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REVIEW ARTICLE **OPEN ACCESS**

A Review on a Analytical and Bio-Analytical Methods for Determination of Silodosin and Mirabegron

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ABSTRACT
Silodosin is used to smooth muscle in bladder and prostate tissues, it increases bladder blood flow in conditions of chronic bladder ischemia. Now this combination is in clinical approval phase III conduct by Mascot health series Pvt. Ltd in India. The aim is to conduct review of this is two drug to know about the estimation method status in this two drug combination. There is many method available like High performance liquid chromatography, UV-Visible Spectroscopy, Liquid Chromatography – Mass spectroscopy and related substance method, but there is no any single method available of estimation of Silodosin and Mirabegron combine dosage form. In this article include all method of silodosin and mirabegron in separate dose and combination with other drug.
Keyword: *HPLC, Chromatography, silodosin-Mirabegron, UV-Visible, LC-MS, Analytical-Bio analytical.*

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INTRODUCTION

Silodosin determine smooth muscle relaxation in bladder and prostate tissues, it increases bladder blood flow in condition of chronic bladder ischemia and regulate the activity of transcriptional factor responsible for stoma growth and prostate hyperplasia.[1] Silodosin is a new uro-selective alpha-blocker with high pharmacological selectivity for the 1A adrenoceptor. It is a effective and well-tolerated treatment in men with lower urinary tract symptoms (LUTS), due to presume bladder outlet obstruction secondary to benign prostatic hyperplasia (BPH). The efficacy of silodosin is at least equivalent to existing selective alpha-1 antagonists like tamsulosin. A beneficial consequence of its high selectivity is improved cardiovascular safety and failure to interact with other therapies like anti-hypertensives and phosphodiesterase type-5 inhibitors.[2]

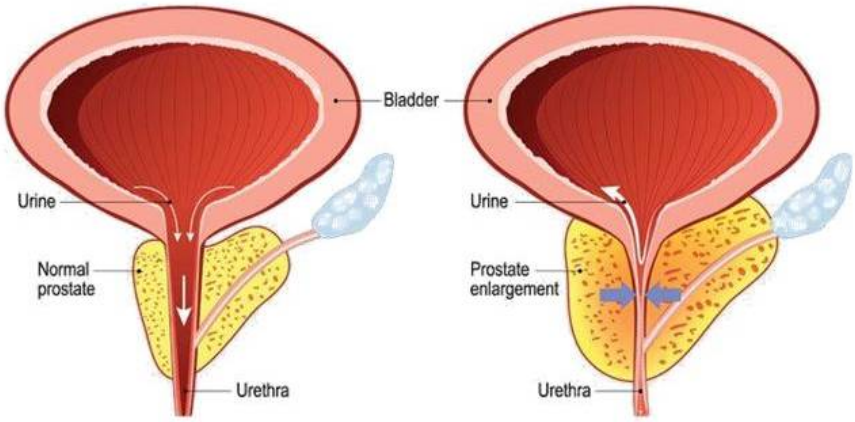


Figure1. Normal prostate and prostate enlargement [3]

Table 1: Drug profile: Silodosin

Sr. No	Parameter	silodosin
1	Chemical name	(-)-1-(3-hydroxypropyl)-5-[(2R)-2-({2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl}amino)propyl]-2,3-dihydro-1H-indole-7-carboxamide
2	Molecular formula	$C_{25}H_{32}F_3N_3O_4$
3	Molecular weight	495.534 g/mol
4	Solubility	aqueous buffers
5	Log P	2.87
6	pKa	pKa1: 8.53, N-ethylaminopropyl group pKa2: 4.03, N- indoline ring
7	Melting point	***105- 109°C***
8	Pharmacological effect	promotes prostatic and urethral smooth muscle relaxation, thereby improving lower urinary tract symptoms such as voiding.
9	Chemical structure	
10	BSC class	class III
11	Half life	About 11 hours[4]

Mechanism of action of Silodosin

The α1 -ARs belong to the family of G protein-coupled receptors. Binding of norepinephrine and epinephrine induces phospholipaze C activation, leading to generation of second messengers, calcium levels and smooth muscle contraction.25 Consequently, blockage of α1A-AR induced prostatic including inositol triphosphate and diacylglycerol. Finally, these induce an increase in intracellular and urethral smooth muscle relaxation, and may improve voiding symptoms. However, silodosin also seems to target afferent nerves in the bladder, then an thereby acts on bladder over activity and storage symptoms.[5]"

