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Simultaneous Determination of Ivabradine and Metoprolol by Ultra-Performance Liquid Chromatography Bulk and Pharmaceutical Dosage Form and Its Stability Studies

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Abstract

A precise and efficient method for measuring Ivabradine and Metoprolol in bulk and pharmaceutical products has been developed using Reversed-Phase Ultra-Performance Liquid Chromatography (RP-UPLC). The experiment utilized an SB C8 100 x 3.0mm, 1.8mm column with a running phase consisting of a 50:50v/v ratio of Buffer 0.01N Potassium dihydrogen ortho phosphate to Acetonitrile. The flow rate was set at 0.3 ml/min. A wavelength of 260 nm was used for UV detection. The correlation parameters for Ivabradine and Metoprolol were highly significant, with values close to 99.9% and % MSD, respectively.

Keywords: Ivabradine, Metoprolol, UPLC, Heart Failure, Uv Detection

Introduction

Ivabradine, [1] sold under the brand name Procoralan among others, is a medication, which is an If inhibitor, used for the symptomatic management of stable heart-related chest pain and heart failure [2, 3]. Patients who qualify for use of Ivabradine for coronary heart failure are patients who have symptomatic heart failure, with reduced ejection volume and heart rate at least 70 bpm, which condition cannot be fully managed by beta blockers. [4-6] Ivabradine acts by allowing negative chronotropy in the sinoatrial structure thus reducing the heart rate via specific inhibition of the pacemaker current, a mechanism different from that of beta blockers and calcium channel blockers[7,8,] two commonly prescribed antianginal classes of cardiac pharmaceuticals. Ivabradine has no apparent inotropic properties and may be a cardio tonic agent.

Metoprolol [9,10], sold under the brand name Lopressor, among others, is a selective β1 receptor blocker. It is used to treat high blood pressure, chest pain due to poor blood flow to the heart, and a number of conditions involving an abnormally fast heart rate. By working on the beta-1 receptor of the cardiac muscle cells, it yields both a chronotropic and inotropic effect. It is also used to prevent further heart problems after myocardial infarction [11, 12] and to prevent headaches in those with migraines. [13, 14] For ascertaining quality, various analytical methods are used. Various methods used for evaluation of Ivabradine and Metoprolol Were Titrimetric, UV, Visible spectroscopy, dissolution study using HPLC, IR, HPLC, HPLC coupled with MS (LC-MS), HPTLC, UPLC, UPLC coupled to MS, UPLC-MS/MS. Out of the available methods, UPLC-MS method is the generally used for the analysis of biological samples, whereas the HPLC method is the used for the analysis of pharmaceutical samples. Ivabradine and Metoprolol in pharmaceutical or biological matrixes can be evaluated by different methods of analysis[15]. Effective and reliable results for Pharmaceutical analyses are essential as they have an impact on making analytical decisions besides, the method must be suitable for the intended investigation. Ivabradine is a newly approved drug, hence analytical methods are not available in any compendia, whereas analysis of Metoprolol is available in IP[16] and USP[17-22] for various salt forms. However, simultaneous quantification of both Ivabradine and Metoprolol is not available to date. Hence, in this study a novel, quick, sensitive, and easy-to-use UPLC method was attempted for simultaneous estimation of Ivabradine and Metoprolol in API and pharmaceutical dosage types without having to separate the drugs beforehand [23-26]

Materials and Methodology

Instrumentation

Empower 2 software developed by Waters and a TUV detector. The isocratic analytical approach utilized an SB C8 100 x 3.0mm, 1.8µm column. Buffer and Acetonitrile was pumped through the column at a flow rate of 0.3ml/min. The

temperature was kept at 30 degrees Celsius throughout the experiment.

Chemicals and Reagents
Dr. Reddy labs, provided the Ivabradine and metoprolol samples used in this study. This HPLC-grade water and other chemicals were purchased from Merck India's Mumbai for use in this experiment. These chemicals included Acetonitrile, Methanol, Potassium Dihydrogen, Orthophosphate Buffer, Ortho-phosphoric Acid, and Triethylamine.

