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Review Article

ANALYTICAL TECHNIQUES FOR DETERMINATION OF MIRABEGRON FROM BULK, PHARMACEUTICAL FORMULATION, AND BIOLOGICAL MATRICES: A CRITICAL REVIEW

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ABSTRACT

Mirabegron is a beta-3 adrenergic receptor agonist and is specified for the treatment of overactive Bladder. This review covers analytical methods aimed at the identification and quantification of mirabegron in bulk, commercial dosage forms, and Biological fluids. Using various techniques such as UV-spectroscopy, spectro-fluorimetry, planer chromatography, High Performance-Thin Layer Chromatography (HPTLC), HPLC, High-Performance Liquid Chromatography-MS/MS (HPLC-MS/MS), Ultra-Pressure Liquid Chromatography-MS/MS (UPLC-MS/MS), and capillary electrophoresis. HPLC is the most used analytical technique for the identification and quantification of mirabegron in bulk and commercial dosage forms.

Keywords: Mirabegron, Analytical techniques, Chromatography, Spectroscopy

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INTRODUCTION

Overactive Bladder (OAB) is an uncomfortable condition described as urine urgency, which has a remarkable effect on routine life performance in both men and women patients [1]. Inadequate sleep and depression are common in OAB, with adverse impacts on physical and mental health. [2]. According to epidemiological studies, in 12% of both adult and female populations, the OAB rate increased from 7 % to 26% with age and time [3]. the main purpose of medication of is OAB to get relief from symptoms without disturbing the empty phase of the micturition cycle [4]. Mirabegron is a clinically beta-3 agonist receptor and is a first-line treatment in OAB. It relaxes the smooth muscles of the urinary Bladder by stimulating beta-3 adrenergic receptors; eventually, it promotes the filling of the Bladder and increases urine storage amount [5, 6]. Mirabegron is considered a first-line therapy because of its higher efficacy in treating OAB with a moderate adherence rate at 6 mo. According to the study, out of 196 patients, 128 received mirabegron monotherapy; urinary urgency was improved in them ($P<0.05$), and 68.0, 54.4 and 39.4% at 3, 6, and 12 mo respectively was the persistence of monotherapy [7]. It is available in the market since 2013 [8]. Mirabegron is an official drug indicated for OAB in Japan, USA, Canada, and Europe [9]. Mirabegron is used with or without combination with anti-cholinergic drugs such as solifenacin succinate, darifenacin, and fesoterodine to treat urinary incontinence [10]. This review focuses on analytical methods such as Ultraviolet (UV) spectroscopy, Spectrofluorimetry, Thin-layer chromatography, High Performance-Thin Layer Chromatography, High-Performance Liquid Chromatography, High-Performance Liquid Chromatography-Mass spectrometry/Mass Spectrometry, Ultra HPLC-Mass Spectrometry/Mass Spectrometry and Capillary electrophoresis are used for estimation of quantity and quality of mirabegron present in the formulation and biological sample in last 20 y. Some adverse effects of MIR are shown in fig. 2. Analytical method-wise distribution of mirabegron in the public domain is shown in fig. 3.

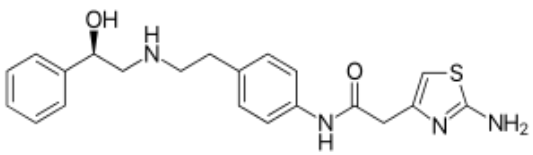

Fig. 1: Mirabegron chemical structure

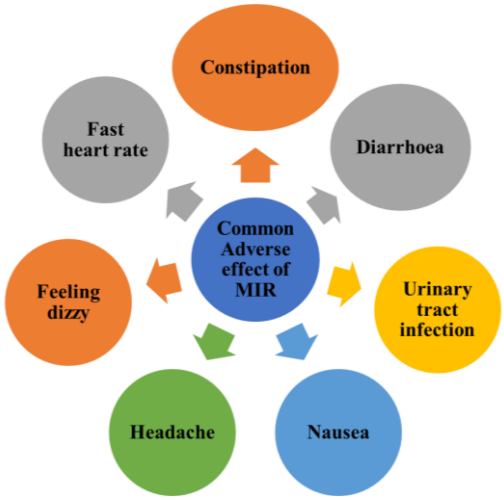

Fig. 2: Common adverse effect of mirabegron [11]

Physical and chemical properties

It is available as a white amorphous powder. It is insoluble in water and soluble in methanol and dimethyl sulphoxide. [12]. chemically, it is 2-{2-aminothiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-phenylethyl] amino} ethyl) phenyl] acetamide. Its molecular formula is $C_{21}H_{24}N_4O_2S$, molecular weight is 396.509 g/mol [13] and melting point is 138-140 °C.

