RESEARCH ARTICLE

Formulation and Development of Solifenacin Succinate Oral Suspension

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ABSTRACT

Solifenacin succinate is prescribed for patients with overactive bladder (OAB) syndrome to address symptoms such as urge incontinence, increased urinary frequency, and urgency. Tablet formulations can be challenging or impossible to administer to patients who are unable or unwilling to swallow solid dosage forms like tablets or capsules. For these patients, a liquid formulation of Solifenacin succinate is a more suitable alternative. The goal was to develop a liquid formulation with reduced astringency and bitterness compared to Solifenacin succinate in its raw form, while ensuring good drug content homogeneity. A Solifenacin succinate suspension was developed and evaluated based on parameters including pH, density, viscosity, % assay, and drug release profile. Batch optimization was carried out using design of experiment (DoE) software. The optimized formulation was subjected to stability studies as per ICH guidelines. Trial batches played a crucial role in formulating the suspension. Suspending agent (MCC/CMC sodium), viscosity modifier (Xanthan gum) and sweetener (Xylitol) were considered as independent variables and viscosity, dissolution and content uniformity, the suspension batch was optimized with a desirability score of 0.63 using DoE software. The optimized batch demonstrated stability and successfully passed the stability tests. A stable oral suspension dosage form of the anti-muscarinic drug Solifenacin succinate was successfully developed, meeting pharmacopoeial standards and offering a patient-friendly alternative for those with difficulty swallowing solid dosage forms.

Key words: Quality by design, Quality target product profile, Critical quality attributes, Design of Experiment

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INTRODUCTION

Among all drug administration routes, oral delivery is the most common. For years, oral pharmaceutical suspensions have been a preferred dosage form for children and patients unable to tolerate solid formulations. A pharmaceutical suspension is a coarse dispersion in which the internal phase is uniformly distributed within the external phase. Due to the thermodynamic instability of suspensions, a suspending agent is essential. This agent increases the viscosity of the medium, reduces the settling rate of suspended particles, and enables easy redispersion of settled particulate matter through protective colloidal action[1–3]. Solifenacin succinate belongs to the anti-muscarinic class of urinary antispasmodics. It is Biopharmaceutical Classification System (BCS) Class I drug. It is used in the formulation of oral suspensions to treat overactive bladders, including cases associated with urge incontinence. A comprehensive review of the literature indicates the absence of a dedicated oral suspension formulation for managing overactive bladders in pediatric patients[4–7]. Currently, immediate-release tablet formulations are available on the market; however, these options are limited in suitability for the pediatric population. As a result, oral suspensions represent a more appropriate choice for this demographic. Such formulations are not only cost-effective but also significantly enhance compliance among pediatric patients.

MATERIALS AND METHODS

The Solifenacin succinate was procure from MSN laboratories Pvt. Ltd, Hyderabad, Telangana, India as gift sample.

Preformualtion study

The preformulation study involved comparing the properties of Solifenacin succinate with certificate of authentication, solubility study, and drug- excipient compatibility study. Solubility studies were conducted in purified water, 0.1N hydrochloric acid, sodium acetate buffer (pH 4.5), and phosphate buffer (pH 6.8). Drug-excipient compatibility was assessed by observing binary mixtures of the drug and excipients in dry form, prepared in specific ratios and stored under closed conditions. The samples were stored for one month at 40±2 °C and 5±5 % relative humidity (RH) and 25°C and 60% RH[4,6,8].

Formulation of Solifenacin succinate suspension

Solifenacin succinate was dissolved in water. Beta-cyclodextrin and a taste-masking agent 566038T bitter blocker flavour 68 were added to the Solifenacin succinate solution under stirring until a clear solution formed, and stirring continued for 60 minutes. Tutti-frutti flavor and a 30% simethicone emulsion were added to this dispersion. Microcrystalline cellulose (MCC) and carboxymethyl

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Table 1: Formula for trial batches.