Method Development
Preparation of Standard Solution:
5mg of Ivabradine and 25mg of Metoprolol working standards were accurately weighed and transferred to 25mL clean dry volumetric flasks, and 10ml of diluent was added, sonicated for 10 minutes, and the total volume was made up using diluents. 200 µg/ml Ivabradine and 1000 µg/ml Metoprolol are recommended.
1mL from stock solution was pipette out and taken into a 10mL volumetric flask and fill up to the mark with diluent.

Preparation of Sample solution:
Accurately weighed equivalent of the combination (IVA Met XL) powder sample transfer into a 50mL volumetric flask, 25mL of diluents was added and sonicated for 25min, further the volume was made up with diluents and filtered by PVDF filters. 2 mL of filtered sample stock solution was transferred to 10mL volumetric flask and made up with diluent. Ivabradine and Metoprolol concentrations are 20 and 100 micrograms per liter, respectively.

Method Validation [27-35]
System Suitability:
Preparation of standard solutions of Ivabradine 20µg/ml and Metoprolol 100µg/ml helped identify the system suitability characteristics. There were six injections, and the peak tailing and resolution factors were measured. Six standard injections were used to determine the percentage RSD, and RSD was not greater than 2.0 percent.

Linearity:
Ivabradine and Metoprolol standard aliquots were used to generate six working solutions ranging from 5-30 µg/ml and 25-150 µg/ml, respectively. A total of three replicates were used at each linearity point in the experiment. Regression equations and correlation coefficients were calculated on the Ivabradine and Metoprolol calibration curves by plotting observed peak areas versus concentration.

Accuracy:
A percentage recovery study was conducted at three different concentrations of Ivabradine and Metoprolol to verify accuracy (50 percent, 100 percent, and 150 percent).

Precision:
Precision of a method is the degree of agreement among individual test results when the procedure is applied repeatedly to multiple samplings. Precision is measured by injecting a series of standards or analyzing series of samples from multiple samplings from a homogeneous lot.

Limit of Detection (LOD) and Limit of Quantitation (LOQ):
The slope of the calibration plot and the peak area's standard deviation (SD) were used to determine the LOD and LOQ, with LOD = 3.3 σ/s and LOQ = 10 σ/s, respectively.

Robustness:
Variations in flow rate, mobile phase ratio, and column temperature were made to ensure that the process was stable, but no apparent change in results was seen. All of these parameters are within the ICH guidelines. It was essential to keep the flow rate at 0.27ml/min and the flow rate at 0.33ml/min, as well as the temperature minus (25°C) and the temperature plus (35°C) constant to ensure the robustness of the experiment.

Degradation Studies
Oxidation:
Separately, 1 ml of 30% hydrogen peroxide (H_2O_2) was added to 1 ml of Ivabradine and Metoprolol stock solution. At 60°C for 30 minutes, the solutions were held. For UPLC analysis, the resulting solution was diluted to obtain (20ppm & 100ppm) solution, 0.50 µl was injected into the system, and the chromatograms were recorded to test the stability of the sample.

Acid Degradation Studies:
1 ml of 2N hydrochloric acid was added to 1 ml of s tock's solution Ivabradine and metoprolol and refluxed at 60°C for 30 minutes. To test the stability of the sample, the diluted solution was injected into the chromatography system, and the chromatograms were recorded at a concentration of 20 ppm and 100 ppm.

Alkali Degradation Studies:
The stock solution of ivabradine and metoprolol was diluted with 2N sodium hydroxide and heated to 60°C for 30 minutes. To test the sample's stability, the final solution was diluted to 20 ppm and 100 ppm and injected into the system in a volume of 0.50µl.

