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A CRITICAL REVIEW ON ANALYTICAL METHODS FOR NEWLY APPROVED DRUGS: MIRABEGRON AND SOLIFENACIN SUCCINATE

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ABSTRACT

A recently approved FDC of Mirabegron (25mg) and Solifenacin Succinate (5mg) recommended to treat Over Active Bladder. Analytical methods are available for individual quantitation of Mirabegron (MB) and Solifenacin Succinate (SFS), but only one an effective and reliable analytical method reported for their combination. Thus, the objective for this literature survey was to gather information on various analytical instrumental methods used so far for the individual quantitation of Mirabegron and Solifenacin Succinate in various matrices. The reported methods are high performance liquid chromatography, hyphentaed techniques, spectroscopy and high performance thin layer chromatography or thin layer chromatography for mirabegron and Solifenacin succinate respectively.

KEYWORDS: Mirabegron, Solifenacin succinate, UV, RP-HPLC, Analytical Method.

INTRODUCTION

Mirabegron is a beta- 3 adrenergic agonist. The chemical name is 2-(2-amino-1,3-thiazol-4-yl)-N-[4-(2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]acetamide having emphrical formula $C_{21}H_{24}N_4O_2S$ and molecular weight 396.5 g/mol. The structural formula for mirabegron is.

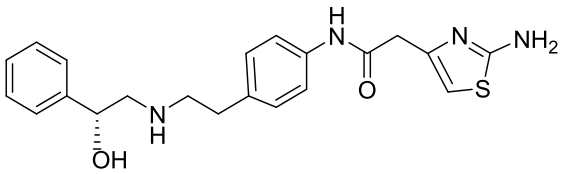

Figure 1: Structure of Mirabegron.

It has CAS number 223673-61-8. It has a (4.2) pKa1 and pKa2 (8.0). Mirabegron is a white powder. It is practically insoluble in water. It is soluble in methanol and dimethyl sulfoxide. It has 138-140^0 C. it is classified as Class 3 biopharmaceutical classification system (high solubility and low premability.

Solifenacin Succinate is a anti-muscarinic selective M3 / anti-cholinergic drugs. The chemical name is [(3R)-1-azabicyclo[2.2.2]octan-3-yl] (1S)-1-phenyl-3,4-dihydro-1H-isoquinoline-2- carboxylate;butanedioic acid having emphrical formula $C_{23}H_{26}N_2O_2$; $C_4H_6O_4$ and molecular weight 480.6 g/ml. the structural formula for Solifenacin Succinate is:

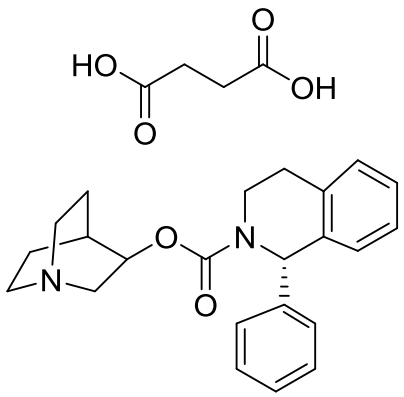

Figure 2: Structure of Solifenacin Succinate.

It has CAS number 242478-38-2. It has a pKa (8.0). Solifenacin Succinate (SFS) is a white powder or crystals. It is freely soluble in water. It is also soluble in methanol. It has 134-136^0 C. It is classified as Class 1 biopharmaceutical classification system (high solubility and high permeability.

Mechanism of Action

Mirabegron

When urine accumulates in bladder, sympathetic nerve stimulation predominates. Non-adrenaline is released from nerve terminals, leads to beta adrenoreceptor activation in bladder muscles. Mirabegron is potent and selective agonist of beta-3 adrenergic receptors. The activation of beta-3 receptors relaxes detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle, which increases the bladder's storage capacity so increase the feelings of urgency and frequency.

