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Research Article

RPHPLC METHOD DEVELOPMENT AND VALIDATION FOR ASSAY DETERMINATION OF SOLIFENACIN SUCCINATE IN SOLIFENACIN SUCCINATE TABLETS

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A B S T R A C T

Solifenacin succinate is a competitive muscarinic acetylcholine receptor antagonist. The binding of acetylcholine to these receptors, particularly the M3 receptor subtype, plays a critical role in the contraction of smooth muscle. By preventing the binding of acetylcholine to these receptors, Solifenacin reduces smooth muscle tone in the bladder, allowing the bladder to retain larger volumes of urine and reducing the number of incontinence episodes. This article describes development and validation for the assay determination of Solifenacin succinate in Solifenacin succinate Tabletsby using a high performance liquid chromatography. The high performance liquid chromatography was achieved on a Inertsil ODS 3 150 x 4.6, 5µ, column with an isocratic elution at a flow rate of 1.0mL/min.The detection was performed by a photo diode array Detector. The method was validated in the concentration range of 50% to 150% of working concentration. The intra and inter-day precision and accuracy were within Limit. The overall mean recoveries of Solifenacin succinatewere in the range of 98.0% to 102.0% for 50%, 100% and 150%.

INTRODUCTION

Solifenacin succinate is a competitive muscarinic acetylcholine receptor antagonist. Muscarinic receptor antagonists are widely used for treatment of the syndrome of overactive bladder and urge urinary incontinence [1-4]. M2 and M3 receptors are mainly distributed in the bladder while M3 subtype is distributed predominantly in the salivary gland and that M3 subtype plays a major role in the physiological function of both organs. Solifenacin compared with oxybutynin binds to a greater extent to bladder M3 muscarinic receptors in the bladder while it may exert a relatively little activity to bind exocrine M3 muscarinic receptors [5-6].Various methods are available for the analysis of Solifenacin in literature like LC–ESI-MS/MS, semi-micro high performance liquid chromatography. Analytical method for the estimation of Solifenacin in bulk drug was not reported by HPLC method or HPTLC method [7-8]. Analytical method is validated that allows the determination of Solifenacin succinate assay in Solifenacin succinate Tablets. The validation parameters, Specificity, Forced degradation, linearity, repeatability, precision, Accuracy, Solution Stability and robustness were validated [9-10].

MATERIAL AND METHODS

Working standard used in Experiments reported in table No.1. Apparatus and instruments used in experiment are listed in table No: 2. Reagents and solvents used: Water (HPLC grade, Milli Q), Potassium dihydrogen phosphate (AR grade), Sodium dihydrogen phosphate anhydrous (AR grade), Acetonitrile (HPLC grade), Methanol (HPLC grade), Triethyl amine (AR Grade), Orthophosphoric Acid (AR Grade).

Table 1 Standard details

S No.	Name of Standards	Potency (%)
1	Solifenacin succinate	99.7

Table 2 List of Instruments used

Sr No	Instrument	Make	Software	Detector/Model No
1	HPLC	Waters	Empower Software	2489 dual wavelength
2	HPLC	Waters	Empower Software	2998 PDA Detector
3	Sonicator	Lab India	NA	NA
4	Weight balance	Mettler Toledo	NA	ML204
5	Oven	Thermo lab	NA	GMP
6	Photolytic Chamber	Thermo lab	NA	GMP

Development Trials: Standard, **i**mpurities and spiked sample were injected in to HPLC using following trials

Trail -05

Preparation of Buffer 1: Added 4.0ml of trimethylamine in 2.0 litres of water and adjust pH 3.0 with orthophosphoric acid.

