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ORIGINAL ARTICLE

Development and Validation of Stability-Indicating RP-HPLC Method for Estimation of Mirabegron in Bulk and Pharmaceutical Dosage form

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ABSTRACT
A new, simple, rapid, accurate, and precise stability indicating reverse phase HPLC method has been developed for estimation of mirabegron in bulk and pharmaceutical dosage form. Chromatographic separation was successfully carried out on Oyster ODS 3 C_{18} column (150mm×4.6mm, 5µm) at a flow rate of 1.0ml/min and the detection wavelength set at 249nm in an isocratic mode. The mobile phase composed of buffer Potassium dihydrogen orthophosphate (pH:3) adjusted with orthophosphoric acid and Acetonitrile in the ratio of 70:30 v/v. The retention time of mirabegron was found to be 2.327min and the injection volume was 20µL. linearity of the developed method was confirmed over concentration range of 10-60µg/ml and the correlation coefficient (r^2) were found to 0.9999. The LOD and LOQ were found to be 0.3022 & 0.9159 µg/ml respectively. The precision of the method was found to be 0.35-0.79 (%RSD) for intraday and 0.57-0.93 (%RSD) for inter-day that indicates good precision of mirabegron analysed. A % recovery of the method was found in the range of 99.77-101.31%. The percentage assay of mirabegron was found to be 100.34%. All the parameters of validation were in the acceptable limit. The degradation product peak was well resolved from the primary peak of mirabegron and also there was no interference of excipients and degradation product on retention time of mirabegron, indicating that the method is specific and stability indicating. The developed HPLC method was validated as per ICH guidelines.
Keywords: Mirabegron, RP-HPLC, Method development, Validation, Forced degradation.

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INTRODUCTION

The chemical name for Mirabegron is 2-(2-amino-1, 3 thiazol-4-yl)-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl] acetamide, havinga molecular formula of $C_{21}H_{24}N_4O_2S$ and a molecular weight of 396.509 g/mol. Mirabegron is an agonist of β-3 adrenergic receptor, is used to treat overactive bladder (OAB), a condition in which the bladder muscles contract involuntarily and results in frequent urine, the need to urinate immediately and the inability to regulate urination [1]. Urgency with or without urine incontinence is what the International Continence Society refers to as an overactive bladder,typically accompanied by frequency and nocturia [2], is a multifactorial and common health disorder associated with detrimental effects on quality of life and huge economic burden [3, 4]. Caffeine consumption that is very high leads to issues with an overactive bladder [5]. Its benefits are similar to other antimuscarinic medication such as solifenacin or tolterodine [6]. In the United kingdom it is less preferred to antimuscarinic medication such as oxybutynin [7]. The maximal concentration of Mirabegron is reached after 3.5 hours of oral administration to healthy volunteers. Giving 25 mg of the medication increases the absolute bioavailability to 29%. By providing a dose of 50 mg, the absolute bioavailability increases to 35% [8]. Through activation of the β-3 adrenoreceptor, Mirabegron has recently been demonstrated to relax in-vitro human and rabbit prostate smooth muscle. The same team also demonstrated how mirabegron encourages smooth muscles relaxation by blocking α-1 adrenergic

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receptor [9]. High blood pressure, headache, and urinary tract infections are the common side effects [8]. The majority of methods for determination of Mirabegron in biological fluid and pharmaceutical dosage form includes LC-MS/MS [10], RP-HPLC [11-13], UV spectrophotometric [14-17] analytical method are available in the literature for analyzing Mirabegron in pharmaceutical dosage form or as bulk drug sample. Considering the stability of mirabegron, it was thought to be interesting to develop a simple, sensitive, accurate, precise method for estimating mirabegron in pharmaceutical dosage form. The current study describes the validation parameters stated by the ICH guidelines [18].

MATERIAL AND METHODS

Instruments

Analysis was carried out on a Shimadzu HPLC System equipped with LC Solutions software.The separation was carried out on (Oyster ODS3)C_{18} column(150mm×4.6mm, 5µm)maintained at 30ºC at a Flow rate of 1.0 ml/min.Shimadzu UV-Visible Spectrophotometer, Digital pro plusUltra sonicator, Systronics pH meterand 0.45µ membrane filter.

Chemicals and Reagents:

TheAPI Mirabegron was procured from Mehta API Pvt.Ltd,Navi Mumbai, Tablet(Megatas 50mg)were purchased from the local market.HPLC grade water, Ortho phosphoric acid(OPA), Potassium Dihydrogen Phosphate, Acetonitrile was Procured from Fine Chem Industries.NaOH, HCL, Hydrogen peroxide were Procured from Molychem Pvt. Ltd.