Materials

Qualitative and quantitative analytical techniques for mirabegron

UV-spectrophotometric methods

UV spectroscopy is an absorption technique used for the identification of functional groups and unsaturated bonds (π electron) in the structure of organic molecules. The wavelength range of Ultraviolet (UV) radiation is 200-400 nm. A total of four UV spectrophotometric methods have been reported for mirabegron. The study [14] discussed the development of mirabegron estimation in bulk and tablet formulation. Derivative spectroscopy was the method of analysis for the elimination of spectral interference of zero order, 1st derivative spectroscopy and detection were done at 246 and 213 nm, respectively. Ethanol: water with a ratio of (1:9)

used as a solvent in the method. The linearity was achieved over the range concentration of 2-25 µg/ml. The LOD and quantification was found 0.80 and 0.47 µg/ml and 2.43 and 1.42 µg/ml, respectively for zero-order and 1st derivatives with a recovery of 99.8%.

Another UV spectrophotometric method reported by [15] discussed three Ultraviolet (UV) spectrophotometric methods for the assessment of mirabegron. The first method was founded on the Mirabegron reaction with ninhydrin in the occurrence of sodium molybdate at pH 5.5. The second method was founded on the reaction of the drug with 1, 2-naphthoquinone-4-sulfonate, and cetyl trimethyl ammonium bromide in an alkaline medium. The third method was founded on a redox reaction of the drug with Folin-Ciocalteu reagent in a sodium carbonate medium. Mirabegron was found linear over the range of 2.5-22.5, 5.0-35, and 5.0-70 µg/ml for all methods with good r^2 value in the range of 0.9920-0.9988.

[16] Proposed an alternative UV spectrophotometric method for force degradation simultaneous estimation of vildagliptin and mirabegron in powder and dosage form. Stability indicating studies under different environmental conditions were done and the degradants product was found more than exceeding the limit for both drugs. Drug shows Beer's laws over 10-100µg/ml range with good r^2=98.24. λ_{max} was found to be at 245 nm. All results were found to be in a limited range. A study published by [17] discussed stability, indicating the liquid chromatographic method and UV spectrophotometric method of mirabegron in bulk and formulation. Good linearity was found in a range of 2-18µg/ml with correlation coefficient r^2=0.995 determined at λ_{max} 247 nm. The methods were validated and proven sensitive, accurate, and precise. A summary of UV spectrophotometric methods for mirabegron is obtainable in table 1.

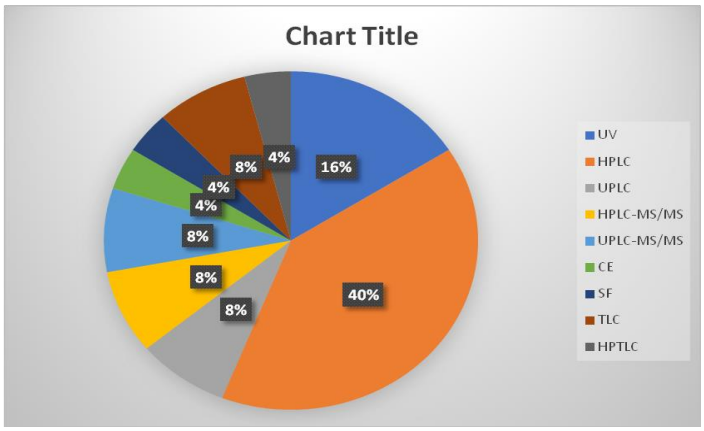

Fig. 3: Overview of analytical methods described in the literature for Mirabegron determination. UV: Ultraviolet spectroscopy; CE: Capillary Electrophoresis; SF: Spectrofluorimetry; HPLC: High-performance liquid chromatography; LC-MS: Liquid chromatography-mass spectrometry; LC-MS/MS: Liquid chromatography-tandem mass spectrometry; UPLC: Ultra performance liquid chromatography; UPLC-MS/MS: Ultra performance liquid chromatography-tandem mass spectrometry; TLC: Thin Layer Chromatography; HPTLC: High-Performance Thin layer chromatography [11]