Solifenacin Succinate

Solifenacin is a competitive muscarinic receptor antagonist. It has the highest affinityfor M3, M1 and M2 muscarinic receptors. Most (80%) of the muscarinic receptors in the bladder are M2 while 20% are M3. Solifenacin antagonism of the M3 receptor prevents contraction of the detrusor muscle, while antagonism of M2 receptor may preventcontraction of smooth muscle in bladder.

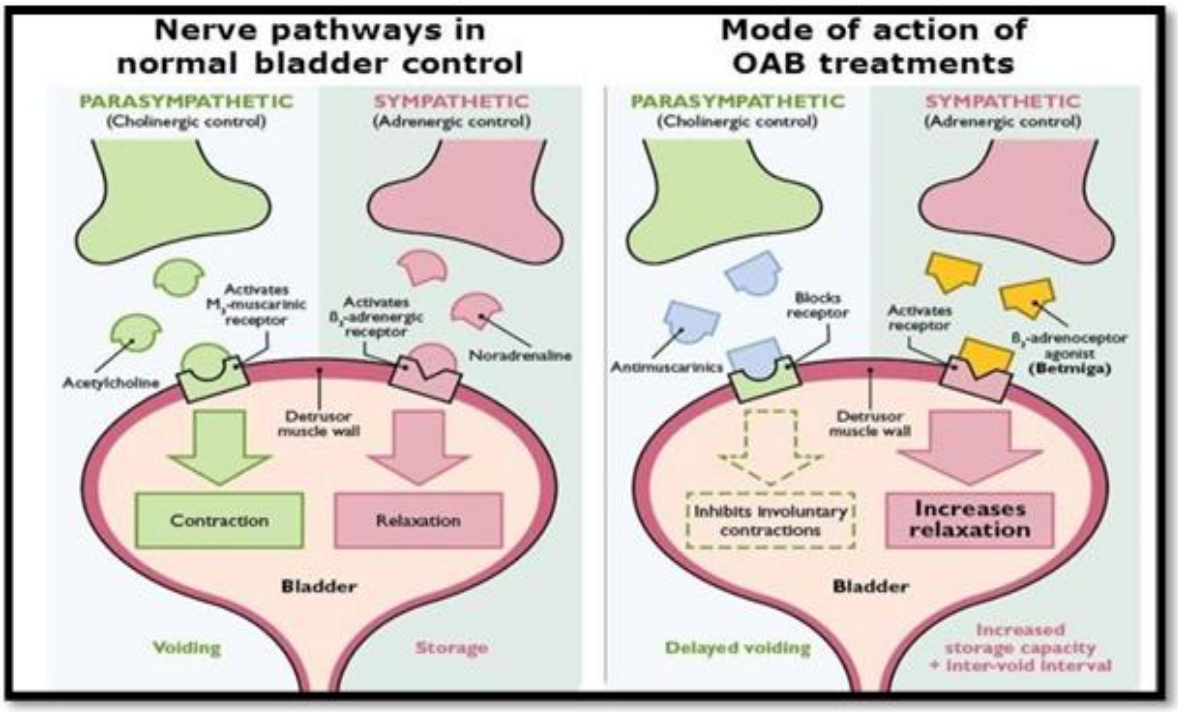

Figure 3: Site of action of drugs.

Pharmacokinetics

Mirabegron absolute bioavailability of orally administered mirabegron ranges from 29% at a dose of 25 mg to 35% at a dose of 50 mg. The T_{max} for the extended-release tablet and suspension formulations are approximately 3.5 hours, while the T_{max} for the granule formulation is 4-5 hours. Steady-state concentrations of mirabegron are achieved after approximately 7 days of once-daily administration. Volume of distribution (Vd) of 1670 L indicating extensive distribution. Mirabegron is approximately 71% protein-bound in plasma, primarily to albumin and alpha-1-acid glycoprotein. metabolic pathways and their resultant metabolites include amide hydrolysis (M5, M16, M17), glucuronidation (mirabegron O-glucuronide, N-glucuronide, N-carbamoylglucuronide, M12), and secondary amine oxidation or dealkylation (M8, M9, M15), amongst others. The enzymes responsible for the oxidative metabolism of mirabegron are thought to be CYP3A4 and CYP2D6 hile the UDP-glucuronosyltransferases responsible for conjugation reactions have been identified as UGT2B7, UGT1A3, and UGT1A8. Other enzymes that may be involved in the metabolism of mirabegron include butylcholinesterase and possibly alcohol dehydrogenase. Renal elimination is achieved primarily via active tubular secretion with some contribution by glomerular filtration. elimination half-life of mirabegron approximately 50 hours in adults and elimination half-life is approximately 26-31 hours for pediatric patients. Total plasma clearance following intravenous administration is approximately 57 L/h, with renal clearance accounting for roughly 25% at approximately 13 L/h. symptoms of overdose included palpitations and increased heart rate. Symptoms of chronic overdosage are similar in presentation and may also include a rise in systolic blood pressure.