Chromatographic conditions:

Chromatographic analysis was performed on Shimadzu HPLC system and separation done on Oyster ODS3 C_{18} (150mm×4.6mm, 5µm) Column, maintained at30ºC. The mobile phase contains potassium Dihydrogen phosphate 20Mm (pH-3) and Acetonitrile (70:30) v/v. Prior to usage, it was filtered using a 0.45µ membrane and sonicated for 15 minutes and set to 1.0 ml/min isocratic elution flow rate and injection volume of 20µL.Eluted sample was monitored at 249nm and run time was 8min.

Preparation of Buffer:

A precise 1.36g of potassium dihydrogen phosphate was weighed, transferred, and sonicated into a 500ml volumetric flask with water (20Mm Conc). The pH was raised to 3 using OPA, and it was degassed and filtered through 0.45µ filter paper.

Preparation of Mobile phase:

Mix Buffer and Acetonitrile in the ratio of 70:30v/v and filtered through 0.45µ nylon membrane filter and sonicated for about 30 minutes to degas.

Preparation of standard stock solution:

An accurately weighed 100mg of Mirabegron was transferred to 100ml of volumetric flask to this add 20ml of diluent it is sonicated for 15min and makeup the volume upto (100ml) the mark (1000µg/ml). From the above stock solution pipetted 1ml in to a 10ml volumetric flask and the volume was made up to mark with diluent(100µg/ml). Stock solution was further diluted with diluent to obtain (10-60µg/ml) conc. standard solution.

Preparation of Working standard solution:

Aliquot of 4ml of standard stock solution of Mirabegron was withdrawn by means of pipette and diluted to 10ml with mobile phase to make resultant solution of 40µg/ml. The solution was sonicated for 15min and used for supplementary study.

Preparation of sample solution:

Weighedaccurately20 tablets and the average weight was calculated. Tablets were crushed in the mortar pestle and the tablet powder equivalent to 10mg of Mirabegron was accurately weighed and transferred in to 100ml volumetric flask, add about 30ml of diluent and sonicated it up to 30min to dissolve it completely and the volume was made up to mark with the mobile phase to obtain concentration of 100ppm.The solution was filtered through 0.45µmembrane filter. Further dilutions were made to obtain concentration of 10-60µg/ml.

Determination of maximum wavelength:

Working standard (40 µg/ml) was scanned between 200 and 800 nm on a UV-Visible spectrophotometer using methanol as a blank to find the ideal maximum wavelength. The drug highest absorbance was detected at 249 nm, which was used as the detection wavelength for Mirabegron estimation.

Method validation:

The analytical method validation was done according to ICH Q2 (R1) guidelines of validation of analytical methods for the parameters of specificity, system suitability, linearity, the limit of detection (LOD), the limit of quantification (LOQ), accuracy, precision and robustness were discussed below.

Linearity and Range:

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The linearity response was determined by analysing solutions having concentrations in the range of 10-60µg/ml Mirabegron. Peak area of each solution was measured using developed method. Calibration curve of Peak area vs Concentration was plotted.
The correlation coefficient and regression line equations for Mirabegron was determined.

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

LOD and LOQ are two different parameters useful for determination of lowest concentration of drug that can be detected and quantified suitably. LOD and LOQ determinations were done using standard deviation of the response (σ) by slope of the calibration curve (S) mathematical values. The σ/S values were multiplied with 3.3 for LOD and 10 for LOQ determinations**.**

Precision:

Precision was analyzed by calculating variation of the method in intraday (Repeatability performed by analyzing standard solution on the same day) and interday (Repeatability carried out by analyzing standard solution on three different days).On the same day and three consecutive days, a precision study was carried out by injecting standard solution six times at three distinct concentrations of 30, 40, and 50 µg/ml.

Repeatability:

Repeatability was confirmed by analyzing the same solution of 40µg/ml of standard solution repeatedly.

Accuracy:

By spiking a precise concentration of pure drug into a previously examined sample solution containing 40 µg/ml of mirabegron, recovery studies were conducted to verify accuracy. A known quantity of standard stock solution was added to the sample solution at levels of 50%, 100%, and 150% to pre-analyze it. The mean % recovery was calculated.