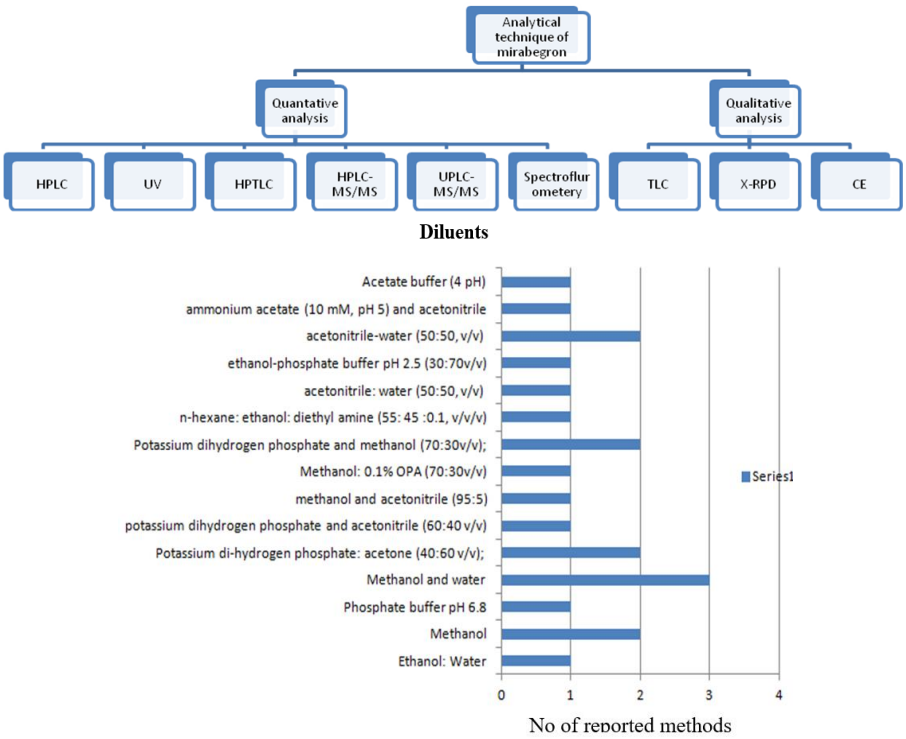

Fig. 4: Diluents used for the analysis of mirabegron [12]

Chromatographic methods

Reverse phase-high performance liquid chromatography (RP-HPLC)

HPLC is a powerful separation technique that pumps a mobile phase and sample mixture at high pressure and separates the analyte. It is useful to separate, identify, and quantify the individual components from the mixture. The pressure used normally ranges from 30 to 200 atm. HPLC was drastically used for the analysis of mirabegron in different samples [18].

A total of nine RP-HPLC methods have been reported for Mirabegron. In the study, [19] developed a simple RP-HPLC technique for the quantitative estimation of mirabegron in bulk and tablet dosage form. Mirabegron has successfully separated on Waters Acquity HSS C18 (100 × 2.1 mm, 1.7µm) column with mobile phase potassium di-hydrogen phosphate: acetone in the ratio (40:60 v/v) at flow rate 1.0 ml/min. It was eluted at 2.754 min and detected at wavelength 243 nm. Limit of Quantification (LOD) and Limit of quantification (LOQ) were 0.049 and 0.15µg/ml. Good linearity was found over the range of 10-50µg/ml. A study published by the author [20] discussed the quantitative assessment of mirabegron in extended-release tablets. System suitability parameters were found in the ideal range and a sharp peak was obtained at 4.5 min. Mirabegron follows Beer's law and r^2 was found 0.99. Restek C18 column (250 mm × 4.6 mm, 5µm) was used for efficient separation at pH: 7.0 potassium dihydrogen phosphate and acetonitrile (60:40 v/v) as mobile phase. Percent recovery was found between 99.00 and 101.17%.