Solifenacin Succinate is well absorbed in the duodenum, jejunum, and ileum but not the stomach. Absorption occurs via passive diffusion and so no transporters are involved. The mean oral bioavailability of solifenacin is 88%.The T_{max} of solifenacin is 3-8 hours with a C_{ss} of 32.3ng/mL for a 5mg oral dose and 62.9ng/mL for a 10mg oral dose. The volume of distribution of solifenacin is 600L. Solifenacin is 93-96% protein bound in plasma, mainly to alpha-1-acid glycoprotein. Metabolism of Solifenacin undergoes N-oxidation at the quinuclidin ring by cytochrome P450, though the exact enzymes are not revealed in the literature. The tetrahydroisoquinolone ring is 4R-hydroxylated by CYP3A4, CYP1A1, and CYP2D6. A 4R-hydroxy N-oxide metabolite is also formed by CYP3A4. Finally, solifenacin can undergo direct glucuronidation.The elimination half life of solifenacin ranges from 33-85 hours. The clearance of solifenacin is 7-14L/h and a renal clearance of 0.67-1.51L/h. toxicity is Signs of overdose include severe anticholinergic effects, mental status changes, and decreased consciousness.

Pharmacodynamics

Mirabegron exerts its pharmacologic effects by forcing bladder smooth muscle to relax, thereby expanding its capacity and relieving urgency. Mirabegron does not appear to adversely affect the mean maximum flow rate or mean detrusor pressure at maximum flow rate in patients with lower urinary tract symptoms and bladder outlet obstruction (BOO), but should be used with in patients with BOO due to reports of significant urinary retention. Furthermore, mirabegron increases both blood pressure and heart rate in a dose-dependent manner and should therefore be used with caution in patients with severely uncontrolled hypertension or others for whom these increases may prove dangerous.

Solifenacin antagonizes the M2 and M3 muscarinic receptors in the bladder to treat an overactive bladder. It has a long duration of action as it is usually taken once daily. Patients taking solifenacin should be aware of the risks of angioedema and anaphylaxis.

Pharmaceutical analysis profiles for Mirabegron and Solifenacin Succinate

Various analytical methods for the individual estimation of MB as well as SFS have been published in literature since 2010. Figure 4 shows a year wise paper published for both the drugs. Both drugs are non-offical in any of compendia.