Robustness:

A robustness method was performed to confirm whether the method is capable of reproducibility during the deliberate changes taken place in the proposed method. The modification includes different flow rates of the mobile phase (±0.2ml/min), change in mobile phase organic content ratio in the mobile phase (±5%), change in the wavelength for detection (±5nm).

Stress Degradation studies:

Stress testing must be done in order to clarify the inherent stability properties of the active substance, according to International Conference on Harmonization (ICH) standards titled stability testing of new drug substance and products.

Acid Degradation:

Forced Degradation in acidic media was performed by taking 1 ml stock solution of Mirabegron to 10 ml volumetric flask. Add 2ml of 0.1 N HCL in volumetric flask and kept at 60 ºC for 30 min then Neutralized it with 0.1N NaOH and diluted up to the mark with mobile phase.Solution was injected in to the HPLC.

Basic Degradation:

Forced Degradation in Basic media was performed by taking 1 ml stock solution of Mirabegron to 10 ml volumetric flask. Add 2ml of 0.1 N NaOH in volumetric flask and kept at 60 ºC for 30 min.Then Neutralized it with 0.1N HCL and diluted up to the mark with mobile phase. Solution was injected in to the HPLC.

Hydrolytic Degradation under neutral Condition:

Forced Degradation in Neutral Degradation was performed by taking 1 ml stock solution
of Mirabegron to 10 ml volumetric flask. Add 2ml of HPLC grade water and heated at 60 ºC for 30 min and diluted up to the mark with mobile phase.Solution was injected in to the HPLC.

Oxidative degradation:

Forced Degradation in Oxidative Degradation was performed by taking 1 ml stock solution of Mirabegron to 10 ml volumetric flask. Add 2ml of 3% H_2O_2 and heated at 70 ºC for 1 hr. and diluted up to the mark with mobile phase.Solution was injected in to the HPLC.

Thermal Degradation:

Forced Degradation in Thermal Degradation was performed by taking 10mg accurately weighed amount of Mirabegron and was exposed at 70ºC for 24 hrs. after this exposure, the drug powder was mixed and transferred in to 10 ml volumetric flask and volume made up to the mark with mobile phase.Solution was injected in to the HPLC.

Photolytic degradation:

1ml of solution from the sample stock solution was taken in a 10ml volumetric flask, and exposed it to sunlight for 24 hrs. and diluted up to the mark with mobile phase. Solution was injected in to the HPLC.

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RESULTS AND DISCUSSION

Determination of maximum wavelength (λ max):

The wavelength corresponding to maximum absorbance (λ max) was determined as 249nm from the UV spectrum of standard solution as shown in figure no.1

Optimization and method development:

Several mobile phases, stationary phases, flow rates, and buffer pH levels were appropriately examined in order to obtain optimal HPLC conditions the first time. In the end, it was determined that a mobile phase made of Potassium Dihydrogen Orthophosphate Buffer and acetonitrile mixed in a ratio of 70:30 v/v and a stationary phase made of an Oyster ODS 3 C18 Column with a (150 mm×4.6mm, 5µm) were the best for analyzing mirabegron. At room temperature for the column, the mobile phase flow rate and detection wavelength were set to 1.0 ml/min and 249 nm respectively. A Standard peak of Mirabegron is shown in figureno.2

Method Validation:

Following the ICH guidelines (Q2R1), the following parameters were determined after the chromatographic and experimental conditions had been established: Specificity, System appropriateness, Linearity, Precision, Accuracy, Robustness, Limit of Detection, Limit of Quantitation, and Solution Stability.

Linearity:

A series of solutions (10-60 µg/ml) were prepared from the MIRA stock solution, and 20 µL of each solution was injected into the HPLC system and the peak area of the chromatogram was noted. A calibration curve was plotted by taking the concentration of the solutions on the x-axis and the corresponding peak area values on the y-axis. The calibration curves were constructed by plotting absorbance versus concentration, and the linearity was calculated by the least square regression method. A calibration curve is shown in Figure no3. The linearity of response for the MIRA standard was estimated in the range of 10-60 µg/ml. The correlation coefficient was found to be 0.9999. The results are shown in Tableno1. Therefore, the HPLC method was found to be linear.

Precision:

The precision of the method was determined by repeatability (intra-day) and intermediate precision (interday). Repeatability was determined by performing six repeated analyses of the same working solution of MIRA on the same day, under the same experimental conditions. The intraday and interday study was performed by injecting six times of standard solution at three distinct concentrations 30, 40, 50 µg/ml on the same day and three consecutive days and also by another analyst performing the analysis in the same laboratory. It was noted that the %RSD values of precision for intraday and interday precision was (0.35-0.79 and 0.57-0.93) respectively. The values found to be lower than 2% assuring that this method was found to be fairly precise and reproducible. Precision results are tabulated in Tableno.2, 3, 4.