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Table 3 Method Development Trial 01 and 02

Chromatography Parameters	Trial 01	Trial 02
Column	Hyber® 100-4.6 purosphere star RP18e,3µm	Hyber® 100-4.6 purosphere star RP18e,3µm
Buffer	6.8 gm Potassium dihydrogen phosphate transferred to 2000ml with water. Add 4ml TEA. Adjust pH 3.0 with OPA.filter mixed and degas.	6.8 gm Potassium dihydrogen phosphate transferred to 2000ml with water. Add 4ml TEA. Adjust pH 3.0 with OPA.filter mixed and degas.
Mobile phase	Buffer : ACN: MeOH (50:25:25)	Buffer:ACN:MeOH (40:40:20)
Diluent	Mobile phase used as diluent.	Buffer:MeOH (1:1)
Flow Rate	1.5 mL/min.	1.5 mL/min.
Injection Volume	20 µL	20 µL
Wavelength	215 nm	215 nm
Column Temp.	40°C	30°C
Elution	Isocratic Elution	Isocratic Elution
Standard Concentration	Solifenacin Succinate 80ppm	Solifenacin Succinate 80ppm
Sample Concentration	Solifenacin Succinate 80ppm	Solifenacin Succinate 80ppm
Retention Time	About 3.4 min. for Solifenacin Succinate peak	About 5.15 min. for Solifenacin Succinate peak.
Observations	System precision found ok.(RSD of 5 replicate injections is 0.04%) Blank, Standard, Sample injected. Assay of sample was found much on lower side. Column performance is found poor.Theoretical plates not found satisfactory.(4000) Assay is below the accepted limits of 90-110%.Assay value coming on much lower side (88%).	System precision found ok.(RSD of 5 replicate injections is 0.24%) Blank, Standard, Sample injected. Theoretical plates increase upto 5330. But Assay of sample was found again on lower side of acceptance criteria.(89%).
Conclusion	As the assay found on much lower side, might be the diluent used is not capable to extract the drug from the matrix. Need to modify the extraction efficiency of diluent. Also as theoretical plates are much lower peak symmetry need to be enhance in further Trial-02.	Need to enhance the extraction efficiency of diluent again in next Trial -03.

Table 4 Method Development Trial 03 and 04

Chromatography Parameters	Trial 03	Trial 04
Column	Hyber® 100-4.6 purosphere star RP18e,3µm	Inertsil ODS 3, 150x4.6, 5µ
Buffer 1	6.8 gm Potassium dihydrogen phosphate transferred to 2000ml with water. Add 4ml TEA. Adjust pH 3.0 with OPA.filter mixed and degas.	6.8 gm Potassium dihydrogen phosphate diluted to 2000ml with water. Added 4ml TEA. Adjusted pH 3.0 with OPA. Filter mixed and degas.
Buffer 2	Not applicable	7.1 gm sodium dihydrogen phosphate anhydrous diluted to 5000ml of water. Adjusted pH 6.8 with TEA.
Mobile phase	Buffer:ACN (60:40)	Buffer 1:ACN:MeOH (40:40:20)
Diluent	Buffer:ACN (60:40)	Diluent 1:Buffer 2 Diluent 2: ACN:Methanol (1:1) Diluent 3: Buffer 2 : ACN: Methanol (20:40:40) Final diluent for sample extraction
Flow Rate	1.5 mL/min.	1.0 mL/min.
Injection Volume	20 µL	20 µL
Wavelength	215 nm	215 nm
Column Temp.	30°C	30°C
Elution	Isocratic Elution	Isocratic Elution
Standard Concentration	Solifenacin Succinate 80ppm	Solifenacin Succinate 100ppm
Sample Concentration	Solifenacin Succinate 80ppm	Solifenacin Succinate 100ppm
Retention Time	About 5.20 min. for Solifenacin Succinate peak.	About 2.6 min. for Solifenacin Succinate peak.
Observations	Blank, Standard, Sample injected. System precision found ok.(RSD of 5 replicate injections is 0.16%). Assay of sample was found bit comfortable 95% and Theoretical plates found 4100.	Blank, Standard, Sample injected in same method. System precision found ok.(RSD of 5 replicate injections is 0.04%). Assay in this Trial-04 found is 99.0%. In spiked sample at 1% of sample concentration known impurity A, C are well separated from main peak but impurity B was eluting at the tailing of Solifenacin Succinate peak.
Conclusion	Though the Assay is enhanced upto 95% but still need to work on the extraction efficiency of the diluent in next Trial-04	To achieve well separation of main peak and impurity mobile phase buffer was modified and injected as Trial-05.