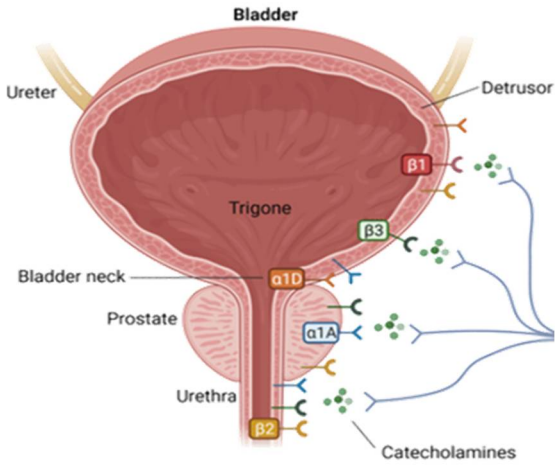


Figure2. Mechanism of action of Silodosin[6]

Analytical methods of silodosin

Table2: Official analytical method for silodosin

Sr. no.	Drug	Method Description
1	Silodosin Dosage form: Bulk/Dosage form Method: HPLC	**Stationary phase:** A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 mm in particle diameter). **Column temperature:** 40°C **Mobile phase:** Hexane : diethylamide : ethanol (93:10:7) **flow rate:** Adjust so that the retention time of silodosin is about 29 minutes **Wavelength:** 270 nm **Loop injecter:** 5 mL **peak area %RSD:** not more then 5%[7]

Table3. Reported analytical method for silodosin in bulk and pharmaceutical formulation

Sr. no.	Drug	Method Description
1	Silodosin Dosage form: Bulk Method: HPLC	**Stationary phase:** RP- C18 column **Mobile phase:** methanol, acetonitrile and water (40:40:20) **flow rate:** 1.0 ml/min **Wavelength:** 269 nm **Loop injecter:** 20µl **Linearity range:** 10-60µg/ml **Correlation coefficient:** 0.9997 **Retention time:** 2.5 **LOD(µg/ml):** 5.46 µg/ml **LOQ(µg/ml):** 16.57µg/ml[8]

Sr. no.	Drug	Method Description
2	Silodosin Dosage form: Capsule Method: HPLC	**Stationary phase:** Agilent ZORBAX CN **Mobile phase:** methanol : acetonitrile : ammonium acetate (40:30:30, v/v/v) **flow rate:** 1.3 mL min−1 **Wavelength:** 270nm **Linearity range:** 4-600µg/ml **Correlation coefficient:** 0.9988 **Retention time:** 2.5 Min **LOD(µg/ml):** 2µg/ml **LOQ(µg/ml):** 6 µg/ml[9]
Sr. no.	**Drug**	**Method Description**

3	Silodosin Dosage form: Bulk/Dosage form Method: UV-Visible spectroscopy	**Solvent:** methanol **Wavelength:** 269nm **Concentration Range:** 5-50µg/ml **Correlation coefficient:** 0.994 **Accuracy (% Recovery):** 98.9-101.9% **LOD: 0.5** (µg/ml) **LOQ: 1.55** (µg/ml) **Precision(%RSD):** **Intraday:**0.16% **Interday:**0.16%[10]

Sr. no.	**Drug**	**Method Description**
4	Silodosin Dosage form: Bulk/Dosage form Method: HPTLC	**Stationary phase:** silica gel 60 F254 **Mobile phase:** toluene/methanol/diethylamine (8:1:1) **Rf value :** 0.37 **Linearity range** :140-1400 ng/spot **Correlation coefficient:** (r2) 0.99916 **LOD:** 85 ng/spot **LOQ:**260 ng/spot **% Accuracy:** 101.02% **% Assay** :95.58%[11]

Sr. no.	**Drug**	**Method Description**
5	Silodosin Dosage form: Bulk/Dosage form Method: Spectrofluorimetric	**Solvent:** methanol **excitation wavelength:** 272 nm **emission wavelength:** 450 nm **range:** 0.01 to 1µg/ml **LOD:** 0.003µg/ml **LOQ:** 0.0091µg/ml **%Drug recovery:** 98.53% to 99.27% **Correlation coefficient(R2) :** 0.9989 **Precision (%RSD)*:** Intraday: 0.63 Interday: 1.39 **%Assay:** 99.19[12]

Table 4. Silodosin Quantification in human plasma by LC-MS:

Sr. no.	**Drug**	**Method Description**
1	Silodosin Dosage form: Bulk Method: LC-MS	**Stationary phase:** ZORBAX SB-C8, 100 mm × 4.6 mm, 3.5 µm **Mobile phase:** Buffer:(5 mM Ammonium Acetate) approximately weighed 0.385 g of ammonium acetate dissolve in 1000 ml of Milli-Q-water and adjusted solution pH to 9.0 with Ammonia and filtered. Buffer : ACN (200:400) **flow rate:** 0.800 ml/min **Injection volume:** 10 µl. **Linearity range:** 0.502 ng/ml to 207.376 ng/ml **Retention time:** 3.5 min Biological Matrix: K2 EDTA Human Plasma Precision (%RSD): 4.61% **%Accuracy :** 91% [13]