Thermal Degradation Studies:
An oven was set to 105°C for six hours to evaluate the dry heat degradation of a typical medication solution. As part of the study for UPLC, the resulting solution was diluted, and 0.50 µL was introduced into the system to record chromatograms to determine the sample's stability.

Photo Stability studies:
After subjecting the (200ppm and 1000ppm) solution to UV light for 7 days or 200-Watt hours/m in a photo stability chamber, the photochemical stability of the medication was also examined. The final solution was diluted to produce 20ppm and 100ppm solutions, and 0.50 µl of each was fed into the UPLC machine to record the chromatograms.

Neutral Degradation Studies:
In neutral environments, stress testing was carried out by recirculating the drug for six hours in water heated to 60°C (deg. C). To test the sample's stability using UPLC, the final solution was diluted to 20ppm and 100ppm concentrations and then injected into the system in a volume of 0.50 µl.

Results and Discussions
It was found that ivabradine and Metoprolol dilutions could be made using a 0.2N Potassium dihydrogen ortho-phosphate; Acetonitrile (50:50) SB C8 100-x-4.6mm, 3-m. a column with a flow rate of 0.7ml/min and run time of 3 minutes. The Metoprolol and Ivabradine peaks are clearly separated in the chromatogram above. Metoprolol has a half-life of 0.810 minutes. Ivabradine's retention time was 1.156 minutes. Method validation was performed by following ICH guideline Q2 (R1) to verify that the UPLC method is accurate for use in laboratory quality control testing procedures.

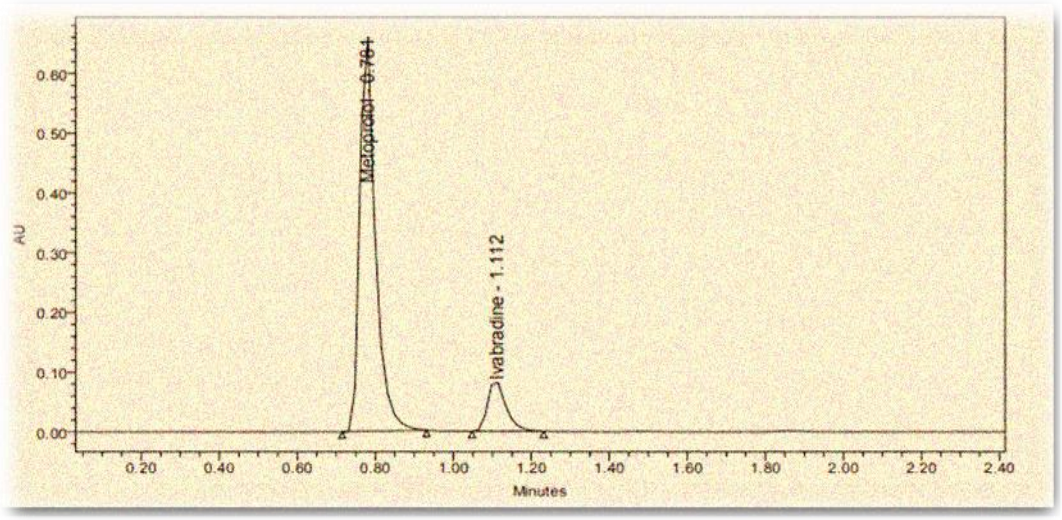

Figure 1: Optimized Chromatogram

Table: 1 Peak results of Chromatogram Trial-4

Drug Name	Rt	Area	Usp Tailing	Usp Plate Count
Metoprolol	0.781	1950050	1.3	5977.8
Ivabradine	1.112	274943	1.3	2745.2

System suitability

Table: 2 Parameters of system suitability

Parameters	Metoprolol	Ivabradine
Retention Time (min)	0.810 min	1.156
Theoretical plates (N)	5970	2355
Tailing factor	1.45	1.30
Resolution	NA	4.2
%RSD	0.9	0.8

Linearity

Ivabradine and Metoprolol concentrations of 5-30 and 25-150 g/ml were linear with correlation values of 0.999.