In this trail mobile phase composition was changed to Buffer 1: Acetonitrile in the ratio (60: 40) and rest all are same as Trail-04.

Observation

Blank, Standard, Sample injected in same chromatographic system as mentioned in Table 6. System precision found ok.(RSD of 5 replicate injections is 0.20%).
Assay value observed was 100.0%.
Resolution between Solifenacin and Impurity B enhanced significantly from 1.2 to 2.8 in this trial.

Hence Trial 05 was considered as final optimised method and validation was performed on following final methodology (Trail-05).

Proposed Final methodology for Method Validation:
Preparation of Buffer 1: Added 4.0ml of trimethylamine in 2.0 litres of water and adjust pH 3.0 with orthophosphoric acid.

Preparation of Mobile phase: Prepare a mixture of Buffer 1: Acetonitrile in the ratio (60: 40)

Preparation of Buffer 2: Dissolve 1.42g Sodium dihydrogen phosphate anhydrous in 1.0 liters of water; adjust pH 6.8 with triethylamine.
Preparation of Diluent 1: Buffer 2
Preparation of Diluent 2: ACN: Methanol (40:40)
Preparation of Diluent 3: Buffer 2: ACN: Methanol (20:40:40)

Preparation of Standard Stock Solution:Weigh accurately and transfer about 25 mg of Solifenacin succinate working standard into a 100 mL volumetric flask, add 50ml diluent 3 and sonicate it to dissolve. Cool to room temperature and make up to the mark with diluent 3 and mix.

Preparation of Standard solution: Accurately transfer 10 ml of Standard stock solution into 25 mL volumetric flask and dilute up to mark with diluent 3 and mix.

Preparation of sample stock solution: Weigh and transfer 10tablets into 250mL volumetric flask, add 50ml diluent 1 and sonicate for 10minutes with intermittent shaking again add 150ml of diluent 2 and sonicate for 20mins with intermittent shaking. Cool to room temperature and make up to the mark with diluent 2 and mix. Filter this solution with 0.45µ Nylon filter.

Preparation of sample solution: Accurately transfer 5 ml of Sample stock solution into 20 mL volumetric flask and dilute up to mark with diluent 3 and mix.

Chromatographic Conditions

Column	:	Inertsil ODS 3 150 x 4.6, 5µ or equivalent
Flow Rate	:	1 mL / min.
Detection	:	215 nm.
Column Temp	:	30°C.
Injection Volume	:	20 µL.
Run Time	:	5 min.
Retention time	:	About 3 minutes

Evaluation of System Suitability: Inject the five replicates injections of standard solution into the chromatograph and record the chromatograms. Measure the area counts for Solifenacin succinate peak. The RSD of five replicate injections should not be more than 2.0%.

RESULT AND DISCUSSION

Specificity: Prepared representative Standard solutions and Sample solutions ofSolifenacin succinate Tablets and Injected each of the Diluent, Placebo solutions, Sample solutions and Standard solutions into the HPLC using the Chromatographic system utilizing a photodiode array detector. No interference was observed from Blank and Placebo at the retention time of Solifenacin succinate peak. Also, The Solifenacin succinate peak is pure in Standard solution and Sample solution. Therefore, the HPLC method for the determination of Assay of Solifenacin succinatein Solifenacin succinateTablets is specific. Specificity reported in table no.5.