Batch size (Litre)		2.0	2.0	2.0	2.0	2.0
Sr. No.	Ingredient	T1	T2	T3	T4	T5
		Qty. (mg/mL)	Qty. (mg/mL)	Qty. (mg/mL)	Qty. (mg/mL)	Qty. (mg/mL)
1	Solifenacin Succinate	1.0	1.0	1.0	1.0	1.0
2	Microcrystalline Cellulose and Carboxymethyl Cellulose Sodium RC 591	10.0	14.0	15.0	12.0	12.0
3	Beta Cyclodextrin	1.0	2.0	3.0	4.0	4.0
4	Sodium Benzoate	0.3	0.3	0.3	0.3	0.3
5	Hydroxypropyl cellulose 6cps	20.0	-	-	-	-
6	Hydroxy ethyl Cellulose 250 HHX	-	2.0	-	-	-
7	Xylitol	90.0	90.0	90.0	90.0	-
8	Sucralose	1.2	1.2	1.2	1.2	0.5
9	Xantun Gum (Xantural 180)	-	-	-	2.0	2.0
10	Acesulfame Potassium	-	-	-	-	5.0
11	Simethicone emulsion 30%	1.1	1.1	1.1	1.1	1.1
12	Citric Acid Monohydrate	1.28	1.28	1.28	1.28	1.28
13	Taste masking agent (566038T bitter blocker flavour 68)	2.0	2.0	1.0	1.0	1.0
14	Tutti-frutti Flavour	1.0	1.0	1.0	1.0	1.0
15	Purified water	q.s.	q.s.	q.s.	q.s.	q.s.

Table 2: DOE for Solifenacin succinate suspension

File Version	13.0.9.0		
Study Type	Factorial	Subtype	Randomized
Design Type	2 Level Factorial	Runs	11.00
Design Model	3FI	Blocks	No Blocks
Center Points	3.00	Build Time (ms)	5.00

cellulose sodium (CMC-Na) were dispersed in water and homogenized for 45 minutes at 2000–3000 rpm. Sodium benzoate was dissolved in purified water, followed by the addition of a viscosity modifier under continuous stirring followed by addition of Xylitol and acesulfame potassium until a clear solution formed.

The pH was then adjusted with citric acid monohydrate, and the mixture was stirred for 15 minutes. Finally, the suspension was filtered through a #40 mesh, filled into tightly sealed containers, and stored at room temperature.

The trial batches were formulated by changing viscocity modifiers like Hydroxypropyl cellulose 6cps, Hydroxy ethyl Cellulose 250 HHX or Xantun Gum (Xantural 180) as specified in Table no 1. The trial batches were thoroughly evaluated for pH, density, viscosity, dissolution profile using Type II (Paddle) dissolution apparatus and % assay using HPLC analysis. An Inertsil ODS 3V column (250 x 4.6 mm, 5 µm) was employed for the HPLC analysis. The mobile phase consisted of Buffer solution, Acetonitrile and Methanol in the ratio of 100:550:350, with a 1 µL injection volume and flow rate of 1.0 mL/min. The total runtime was 28 minutes, with the peak detection retention time at 10 minutes and UV detection set at 220 nm[9].

$$\% \text{ Assay} = \frac{Su}{Ss} * \frac{WS}{50mL} * \frac{5 \text{ ml}}{50\text{ml}} * \frac{100 \text{ ml}}{Wt} * \frac{1}{\text{LC}} * \frac{P}{100} * 100 * F$$

Where,

Su = Average area of Solifenacin peak in the chromatogram of sample solution.

Ss = Average area of Solifenacin peak in the chromatogram of standard solution.

Ws = Weight of Solifenacin Succinate standard (mg).

Wt. = Weight of test sample (g).

P = Percent potency of Solifenacin succinate standard on as is basis.

F = Weight per mL (g/mL).

LC = Label claim in mg/mL.

Batch optimization of Solifenacin succinate suspension

The fractional factorial design was employed using experiment (DoE) version 13 was employed for batch selection by considering suspending agent (MCC/CMC sodium), viscosity modifier (Xanthan gum) and sweetener (Xylitol) as independent parameters. Three responses namely Viscosity, Dissolution and Content Uniformity were considered for batch optimization of Solifenacin succinate. An Inertsil ODS 3V column (250 x 4.6 mm, 5 µm) was employed for the HPLC analysis. The mobile phase consisted of Acetonitrile and Methanol in the ratio

Table 3: Independent parameters

Factor	Name	Units	Type	Sub Type	Minimum	Maximum	Mean	Std. Dev.
A	MCC/CMC Sodium	mg	Numeric	Continuous	10.00	14.00	12.00	1.79
B	Xanthan gum	mg	Numeric	Continuous	1.0000	3.00	2.00	0.8944
C	Xylitol	mg	Numeric	Continuous	80.00	100.00	90.00	8.94