Tables: 3 Results of Linearity

Parameters	Metoprolol	Ivabradine
Y intercept	19132	13738
Correlation coefficient r2	0.9997	0.9993
Regression Equation	Y=19132x+26914	Y=13738x+4034
Linearity range	25-150 µg/ml	5-30 g/ml

Accuracy

From the Accuracy Method, we observed that the mean %Recovery of the drugs are 100.23%, 99.96% and 99.88 % which is within the range of 98- 102% and %RSD is within the range <2 i.e. 0.54 %, 0.09% and 0.38% respectively. From the Accuracy Method, we observed that the mean %Recovery of the drugs are 100.26%, 99.95%, and 99.87 %, which is within the range of 98- 102% and %RSD is within the range <2 i.e., 0.57 %, 0.48% and 0.32% respectively.

Table: 4 Accuracy Results of Metoprolol

Concentration	Peak Area	%Recovery of pure drug	Statistical Analysis
50	2904915	100.86	Mean =100.23% S. D=0.541073 %RSD=0.54
	2896539	99.98	
	2895459	99.87	
100	3853467	100.01	Mean=99.96% S. D=0.090322 %RSD =0.09
	3850568	99.86	
	3853647	100.02	
150	4818522	100.30	Mean=99.883% S. D=0.377759 %RSD=0.38
	4803497	99.78	
	4797472	99.57	

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Table: 5 Accuracy results of Ivabradine

Conc Found	Peak Area	%Recovery of pure drug	Statistical Analysis
10	415817	99.74	Mean=100.26% S. D=0.568659 %RSD=0.57
	417368	100.87	
	416429	100.19	
20	552051	99.45	Mean=99.95% S. D=0.478138 %RSD =0.48
	554670	100.41	
	553543	100.00	
30	689058	99.54	Mean=99.87% S. D=0.323348 %RSD=0.32
	690462	99.89	
	691722	100.19	

Precision

RSD of 0.4 percent for Metoprolol and 1.0 percent for Ivabradine were found in the reproducibility research on the solution containing roughly 100µg/ml for Metoprolol and 20µg/ml for Ivabradine. Good reproducibility was found in the analytical method.

Table :6 Data showing reproducibility analysis for Metoprolol and Ivabradine

Preparations	Metoprolol		Ivabradine	
	Area	% Assay	Area	% Assay
AVERAGE	1930186	99.82	276563	99.75
STANDARD DEVIATION	8667.3	0.448	2767.1	1.00
%RSD	0.4	0.4	1.0	1.0

Limit of Detection and Limit of Quantification

Limit of detection of target assay concentration of Ivabradine and Metoprolol by using formula method 0.03µg/ml and 0.12µg/ml. Limit of quantification of the target assay concentration of Ivabradine and Metoprolol by using formula method 0.08µg/ml and 0.35µg/ml were within the limits**.**

Table: 7 Peak results of LOD and LOQ

	LOD		LOQ	
Drug Name	**RT**	**S/N**	**RT**	**S/N**
Metoprolol	0.811	595.3	0.806	1067.5
Ivabradine	1.151	74.7	1.153	149.6