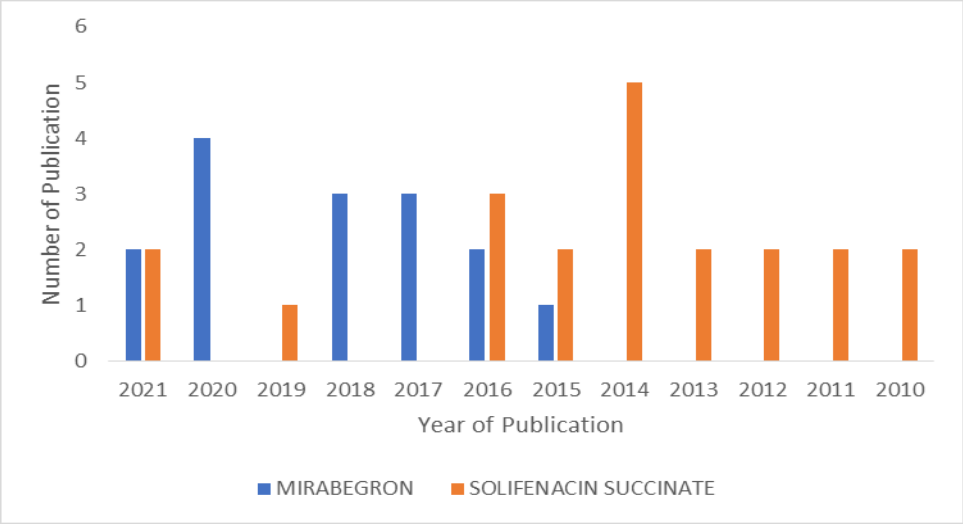

Figure 4: Year wise paper published of MB and SFS.

Non-compendial analytical methods

Non-compendial methods of analysis developed by various researches. These are spectroscopic, chromato-graphic and hyphenated techniques represented graphically in figure 5.

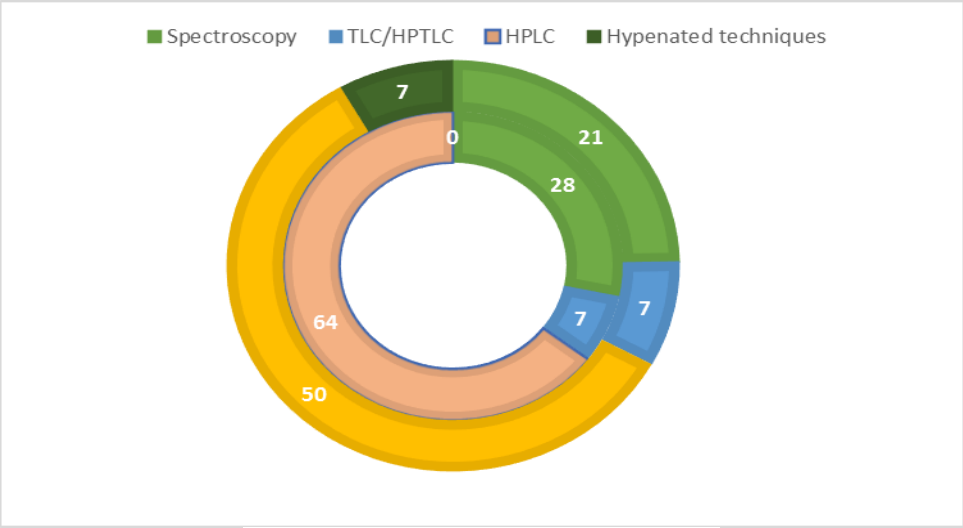

Figure 5: Non-compendial methods chart.

Spectroscopy methods

Spectroscopy is the interaction of matter and electromag- netic radiation that, as a function of wavelength, provides a quantitative evaluation of the reflecting or transmitting properties of a material. These methods have many benefits, such as being simple,

inexpensive and taking less time. They are the most widely used method by researchers and those who do not have access to advanced analytical tools. It was claimed that these methods were simple, quick, and relatively cost-effective.

There are many spectrophotometric methods developed so far for estimation of Mirabegron in various sample matrices including capsule formulation, bulk, dissolution medium and human plasma. The maximum UV-visible wavelength range was between 400-200nm. The solvent used for the detection of mirabegron was found according to solubility.There are many estimation of Solifenacin Succinate in bulk and tablet formulation.

Chromatographic methods

Chromatography is defined as separation of the components of a sample, in which the components are distributed between two phases, one of which is stationary phase while other is mobile phase. The stationary phase may be solid or liquid supported on a solid or gel, and maybe packed in a column, spread as a layer or distributed as a film. The mobile phase may be gaseous or liquid.

It is categorized as thin-layer (TLC) chromatography, gel permeation chromatography, affinity chromatography, gas chromatography (GC), high- pressure liquid chromatography (HPLC), ion-exchange chromatography, ultra-high-performance liquid chromatography (UHPLC) etc.