Table 4: Dependent parameters

Response	Name	Units	Observations	Minimum	Maximum	Mean	Std. Dev.	Ratio
R1	Viscosity	Cp	11.00	370	460	413.82	30.59	1.24
R2	Dissolution	%	11.00	87	94	90.82	2.56	1.08
R3	Content Uniformity	Av Value	11.00	2.9	6.4	4.29	1.20	2.21

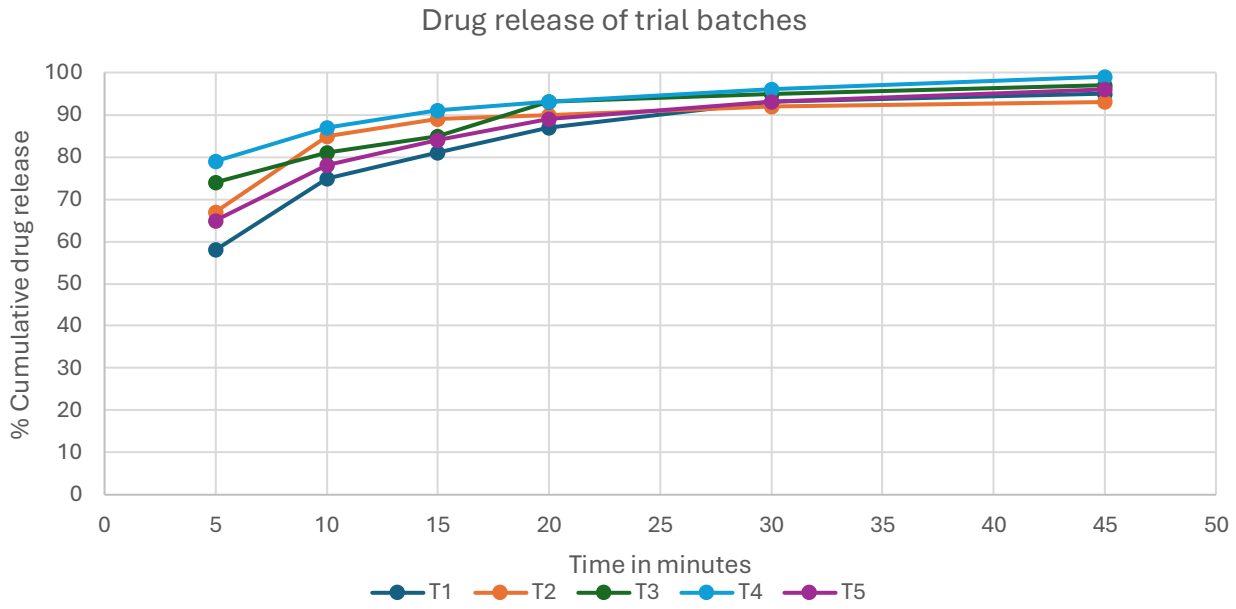

Figure 1: Dissolution study of trial batches

of 900:50:50, with a 10 µL injection volume and flow rate of 1.0 mL/min.

The total runtime was 28 minutes, with the peak detection retention time at 10 minutes and UV detection set at 220 nm.

$$\%\ Content\ uniformity = \frac{Su}{Ss} * \frac{Ws}{50mL} * \frac{100mL}{Wt} * \frac{1}{LC} * \frac{P}{100} * 100 * F$$

Where,

Su = Area of Solifenacin peak in the chromatogram of sample solution.

Ss = Average area of Solifenacin peak in the chromatogram of standard solution.

Ws = Weight of Solifenacin Succinate standard (mg).

Wt. = Weight of test sample (g).

P = Percent potency of Solifenacin succinate standard on as is basis.

F = Weight per mL (g/mL).

LC = Label claim in mg/mL.

Stability Study

The optimized batch was subjected to a Six-months stability study in accordance with ICH guidelines at 25°C/60±5% RH and 40±2°C/75±5 % RH. Evaluation parameters included pH, Density, assay, related substances, and dissolution profile[10].

RESULTS

Pre-formulation study

The Solifenacin succinate showed physical characteristics which matched with the Certificate of Analysis.

Formulation of Solifenacin succinate suspension

The details of trail batches are as per table no 8. The dissolution study of the trail batches are as per figure no 1. The factorial design suggested 11 batches and their results are as per table no 8. The data for response 1 Viscosity is shown in table no 9. The 3D contour plot for Viscosity is as per fig no 2. The data for response 2 dissolution is shown in table no 10.