In a study by [21], a sensitive, specific RP-HPLC technique was developed for mirabegron. At 2.754 min, mirabegron separation was achieved on column Waters Acquity HSS T-3 C18 (100 × 2.1 mm, 1.7µm). A mobile phase was a mixture of potassium di-hydrogen phosphate: acetone in the ratio (40:60 v/v) at pH 6. The 30-70µg/ml concentration range was used to obtain a linear graph with good r^2-0.999. System suitability parameters were found within the limit. LOD and LOQ were found to be 0.01µg/ml and 0.05µg/ml. According to [22], mirabegron appeared on a chromatogram at 2.58 min on a 250X4.6 mm, 5µm column with a mobile phase methanol: water mixture in the ratio of 70:30 at pH 5.0 adjusted with ortho-phosphoric acid and at a flow rate of 1.0 ml/min. The linear graph was obtained over the range of 50µg/ml to 150µg/ml. The LOD and LOQ were found to be 0.149 and 0.498 with r^2 value 0.999. The percentage recovery was almost 100%. All results were found within the limit and the method was found to be highly accurate.

In a study reported by [23], a novel and simple RP-HPLC method was developed for the resolve of mirabegron in a dosage form. Successful separation was achieved on the eclipse XDB C18 column (4.6 mm i.d. × 250 mm, 5 µm particle size). The mixture of methanol and acetonitrile in the ratio of 95:5v/v was used as a mobile phase at a 1 ml/min flow rate. Linearity was found over the range of 0.2-1.0 µg/ml with a good correlation coefficient, r^2= 0.999. Percentage recovery was initiated in a range of 99.6-99.8. The reported method was found utmost suitable for analyzing mirabegron.

[24] Developed RP-HPLC method for mirabegron. They carried out separation of the mixture on Enable C18G (250 x 4.6 mm, 5µm) column using a mixture of methanol: 0.1% o-phthalaldehyde (pH 5) in the ratio of 70:30 v/v as mobile phase at 1 ml/min flow rate. Sample detection was carried out at wavelength 246 nm. The calibration curve was found linear at the range of 10-50µg/ml with r^2=0.999. The LOD and LOQ were found to be 0.202µg/ml and 0.612 µg/ml respectively. All results were found in a limited range. In the study, [25] proposed a simple, accurate RP-HPLC method for the drug mirabegron. The drug was successfully separated on column THERMO, C18 (250X4.6 mm, 5 µm), and a mixture of 0.1M Potassium dihydrogen phosphate: methanol in the ratio of (60:40) used as a mobile phase. The retention time was found to be 3.684 min at 248 nm wavelength. The response was found linear at a concentration range of 50µg/ml to 150 µg/ml with r^2=0.999. System suitability parameters were found optimized.

In the study, [17] proposed a selective, simple, and accurate force degradation RP-HPLC method for drug mirabegron. Physical separation was achieved on a simple column with a mixture of acetonitrile: water with a 50:50 (v/v) ratio used as a mobile phase for better elution; the mobile phase was adjusted with pH 9 with 1% triethylamine (1 ml). The sample was scanned and detected at 247 nm. Linearity was in the range of 0.01-20 µg/ml. The LOD and LOQ were found to be 0.006 and 0.01 (µg/ml) respectively. Mirabegron was found susceptible to acid and base hydrolysis, oxidation, photolytic, and dry heat degradation conditions. [26]. constructed a new Liquid Chromatographic method for separation and thermodynamic investigation of mirabegron enantiomers, in which the author used columns (Chiralpak AD-H and AY-H) for separation of mirabegron and its (S)-enantiomer. Chiralpak AY-H, a column was coated with amylose tris-(5-chloro-2-methylphenyl carbamate) as a chiral stationary phase and a mixture of n-hexane, ethanol, and diethyl amine with 55: 45: 0.1 (v/v/v) ratios were used as a mobile phase. Detection was set at 254 nm. System suitability was achieved by the analysis of the standard solutions containing MI-I and II in sextuplicate. Linearity for I enantiomer was achieved over the concentration range of 251.4-603.2 (mg/ml), while for II enantiomers, it was over a range of 0.129-5.190 (mg/ml) and the Correlation coefficient, r^2 was found 0.99 for both enantiomers.

Ultra-performance liquid chromatography (UPLC)

UPLC is a modern form of HPLC that operates at higher pressure (15,000 psi) and mainly enhances speed, sensitivity, and resolution. Due to the high pressure and small particle size of the stationary phase, the sample run time was cut from days to hours or minutes. [27] Developed a new forced degradation RP-UPLC method for assessment of mirabegron in pharmaceutical dosage forms. Separation was done on Waters Acquity C18 (50 mm x 2.1 mm ID, 1.8µm) column using a mixture of potassium di-hydrogen phosphate: methanol in the ratio of 70:30 (v/v) with detection set at 254 nm. The linearity was good over the range of 50-150 µg/ml (r2 =0.998). Percent recovery was found 100.1%. A summary of UPLC and HPLC methods for Mirabegron is presented in table 2.