Hypenated techniques

Hypenated techniques are a combination of chromatographic techniques with spectral techniques. For the estimation of drugs in biological fluids such as plasma and urine, various advanced chromato-graphic techniques such as GC-MS, LC-MS/MS, UHPLC have been used.

Table 1: Spectroscopic methods for the determination of Mirabegron.

Sample matrix	Instrument model UV-Visible spectrophotometer	Solvent/Solution	Wavelength (nm)	LQ µg/ml	LD µg/ml	Author and year publication
Bulk and tablet	UV-Visible spectrophotometer	1N HCl	249	0.568	0.187	Badike S, et al. [2020]
Bulk and tablet	ElicoSL164 UV-Visible spectrophotometer	phosphate buffer pH 6.8.	245	7.67	23.24	Raveendra G, et al. [2017]
Bulk and tablet	UV-Visible spectrophotometer	Ethanol and water (1:9)	246 zero order 213 1st derivative	0.80 & 2.43	0.47 & 1.42	Rani K, et al. [2017]
Bulk and tablet	ELICO Double beam SL 210 UV-VIS spectrophotometer	Methanol	251	0.029	0.00957	Sankar P, et al. [2016]

Table 2: Spectroscopic methods for the determination of Solifenacin Succinate.

Sample matrix	Instrument model UV-Visible spectrophotometer	Solvent/Solution	Wavelength (nm)	LQ µg/ml	LD µg/ml	Author and year publication
Tablets	UV-visible spectrophotometer (LABINDIA)	Distilled water	250 265 nm First derivative	3.196	1.054	Srinivasaroa Y, et al. [2021]
Tablets	Shimadzu UV/VIS double beam spectrophotometer (model 1800)	Methanol	223	0.09992	0.9985	Saiyed N, et al. [2015]
Tablets	UV-visible spectrophotometer (Shimadzu, model 1800)	0.1N HCl	210	-	-	Kumar A, et al. [2015]
Tablets	UV-visible spectrophotometer (Shimadzu, model 1800)	100% TEA phosphate buffer (pH 2.5)	215	3.35	1.106	Kumar A, et al. [2014]
Tablets	UV-visible spectrophotometer (Shimadzu, model 1800)	Distilled water	220	0.914505	0.301786	Teja G, et al. [2013]
Tablets	Shimadzu UV 1700 UV-visible spectrophotometer	Bromo thymol blue (0.3%w/v) added to Chloroform	415.6 and 412	-	-	Singh L, et al. [2011]

Table 3: HPLC methods for the determination of Mirabegron.

Analytical system	Sample matrix	Column	Mobile Phase	Detection (nm)	Flow rate (ml/ min)	Retention time (min)	Author and publication year
RP HPLC	Bulk	Puratis C18 column (250 × 4.6mm, 5µm)	mobile phase A consisted, 20 Mm Ammonium acetate, Ph adjusted to 4.5 and mobile phase B consisted methanol	247	1.0	10.8	Bharathi T, et al. [2021]
RP HPLC	Bulk and tablets	C18, 250 ×4.6mm, 5µm	methanol water (70:30) at Ph 5.0 Adjusted to OPA	243	1.0	2.548	Suryawanshi R, et al. [2020]
HPLC- UV	Bulk and tablets	-	Acetonitrile: water (50/50 v/v) adjusted Ph 9 with 1 % TEA	247	1.0	3.93	Chhalotiya U, et al. [2020]
Agilent technologies-1260 infinity system HPLC	Dosage form	eclipse XDB C18 column (4.6mm i.d × 250 nm, 5µm particle size)	methanol and acetonitrile (95: 5v/v)	251	1.0	5.813	Sankar P, et al. [2020]
RP HPLC	Tablets	Restek C18 column (250 × 4.6mm, 5µm)	buffer Ph: 7.0 potassium dihydrogen phosphate and acetonitrile (60:40 v/v)	249	1.0	4.576	Ramazani A, et al. [2018]
RP HPLC	Bulk and dosage form	THERMO, C18, 250X4.6mm, 5µm	0.1M KH2PO4 : Methanol (60:40)	248	1.0	3.684	Jyothsna M, et al. [2018]
RP HPLC	Tablets	Waters Acquity HSS T-3 C_{18} (100 × 2.1 mm, 1.7µm	Potassium di-hydrogen phosphate: acetone in the ratio (40:60 v/v) at Ph 6.0	243	1.0	2.574	Mounika B, et al. [2017]
RP HPLC	Tablets	EnableC18 G (250 × 4.6mm, 5µm) column	methanol: 1% OPA (70: 30v/v) at Ph 5	246	1.0	3.601	Spandana R, et al. [2016]
LC	Enantio meres	Chiralpak AY-H, column coated with amylose tris-(5-chloro-2-methylphenylcarbamate) with influence of ethanol (30-45%)	mixture solution of n-hexane, ethanol, and diethyl amine (55: 45: 0.1, v/v/v)	254	1.0		Zou Q, et al. [2015]

