MET

Derivatized overlay spectra in first derivative 4 λ

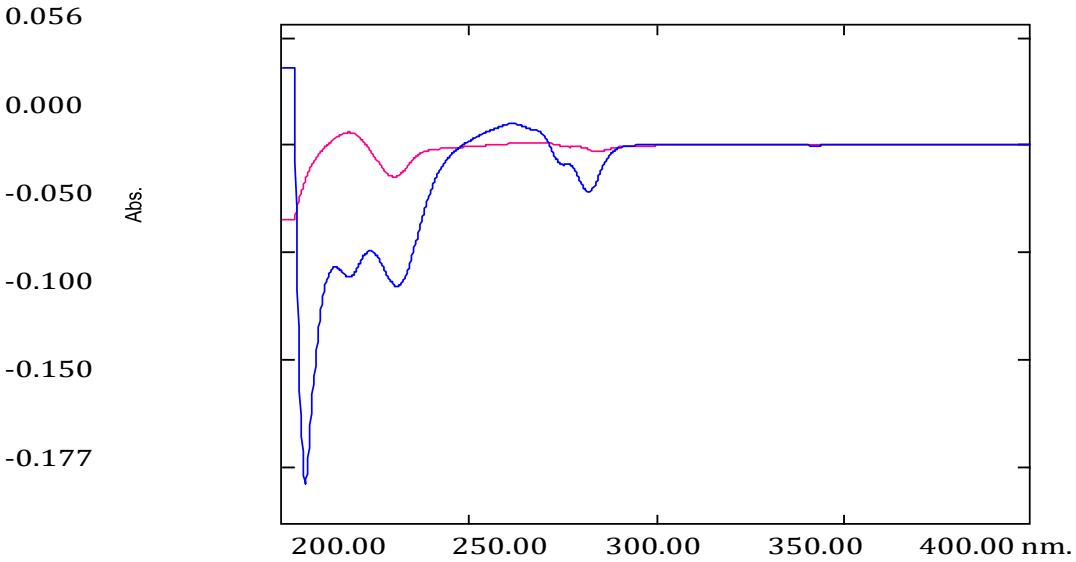

Figure 4. Derivatized overlay spectra in first derivative 4 λ

Determination of Zero Crossing Point (ZCP)-

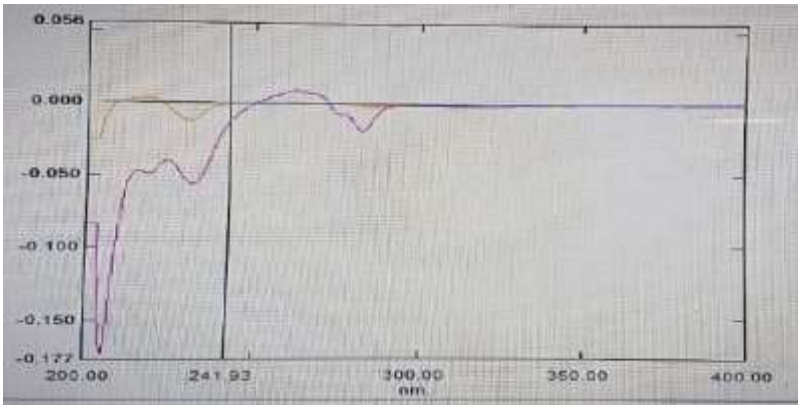

Figure 5. determination of Zero Crossing Point (ZCP)

Preparation of Calibration curve of RAN in first derivative

Table 3 Preparation of Calibration curve of RAN in first derivative

Concentration(ppm)	Abs.	Abs.	Abs.	Mean Absorbance	Standard Deviation(+/-)
0	0.005	0.005	0.005	0.005	0
7.5	0.012	0.012	0.012	0.012	2.1245E-18
15	0.025	0.031	0.025	0.029	0.0034
22.5	0.040	0.044	0.044	0.042	0.00230
30	0.054	0.058	0.057	0.056	0.00208
37.5	0.065	0.074	0.074	0.071	0.00519