Accuracy:

By injecting a precise concentration of pure drug into a previously examined sample solution containing 40 g/ml of mirabegron, recovery studies were conducted to verify accuracy.To pre-analyze the sample solution, a known amount of standard stock solution was added which was at the different levels of 50%, 100%, 150%. The %Recovery determined was between**99%-101%**which is the acceptance limit as per the ICH guidelines. %RSD values for all analysis were less than 2% indicating that the analytical method is very accurate. Table no.5 shows the results of Accuracy.

Robustness:

The %RSD of the robustness was found to be within the permissible amount.Thus, the method was found to be robust. The results of this study were presented in Table no.6

LOD and LOQ:

The LOD and LOQ were found to be **0.3022 µg/ml** and **0.9159 µg/ml** respectively. Shown in Table No 7.

Analysis of Marketed Formulation using developed HPLC method:

The developed and validated method was successfully applied for the determination of Mirabegron in their tablet dosage form. The % assay was found to be **100.34 %** which is permissible as per the ICH guidelines. The result of assay was shown in Table no.8. The chromatogramis shown in Figure no.4 and Figure no.5

Degradation studies:

Mirabegron was subjected to different stress conditions as per ICH specified conditions. Mirabegron was found to be stable under neutral, thermal and photolytic stress conditions, as shown in Figure No8, 10, 11 respectively. However, the drug showed degradation under acid, alkali and peroxidation stress conditions. Under acid condition, a significant decrease in the peak area of mirabegron was exhibited with three additional peaks detected at 4.09, 9.81and 10.95 min. as shown in Figure No6.Under the alkali

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condition, a significant decrease in the peak area of mirabegron was observed with two additional peaks detected at 3.33 and 11.57 min. as shown in Figure No7. Under the oxidative condition, a significant decrease in the peak area of mirabegron was observed with two additional small degradation peaks detected at 3.33 and 10.97 min. as shown in Figure No9.The results for % of degradation was tabulated in Table no 9.

Sr. No	Conc(µg/ml)	Mean peak Area ± S.D	%RSD	Statistical Analysis
1	10	75042±805.02	1.08	Slope = 4982.3 Intercept = 24795 Correlation Coefficient = 0.9999
2	20	123736±540.39	0.44	
3	30	173652±840.55	0.49	
4	40	224935±538.72	0.24	
5	50	274756±1271.22	0.47	
6	60	322935±778.92	0.25	

Table No1: Linearity Data of the Mirabegron HPLC method (n=5)

Sr. No	Conc (µg/ml)	Mean Peak Area ± S.D	% RSD
1	40	225390±1114	0.49

Table No 2: Repeatability Data of Mirabegron (n=6)

Sr. No	Conc (µg/ml)	Mean Peak Area ± S.D	% RSD
1	30	173605±615.57	0.35
2	40	225263±1579.6	0.79
3	50	274766±1501.36	0.55

Table No 3: Intraday Precision Data of Mirabegron (n=3)

Sr. No	Conc (µg/ml)	Mean Peak Area ± S.D	% RSD
1	30	175605±1231	0.71
2	40	226261±1295	0.57
3	50	274326±2544	0.93

Table No 4: Inter-day Precision Data of Mirabegron (n=3)

Sr. No	% Spike Level	Amount (µg/ml)	Amount Added (µg/ml)	Mean amount Recovered ± S.D	Mean % Recovery ±S.D	%RSD
1	50%	40	20	20.00±0.172	100.06±0.876	0.88
2	100%	40	40	40.14±0.365	100.37±0.913	0.92
3	150%	40	60	60.48±0.336	100.81±0.557	0.56

Table No 5: Results for Accuracy of Mirabegron (n=3)

Sr.No.	Parameter	Optimized	Used	RT	Mean Peak Area ±S.D	%RSD
1	Flow Rate (+/- 0.2 ml/min)	1.0 ml/min	0.8 ml/min	2.39	223120±1571	0.71
			1.0 ml/min	2.31	224250±712	0.31
			1.2 ml/min	2.36	227538±1296	0.57
2	Detection wavelength (± 5nm)	249 nm	244 nm	2.31	223918±1254	0.56
			249 nm	2.38	225659±704	0.31
			254 nm	2.34	226624±1090	0.49
3	Mobile Phase Comp. (Buffer: ACN)	70:30 (v/v)	65:35:00	2.33	222977±1788	0.81
			70:30:00	2.39	224756±1002	0.45
			75:25:00	2.31	226939±1572	0.71