Table 4: HPLC methods for the determination of Solifenacin Succinate.

Analytical system	Sample matrix	Column	Mobile Phase	Detect-ion (nm)	Flow rate (ml/min)	RT (min)	Author and publication year
RP-HPLC	Bulk and tablets	Sunfire C8 (4.6 ×150mm,5µm)	buffer: methanol: Acetonitrile (45: 45: 10v/v/v)	220	1.0	2.894	Tanuja A, et al. [2021]
RP-HPLC	API and tablets	Enable ODS reverse phase (250mm ×4.6 mm, 5µm)	Acetonitrile and water (80: 20v/v)	225	1.0	2.92	Kumar H, et al. [2019]
HPLC	Tablets	Capcell Pak C18, MG, (150 × 4.6mm, 5µm) column	A- (pH 6.6 phosphate buffer + 0.5% Triethylamine) B- (Milli-Q water 90%Acetonitrile (10: 90)).	225	0.9	10	Ganthi R, et al. [2016]
RP-HPLC	API	Xterra RP-18 (25cm×4.6mm i.d. 5µm)	0.05M pentane sulfonic acid sodium salt and acetonitrile (50:50 v/v)	200	1.0	4.1	Attia A, et al. [2016]
RP-HPLC	Tablets	EnableMake C18 G (250mm	Triethylammonium phosphate buffer pH 3:	210	1.0	3.5	Kumar A, et al. [2014]

		×4.6mm i.d., 5µm) column.	acetonitrile (30: 70v/v)				
RP-HPLC	Tablets	Inertsil ODS 3V C18 column (150mm ×4.6mm, 5µm)	potassium phosphate at pH 3.5 containing 0.1% triethylamine and methanol	220	1.5	5.12	Shaik R, et al. [2014]
LC	Tablets	C18 column	aqueous tetra butyl ammonium hydrogen sulphate (10mM): Acetonitrile (40: 60)	254	0.8	3.071	Annapurna M, et al. [2014]
HPLC	API	RP-18 (150mm × 4.6mm, 5µm)	0.01M phosphate bufferpH 3.5 with orthophosphoric acid (88%) and second mobile phase B contains mixture of acetonitrile and water (90: 10 v/v)	220	1.0	-	Rambabu C et al. [2013]
RP-HPLC	Bulk and Tablets	eclipse XBD-C18 (4.6 mm × 150mm, 5µm)	CAN: 20mM sodium phosphate buffer (0.2% TEA) (30:70)	225	1.0	10.95	Israel D, et al. [2013]
RP-HPLC	Bulk and Tablets	Xterra C18 (150 ×4.6mm, packed with 5µm)	Acetonitrile: Phosphate buffer (50: 50v/v)	210	1.0	2.4	Raul S, et al. [2012]
RP-HPLC	Bulk and tablets	OysterBDS C8 (250mm ×4.6mm i.d., 5µm)	10mM ammonium formate buffer: acetonitrile: methanol (52.5: 37.5:5.10, v/v/v)	210	0.7	13.8	Rajput S, et al. [2012]
HPLC	Bulk and tablets	Hypersil C8(250mm ×4.6mm i.d., 5µm)	10mM potassium dihydrogen phosphate with 0.1%v/v TEA in Milli-Q water pH 3: Acetonitrile (60: 40)	210	1.0	7.8	Vasanthraju S, et al. [2011]
HPLC	SFS in Rat plasma	TSK gel ODS-80Ts (5µm, 150mm ×2.0 mm i.d)	0.1M phosphate buffer: acetonitrile (71: 29v/v)	220	0.2	7.3	Yanagihara T, et al. [2007]
UFLC	API	Simpak XR-ODS column	10mM buffer potassium dihydrogen orthophosphate in water the pH adjusted by using TEA		0.5		Saipriya P, et al. [2010]

