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AN IMPROVED PROCESS FOR THE PREPARATION OF HIGHLY PURE SOLIFENACIN SUCCINATE VIA RESOLUTION THROUGH DIASTEREOMERIC CRYSTALLISATION

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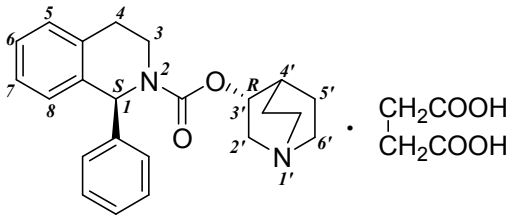
KEYWORDS: Solifenacin succinate, (RS)-3-Quinuclidinol, diastereomeric crystallisation.

ABSTRACT

An improved process for the preparation of solifenacin succinate (**1**) involving resolution through diastereomeric crystallisation is described. (1S)-IQL derivative (**5**) is esterified to form (1S)-ethoxycarbonyl IQL derivative (**6**) which is condensed with (RS)-3-Quinuclidinol (**7**) to form solifenacin diastereomeric mixture (**8**), this is subjected to resolution through diastereomeric crystallisation to produce solifenacin succinate (**1**), which is used for the treatment of overactive bladder.

INTRODUCTION

Solifenacin (**1**) is a quinoline derivative which is chemically known as (1S)-3,4-dihydro-1-phenyl-2-(1H)-isoquinolinecarboxylic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester. The chemical structure of solifenacin succinate (**1**) is as represented in Figure-1.



1

Figure-1. Structure of solifenacin succinate.

Molecular structure of solifenacin has two chiral centers and hence exists in two racemic pairs (four stereoisomers) viz., [(1S,3'R)-isomer, solifenacin] (**1a**), [(1S,3'S)-isomer, diastereomer of solifenacin] (**2**), [(1R,3'S)-isomer, enantiomer of solifenacin] (**3**), [(1R,3'R)-isomer, diastereomer of solifenacin] (**4**), (Figure-2)**.**[1] Solifenacin i. e., (1S,3'R)-isomer (**1a**) is the therapeutically active and approved isomer.

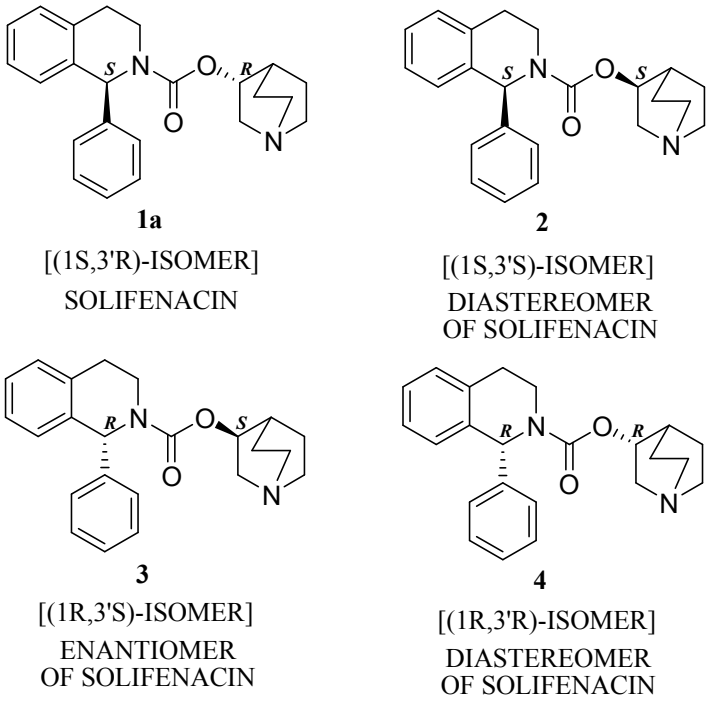


Figure-2. Structures of solifenacin stereoisomers.

Solifenacin is a potent muscarinic M_3 receptor antagonist. Muscarinic receptors play an important role in several major cholinergically mediated functions, including contractions of the urinary bladder, gastrointestinal smooth muscle, saliva production, and iris sphincter function. Solifenacin has great affinity for the M_3 receptor than the other known muscarinic receptors.[2-5] Solifenacin also shows a wide spectrum of bowel dysfunction through the blockade of M_3 receptors, its therapeutic potential for treating irritable bowel syndrome (IBS).[6] Solifenacin succinate is commercially available and it has been approved for the treatment of overactive bladder with symptoms of urinary urgency and urinary frequency.