Table No 6: Robustness studies of Mirabegron (n=3)

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Sr.No.	Parameter	Results
1	LOD	0.3022 µg/ml
2	LOQ	0.9159 µg/ml

Table No 7: LOD and LOQ results of Mirabegron

Formulation	Label Claim	Amount Found	Assay	SD	%RSD
Megatas 50	50 mg	50.171 mg	100.34	0.977	0.98

Table No 8: Assay studies for Mirabegron (n=5)

Parameter	Peak Area	% Degradation	Peak Purity
Standard	225306	00	Passes
Acid	205698	8.78	Passes
Alkali	215748	4.32	Passes
Neutral	225478	00	Passes
Oxidative	210856	6.49	Passes
Thermal	225986	00	Passes
Photolytic	226148	00	Passes

Table No9: Degradation studies

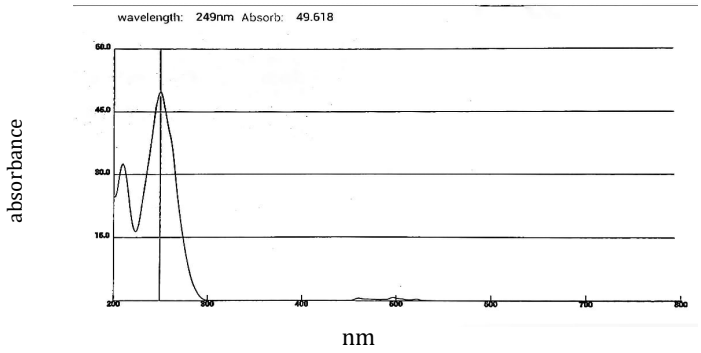

Figure No 1: UV spectra of Mirabegron for the selection of wavelength

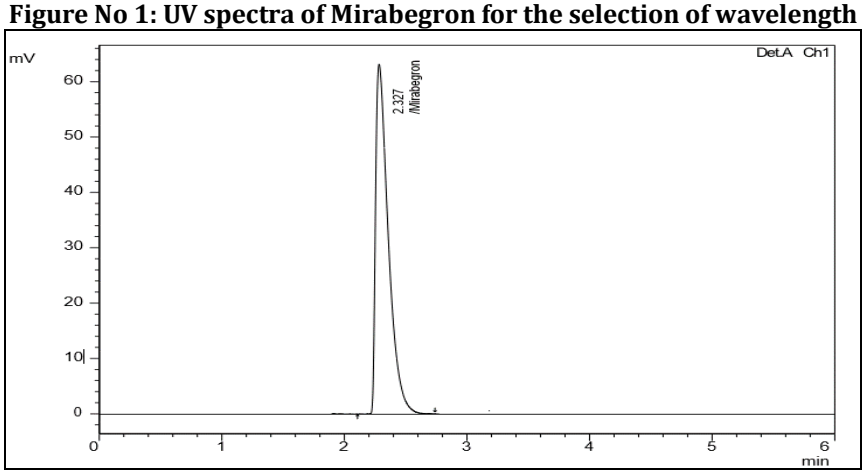

Figure No 2: Chromatogram of standard

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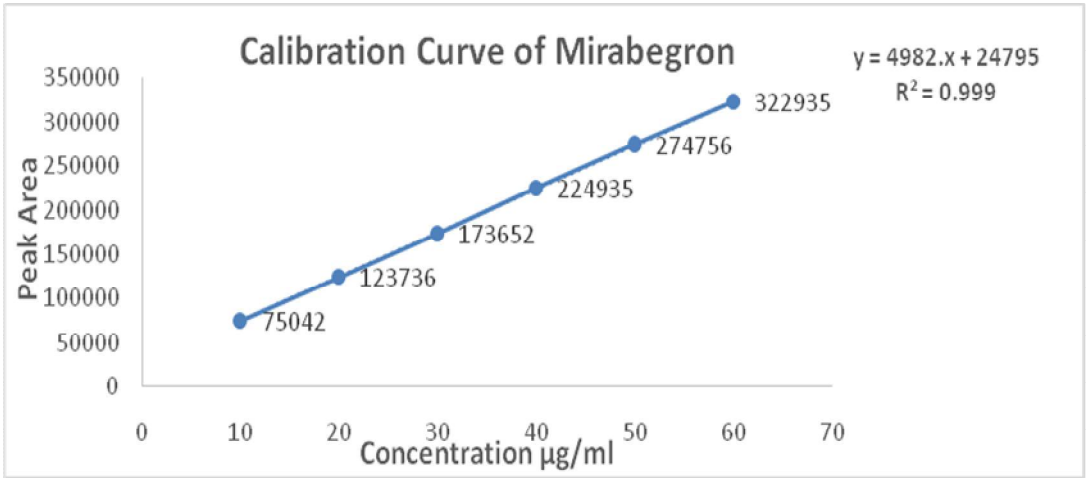