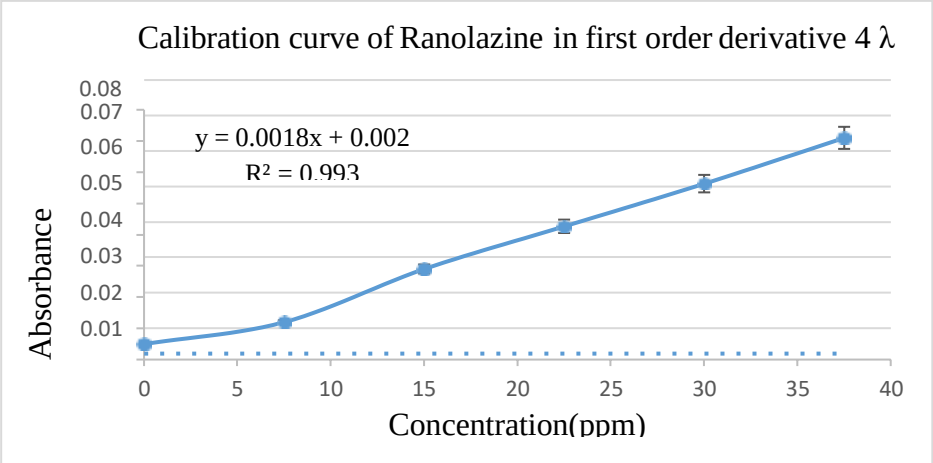

Figure 6. Calibration curve of Ranolazine in first order derivative 4 λ

➢ **For Metoprolol succinate**

Preparation of stock solution-

10 mg of Metoprolol Succinate is dissolved in 0.1 N Hydrochloric acid and made up to 100 ml byadding 0.1 N Hydrochloric acid to make 100 ppm.

Table 1: Preparation of Calibration curve of MET in first derivative

Concentration(ppm)	Abs.	Abs.	Abs.	Mean absorbance	Standard Deviation(+/-)
0	0.003	0.003	0.003	0.003	0
1	0.012	0.011	0.011	0.011	0.00058
2	0.018	0.017	0.017	0.017	0.00058
3	0.025	0.022	0.022	0.023	0.00173
4	0.03	0.027	0.028	0.028	0.00153
5	0.035	0.031	0.033	0.033	0.00200

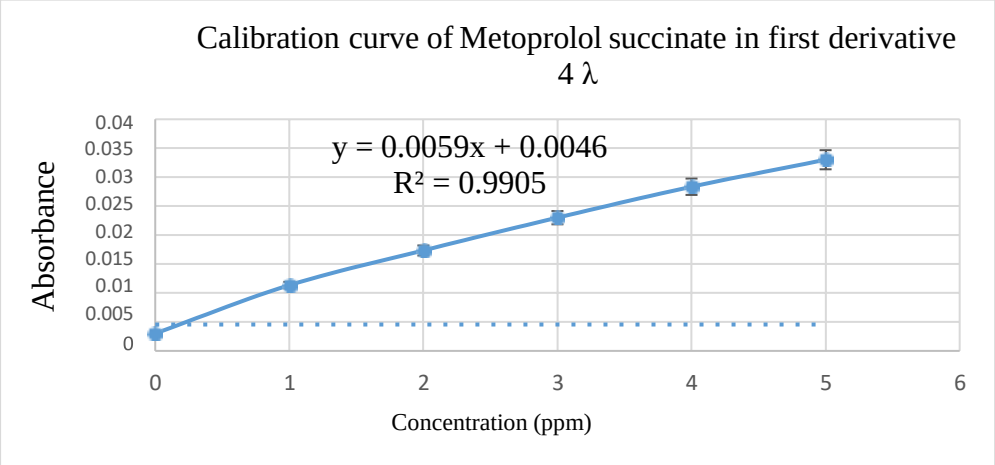

Figure 7. Calibration curve of Ranolazine in first order derivative 4 λ

Linear equation for RAN, Y=0.0017x+0.002Linear equation for MET, Y=0.0058x+0.006

➢ For linearity study- Select five concentrations which are in the ratio of both drugs' assay concentration. Dose of RAN is 375 mg and for MET it is 50 mg so here the assay concentration ratio becomes 1:7.5 ppm (MET: RAN). Prepare solutions of both drugs were prepared in this ratio. Series of solutions was prepared ranging from 1:7.5 to 5:37.5 ppm. Absorbance were taken at 212nm and 203 nm for Ranolazine and Metoprolol succinate respectively.