Naito, R. *et al*. first designed and developed potent and more bladder selective muscarinic M_3 receptor antagonist solifenacin (**1**).[7] Takuchi, M. *et al*. disclosed the synthesis of solifenacin and its pharmaceutical acceptable salts.[8] In general solifenacin has been prepared by two synthetic

approaches: in the first one, (1S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid ethyl ester (**6**) was transesterified with pure (R)-3-quinuclidinol to provide pure isomer solifenacin (**1**), the second approach involves the preparation of solifenacin as its diastereomeric mixture by the transesterification of (1RS)-1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid ethyl ester with (R)-3-quinuclidinol and this mixture was either resolved by chiral HPLC[2] or through crystallisation[9] to produce pure solifenacin (**1**). The resolution process of (RS)-3-quinuclidinol (**7**) involves acetylation, resolution and deacetylation through hydrolysis to yield only 10% of (R)-3-quinuclidinol[10] or asymmetric hydrogenation of (RS)-3-quinuclidinol (**7**) catalysed by the use of highly costly Ruthinium (II) complex[11] or by means of enzymatic resolution process of acetylated (RS)-3-quinuclidinol (**7**) to access pure isomer.[12]

The present invention discloses an improved synthetic strategy for the preparation of solifenacin succinate (**1**) as depicted in scheme 1. The present authors selected less expensive racemic (RS)-3-quinuclidinol (**7**) rather than the expensive pure isomer, (R)-3-quinuclidinol as one of the key raw materials to develop the process for the preparation solifenacin succinate (**1**).