Ultra Performance Liquid Chromatography-Mass Spectrometer/Mass Spectrometer (UPLC-MS/MS)

When UPLC is coupled with a mass spectrometer (MS), a novel technique UPLC-MS forms with good resolution power. It combines the separation feature of UPLC and mass determination of Mass spectrometry. It has greater precision, accuracy, and sensitivity [28]. Author [29] proposed mirabegron determination in rat plasma after oral and intravenous administration by UPLC-MS/MS method. The sample was extracted using a protein precipitation method and acetonitrile was used as a solvent for precipitation. The molecule appears in a chromatogram at 2.5 min using a UPLC BEH C18 column (2.1 mm × 50 mm, 1.7 µm) with a mixture of acetonitrile water used as a mobile phase at a flow rate of 0.35 ml/min. Deproteinization was done using acetonitrile. Peak of protonated mirabegron and tolterodine was obtained at m/z 397.34 and 326.47, respectively, using electrospray ionization positive ion mode. The linearity of the drug in rat plasma was found linear over the range of 5-2500 ng/ml (r^2=0.999). Forced degradation of mirabegron in rat plasma was found in the ideal range of 5-2500ng/ml. Sample preparation procedure that is schematically shown in fig. 5. Male Sprague-Dawley rats were used in ten no. for pharmacokinetic study by administering the drug via oral and intravenous routes and UPLC-MS/MS method validated. The Limit of Quantification for the drug in rat plasma was achieved 5ng/ml.

[30] Developed UPLC-MS/MS method and *in silico* toxicity prediction of all degradation products of mirabegron. Seven degradation products were characterized in positive ion mode after exposure to various environments. *In silico* toxicity was determined for all degradants using TOPKAT and DEREK software. Separation was achieved on Waters CSH C18 column (100 mm, 2.1 mm, 1.7 mm) using a gradient elution of ammonium acetate (10 mmol, pH 5) and acetonitrile as mobile phase. The drug sufficiently degrades in hydrolytic and oxidative stress conditions, while it was found stable in thermal and photolytic conditions. The potential impurities of mirabegron were well separated. A summary of UPLC-MS/MS methods for mirabegron is presented in table 3.

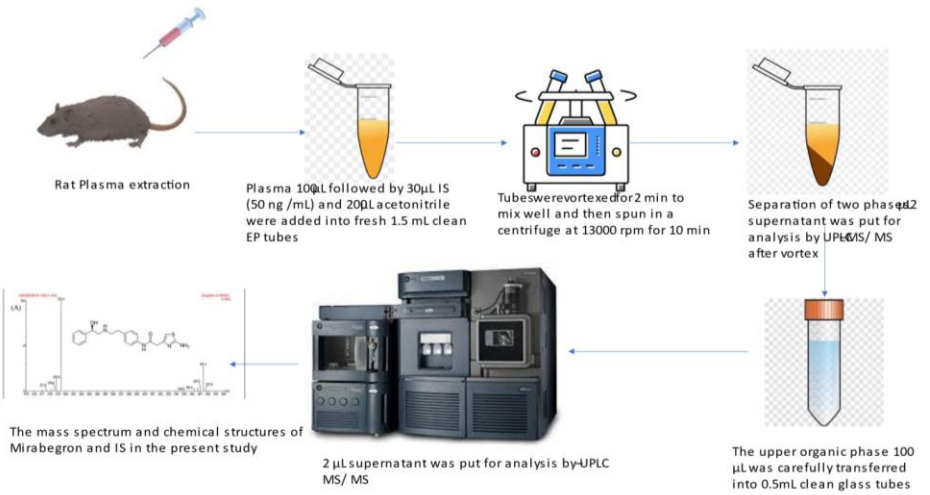

Fig. 5: Schematic illustration of a procedure of sample formation and ultra-high performance liquid chromatography analysis for mirabegron [30]

High-performance-Tendom Mass Spectrometer (HPLC-MS/MS)