Figure No 3: Calibration curve of Mirabegron by HPLC

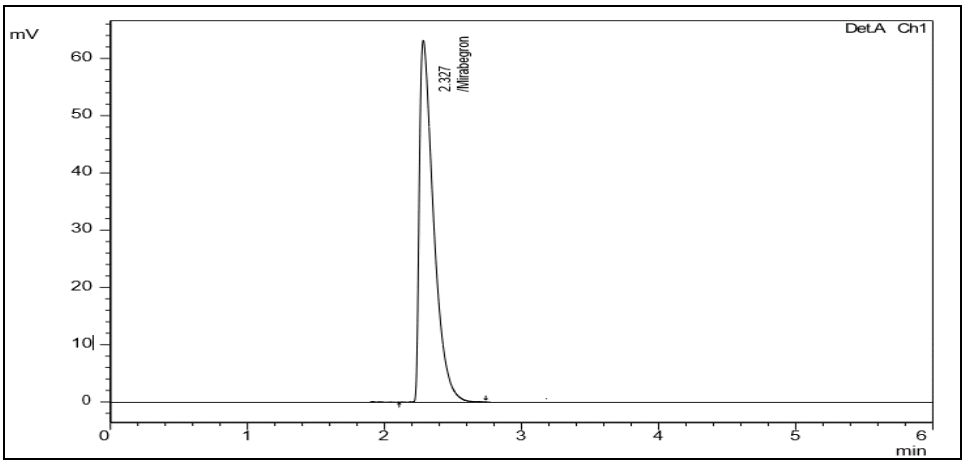

Figure No 4: Typical Chromatogram of Mirabegron standard

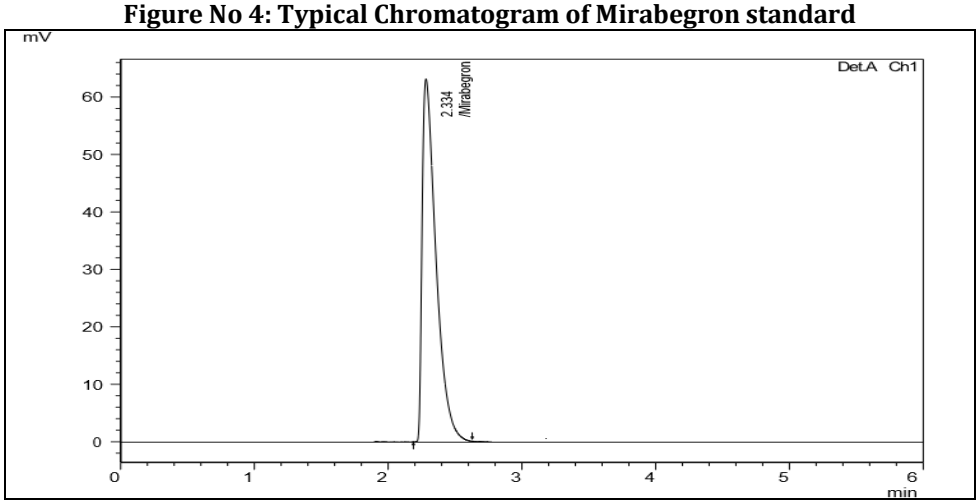

Figure No 5: Typical Chromatogram of Mirabegron Assay

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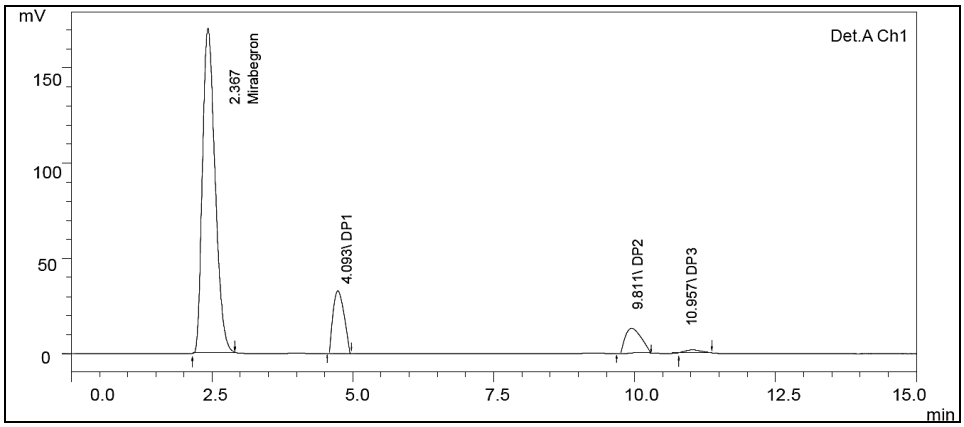