Table 5 Table for Specificity

Sr. No.	Name	Purity Angle	Purity Threshold
1	Standard solution	0.288	1.101
2	Sample solution -5 mg	0.282	1.087
3	Spiked Sample -10 mg	0.360	1.167

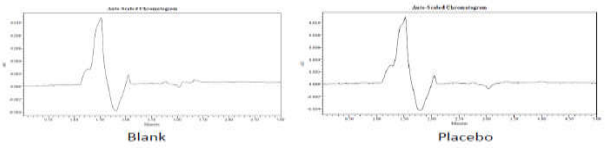

Figure No 1 Blank and Placebo Chromatogram

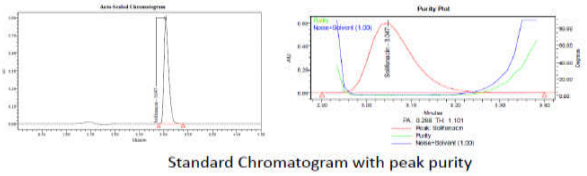

Figure No 2 Standard Chromatogram

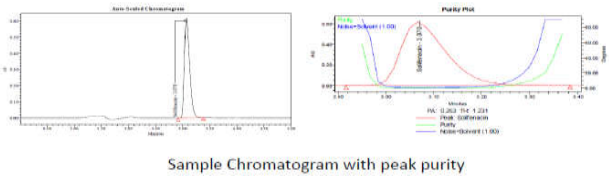

Figure No 3 Sample Chromatogram

Forced Degradation Studies**:** Summary of Forced degradation data is reported in Table no 6

Linearity and Range: A series of Standard preparations of Solifenacin succinatewere prepared over a range of 50% to 150% of the working concentration of Solifenacin succinate in Solifenacin succinateTablets. Since the working concentration is 100 µg per ml, of Solifenacin succinate, the range proposed is about 50 µg per ml to 150 µg per ml of Solifenacin succinate. Linearity of Solifenacin succinate reported in table No. 7.

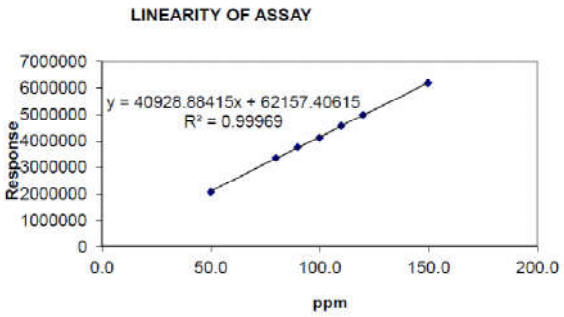

Figure No 4 Linearity Plot

Accuracy (Recovery): Placebo of Solifenacin succinatewas spiked with Solifenacin succinatedrug substance at three different levels: 80%, 100% and 120% in triplicate (total nine determinations). Each of the sample preparations was injected in duplicate and the average area count to be taken for calculation. Accuracy reported in table no.8

Precision: System PrecisionFive replicate injections of the Standard preparation were made into the HPLC. The RSD of system precision is reported in Table no. 9

Method Precision**:** Six sample preparations of Solifenacin succinateTablets were prepared and injected into the HPLC. The HPLC method for the determination of Assay of Solifenacin succinate in Solifenacin succinateTablets is reproducible. Result of method precision reported in Table no.10

Table No 6 Table for Forced Degradation Studies

Sr. No.	Experiment	Degradation Condition	% Assay	% Degradation	Purity Angle	Purity Threshold
1	Control Sample	--	100.3	--	0.282	1.087
2	Acid Degradation	5N HCl/ RT - 0 hours	100.3	--	0.275	1.041
		5N HCl/ RT-24 hours	100.6	--	0.408	1.107
		5N HCl/ 70°C - 3 hours	107.4	--	0.640	2.045
3	Base Degradation	2N NaOH/ RT-0 hours	102.1	--	0.290	1.042
		2N NaOH/ RT-24 hours	99.3	--	0.445	1.419
		2N NaOH/ 70°C - 3 hours	76.7	23.5	5.476	26.687
4	Peroxide Degradation	50% H_2O_2/RT-0 hours	4.3	95.7	16.831	24.206
		5% H_2O_2/RT-0 hours_10ml	87.7	12.6	0.250	1.103
5	Thermal Degradation	105°C/72 hours	97.2	--	0.239	1.205
6	Humidity Degradation	25°C/92%RH – 72 hours	101.2	--	0.284	1.034
7	Photolytic Degradation	1.2 million lux hours of Light	96.3	--	0.243	1.042