Table5. Reported analytical method of Silodosin with other drug

SN.	Drug	Method Description
1	Silodosin and solifenacin Dosage form: Bulk/Dosage form Method: Spectrofluorimetric	**Solvent:** methanol **excitation wavelength:** 272 nm **emission wavelength:** 450 nm **range:** 0.01 to 1µg/ml **LOD:** 0.003µg/ml **LOQ:** 0.0091µg/ml **%Drug recovery:** 98.53% to 99.27% **Correlation coefficient(R2) :** 0.9989 **Precision (%RSD)*:** Intraday: 0.63 Interday: 1.39 **%Assay:** 99.19[12]

SN	Drug	Method Description
2	Silodosin and solifenacin Dosage form: Bulk/Dosage form Method: HPLC	**Stationary phase:** Agilent ZORBAX CN **Mobile phase:** acetonitrile:methanol:buffer (50:20:30, v/v/v) **flow rate:** 1 ml/min **Wavelength:** Silodosin:270 nm Solifenacin:210nm **Linearity range:** Silodosin: 0.9994 Solifenacin: 0.9982 **Retention time:** Silodosin: 3.626 min Solifenacin: 5.754 min %RSD: less then 2%[14]

SN	Drug	Method Description
3	Silodosin and solifenacin Dosage form: Bulk/Dosage form Method: HPTLC	**Stationary phase:** silica gel 60 F254 **Mobile phase:** ethyl acetate, ethanol & 25% w/w ammonia (3.0: 7.0: 0.3, by volume) **Linearity range** : silodosin: 0.1 to 7.0 µg/band solifenacin: 0.1–6.0 µg/band. **Wavelength:** silodosin:270nm solifenacin:215nm[15]

SN	Drug	Method Description
4	Silodosin and Tadalafil Dosage form: Bulk/Dosage form Method: RP-HPLC	**Stationary phase:** C8 (150mmx4.6mm, 5µm) **Mobile phase:** potassium phosphate dibasic buffer pH (4.3) and acetonitrile (70:30 v/v) **detector:** PDA **retention time:** Silodosin:8.2min Tadalafil :9.6min **Correlation Coefficient** **Silodosin:** 0.9991 **Tadalafil:** 0.9992 **concentration ranges:** **Silodosin:** 80-240 µg/ml **Tadalafil :** 50-150 µg/ml **% Mean Recovery:** Between 98.0% -102.0% **Wavelength:** **Silodosin:** 270nm **Tadalafil :** 284 nm[16]

SN	Drug	Method Description
5	Dutasteride And Silodosin Dosage form: Bulk/Dosage form Method: Rp-HPLC	**Stationary phase:** Agilent C18 Column(250×4.6mm,5µm) **Mobile phase:** 20% Buffer, 40% Methanol, 40% Acetonitrile. **flow rate:** 1.0 ml/min **detector:** PDA **Flow rate:** 1.5 ml per min **retention time:** Silodosin:2.623 min Dutasteride: 2.050 min **range:** 10-50 µg/ml **Run time:** 7min **Wavelength:**260 nm correlation coefficient: Silodosin 0.999 Dutasteride of 0.999 **Precision (% RSD):** Silodosin: 0.1136 Dutasteride: 0.10229 **%accuracy:** 99.26 to 104.81[17]