The 3D contour plot for dissolution is as per figure no 3. The data for response 3- % content uniformity is shown in table no 11.

The 3D contour plot for dissolution is as per figure no 4.The ANOVA suggested solution as discussed in 12 with desirability was 0.635.

The results for batch optimization are disclosed in table no 12. Figure shows 3 D contour plot for desirability.

Table 5: Physical properties of Solifencin succinate

Parameter	Observation
Description	A white to light yellowish-white crystalline powder or solid.
Solubility	Soluble to freely soluble in water, glacial acetic acid, and dimethyl sulfoxide; shows solubility in methanol; exhibits very limited solubility in acetone and ethanol.
Hygroscopicity	Non hygroscopic
Melting point	143.0°C - 153.0°C
Molecular weight	480.6
pKa	9.6

Table 6: Compatibility study of Solifenacin succinate with excipients

Mixture	Stability condition	Ratio	Description
API	Initial	NA	White coloured powder
	After 1 Month at 25^0C & 60% RH		No changed
	After 1 Month at at 40^0C &75% RH		No changed
API+Sodium benzoate	Initial	1:1	White coloured powder
	After 1 Month at 25^0C & 60% RH		No changed
	After 1 Month at at 40^0C &75% RH		No changed
API+Microcrystalline cellulose and Sodium CMC	Initial	1:25	White coloured powder
	After 1 Month at 25^0C & 60% RH		No changed
	After 1 Month at at 40^0C &75% RH		No changed
API+Simethicone 30%	Initial	1:3	White coloured mixture
	After 1 Month at 25^0C & 60% RH		No changed
	After 1 Month at at 40^0C &75% RH		No changed
API+Citric acid monohydrate	Initial	1:5	White coloured powder
	After 1 Month at 25^0C & 60% RH		No changed
	After 1 Month at at 40^0C &75% RH		No changed
API+Sucralose	Initial	1:2	White coloured powder
	After 1 Month at 25^0C & 60% RH		No changed
	After 1 Month at at 40^0C &75% RH		No changed
API+Xylitol	Initial	1:50	White coloured powder
	After 1 Month at 25^0C & 60% RH		No changed
	After 1 Month at at 40^0C &75% RH		No changed
API+Hydroxy propyl cellulose	Initial	1:25	Off White coloured powder
	After 1 Month at 25^0C & 60% RH		No changed
	After 1 Month at at 40^0C &75% RH		No changed
API+Hydroxy ethyl cellulose	Initial	1:5	Off White coloured powder
	After 1 Month at 25^0C & 60% RH		No changed
	After 1 Month at at 40^0C &75% RH		No changed
API+Beta cyclodextrin	Initial	1:10	White coloured powder
	After 1 Month at 25^0C & 60% RH		No changed
	After 1 Month at at 40^0C &75% RH		No changed
API+Xantun Gum	Initial	1:5	Off White coloured powder
	After 1 Month at 25^0C & 60% RH		No changed
	After 1 Month at at 40^0C &75% RH		No changed
API+Acesulfame Potassium	Initial	1:10	White coloured powder
	After 1 Month at 25^0C & 60% RH		No changed
	After 1 Month at at 40^0C &75% RH		No changed
API+Taste masking agent	Initial	1:3	Pale yellow coloured Mixture
	After 1 Month at 25^0C & 60% RH		No changed
	After 1 Month at at 40^0C &75% RH		No changed
API+Tutti-fruti flavour	Initial	1:3	Off White coloured powder
	After 1 Month at 25^0C & 60% RH		No changed
	After 1 Month at at 40^0C &75% RH		No changed

Table 7: Trial batches of Solifenacin succinate suspension

Batch	pH	Density (gm/mL)	Assay (%)	Viscosity (Cp)
T1	4.89	1.010	98.8	295
T2	5.22	1.190	97.9	510
T3	4.75	1.280	99.1	618
T4	5.05	1.033	99.8	415
T5	4.91	1.038	99.4	472