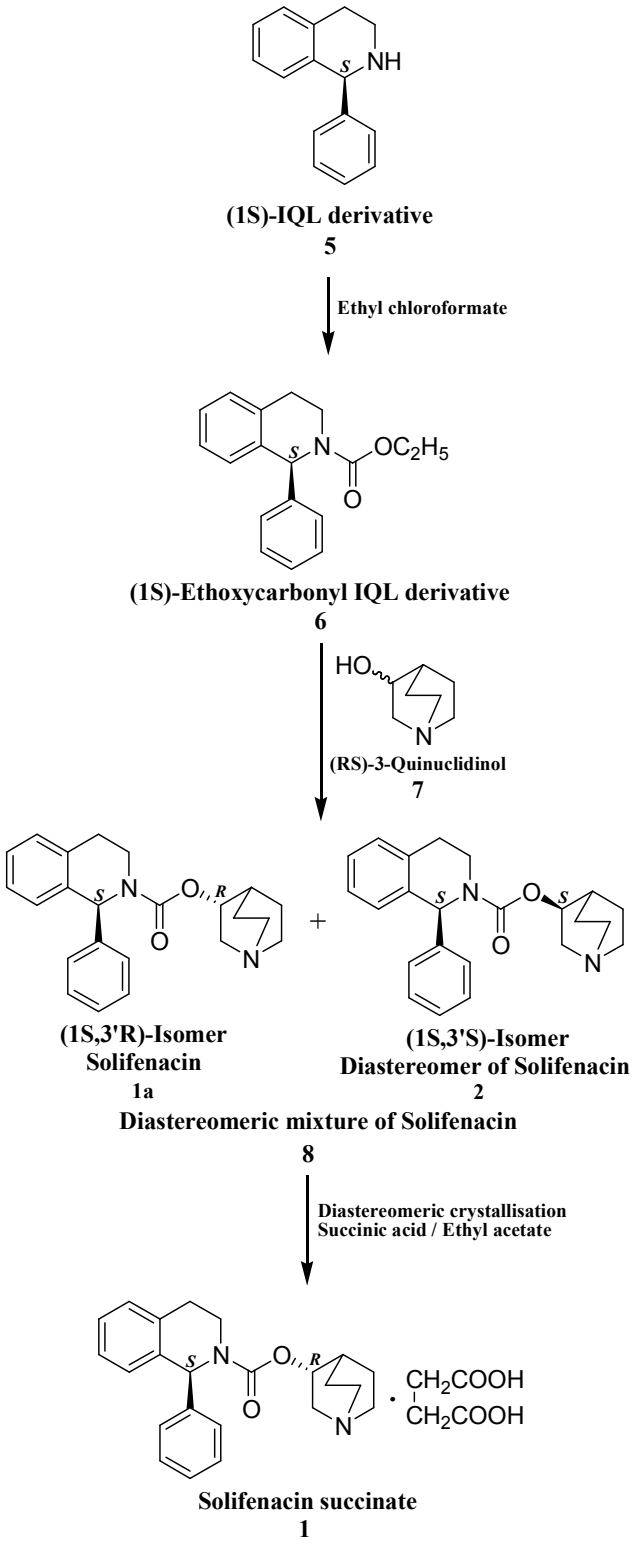
RESULTS AND DISCUSSION

To carry out the synthesis of solifenacin succinate, (1S)-IQL derivative (**5**) is condensed with ethyl chloroformate in presence of a base such as triethylamine. We studied the optimal quantity of ethyl chloroformate for the condensation with (1S)-IQL derivative (**5**) in the presence of triethylamine and found that 1.05 molar equivalents of ethyl chloroformate and triethylamine w.r.t. (1S)-IQL derivative (**5**) are sufficient to achieve desired conversion consistently. We carried out this reaction in different solvents like methylene chloride and toluene and found that toluene is the suitable solvent for this reaction. Since toluene solution containing (1S)-

ethoxycarbonyl IQL derivative (**6**) was obtained after aqueous work-up, it can be used as such in the subsequent stage. We also carried out this reaction at different temperatures and observed that 25-30°C is ideal temperature for this reaction.[#] After completion of the reaction, the reaction mass is washed with water to remove the triethylamine hydrochloride by-product and the toluene solution containing (1S)-ethoxycarbonyl IQL derivative (**6**) is taken to the next stage as such without isolation for the condensation reaction with (RS)-3-Quinuclidinol (**7**) to produce solifenacin and its diastereomer (**8**).

[#] We have observed that ethyl chloroformate addition was exothermic, therefore, we have started the addition of ethyl chloroformate at low temperature ~5 °C and during the addition of ethyl chloroformate, the temperature raises to 25-30 °C on its own due to exothermicity. Thereafter, the reaction mass is allowed to be stirred at the same temperature which is an ideal temperature for this reaction to achieve desired conversion. It was also observed that this reaction at higher temperature (35-40 °C) yielded lesser purity product and at lower temperature (10-15°C) the reaction mass becomes a thick mass and further stirring was observed to be difficult.

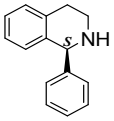
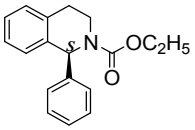
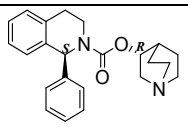
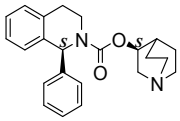
Scheme 1


(1S)-IQL derivative
5
Ethyl chloroformate
(1S)-Ethoxycarbonyl IQL derivative
6
(RS)-3-Quinuclidinol
7
(1S,3'R)-Isomer
Solifenacin
1a
(1S,3'S)-Isomer
Diastereomer of Solifenacin
2
Diastereomeric mixture of Solifenacin
8
Diastereomeric crystallisation
Succinic acid / Ethyl acetate
Solifenacin succinate
1

It is known from the literature[2] that (1S)-ethoxycarbonyl IQL derivative (**6**) can be transesterified with 3-quinuclidinol in presence of a strong basic metal hydride such as sodium hydride or metal alkoxides like sodium ethoxide in an organic solvent at elevated temperatures to obtain solifenacin. We conducted our initial experiments by using sodium hydride as base in toluene at reflux temperature of 110-115°C. In this reaction, (1S)-ethoxycarbonyl IQL derivative (**6**) is reacted with (RS)-3-Quinuclidinol (**7**) in presence of sodium hydride base in toluene solvent at reflux temperature to produce 1:1 mixture of solifenacin and its diastereomer (**8**). It has been also observed that ethanol is formed as a by-product during this reaction and is required to be removed from the reaction mass to facilitate the forward reaction to yield desired product. Therefore, the by-product ethanol is azeotropically distilled out with toluene and an additional amount of toluene is added simultaneously to maintain the volume of the reaction mass.

The progress of the reaction is monitored by HPLC. It was observed that in this transesterification reaction the formation ~ 85% of desired product and one major impurity around ~10-15% was formed and this impurity was identified as (1S)-IQL derivative (**5**) based on its retention time and LC-MS. It is anticipated that (1S)-IQL derivative (**5**) could form during reaction not only by the hydrolysis of (1S)-ethoxycarbonyl IQL derivative (**6**) but also hydrolysis of solifenacin and its diastereomer (**8**). To optimize the conditions to control the formation of this impurity, we carried out this reaction by using varying amount of sodium hydride base and the results are summarized in Table 1.

Table 1 Effect of sodium hydride base quantity on transesterification reaction.