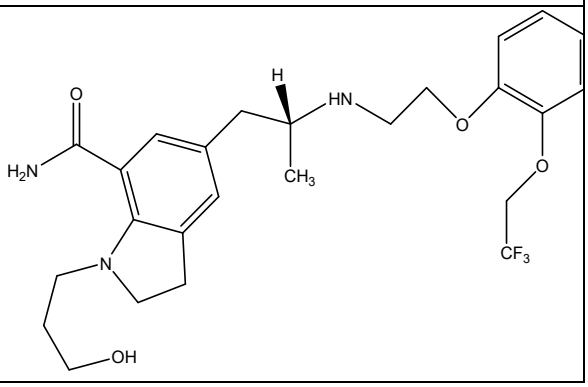
Organic Impurity study of Silodosin

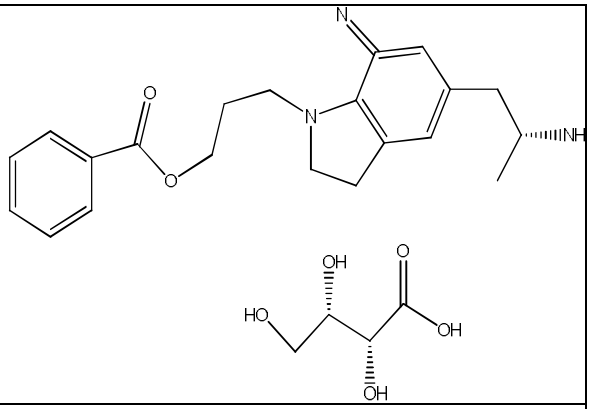
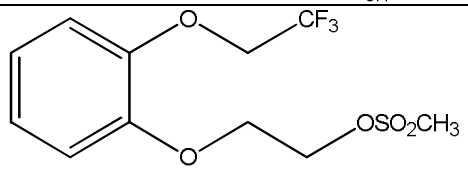
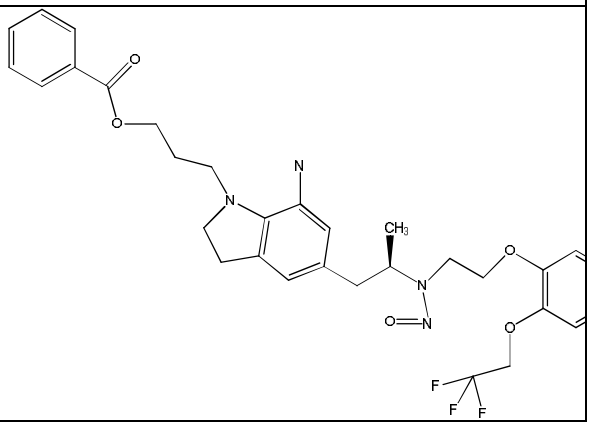
Many type of impurity present in API of any drug like, Organic, Inorganic, residual solvent, elemental impurity. So this described impurity is organic and process related impurity.

Table6. Chromatographic condition for estimation Silodosin organic impurity in HPLC

parameter	Condition		
Column	Agilent Poroshell 120EC-C18 column (50×4.6 mm i.d.; particle size, 2.7 mm)		
Temperature	28°C		
Flow rate	0.7 mL/min		
Mobile phase	10 mM ammonium acetate buffer mixed with 0.1% triethyl amine, pH 6.0 adjusted with glacial acetic acid(A): acetonitrile(B) (50:50)	Time	Flow(solution B)
		0	10%
		6	90%
		8	90%
		12	10%
Run time	15 min		
Injection volume	10 µL		
wavelength	273 nm		

Table7. Structure of organic Impurity of Silodosin

IUPAC name of Impurity	Structure of Impurity
IUPAC name: 1-(3-hydroxypropyl)-5-(2-(2-(2-(2,2,2- 2-(2-(2, D carboxamide trifluoroethoxy)phenoxy)ethylamino)propyl)indoline-7 Chemical Formula: $C_{25}H_{32}F_3N_3O_4$ Molecular Weight: 495.53 **(Silodosin)**	

IUPAC name: 3-(5-(2-aminopropyl)-7-cyanoindolin-1-yl)propyl benzoate 2,3-dihydroxysuccinate Chemical Formula: $C_{26}H_{31}N_3O_8$ Molecular Weight: 513.54 **(impurity-1)**	
IUPAC name: 2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethyl methanesulfonate Chemical Formula: $C_{11}H_{13}F_3O_5S$ Molecular Weight: 314.28 **(impurity-2)**	
IUPAC name: 3-(7-cyano-5-(2-(2-(2-(2,2,2-trifluoroethoxy)phenoxy)ethylamino)propyl)indolin-1-yl)propyl benzoate Chemical Formula: $C_{32}H_{34}F_3N_3O_4$ Molecular Weight: 581.63 **(impurity-3)**	

Preparation of stock solution of silodosin Organic Impurity:
The stock solutions of the three impurities of silodosin were prepared by separately dissolving 10 mg of each impurity in 20 mL of diluents (100%).
A series of dilutions were made by using 100% solutions of Impurity 1, Impurity 2 and Impurity 3.
The sample solution was prepared by weighing approximately 10 mg of silodosin into a 20 mL volumetric flask; the drug was dissolved and diluted to 20 mL with diluents.

Method validation results of Silodosin organic Impurity

Table8. Potency and RRF and retention time of Silodosin and it`s Impurity

Sample	Name	Potency%	RRF values	Retention time
1	Silodosin	98.90	1.00	3.81
2	Impurity 1	96.78	1.36	4.5
3	Impurity 2	99.83	0.33	5.6
4	Impurity 3	97.45	1.03	7.4

Table9. Linearity response of Silodosin And it`s Impurity

Sample	Name	Range (mg/mL)	Correlation coefficient (r)
1	Silodosin	0.25-1.5	0.998
2	Impurity 1	0.20-1.5	0.9998
3	Impurity 2	0.36-1.5	0.9997
4	Impurity 3	0.24-1.5	0.9997

Table10. Accuracy Results of Silodosin and it`s impurity

Level of accuracy	Impurities	Impurities added (PPM)	Impurity recovered(PPM)	Impurity recovered (%)
50%	1	0.375	0.38	100.4
	2	0.375	0.39	102.7
	3	0.375	0.37	98.7
100%	1	0.75	0.75	99.6
	2	0.75	0.76	101.6
	3	0.75	0.74	98.7
105%	1	0.1125	0.1143	101.6
	2	0.1125	0.1147	101.9
	3	0.1125	0.1142	101.5