Table 7 Table for Linearity and Range

% Concentration	Concentration (PPM) (µg per mL)	Response (Area)	Statistical analysis	
50%	49.960	2076804	Slope	40929
80%	79.935	3360168		
90%	89.927	3766965	Intercept	62157
100%	99.919	4134174		
110%	109.911	4565832	Correlation Coefficient	0.9998
120%	119.903	4982696		
150%	149.879	6175516		

Table 8 Table for Accuracy

Sample No.	Amount added (mg)	Amount recovered (mg)	% Recovery
Acc. 80% -1	79.98	81.19	101.5
Acc. 80% -2	80.04	81.21	101.5
Acc. 80% -3	79.99	80.64	100.8
Acc. 100% -1	99.91	100.88	101.0
Acc. 100% -2	99.88	100.74	100.9
Acc. 100% -3	99.95	100.77	100.8
Acc. 120% -1	119.92	121.15	101.0
Acc. 120% -2	119.93	120.96	100.9
Acc. 120% -3	119.93	121.24	101.1
	Mean		101.1
	SD		0.208
	% RSD		0.206

Table 9 Table for System Precision

Injection	Area
1	4177699
2	4188000
3	4177209
4	4168530
5	4192120
Mean	4180712
SD	9394.250
%RSD	0.225

Ruggedness (Intermediate Precision): Six sample preparations of the same lot (as used in Precision) of Solifenacin Succinate Tablets, was made by a different analyst, using different column on a different day and injected into a different HPLC system. Ruggedness reported in table no. 10

Table 10 Table for Precision and Ruggedness % Assay

Sample	Precision	Ruggedness
1	99.8	101.4
2	99.2	100.4
3	99.6	101.5
4	99.2	101.1
5	99.0	101.0
6	99.8	100.5
Mean	99.4	101.0
SD	0.344	0.454
%RSD	0.346	0.450
Overall Mean	100.2	
Overall SD	0.896	
Overall %RSD	0.894	
Mean Difference	1.6	

Stability of Analytical solution: The sample and standard preparations were stored at room temperature and tested against freshly prepared standard preparations for 72 hours. Solution Stability of Solifenacin succinate Reported in Table no. 11

Table 11 Stability of Analytical solution at Room Temperature

Sr. No.	Name	% Content	% Correlation
1	Standard Solution - 0 hours	100.0	--
2	Standard Solution -24 hours	100.7	100.7
3	Standard Solution -48 hours	102.3	102.3
4	Sample Solution - 0 hours	99.8	--
5	Sample Solution -24 hrs	99.6	99.8
6	Sample Solution -48 hrs	101.2	101.4

Conclusion: Standard and sample solutions are stable for 48 hours at room temperature

Robustness: Three Sample preparations of the same lot of Solifenacin succinateTablets were prepared and the samples along with standard was injected in duplicate under different chromatographic conditions as shown below. Result of robustness reported in table no. 12 to 16.

Table 12 Table for Change in organic phase composition. (± 2% absolute)

Control	(+2% absolute)	(-2% absolute)
101.6	100.2	100.6
103.0	100.5	101.6
102.5	100.0	100.3
Cumulative Mean	101.3	101.6
Cumulative SD	1.262	1.045
Cumulative %RSD	1.246	1.029

Table 13 Table for Change in pH of Buffer (± 0.2 units)

Control	(+0.2 units)	(-0.2 units)
101.4	101.6	101.3
100.4	100.6	100.3
101.5	101.3	101.1
Cumulative Mean	101.1	101.0
Cumulative SD	0.505	0.522
Cumulative %RSD	0.500	0.517

Table 14 Table for Change in Flow rate (±0.1 mL/min.)