Quantity of sodium hydride used	Reaction monitoring data[a]			
			 (1S,3'R)-isomer **(1a)** +  (1S,3'S)-isomer **(2)**	
	IQL derivative **(5)**	(1S)-ethoxycarbonyl IQL derivative **(6)**	Diastereomeric mixture of Solifenacin **(8)**	
1.00 m. eq.	25.30	14.76	57.17	
0.50 m. eq.	16.89	2.06	79.93	
0.20 m. eq.	10.68	5.88	81.49	

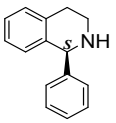
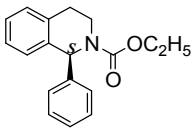
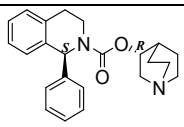
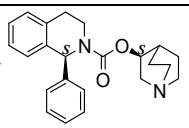
[a]By HPLC, by area normalization.

The results indicate that higher molar quantity of the base, sodium hydride facilitates the formation of higher amount of undesired impurity (1S)-IQL derivative (**5**). It was also observed that the experiment which was performed by using 1.0 m. eq. of sodium hydride has resulted in the isomerisation, leading to the formation of other undesired (1R,3S)-isomer and (1R,3R)-isomer of solifenacin ~ 6% by chiral HPLC analysis. It is reported[13] that in this transesterification reaction sodium ethoxide is generated in-situ from reaction of sodium hydride with the by-product, ethanol. Therefore, it was concluded that 0.2 m. eq. of sodium hydride w.r.t. (1S)-IQL derivative (**5**) is sufficient to carry out this transesterification reaction.

Effect of temperature on this transesterification reaction was also studied at different temperatures such as 80-85°C, 110-115°C and 120-125°C. *o*-Xylene was used as the solvent

where the condensation reaction was carried out at 120-125°C. It was observed that in case of experiments with toluene at low temperature and with *o*-xylene at high temperature, the by-product ethanol could not be removed effectively and hence resulted in low conversion and lesser amount of product formation. The reaction was very slow and the unreacted (1S)-ethoxycarbonyl IQL derivative remained in higher amount. Therefore, the removal of ethanol by-product is essential to move forward the reaction towards the formation of desired product. Therefore, 110-115°C is the suitable temperature for this reaction to achieve the desired conversion. The experimental results of the temperature study are tabulated in Table 2.

Table 2 Effect of temperature on the transesterification reaction.

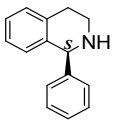
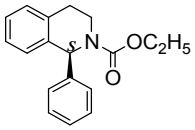
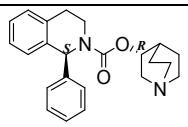
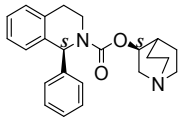
Solvent used for the reaction	Reaction Temperature	Reaction monitoring data[a]			
				 (1S,3'R)-isomer **(1a)**	 (1S,3'S)-isomer **(2)**
		IQL derivative **(5)**	(1S)-ethoxycarbonyl IQL derivative **(6)**	Diastereomeric mixture of Solifenacin **(8)**	
Toluene	80-85°C	6.54	48.91	42.71	
Toluene	110-115°C	10.68	5.88	81.49	
o-Xylene	120-125°C	11.14	29.22	36.53	

[a]By HPLC, by area normalization.

Next we focused to study the effect of solvent quantity used in the reaction. We have carried out this reaction by using 10, 7.5 and 4 volumes of toluene and observed that toluene quantity during

transesterification reaction plays an important role. It was observed from these reactions that the rate of the reaction is slower with higher volume of toluene and the rate of reaction is faster with higher conversion when lesser volume of toluene is used. The results obtained from the effect of reaction volume study are summarized in Table 3.

Table 3 Effect of Toluene quantity on the transesterification reaction.

Reaction volume	Reaction time	Reaction monitoring data[a]			
				 (1S,3'R)-isomer **(1a)**	 (1S,3'S)-isomer **(2)**
		IQL derivative **(5)**	(1S)-ethoxycarbonyl IQL derivative **(6)**	Diastereomeric mixture of Solifenacin **(8)**	
10 times	42 h	10.68	5.88	81.49	
7.5 times	42 h	5.88	10.68	81.49	
4 times	20 h	2.94	3.97	92.68	

[a]By HPLC, by area normalization.

It was concluded that toluene solution of (1S)-ethoxycarbonyl IQL derivative (**6**) product obtained from stage-I reaction was concentrated to about four volumes w.r.t. (1S)-IQL derivative (**5**) and proceed for the transesterification reaction. We have also carried out this transesterification reaction by using 0.2 m. eq. of sodium ethoxide base and identical results were obtained when sodium ethoxide base was used in place of sodium hydride.