Table11. Robustness Data of Silodosin and it`s impurity: (relative retention time)

sample	name	0.5ml/min	0.9ml/min	23° C	33° C	pH5.8	pH6.2
1	Impurity 1	1.19	1.19	1.19	1.16	1.18	1.40
2	Impurity 2	1.35	1.51	1.51	1.44	1.47	1.89
3	Impurity 3	1.91	2.04	1.96	1.94	1.94	2.68

Force degradation study of silodosin

Table12. Stress condition result

Sample	Stress condition	Degradation observed (%)	Retention times of major degradants (min)
1	Acid hydrolysis	4.63	3.64,4.73
2	Base hydrolysis	0.27	No major degradants
3	Water hydrolysis	0.37	No major degradants
4	Oxidative degradation	14.82	1.30
5	Thermal degradation	4.64	4.27,5.14
6	Photo degradation	0.25	No major degradants
7	UV degradation	0.34	8No major degradants[18]

MIRABEGRON

Introduction of Mirabegron

It is an human β3-adrenoceptor agonist for the treatment of OAB.

Mirabegron is the first of a new class of drugs licensed for the managing of overactive bladder syndrome (OAB) in over 30 years. It's a great human β3-adrenoceptor agonist for the treatment of OAB that can treat your issues real good. OAB, oh boy, it's when you have an urgent need to pee a lot, and you can't hold it in, even at night. It's like, bothersome, man. It happens to both men and women and it's a bummer, seriously ruins your quality of life. But don't worry, there's hope. You can try losing weight, changing how you handle fluids, and cutting back on stuff like caffeine, alcohol, and other things that make your bladder mad. Oh, and there's this thing called bladder training, too. It can help. But if none of that works, like seriously, nada, then you can take some anti muscarinics. But wait, there's something cooler now. It's called Mirabegron, and it's been gaining fame, like on the Hollywood scene, for helping people with OAB. It was given the thumbs up for treating OAB in Japan in 2011 (Betanis), the USA and Canada in 2012 (Myrbetriq), and Europe in 2013 (Betmiga). [19]

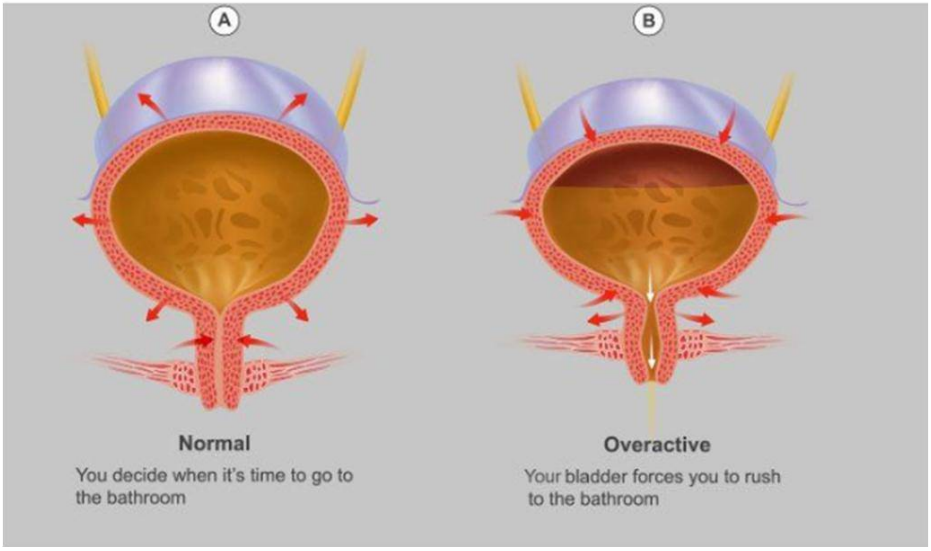
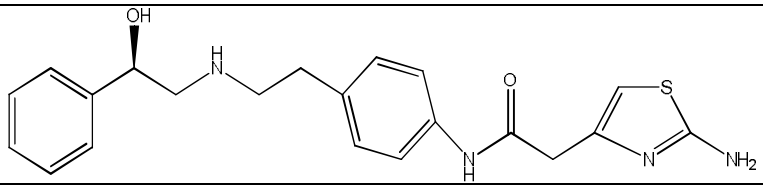


Figure3. Difference between normal bladder and over active bladder [18]