Table 8: Summary of Design of experiment software

Std	Run	Space Type	Factor 1 A:MCC/CMC Sodium mg	Factor 2 B:Xanthan gum mg	Factor 3 C:Xylitol mg	Response 1 Viscosity Cp	Response 2 Dissolution in 30 min %	Response 3 Content Uniformity Av Value
1	7	Factorial	10	1	80	370	94	3.1
2	6	Factorial	14	1	80	386	93	3.4
3	3	Factorial	10	3	80	431	90	3.2
4	5	Factorial	14	3	80	456	87	4.8
5	4	Factorial	10	1	100	375	94	3.6
6	11	Factorial	14	1	100	390	92	2.9
7	10	Factorial	10	3	100	432	88	3.8
8	9	Factorial	14	3	100	460	87	6.4
9	8	Center	12	2	90	417	92	5.6
10	2	Center	12	2	90	415	91	4.9
11	1	Center	12	2	90	420	91	5.5

Table 9: ANOVA result for Response 1-Viscosity

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	9202.50	2	4601.25	240.37	< 0.0001	significant
A-MCC/CMC Sodium	882.00	1	882.00	46.08	0.0001	
B-Xanthan gum	8320.50	1	8320.50	434.67	< 0.0001	
Residual	153.14	8	19.14			
Lack of Fit	140.47	6	23.41	3.70	0.2282	not significant
Pure Error	12.67	2	6.33			
Cor Total	9355.64	10				

Table 10: ANOVA result for response 2- Dissolution

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	61.25	2	30.63	55.85	< 0.0001	significant
A-MCC/CMC Sodium	6.13	1	6.13	11.17	0.0102	
B-Xanthan gum	55.13	1	55.13	100.54	< 0.0001	
Residual	4.39	8	0.5483			
Lack of Fit	3.72	6	0.6199	1.86	0.3902	not significant
Pure Error	0.6667	2	0.3333			
Cor Total	65.64	10				

Table 11: ANOVA result for response 3- % content uniformity

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	3.38	1	3.38	2.78	< 0.0001	significant
B-Xanthan gum	3.38	1	3.38	2.78	0.0102	
Residual	10.93	9	1.21		< 0.0001	
Lack of Fit	10.64	7	1.52	10.61	0.0888	significant
Pure Error	0.2867	2	0.1433			
Cor Total	14.31	10				

Stability study

The results for Six-month stability study at 25°C/60% RH & 40°C/75% RH is as per table no 13**.**

DISCUSSION

Pre-formulation study

The physical evaluation parameters complied with the certificate of analysis standards. Figure 1 demonstrated that Solifenacin succinate API is completely soluble across the studied pH range. Furthermore, no physical or