Figure No 6: The chromatogram of Mirabegron from Acid Degradation

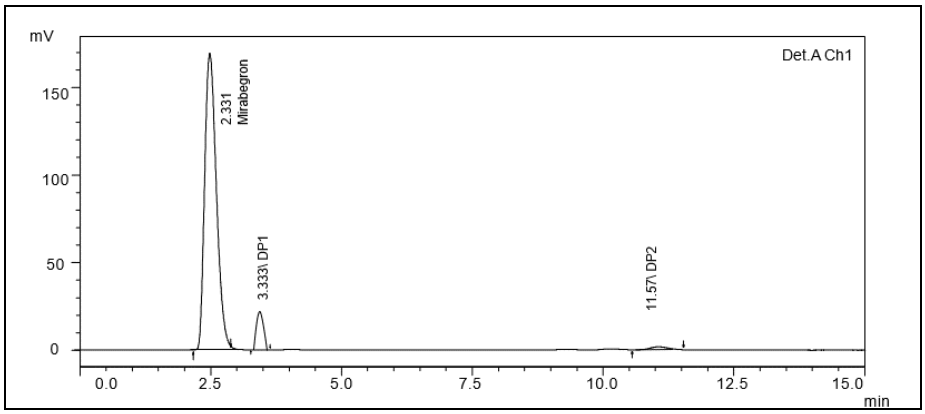

Figure No 7: The chromatogram of Mirabegron from Alkali Degradation

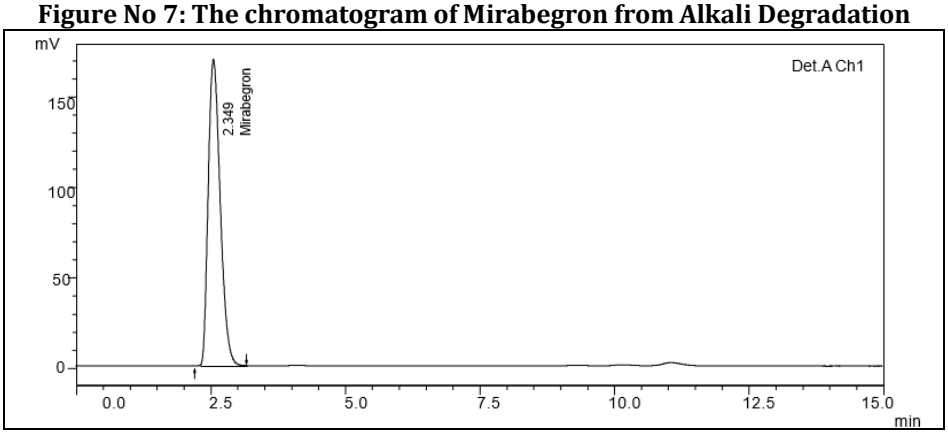

Figure No 8: The chromatogram of Mirabegron from Neutral Degradation

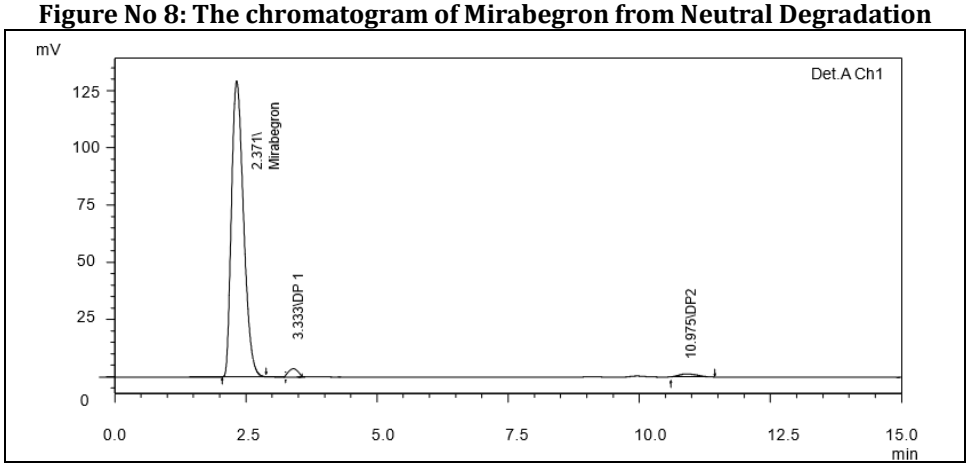

Figure No 9: The chromatogram of Mirabegron from Oxidative Degradation

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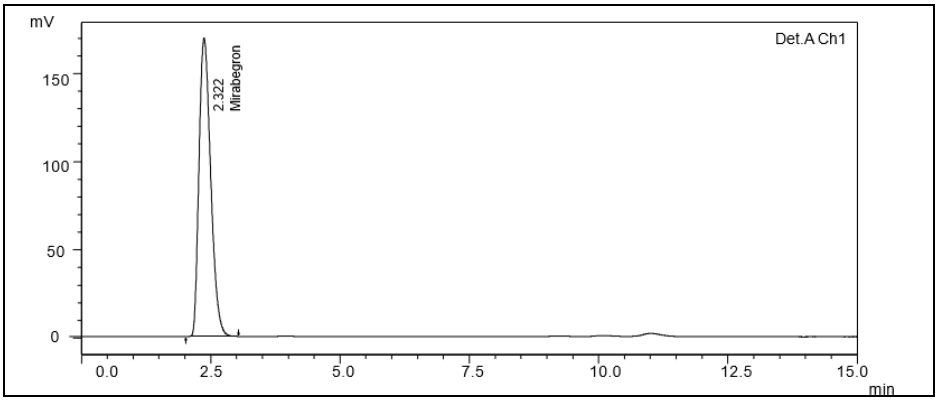

Figure No 10: The chromatogram of Mirabegron from Thermal Degradation

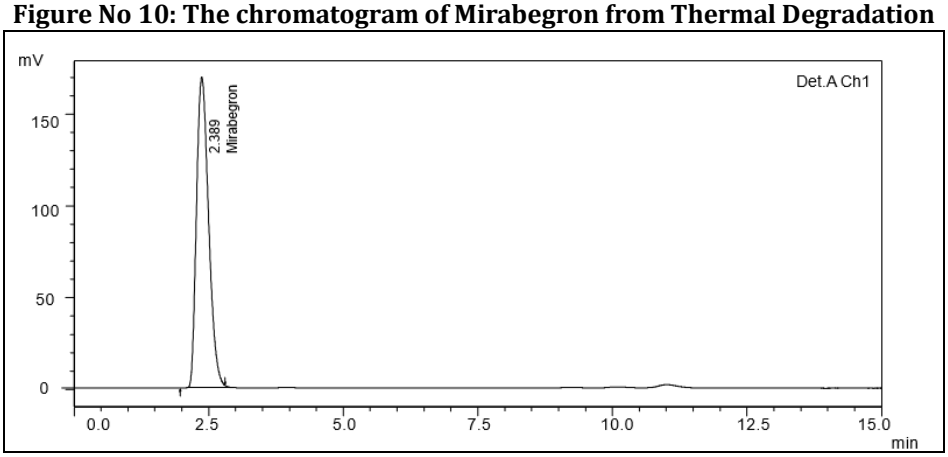

Figure No 11: The chromatogram of Mirabegron from Photolytic Degradation

CONCLUSION:

An accurate, precise, robust, sensitive stability indicating RPHPLC method was developed for estimation of Mirabegron in pharmaceutical dosage form. According to the findings of the recovery studies, there is no interference from the excipient utilised in formulation.Accuracy, precision, robustness, ruggedness, LOD, and LOQ scores all fell within acceptable ranges. The results of the established method's assay of a pharmaceutical dosage form were very repeatable, dependable, and also in high quality agreement with the drug's label claim. We also conclude that this RPHPLC method is efficient and effective for research studies, quality control, and routine analysis of mirabegron in the pharmaceutical industries.

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