Table13 Drug Profile: Mirabegron

Sr.No	Parameter	silodosin
1	Chemical name	2-(2-Amino-1,3-thiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide
2	Molecular formula	$C_{21}H_{24}N_4O_2S$
3	Molecular weight	396.506
4	Solubility	freely soluble in dimethyl sulfoxide, soluble in methanol and insoluble in water
5	pKa	4.5 and 8.0.
6	Melting point	138–140 ºC
7	Pharmacological effect	relaxing the bladder muscles to prevent urgent, frequent, or uncontrolled urination.
8	Chemical structure	
9	Half life	50 hours in adult patients and 26 to 31 hours in pediatric patients[21]

Mechanism of action

Detrusor relaxation, it's mainly mediated by the cyclic adenosine monophosphate pathway, Like, seriously, it's a pathway that's all about cyclic adenosine monophosphate. it's a potent and selective3-adrenoceptorist. causes like, major increased cyclic adenosine monophosphate concentrations in the rat bladder tissue, It shows a major bladder relaxant effect. But wait, there's more! It also results in, like, totally making the bladder smooth muscle chill out in rat and human isolated tissue, It's like magic or something, new level of relaxation.

Mirabegron, that dude is a game-changer. It's all about making those bladder muscles say With Mirabegron and the cyclic adenosine monophosphate pathway, we're on a journey to uncover the secrets of bladder relaxation.

Analytical method of Mirabegron

Table14. Reported analytical methods of mirabegron

Sr. no.	Drug	Method Description
1	Mirabegron Dosage form: Bulk/Dosage form Method: RP-HPLC	**Stationary phase:** C18G (250 x 4.6 mm, 5µm) **Column temperature:** 30°C **Mobile phase:** Methanol: 0.1% OPA (pH5) (70:30v/v) **flow rate:** 1ml/min **Retention time:**3.601min **Wavelength:** 246nm **detector :** PDA **concentration rang:** 10-50µg/ml (R^2 =0.999). **LOD:** 0.202µg/ml **LOQ:**0.612µg/ml **Intraday precision:(%RSD):** 0.35 **Interday precision:(%RSD)**: 0.196 **%accuracy: 99.3-100%**[23]

Sr. no.	Drug	Method Description
2	Mirabegron Dosage form: Bulk/Dosage form Method: UV-visible spectroscopy	**Solvent:** 1N Hcl **Wavelength:** 249 nm **Concentration Range:** 3-15µg/ml, **Correlation coefficient:** 0.999 **Accuracy (% Recovery):** 98% -105% **LOD:**0.187 µg/ml **LOQ:**0.568 µg/ml[24]

Sr. no.	Drug	Method Description
3	Mirabegron Dosage form: Pharmaceutical Dosage form Method: HPTLC	**Stationary phase:** Gel 60F-254 and **Mobile phase:** n-butanol: acetic acid: water (6:2:2 V/V **wavelength:** 249 nm **Rf value**: 0.64 **linear range:** 2- 8 µg per band. **LOD [µg per band]:** 0.047 **LOQ [µg per band] :**0.12 **Accuracy [%]:**98.53-99.78% **Intra-day precision [%RSD]**: 0.87% **Inter-day precision [%RSD]:** 1.42%[25]

Table15. Mirabegron Quantification in human plasma

Sr. no.	Drug	Method Description
1	Mirabegron Dosage form: Bulk Method: LC-MS	**Stationary phase:** InertsilTM C8-3 (50 mm × 2.1 mm) **Column temperature:** 40 **Mobile phase:** 10 mmol/500 ml water ammonium acetate :acetonitrile at a 70/30 (v/v) **flow rate: 0.3ml/min** **Retention time: 2.5min** **Injection volume:** 3 µl **concentration rang:** **LOD:** 80.0 ng/mL **LOQ:** 8.0 ng/mL **Intraday precision:(%RSD):** 15% RSD **%accuracy: 99%** [26]

Table16. Reported analytical method of mirabegron with other drug

Sr. no.	Drug	Method Description
1	Mirabegron And Solifenacin Succinate Dosage form: Pharmaceutical Dosage form Method: UHPLC	**Stationary phase:** Agilent-Poroshell (3 x 100 mm; 2.7µ particle size) **Column temperature:** (45- 60˚C) **Mobile phase:** methanol-acetonitrile (50:50 v/v) at **flow rate:** 0.8ml/mins **Retention time:** 18min **Wavelength:** 210 nm **concentration rang:** mirabegron: 25-75 µg/ml solifenacin: 2.5-7.5 µg/ml **LOD:** mirabegron:3.57 µg/ml solifenacin:1.75 µg/ml **LOQ:** mirabegron: 11.89 µg/ml solifenacin: 5.82 µg/ml **linearity:** mirabegron: 0.999 solifenacin: 0.999 **Interday Precision: (Range of % RSD)** mirabegron: 0.82-1.10 solifenacin: 0.30 -1.26 **%Accuracy:** mirabegron: 99.21 % - 102.57% solifenacin: 98.47% - 107.98%[27]