After completion of the reaction, the mass was cooled and quenched with DM water and subjected to acid-base treatment. Thereafter, the product was extracted in ethyl acetate and the

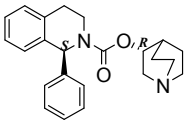
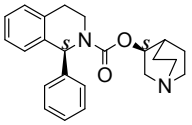
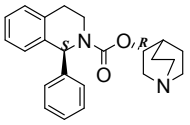
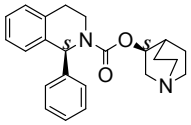
ethyl acetate solution containing solifenacin and its diastereomer was dehydrated and used as such directly to produce solifenacin succinate by treating it with succinic acid through diastereomeric crystallisation in the next stage.

The next focus of our study was to resolve the solifenacin and its diastereomeric mixture by resolution through diastereomeric crystallisation to obtain our target product solifenacin succinate (**1**) in pure form. In general, the conventional diastereomeric resolution is carried out by using a chiral resolving agent. It was reported in the literature that the diastereomeric mixture of (1S,3'R)-isomer and (1R,3'R)-isomer was resolved through crystallisation using succinic acid as achiral resolving agent.[9] Even though solifenacin molecule can exist in four stereoisomers, from our reaction only one diastereomeric pair is obtained. Since the product itself obtained as diastereomeric pair and the diastereomeric resolution is carried out with a achiral resolving agent by converting into its succinate salt through diastereomeric crystallisation.

To select the suitable solvent medium for this diastereomeric crystallisation, we have carried out the experiments for preparation of solifenacin succinate by using 0.60 m. eq. of succinic acid in solvents mixture comprising of 30%, 10%, 5%, 2.5% and 0% ethanol in ethyl acetate. Solifenacin succinate crystallisation is induced by adding solifenacin succinate seed and stirring at 25-30°C for about 15 h to complete the crystallisation process. Thereafter, the slurry mass was heated to 70-75°C, stirred for about 2 h at the same temperature and then cooled to 25-30°C. The product was filtered and washed with ethyl acetate. This solifenacin succinate-crude product was analysed by chiral HPLC and observed that the undesired (1S,3'S)-isomer is < 6%. Therefore, The obtained solifenacin succinate-crude product was then purified from ethyl acetate by heating

at 70-75°C, cooling to 25-30°C, filtration and washing with ethyl acetate to remove undesired (1S,3S)-isomer. The results of these experiments are summarized in Table 4.

Table 4 Effect of solvent during resolution through diastereomeric crystallisation.

Quantity of ethanol in ethyl acetate	% of Product[a] Solifenacin succinate-crude				Yield (w/w based on)
	Before EtOAc slurry wash		After EtOAc slurry wash		
	 Solifenacin **(1a)**	 (1S,3'S)-isomer **(2)**	 Solifenacin **(1a)**	 (1S,3'S)-isomer **(2)**	
30% v/v	96.00	4.00	99.60	0.40	36%
10% v/v	93.83	6.17	99.40	0.60	41%
5% v/v	94.13	5.87	99.23	0.77	49%
2.5% v/v	95.62	4.38	99.39	0.61	55%
0%	94.30	5.70	99.45	0.55	65%

[a]Chromatographic purity (by chiral HPLC, by area normalization).

Based on the experimental results, it was found that ethyl acetate is better solvent for resolution of solifenacin succinate and further to obtain desired chiral purity of solifenacin succinate. Finally, the above obtained solifenacin succinate-crude was purified from 30% v/v ethanol in ethyl acetate solvent mixture to obtain solifenacin succinate drug substance containing ≤ 0.10% of (1S,3'S)-isomer.

We also studied the quantity of succinic acid required for this diastereomeric crystallisation by using 0.50, 0.60 and 0.80 m. eq. of succinic acid and found that 0.50 molar equivalent resulted in lower yield whereas 0.80 molar equivalent gave impure product contaminated with higher amount of undesired (1S,3'S)-isomer. Thus, it was concluded that 0.60 m. eq. of succinic acid is suitable in order to obtain solifenacin succinate drug substance containing ≤ 0.10% of (1S,3'S)-isomer. The results of these experiments are summarized in Table 5.

Table 5 Effect of organic acid (succinic acid) quantity on the diastereomeric crystallisation.

Quantity of succinic acid used	Content of (1S,3'S)-isomer [a]			Yield (w/w based on)
	Solifenacin succinate-crude		Solifenacin succinate pure	
	Before EtOAc slurry wash	After EtOAc slurry wash		
0.50 m. eq.	4.25%	0.69%	0.10%	45%
0.60 m. eq.	6.85%	0.51%	0.09%	57%
0.80 m. eq.	33.82%	12.90%	2.27%	60%

[a]By chiral HPLC, by area normalization.