Table 5: TLC (Thin layer chromatography) or HPTLC (High performance liquid chromatogrpahy) methods for Mirabegron.

Sample matrix	Stationary Phase	Mobile Phase	Wavelength (nm)	Author and publication year
Bulk and Tablets	Aluminium Plates pre-coated with silica gel 60F- 254	methanol: acetonitrile: triethylamine (4: 6: 0.1, v/v/v)	247	Kachhiya H, et al. [2021]

Table 6: TLC (thin layer chromatography) or HPTLC (High performance liquid chromatogrpahy) methods for Solifenacin Succinate.

Sample matrix	Stationary Phase	Mobile Phase	Wavelength (nm)	Retention Factor	Author and Publication year
API	plates precoated with silica gel 60F254 column with 250µm thickness	methanol: water: Glacial acetic acid (9: 1: 0.1v/v/v)	216	0.49 ± 0.03	Damle M, et al. [2016]
Tablets	aluminum plates pre-coated with silica gel F_{254}.	methanol: ethyl acetate: triethylamine (8: 2: 0.1).	222	-	Shah D, et al.

Table 7: Hyphenated techniques for Solifenacin Succinate.

Analytical System	Sample matrix	Stationary Phase	Mobile Phase	Detection	Author and publication year
LC-MS/MS	SFS in rat plasma	Gemini-NX C18 (50 × 4.6mm, 5µm) column	5mM Ammonium formate, pH 3: methanol (20: 80v/v)	proton adducts at m/z 363.2®193.2 and 368.2®198.2 in multiple reaction monitoring mode (MRM).	Shaik R, et al. [2014]
LC-MS	SFS in human plasma	Pentafluoropheny lpropylsilica Column (50 × 4.6mm, 5µm)	methanol- 100mM ammonium acetate containing 1% of formic acid (90: 10 v/v)	m/z 363.2®193.2 and 368.2®198.2.	Macek J, et al. [2010]

CONCLUSION

This review geared toward specializing in numerous analytical stratergies according for the assay of both the drugs. A broad vary of techniques is out there for the estimation of Solifenacin succinate and Mirabegron alone but in combination of both the drugs only HPTLC method is available for estimation. For analysis of Solifenacin succinate and Mirabegron, HPLC-UV provides correct result and low price compared to advance detection techniques. The information provided in the article helps researcher to develop stability indicating method, pharmacokinetic studies and quantification in biological fluids. This review includes the entire detail of analytical stratergies obtainable on Solifenacin succinate and Mirabegron which can be substantiative for any analysis of drug.

Conflicts of Interest: All the authors declared that they have no conflicts of interest.

Abbreviations
MB Mirabegron
SFS Solifenacin Succinate
BCS Biopharmaceutics Classification system
FDC Fixed dose combination
GC Gas Chromatography
HPLC High Performance Liquid Chromatograpy
HPTLC High Performance thin layer Chromatograpy
IUPAC International Union of pure and applied Chemistry
LC-MS/MS Liquid Chromatography mass spectroscopy
mg Milligram
ml Milliliter
TLC Thin Layer Chromatography
UV-Vis Ultra-Violet visible
v/v Volume by volume

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