It is a powerful technique that joins the separation power of liquid chromatography with the detection specificity of mass spectrometry. The system can selectively detect individual compounds from the mixture and mass of the compound [31, 32]. Carried out the separation of potential eight metabolites determined by HPLC-MS/MS of mirabegron in human plasma in a paediatric population. The liquid-liquid extraction was used for the sample method. Metabolites M5, M8, M11–M16 of the drug mirabegron in human plasma were separated. Assays were adjusted to decrease the blood volume (from 10 ml to 2 ml) and increase in sensitivity. The assays were scaled down using 96-well supported liquid extraction (SLE) plates for mirabegron, metabolites M5, M16, and 96-well mixed-mode cation exchange (MCX) solid phase extraction plates for metabolites M8, M11–M15 were used. In a study, [33] carried out the characterization of degradants of mirabegron by the HPLC-MS/MS method. drug and its degradants separation were successfully attained on column XTerra RP-8 (250 mm x 4.6 mm, i.d., 5 µm) and 0.01M ammonium acetate with 60: 40 ratio of Acetonitrile: water as mobile phase. All chromatographic methods were optimized at the beginning. A summary of HPLC-MS/MS methods for mirabegron is presented in table 4.

Capillary electrophoresis (CE) methods

CE is a unique method that uses an electric field to separate components from the mixture. When an electric field is applied on an ionic solution, the cation starts moving toward the cathode, whereas the anion starts moving toward the anode and crude separation occurs [34, 35] have developed the capillary electrophoresis method, which has high analysis speed, reduced use of solvent, green solvent, and easy operate for determination of mirabegron. Separation was achieved on a 50-60 cm capillary (I. D 50 µm) using 50 mmol acetate buffer at pH 4.0, migration was found constant at 3 min and current 5-30kV was applied for better separation. A concentration range of 5.00-45 mg/l was used for the calibration curve. Detection was done using an Ultraviolet-Diode Array detector (UV-DAD) at a wavelength of 249 nm. A summary of capillary electrophoresis methods for mirabegron is presented in table 5.

Spectro-fluorimetry method

Spectro-fluorimetry is a fluorescence detection system. Fluorescence is caused by a sample after irradiation with light. It is a highly precise technique used for the characterization of molecular components in samples [36]. The quenching effect of mirabegron on the fluorescence intensity of Acetoxy Mercuric Fluorescein (AMF) has been measured. The simple, highly sensitive, and economical spectrofluorimetric method was developed for mirabegron in bulk and tablet. The calibration graph was found linear with a range of 1-5 µg ml^{-1} (r^2=0.999) with a LOD (0.140) and LOQ (0.430) at $µg/ml^{-1,}$ respectively. Excitation and emission spectra of mirabegron and AMF were observed at λ_{max} at excitation 498 and at emission λ_{max} 520 nm, respectively. All results were within acceptable limits. The reported method was useful to bulk powder and formulation with a correlation coefficient of r^2=0.9997 in a method developed by [37]. A summary of spectrofluorimetric methods for mirabegron is presented in table 6.

Thin liquid chromatography (TLC)

Thin layer chromatography is a very common solid-liquid separation technique in which stationary phase, solid and mobile phase, and liquid is used to separate compounds to determine purities [38, 39]. Developed TLC Densitometry method for mirabegron. They carried out separation successfully on a silica gel 60 F254 (20x10 cm) plate and toluene-ethyl acetate-methanol-ammonia (5.7:21:5.7:3) used as a mobile phase. The author describes methods that were transferred from TLC screening to HP-TLC for aminophylline, bisoprolol fumarate, griseofulvin, hydrochlorothiazide, pyrimethamine, bupropion HCl, carbamazepine, mirabegron, clomiphene citrate and oxybutynin Cl. Drug spot detected and scanned at 254 nm under UV light. R_f value was found to be 0.50. A study published by [40] successfully determined mirabegron in degraded products by comparison of two TLC and HPLC force degradation chromatographic methods. Further, IR and mass techniques were used to categorize the structure of mirabegron. Sample spots were efficiently separated on a simple TLC plate and chloroform-methanol-ammonia (9:1:0.1) as a mobile phase. R_f value was found to be 0.20. Separated spots were detected and scanned at 250 nm.