Sr. no.	Drug	Method Description
2	Mirabegron And Solifenacin Succinate Dosage form: Bulk/Dosage form Method: RP-HPLC	**Stationary phase:** C18 (150mm × 4.5 mm × 5 µm) **Mobile phase:** Water: Acetonitrile (20:80%v/v) **flow rate:** 1ml/min **Retention time:** mirabegron: 5.82 solifenacin: 3.31 **Wavelength:** mirabegron: 221nm solifenacin: 266nm **concentration rang:** mirabegron: 2.5-12.5 µg/ml solifenacin: 0.5-2.5 µg/ml **LOD:** mirabegron:0.61(µg/ml) solifenacin:006(µg/ml) **LOQ:** mirabegron:1.85(µg/ml) solifenacin: 0.2(µg/ml) **linearity:** mirabegron: 0.9984 solifenacin:0.9993[28]

Sr. no.	Drug	Method Description
3	Mirabegron And Solifenacin Succinate Dosage form: Bulk/Dosage form Method: UV-visible spectroscopy	**Solvent:** methanol **Wavelength:** mirabegron:247nm solifenacin:210nm **Concentration Range:** mirabegron: 7.5- 20 µg/ml solifenacin: 1.5-4 µg/ml **Correlation coefficient:** mirabegron: 0.998 solifenacin:0.999 **Accuracy (% Recovery):** 99.9-100.5% **LOD:** mirabegron:0.17 solifenacin:0.304 **LOQ:** mirabegron:0.484 solifenacin: **0.922**[29]

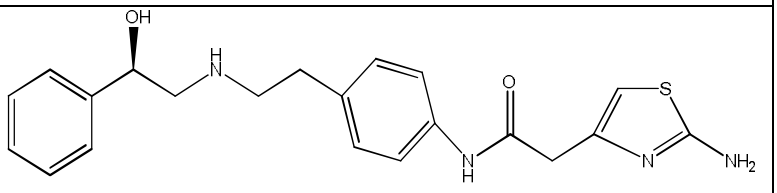
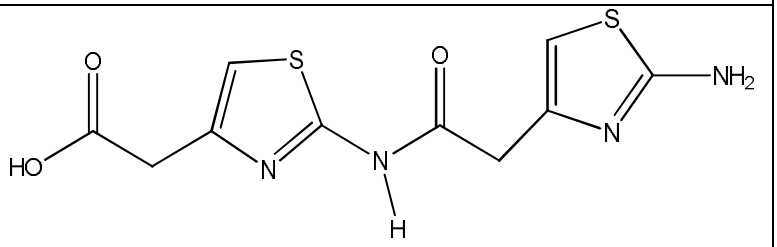
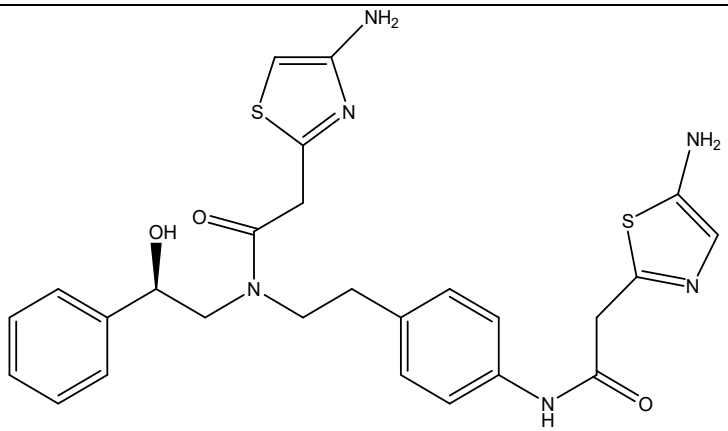
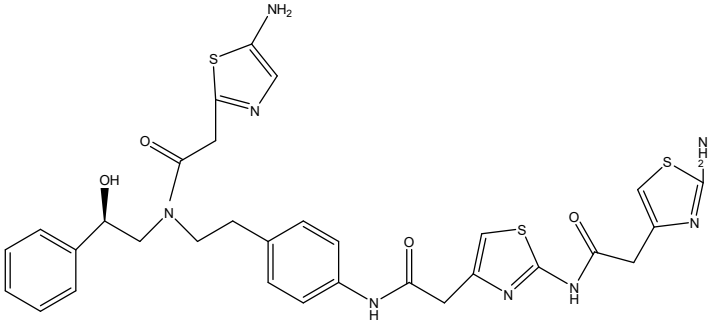
Sr. no.	Drug	Method Description
4	Mirabegron And Solifenacin Succinate Dosage form: Bulk/Dosage form Method: HPTLC	**Stationary phase:** silica gel 60 F254 **Mobile phase:** methanol–ethyl acetate–triethylamine (8:2:0.1, V/V) **wavelength:** 222nm **Rf value**: mirabegron: 0.76 solifenacin: 0.56 **linear range:** mirabegron: 2–5.5 µg per band solifenacin: 0.4–1.1 µg per bands [29]