Forced Degradation Studies

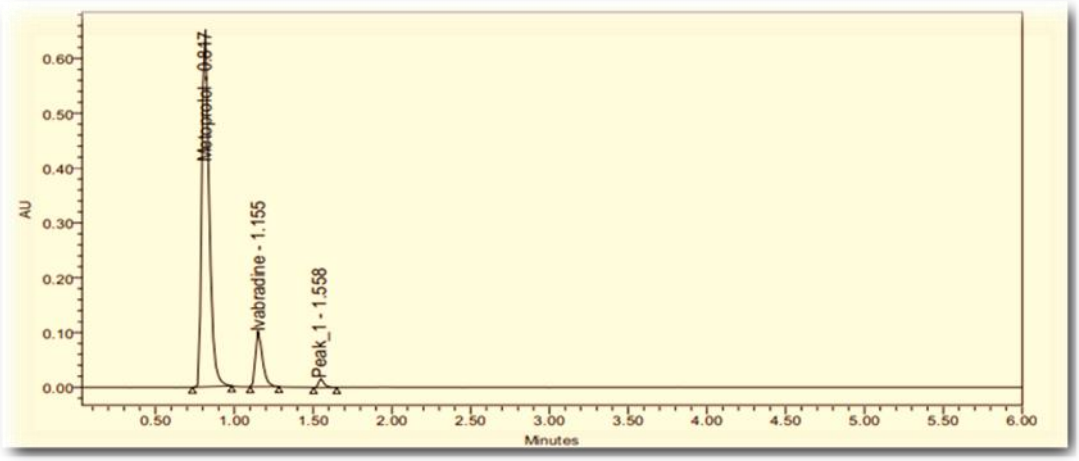

Figure :2 Chromatogram showing Acid Degradation

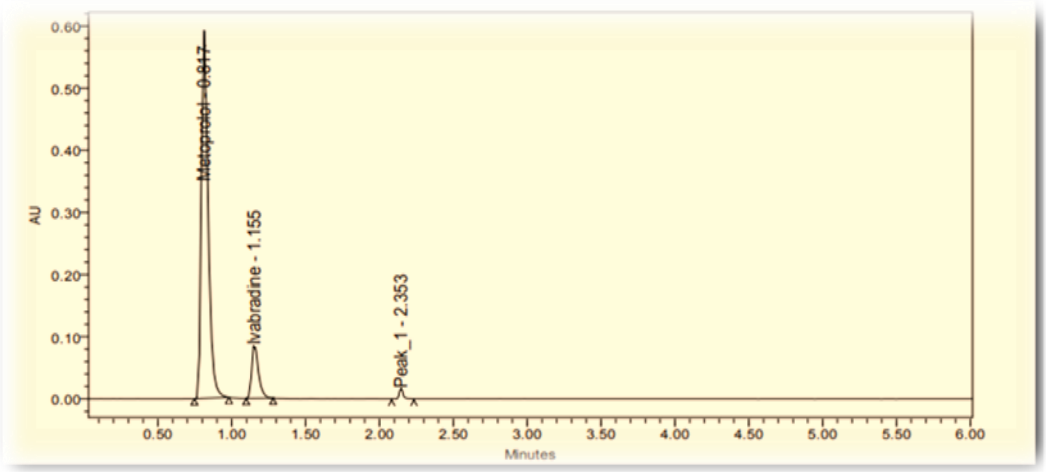

Figure: 3 Chromatogram showing Alkali Degradation

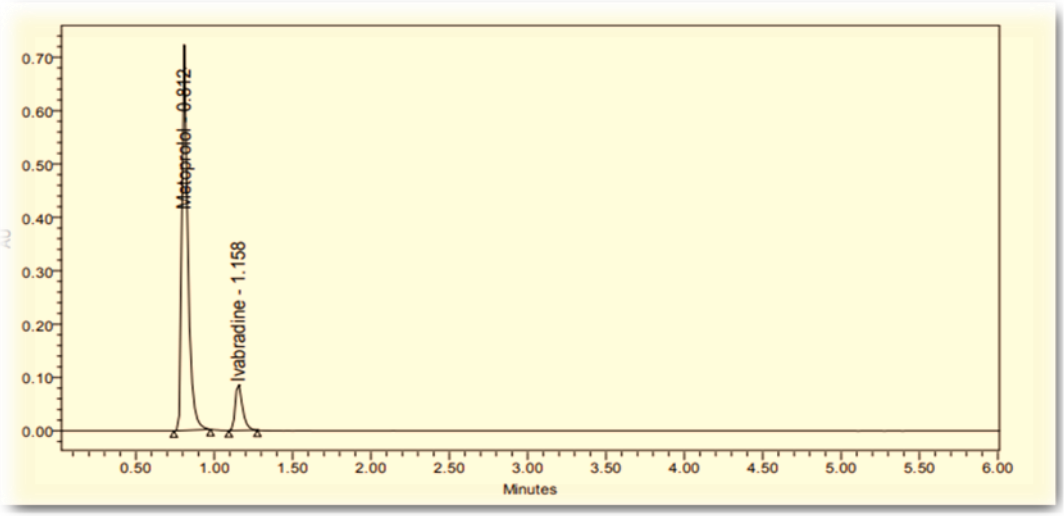

Figure :4 Chromatogram showing Thermal Degradation Studies

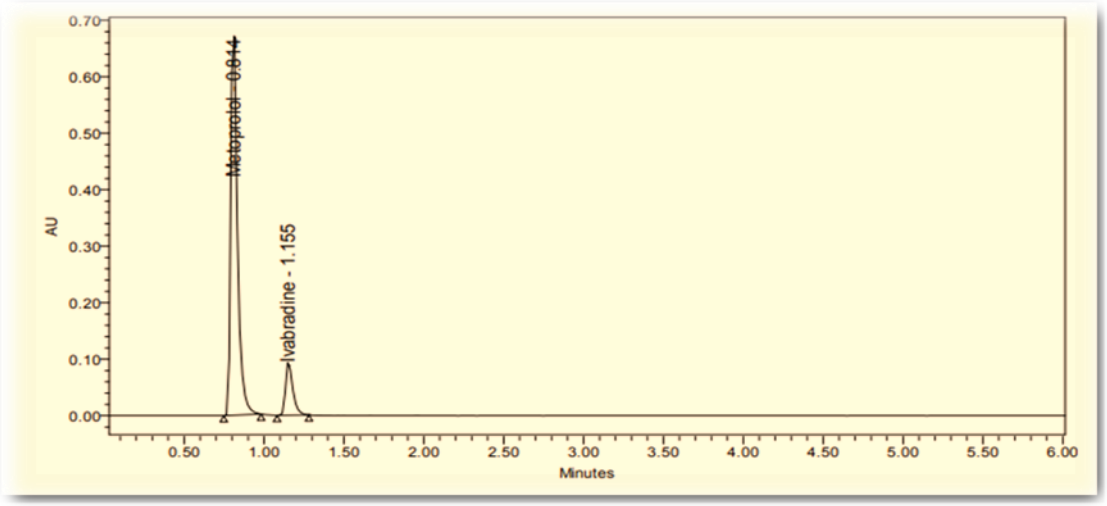

Figure :5 Chromatogram showing Photolytic Degradation Studies

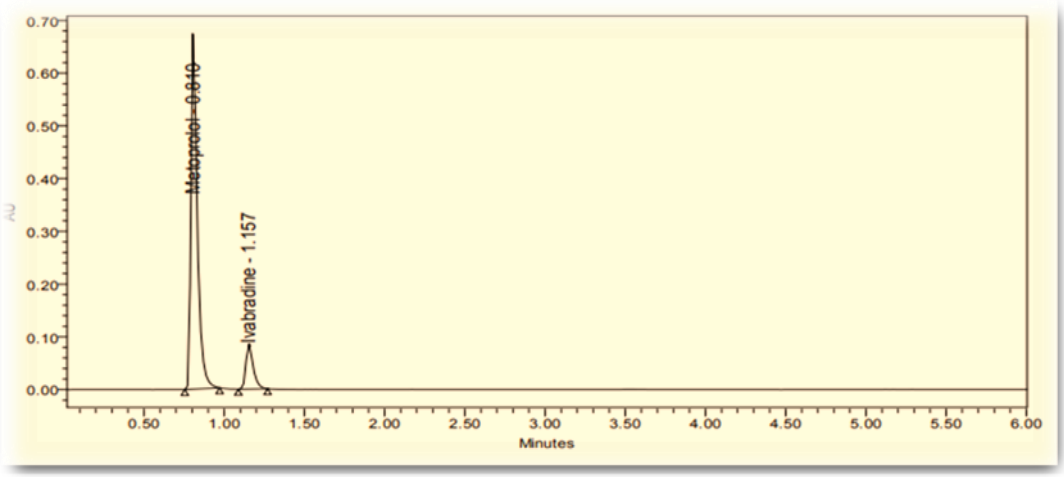

Figure: 6 Chromatogram showing Neutral Degradation

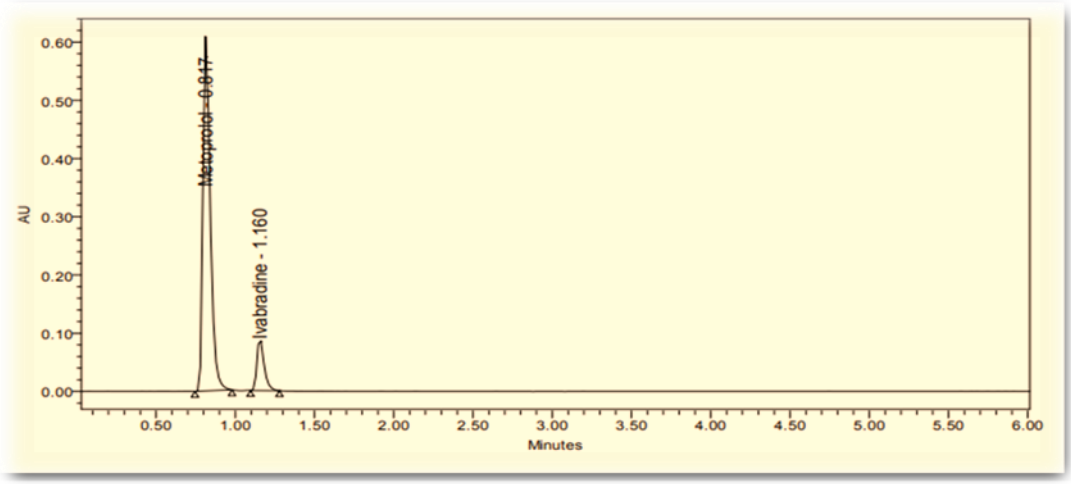

Figure :7 Chromatogram Showing Oxidative Degradation

Table: 7 Results of Force Degradation Studies of Metoprolol and Ivabradine

	Metoprolol		Ivabradine	