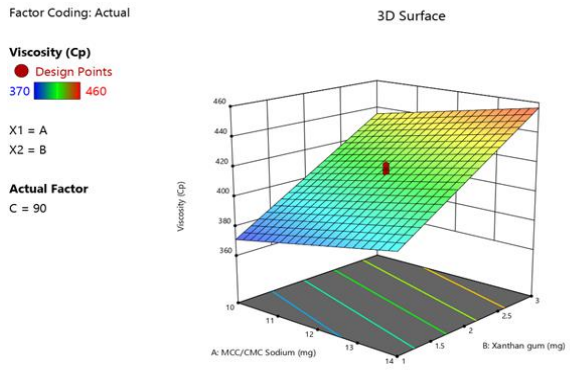

Figure 2: 3D contour plot for Viscosity

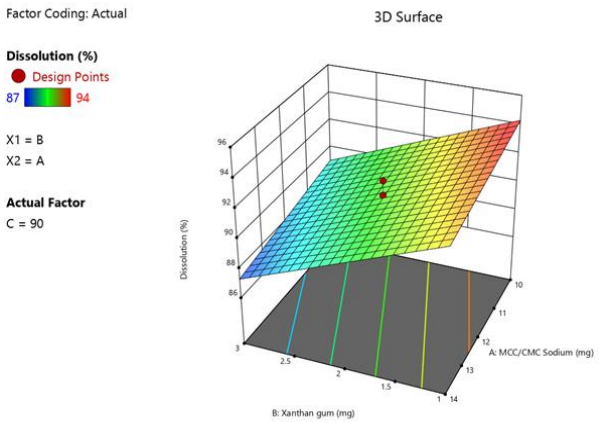

Figure 3: 3D contour plot for dissolution

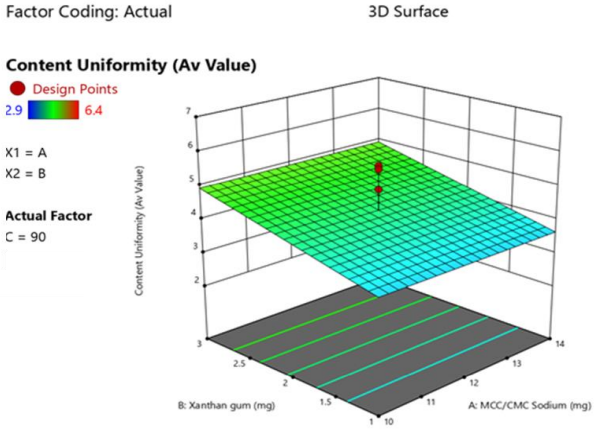

Figure 4: 3D contour plot for dissolution

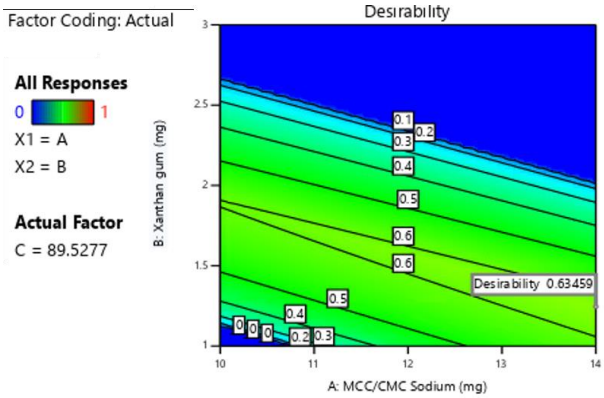

Figure 5: 3D contour plot for desirability

Table 12: Batch optimization for Solifenacin succinate suspension.

Batch	MCC/CMC Sodium	Xanthan gum	Xylitol	Viscosity	Dissolution	Content Uniformity
ANOVA suggested	14.000	1.246	*91.058*	399.999	91.923	3.410
Batch repeated	14	1.2	*91*	400	92.012	3.415

chemical changes were observed in the binary mixtures even after one month at variable temperature and humidity, indicating the compatibility of Solifenacin succinate with the excipients.

Formulation of Solifenacin Succinate Suspension

All trial batches met the specification limits outlined in the standard pharmacopoeia. Batch T4 was selected for optimization based on its % assay and dissolution study results.

The Design of Experiment (DoE) software selected a fractional factorial design with 85 batches, for the optimization of solifenacin succinate suspension. The data for response 1 – viscosity, response 2 - dissolution and response 3- % content uniformity were significant with P-values below 0.0500. The batch optimization was successful as per table no 12.

Stability Study

The table no 13 shows that the optimized batch of Solifenacin succinate was stable during stability testing and passes the test.

CONCLUSION

Based on quality parameters, development data and proposed manufacturing process for oral Suspension, it is concluded that we have developed a stable, robust formulation of Solifenacin Succinate Oral Suspension 1mg/ml. The problem was Solifenacin succinate is its bitter taste. The current study has successfully developed and optimized Solifenacin succinate by using taste masking agents, solubility enhancers and sweetener. The chemical analysis (assay, related substance, pH, weight/mL and dissolution profile) of suspension were studied. The results of suspension indicated that the formulation T4 was the optimized formulation. From all the prepared formulations, T4 was selected as ideal formulations based on physicochemical properties and chemical analysis. The DOE selected a single batch with 0.635 desirability. The stability test results of optimized batch of Solifenacin succinate suspension revealed that the developed suspension was stable and retain their pharmaceutical properties over a period of 3, 6 months at

Table 13: Stability study of optimized batch of Solifenacin succinate suspension

Tests	Specifications	Initial	25°C/60% RH		40°C/75% RH	
			3M	6M	3M	6M
Description	A white to off-white colored aqueous, homogeneous suspension with tutti-fruti flavour	Complies	Complies	Complies	Complies	Complies
pH	Between 4.0 to 6.0	5.05	5.01	4.99	5.03	5.04
Weight/mL	1.000-1.300	1.033	1.032	1.030	1.029	1.032
Assay	NLT 90% and NMT 110% w/w of labelled amount of Solifenacin Succinate.	99.8	99.3	98.9	99.5	98.7
Dissolution at 30 min	NLT 80 %	96	95	93	94	95

controlled ambient conditions (25°C/60% RH) and accelerated conditions (40°C/75% RH).

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