High-Performance Thin Layer Chromatography (HPTLC)

High-performance thin-layer chromatography is advantageous than thin-layer chromatography. This analytical technique provides exact and accurate data in drug discovery and development [41]. Developed HPTLC method along with TLC method for mirabegron [42]. Developed HPTLC method for mirabegron and solifenacin succinate in combination by simultaneous estimation. Samples were run on aluminum plates pre-coated with HPTLC Silica gel 60 F_{254} plate. Methanol-ethyl acetate-triethylamine (8:2:0.1, V/V) was used as the mobile phase. The developed method was linear over 2-5.5 µg per band range of the drug mirabegron. R_f was found 0.76. Spots were scanned and detected at 222 nm. A summary of TLC and High-Performance HPTLC methods for Mirabegron is presented in table 7.

X-ray Powder Diffraction (XRPD)

When constructive interference produces a certain angle because of light incidence on the surface, it gets scattered; this phenomenon is called diffraction. The crystalline nature of the sample is determined

by X-ray diffraction [43]. One can easily differentiate between crystalline and amorphous forms based on the peak intensities and positions by X-ray powder diffraction [44]. Diffraction patterns of powder mirabegron were recorded on BRUKER D8 ADVANCE diffractometer by [44]. In the study presented by [45-49], the solubility of mirabegron was found very poor in organic solvents. To increase the solubility, it was made co-amorphous with fumaric acid, l-pyroglutamic acid, and citric acid. Mirabegron and its co-amorphous form were determined by the X-ray powder diffraction method.

Table 1: Presentation features of UV-spectrophotometric methods

S. No.	Diluent	λ_{max}	Linearity range (µg/ml)	LOD (µg/ml)	LOQ (µg/ml)	Application	Reference
1	Ethanol: Water	246	2-25	0.80,2.43	0.47,1.42	Bulk and tablet dosage form	[14]
2.	Methanol	247	2-18	0.078	0.24	Tablet	[17]
3.	Phosphate buffer pH 6.8	245	1-10	7.67	23.24	Bulk drug	[16]
4.	Methanol and water	567	2.5-22.5	0.368	1.116	Tablet	[15]

Table 2: Performance characteristics of HPLC and UPLC methods

S. No.	Stationary phase mobile phase	UV-detection (nm)	Linear range (µg/ml)	LOD (µg/ml)	LOQ (µg/ml)	Application	Reference
1	Waters Acquity HSS C18(100 × 2.1 mm, 1.7µm), Potassium di-hydrogen phosphate: acetone (40:60 v/v); 1.0 ml/min	243	10-50	0.049	0.15	bulk and tablet dosage form	[19]
2.	Restek C18 column (250 mm × 4.6 mm, 5µm); buffer pH: 7.0 potassium dihydrogen phosphate and acetonitrile (60:40 v/v);1 ml/min	249	10-100	0.015	0.049	Extended-release tablets	[20]
3.	Waters Acquity HSS T-3 C18 (100 × 2.1 mm, 1.7µm; Potassium di-hydrogen phosphate: acetone (40:60 v/v); 1 ml/min	243	30-70	0.01	0.05	Tablets	[21]
4.	C18, 250 X 4.6 mm, 5µm; methanol: water (70:30) at pH 5.0 OPA; 1.0 ml/min	243	50-150	0.149	0.498	Bulk and dosage form	[22]
5.	Eclipse XDB C18 column (4.6 mm i.d. × 250 mm, 5 µm particle size); methanol and acetonitrile (95:5) v/v, 1 ml/min.	251	0.2-1.0	0.0459	0.1391	Dosage form	[23]
6.	EnableC18G (250 x 4.6 mm, 5µm) column; mobile phase Methanol: 0.1% orthophosphoric acid (pH5) (70:30v/v);1 ml/min	246	10-50	0.202	0.612	Dosage form	[24]
7.	Waters Acquity C18 (50 mm x2.1 mm ID) 1.8µm; Potassium dihydrogen phosphate and methanol (70:30v/v);0.5 ml/min	254	50-150	-	-	Tablets	[28]
8.	(250X4.6 mm i.d., 5 mm); n-hexane: ethanol: diethyl amine (55: 45:0.1, v/v/v);1.0 ml/min.	254	I-251.4-603.2 II-0.129-5.190	I-0.73 II-0.77	I-0.43 II-0.58	Enantiomers	[26]
9	THERMO, C18, 250x4.6 mm, 5µm; 0.1M Dipotassium hydrogen phosphate: Methanol (60:40); 1.0 ml/min	248	50-150	0.149	0.498	Tablets	[25]
10	Mobile phase containing acetonitrile: water (50:50, v/v) adjusted pH 9 with 1 ml of 1% triethyl amine.	247	0.01-20	0.006	0.01	Tablets	[17]
11	Agilent C18 column (150 mm × 4.5 mm I.D., particle size 5 µm) using ethanol-phosphate buffer pH 2.5 (30:70v/v); 1 ml min^{-1}.	250	1-25	0.29	0.89	Bulk drug and tablets	[40]
12	Restek C18 column (250 mm × 4.6 mm, 5µm); buffer pH: 7.0 potassium dihydrogen phosphate and acetonitrile (60:40 v/v); 1 ml/min	249	10-100	0.015	0.049	Enantiomers	[20]