Organic Impurity study of Silodosin

Table17. Chromatographic condition for estimation Mirabegron impurity in HPLC

parameter	Condition	
Column	C18 column (250 mm length × 4.6 mm ID with 5µm particle size	
Temperature of column	25 °C	
Flow rate	1.0 mL/min	
Mobile phase: (A) consisted, 20 mM ammonium acetate, pH adjusted to 4.5 and mobile phase (B) methanol	time	Flow(solution B)
	0	10
	10	45
	20	90
	22	90
	25	10
	30	10
Run time	30 min	
Injection volume	10µL	
wavelength	247 nm	

Table18. Structure of organic Impurity of Silodosin

IUPAC name of Impurity	Structure of Impurity
IUPAC name: (R)-2-(2-Aminothiazol-4-yl)- N-(4-(2-(2-(2-(2- aminothiazol-4-yl)a cetamido)thiazol-4-yl)acetamido)phenethyl)-N-(2-hydroxy-2-phenylethyl)acetamide Molecular weight : 396.51 (Mirabegron)	
IUPAC Name:(R)-2-(2-Aminothiazol-4-yl)- N-(4-(2-(2-aminothiazol-4-yl)acetamido)phenethyl)-N-(2-hydroxy-2-phenylethyl)acetamide Molecular weight : 298.34 Impurity 1	
IUPAC name: (R)-2-(2-Aminothiazol-4-yl)- N-(4-(2-(2-aminothiazol-4-yl)acetamido)phenethyl)-N-(2-hydroxy-2-phenylethyl)acetamide Molecular weight: 536.67 Impurity 2	
IUPAC name: (R)-2-(2-Aminothiazol-4-yl)- N-(4-(2-(2-(2-(2- aminothiazol-4-yl)a cetamido)thiazol-4-yl)acetamido)phenethyl)-N-(2-hydroxy-2-phenylethyl)acetamide Molecular weight: 691.87 Impurity 3	

Organic Impurity analysis of Mirabegron

Table19. System suitability result of Mirabegron and it`s impurity

parameter	Impurity 1	Impurity 2	Impurity 3	mirabegron
RT	10.81	18.65	19.42	14.87
RRT	0.72	1.25	1.30	1

Table20. Linearity result of Mirabegron and it`s impurity

parameter	Impurity 1	Impurity 2	Impurity 3	mirabegron
r^2	0.9996	0.9993	0.998	0.9996
LOD(ppm)	0.07	0.07	0.02	0.01
LOQ(ppm)	0.12	0.04	0.21	0.06
Precision(%RSD)	2.01	1.09	1.43	0.22
Repeatability intraday(%RSD)	3.82	0.98	1.98	1.57
Repeatability interday(%RSD)	2.97	0.72	0.93	0.35

Table21. %Accuracy result of Mirabegron and its impurity

parameter	Impurity 1	Impurity 2	Impurity3	Mirabegron
Accuracy at 50% level				
Amount added	0.53	0.53	0.53	13.30
Amount recovered	0.517	0.5131	0.5115	12.71
%Recovery	103.61	104.54	104.98	104.63
Accuracy at 100% level				
Amount added	1.05	1.05	1.05	25.95
Amount recovered	1.03	1.02	1.023	25.36
%Recovery	102.26	102.94	103.24	102.34
Accuracy at 150% level				
Amount added	1.54	1.54	1.54	38.83
Amount recovered	1.55	1.53	1.53	37.703
%Recovery	99.67	100.56	100.59	102.96

Table22. Force degradation study of Mirabegron

Stress condition	Time(min)	Temp. (°C)	%Assay of API	%Of degradation product
Acid Hydrolysis (1N HCl)	120	60	104.2757	1.39
Basic Hydrolysis (1N NaOH)	120	60	90.62859	2.34
Oxidation (10% H2O2)	120	60	55.47937	25.70
Hydrolysis (60 °C)	120	60	101.2761	0.1
UV (254 nm)	3600	-	105.5835	0.1[31]

CONCLUSION

Silodosin and Mirabegron is now clinical approval phase III trial, there are many methods like HPLC, UV-Visible, and LC-MS etc are available for estimation of both this drug in pure form or combination with other drug.

But there is no any single method available for estimation of combine (Silodosin + Mirabegron) dosage form, so this literature review is conduct to gain knowledge about all method of this drug.

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This study is a part of method development in Master of Pharmacy in Quality Assurance Department, this study describe that there are no any Qualitative and Quantitative method available of Silodosin and Mirabegron in combine dosage form. So, I want to conduct research for estimation of Silodosin and Mirabegron in combine drug.

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