We have analysed the samples of solifenacin succinate-crude and solifenacin succinate for succinic acid content and observed that it was between 24.17 to 24.52% w/w which is meeting to the theoretical requirement of 24.58% w/w succinic acid.

Based on the experimental results, the final step of the process for the preparation solifenacin was optimized as the diastereomeric crystallisation was carried out by using 0.60 m. eq. of succinic acid w.r.t. (1S)-IQL derivative (**5**) in ethyl acetate by addition of solifenacin succinate

seed at 25-30°C. The crude product was purified first by slurrying in ethyl acetate and finally purified by recrystallization from a mixture of ethyl acetate (70%) and ethanol (30%).[§]

CONCLUSION

An improved process for the preparation of solifenacin succinate (**1**) was developed and optimized, involving the preparation of solifenacin and its diastereomer (**8**) intermediate and its further, resolution through diastereomeric crystallisation to yield highly pure solifenacin succinate (**1**).[14]

[§] Our aim is to obtain solifenacin undesired isomers <0.15% preferably < 0.10%. In this direction, it is essential to control the undesired (1S,3'S)-isomer before proceeding for final purification by crystallisation from ethanol and ethyl acetate mixture. In order to achieve the suitable / desirable content of (1S,3'S)-isomer in crude product with desired yield, slurry wash in ethyl acetate has been incorporated. To balance the yield and to achieve the desired purity of product (API), it is required to carry out three unit operations.

EXPERIMENTAL SECTION

GENERAL: IQL derivative (**5)** and other reagents and solvents were obtained from commercial suppliers and used without further purification. (RS)-3-Quinuclidinol was prepared by keto reduction of 3-Quinuclidinone. Melting points were determined on a Polmon MP96 capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker 300 MHz spectrometer in DMSO-d_6, chemical shift data are reported in ppm from the internal standard TMS. The reaction monitoring and chromatographic purity (area percentage) was analyzed qualitatively by High Performance Liquid Chromatography (HPLC) on Shimadzu VP series UV using Symmetry C_{18} column (250 mm X 4.6 mm, 5 µ). The chiral purity of Solifenacin were analyzed on a Waters 2695 with 2996 PDA detector using Chiralpak IC (250 mm X 4.6 mm, 5 µ) column respectively High Resolution Mass spectra (HRMS) were taken on Xevo G2 Q TOF HRMS instrument with electrospray ionization (positive) mode in units of mass (m/z). The IR spectra were recorded on KBr pellets on Perkin-Elmer FTIR (spectrum one) spectrophotometer.

Preparation of compound (1S)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolincarboxylate [(1S)-ethoxycarbonyl IQL derivative] (6). Ethyl chloroformate (109 g, 1.005 moles) was slowly added to a mixture of (1S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (IQL derivative) (**5**, 200 g, 0.957 moles) in toluene (2000 mL) in presence of triethylamine (101.50 g, 1.005 moles) at 5-30°C over a period of 30 min. Thereafter the reaction mixture was stirred at 25-30°C for about 30 min. and the completion of the reaction was monitored by qualitative HPLC analysis. The reaction mass was washed with water (2 x 600 mL) to obtain toluene solution (2000 mL) containing (1S)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolincarboxylate **(6)**.

Chromatographic purity: 99.32 % (by HPLC). IR (KBr) (cm^{-1}): 3511, 1694, 1600, 1493. HRMS: *m/z* = 282.1487 $[M + H]^+$. ^1H NMR (DMSO-d_6,): δ 1.20 (t, 3H), 2.81 (m, 2H), 3.28 & 3.86 (2m, 2H), 4.10 (m, 2H), 6.27 (m, 1H,), 7.13-7.33 (m, 9H).