Table 3: Performance characteristics of UPLC-MS/MS

S. No.	Stationary phase, mobile phase	UV-detection (nm)	Linear range (µg/ml)	LOD (µg/ml)	LOQ (µg/ml)	Application	Reference
1.	UPLC BEH C18 column (2.1 mm × 50 mm, 1.7 µm); acetonitrile-water; 0.35 ml/min	-	5-2500	5	1	Bulk	[29]
2.	Waters CSH C18 column (100 mm _ 2.1 mm, 1.7 mm); ammonium acetate (10 mmol, pH 5) and acetonitrile;	248	5-300	-	-	Bulk drug	[30]

Table 4: Performance characteristics of HPLC-MS/MS

S. No.	Stationary phase, mobile phase	UV-detection (nm)	Linear range (µg/ml)	LOD (µg/ml)	LOQ (µg/ml)	Application	Reference
1	Synergi TM Fusion-RP C18 analytical column (150 mm × 2.0 mm, 4 m) and a C18 guard column (4 mm × 2.0 mm) (Phenomenex, Torrance, CA); 0.01% formic acid in water: 0.01% formic acid in methanol: 100 mmol/l: ammonium acetate; 0.4 ml/min.	-	0.05-100	94.2	96.7	Bulk	[32]
2.	XTerraRP-8 (250 mm x 4.6 mm, i.d., 5 µm); 0.01M ammonium acetate 60: 40 ratio of ACN: Water as mobile phase;	240	-	-	-	Bulk drug	[33]

Table 5: Performance characteristics of capillary electrophoresis

S. No.	Buffer	UV detection (nm)	Linearity range (mg/l)	LOD (mg/l)	LOQ (mg/l)	Application	Reference
1.	Acetate buffer (4 pH)	249	5.00-45	0.9	3.1	Tablet	[35]

Table 6: Performance characteristic of spectrofluorometer

S. No.	Diluent	λ_{max} (nm)	Linearity range (µg/ml)	LOD (µg/ml)	LOQ (µg/ml)	Application	Reference
1	Methanol	498	1-5	0.140	0.430	Tablet	[37]

Table 7: Performance characteristics of TLC and HPTLC

S. No.	Plate and mobile phase	λ_{max} (nm)	Linearity range	LOD	LOQ	Application	Reference
1.	Silica gel 60 F_{254}(20 x 10 cm) Toluene-ethyl acetate-methanol-ammonia (5.7:21:5.7:3)	254	-	-	-	Bulk drug	[39]
2.	Simple TLC plate; chloroform-methanol–ammonia (9:1:0.1);	250	2-15	0.15	0.46	Bulk drugs and tablets	[40]
3.	HPTLC aluminum plates pre-coated with silica gel 60 F254 as the stationary phase and methanol–ethyl acetate–triethyl amine (8:2:0.1, V/V)	222	2-5.5	-	-	Tablets	[42]

CONCLUSION

Mirabegron is a beta-3 adrenergic receptor agonist indicated for the treatment of OAB. Different powerful analytical techniques are available for qualitative and quantitative analysis of mirabegron in formulation and matrix. A chromatographic system such as RP-HPLC or UPLC with mass determination by mass spectrometry a preferred technique for the determination of mirabegron due to accurate characterization and quantification of drugs, their degradants, and in-process impurities formed in biological fluids and pharmaceutical formulations. In this review, the authors have covered all published available analytical methods used for the separation, identification, and characterization of mirabegron in the last twenty years.

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Dr. Sanjay Sawant: He is a research guide and principal under his noble guidance; this review article has been prepared. Ms. Shital Godse: She has contributed to preparing the manuscript.

CONFLICT OF INTERESTS

Authors state no conflict of interest

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