Stress condition	**Assay of active substance**	**Assay of degraded products**	**Assay of active substance**	**Assay of degraded products**
Acid Hydrolysis (2N HCl)	95.19	4.81	94.13	5.87
Basic hydrolysis (2N NaOH)	96.29	3.71	95.65	4.35
Thermal degradation (105°C)	97.08	2.92	97.09	2.91
UV	98.17	1.83	98.25	1.75
Water	99.13	0.87	99.26	0.74
30% Hydrogen Peroxide	96.38	3.62	96.25	3.75

Conclusion

An efficient UPLC method was developed for the simultaneous estimation of Ivabradine and Metoprolol in API and pharmaceutical dosage forms. The method is novel, quick, sensitive, and easy-to-use. The approach developed is the most practical option, offering benefits such as shorter run time, low cost, and various other advantageous characteristics. The suitability parameters were thoroughly examined and met all the necessary criteria, such as linearity, accuracy, specificity, robustness, and process precision. The study found that the RSD values for all the parameters were less than 2%, indicating a high level of accuracy in the procedure. Additionally, the results were consistent, further supporting the accuracy of the procedure. The current approach in QC laboratories for routine study in manufacturing pharmaceuticals containing Ivabradine and Metoprolol is highly recommended. It allows for the substances to be analyzed without the need for separation beforehand.

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