Preparation of (1S)-3,4-dihydro-1-phenyl-2-(1H)-isoquinolinecarboxylic acid (3RS) -1-azabicyclo[2.2.2]oct-3-yl ester [(1S,3'R)- & (1S,3'S)-isomeric mixture] (diastereomeric mixture of Solifenacin) (8). (RS)-3-Quinuclidinol (**7**, 145.80 g 1.148 moles) was added to a solution of (1S)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolincarboxylate **(6)** in toluene (2000 mL, as obtained in Stage-I) at 25-30°C under nitrogen atmosphere. The contents were heated to 108-112 °C and concentrated to collect ~1200 mL of distillate to remove traces of water present in the reactants. Thereafter, the contents were cooled to 25-30°C and sodium hydride (60% w/w, 7.70g 0.1925 moles) was added to the reaction mixture and the reaction mass was stirred at reflux for about 20 h. The by-product ethanol was removed azeotropically with toluene and fresh toluene was added simultaneously to maintain the volume of the reaction mass. The completion of the reaction was monitored by qualitative HPLC analysis. The reaction mass was cooled to 20-25°C and DM water (800 mL) was added slowly at 20-30 °C. The reaction was stirred for about 20 min. and toluene layer was separated. DM water (700 mL) was added to the organic layer and cooled to 5-10°C and pH was adjusted to 1.0±0.2 by using ~9% w/w aqueous hydrochloric acid (350 mL). The aqueous layer was separated, cooled to 5-10°C and pH was adjusted to 7.0 to 7.5 by using 10% w/w aqueous sodium hydroxide solution (170 mL). Thereafter ethyl acetate (1600 mL) was added and the pH was further adjusted to 10.0±0.2 using 10% w/w aqueous sodium hydroxide solution (170 mL). The mass was stirred at 25-30°C for 20 min. and separated the upper organic layer. The organic layer was washed with DM water (400 mL) and then it was treated with carbon (10 g) at 25-30°C for 30 min. The carbon was removed by filtration through

hyflo and the residue was washed with ethyl acetate (400 mL) to obtain ethyl acetate solution (2000 mL) of (1S)-3,4-dihydro-1-phenyl-2-(1H)-isoquinolinecarboxylic acid (3RS) -1-azabicyclo[2.2.2]oct-3-yl ester [(1S,3'R)- & (1S,3'S)-isomeric mixture] (diastereomeric mixture of Solifenacin) (**8**).

Chiral purity : 51.14 % (by chiral HPLC). (1S, 3'S)-Diastereomer content: 48.79% (by chiral HPLC). IR (KBr) (cm^{-1}): 3363, 3026, 1693, 1582, 1493. HRMS: *m/z* = 363.2077 $[M + H]^+$. ^1H NMR(DMSO-d_6): δ 1.47 & 1.56 (m, 4H), 1.91 (m, 1H), 2.60 & 2.68 (m, 4H), 2.86 (brs, 1H), 3.05 - 3.09 (m, 1H), 3.83 - 3.89 (m, 1H), 4.63 (brs, 2H), 6.25 (brs, 2H), 7.20 - 7.34 (m, 9H).

Preparation of (1S)-3,4-dihydro-1-phenyl-2-(1H)-isoquinolinecarboxylic acid (3RS) -1-azabicyclo[2.2.2]oct-3-yl ester [(1S,3'R)- & (1S,3'S)-isomeric mixture] (diastereomeric mixture of Solifenacin) (8). (RS)-3-Quinuclidinol (**7**, 24.06 g 0.1894 moles) was added to a solution of (1S)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolincarboxylate **(6)** in toluene (330 mL, as obtained in Stage-I from 33g input of IQL derivative, **5**) at 25-30°C under nitrogen atmosphere. The contents were heated to 108-112 °C and concentrated to collect ~198 mL of distillate to remove traces of water present in the reactants. Thereafter, the contents were cooled to 25-30°C and sodium ethoxide (2.15 g, 0.0316 moles) was added to the reaction mixture and the reaction mass was stirred at reflux for about 20 h. The by-product ethanol was removed azeotropically with toluene and fresh toluene was added simultaneously to maintain the volume of the reaction mass. The completion of the reaction was monitored by qualitative HPLC analysis. The reaction mass was cooled to 20-25°C and DM water (132 mL) was added slowly at 20-30 °C. The reaction was stirred for about 20 min. and toluene layer was separated. DM water (115.5 mL) was added to the organic layer and cooled to 5-10°C and pH was adjusted to 1.0±0.2 by using ~9% w/w aqueous hydrochloric acid (57.8 mL). The aqueous layer was separated,

cooled to 5-10°C and pH was adjusted to 7.0 to 7.5 by using 10% w/w aqueous sodium hydroxide solution (28 mL). Thereafter ethyl acetate (264 mL) was added and the pH was further adjusted to 10.0±0.2 using 10% w/w aqueous sodium hydroxide solution (28 mL). The mass was stirred at 25-30°C for 20 min. and separated the upper organic layer. The organic layer was washed with DM water (66 mL) and then it was treated with carbon (1.65 g) at 25-30°C for 30 min. The carbon was removed by filtration through hyflo and the residue was washed with ethyl acetate (66 mL) to obtain ethyl acetate solution (330 mL) of (1S)-3,4-dihydro-1-phenyl-2-(1H)-isoquinolinecarboxylic acid (3RS) -1-azabicyclo[2.2.2]oct-3-yl ester [(1S,3'R)- & (1S,3'S)-isomeric mixture] (diastereomeric mixture of Solifenacin) (**8**).