Derivatized spectra for linearity study of Ranolazine

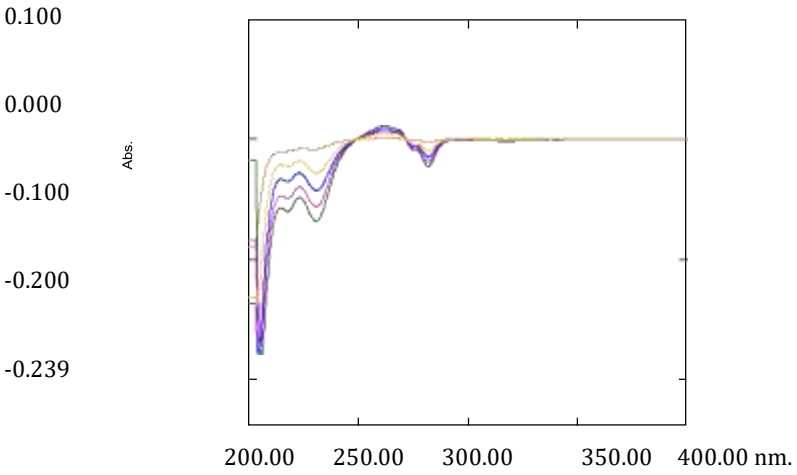

Figure 8. Derivatized spectra for linearity study of Ranolazine

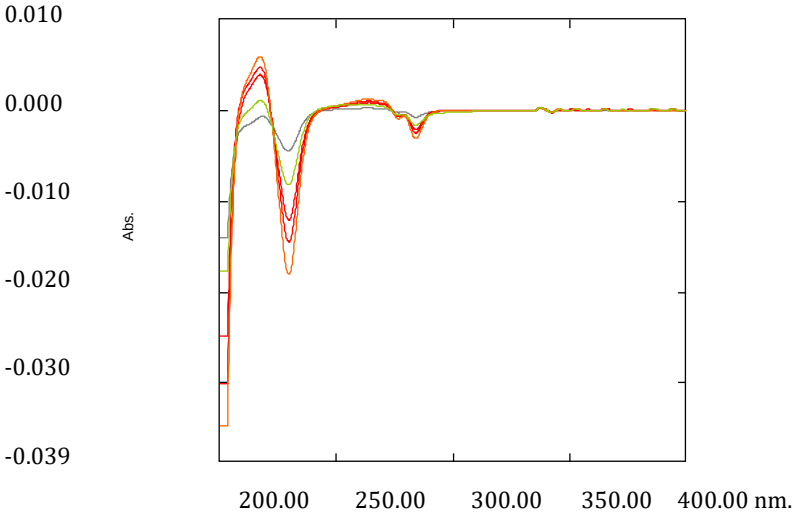

Figure 9. Derivatized spectra for linearity of Metoprolol succinate

Results and Conclusion-1.Linearity study-

Table 4 linearity Study

Parameter	RAN	MET
Linearity range	7.5-37.5 ppm	1-5 ppm
Slope	0.001933	0.005433
Intercept	0.0014	0.0063
Standard deviation of slope	0.000115	0.00404
Standard deviation of intercept	0.0001	0.00052

2. Precision- Precision of the analytical method was ascertained by carrying out the analysis as perthe procedure and as per normal weight taken for analysis. Analysis was repeated for six times. Calculate the % assay, mean assay, % Deviation and % relative standard deviation and %RSD.