Control	(+0.1 mL/min.)	(-0.1 mL/min.)
101.4	101.3	101.8
100.4	99.4	100.9
101.5	99.3	101.7
Cumulative Mean	100.6	101.3
Cumulative SD	1.009	0.534
Cumulative %RSD	1.003	0.527

Table 15 Table for Change in column temperature (+5°C)

Control	(+5°C)	(-5°C)
101.4	99.6	100.7
100.4	98.3	100.8
101.5	99.3	100.1
Cumulative Mean	100.1	100.8
Cumulative SD	1.254	0.549
Cumulative %RSD	1.253	0.545

Table 16 Table for Change in wavelength (± 5 nm)

Control	(+5nm)	(-5nm)
99.4	100.5	99.4
100.9	99.9	100.7
101.1	101.1	100.9
Cumulative Mean	100.5	100.4
Cumulative SD	0.700	0.785
Cumulative %RSD	0.697	0.782

Filter equivalency: Weigh and transfer 10tablets into 250mL volumetric flask, add 50ml diluent 1 and sonicate for 10minutes with intermittent shaking again add 150ml of diluent 2 and sonicate for 20mins with intermittent shaking. Cool to room temperature and make up to the mark with diluent 2 and mix. Centrifuged and filterd in triplicate through different membrane filters such as Teflon 0.45µ, Nylon 0.45µ filters discarding first few mL of the filtrate. Accurately transfer 5 ml of Sample stock solution into 20 mL volumetric flask and dilute up to mark with diluent 3 and mix.. The Mean Filtration Recovery is within limits for Nylon 0.45µ and Teflon 0.45µ filter. Result reported in table no 17.

Table 17 Table for Filter Equivalency

	% Assay		
No.	Centrifuged	Nylon 0.45µ	Teflon 0.45µ
1	99.8	99.7	99.9
2	99.8	99.6	100.0
3	99.6	100.2	99.8
Mean	99.7	99.8	99.9
RSD	0.115	0.322	0.100
% Correlation with centrifuged	--	100.1	100.2

System Suitability:The RSD of five replicate injections of standard solution should not be more than 2.0%. Tailing factor for Solifenacin succinatepeak should not be more than 2.0. Number of theoretical plates should not be less than 3000. Result of system suitability reported in table no 18.

Table 18 Table for System Suitability

Parameter	%RSD
Forced degradation -1	0.180
Specificity	0.153
Linearity, Solution Stability 24 Hrs	0.085
Accuracy, Solution Stability 48 Hrs	0.748
Precision, Filter Equivalency	0.225
Ruggedness, Solution Stability 72 hrs	0.846
Robustness	
Mobile phase - Organic +2%	0.687
Mobile phase - Organic - 2%	0.672
pH +0.2 units	0.976
pH -0.2 units	0.119
Flow -0.1 mL/min.	0.819
Flow +0.1 mL/min.	0.732
Wavelength +5nm	0.190
Wavelength -5nm	0.143
Temp. + 5°C	0.920
Temp. - 5°C	1.077

SUMMARY AND CONCLUSION

The test method is developed and validated for Specificity, Linearity and Range, Precision, Accuracy (Recovery), Ruggedness, Stability of Analytical solution, Filter equivalency and Robustness and found to be meeting the predetermined acceptance criteria. The validated method is Specific, Linear, Precise, Accurate, Rugged and Robust for the determination of Solifenacin assay in Solifenacin Succinate Tablets.

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Competing Interests

This study was performed in Glenmark pharmaceutical limited. The authors have no financial or proprietary interest in the subject matter or material discussed.

List Ofabbreviations

No. Number
HPLC High performance Liquid Chromatography
RSD Relative Standard Deviation
ND Not Detected
NA Not Applicable
hrs Hours
Temp. Temperature
ACN Acetonitrile
MeOH Methanol
PDA Photo diode array
OPA Orthophosphoric acid
TEA Triethy amine

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