Limit of detection

LOD for RAN=0.272179413LOD for MET=0.178319

Limit of quantification LOQ for RAN=0.824786099LOQ for MET=0.540359

Result of Precision study

Table 5 Precision study

Parameter	RAN	MET
% Recovery	99.33-101.57	101.70-99.43
Precision (%RSD)	1.79079	0.9767
Limit of detection (ppm)	0.17069	0.315595
Limit of Quantification (ppm)	0.51724	0.956347

3. Accuracy

Result of Accuracy study

Table 6 Accuracy study

% Level	Amount of drug added (ppm)		Amount recovered (ppm)		% Recovery	
	RAN	MET	RAN	MET	RAN	MET
50	11.25	1.5	11.1743404	1.525577	99.32747	101.705128
100	22.50	3	22.555613	3.064038	99.08075	102.034615
150	33.75	4.5	34.4542162	4.410192	101.5756	98.0042735

4. Ruggedness

Ruggedness of this method was performed by analysis of samples from homogenous slot by different analysts using similar operational and environmental conditions.

Table 7 Ruggedness study

Parameters	RAN	MET
Working wavelengths	212 nm	203 nm
Linearity range (µg/mL)	7.5 to 45 ppm	1 to 5 ppm
Precision [%RSD] Inter-day [n=3] Intraday [n=3]	1.79079	0.9767
% Recovery [n=3] %RSD	99.33-101.57	0.9767
Repeatability (Mean* ±SD)Analyst 1 Analyst 2	0.99 1.0	0.90 0.87

After completion of the method development and validation, a gastro-retentive tablet was formulated and evaluated by this method. After 12 hours % Cumulative Drug Release for Ranolazine and metoprolol was found to be 98.45% and 97.23% respectively. The Dissolution profile and Data is given below-

Time (hr)	% CDR (Ranolazine)	% CDR (Metoprolol)
1	00.03	01.68
2	02.65	04.21
3	06.02	07.64
4	09.48	11.66
5	24.20	18.04
6	35.55	24.66
7	51.60	59.62
8	59.85	62.33
9	64.84	66.30
10	76.02	76.87
11	84.10	87.01
12	98.45	97.23

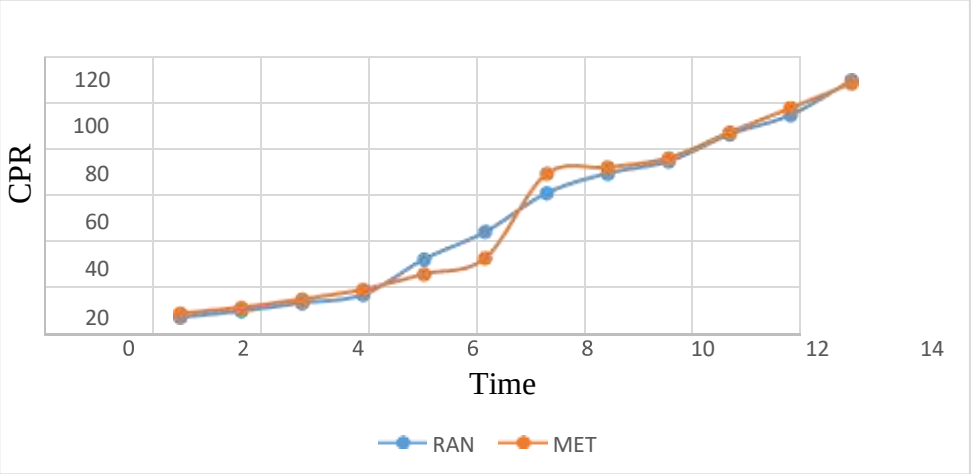

Figure 10. Dissolution data

DISCUSSION

In the treatment therapy of Angina Pectoris mainly used drugs like Beta blockers, etc. have side effect on Blood Pressure and Blood Glucose level, so monitoring is essential. Ranolazine being sodium channel blocker agent doesn't have any side effect on blood pressure. For increasing anti anginal activity of Ranolazine a beta blocker can be given along.

Ranolazine has high solubility in acidic pH and shorter half-life, so here it was formulated as Gastroretentive tablet along with metoprolol Succinate. Analytical method was developed for simultaneous estimation of Ranolazine and Metoprolol in first derivative 4**λ**. A tablet was formulated and Dissolution profile was taken for 12 hours. The results of linearity study, LOD, LOQ, Accuracy, Precision, Ruggedness were found to be were in compliance with Q2 R1 guidelines of ICH.

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