Chiral purity : 51.64 % (by chiral HPLC). (1S, 3'S)-Diastereomer content: 48.24% (by chiral HPLC).

Preparation of (1S)-3,4-dihydro-1-phenyl-2-(1H)-isoquinolinecarboxylic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester. succinate (Solifenacin succinate) (1). Ethyl acetate solution (2000 mL) containing (1S)-3,4-dihydro-1-phenyl-2-(1H)-isoquinolinecarboxylic acid (3RS) -1-azabicyclo[2.2.2]oct-3-yl ester [(1S,3'R)- & (1S,3'S)-isomeric mixture] (diastereomeric mixture of Solifenacin) (**8**) (as obtained in Stage-II) was dehydrated by azeotropic distillation to remove ~600 mL of distillate and cooled to 25-30°C. Added ethyl acetate (~600 mL, equal amount of distillate collected). To this solution succinic acid (67.80 g 0.5746 moles) was added, followed by Solifenacin succinate seed (1 g). The contents were stirred at 25-30°C for 8h. Thereafter, the mass was heated to 75-80 °C and stirred at this temperature for 2h. The slurry was cooled to 25-30°C and stirred at this temperature for 1h. The product was filtered and was washed with ethyl acetate (400 mL).

Chromatographic purity: 98.75% (by HPLC). Chiral purity : 93.69 % (by chiral HPLC). (1S, 3'S)-Diastereomer content: 6.30 % (by chiral HPLC).

Above filtered mass (250 g) was suspended ethyl acetate (2000 mL) at 25-30°C. The suspension was heated to 75-80 °C and stirred at this temperature for 2h. Thereafter, the reaction mass was cooled to 25-30 °C and stirred at this temperature for 1h. The product was filtered, washed with ethyl acetate (240 mL) and then dried under reduced pressure at 50-55 °C to produce Solifenacin succinate-crude (**1**) as cream color crystalline powder. (130 g, 65% w/w yield based on **5**). Chromatographic purity: 99.93 % (by HPLC). Chiral purity: 99.44 % (by chiral HPLC). (1S, 3'S)-Diastereomer content: 0.56% (by chiral HPLC).

Purification of (1S)-3,4-dihydro-1-phenyl-2-(1H)-isoquinolinecarboxylic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester. succinate (Solifenacin succinate) (1). Solifenacin succinate (120 g) as obtained above was stirred in a mixture of ethanol (260 mL) and ethyl acetate (504 mL) at 60-65°C to obtain a clear solution. This was treated with carbon (6 g) at 60-65 °C for 30 min. Carbon was removed by filtration through hyflo at 60-65°C and the residue was washed with pre-heated 30% v/v ethanol-ethyl acetate mixture (240 mL). The filtrate was slowly cooled to 0-5°C and stirred at this temperature for 1h. Thereafter, the product was filtered, washed with ethyl acetate (120 mL) and then dried under reduced pressure at 50-55 °C to produce pure Solifenacin succinate (**1**) as white crystalline powder. (104.50 g, 87% w/w yield based on in-put). Chromatographic purity: 99.94 % (by HPLC). Chiral purity: 99.94% (by chiral HPLC). (1S, 3'S)-Diastereomer content: 0.06% (by chiral HPLC). Mp 145-146 °C. $[\alpha]_D^{25}$ (c=1, in Water): + 40.6°. IR (KBr) (cm^{-1}): 3282, 3024, 3007, 2964, 2937, 2881, 2607, 1722, 1685, 1579, 1491, 1227, 761, 751. HRMS: *m/z* = 363.2071 $[M + H]^+$. ^1H NMR (DMSO-d_6): δ 1.50 - 1.81 (m, 4H), 2.07 (m, 1H), 2.36 (s, 4H), 2.56 - 3.30 (m, 8H), 3.41 & 3.85 (2m, 2H), 4.79 (m, 1H), 6.27 (brs, 1H), 7.20 - 7.32 (m, 9H), 11.79 (brs, 2H). ^{13}C NMR (DMSO-d_6): δ 18.3 (CH_2), 22.3 (CH_2), 24.6 (CH), 27.7 (CH_2), 30.2 (2xCH_2), 38.9 (CH_2), 45.1 (CH_2), 46.0 (CH_2), 54.1 (CH_2), 57.3, 70.2, 126.2 (CH), 127.1 (CH), 127.2 (2xCH), 128.1 (CH), 128.4 (2xCH), 128.7 (CH), 134.7, 135.4, 154.3, 174.5.

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SUPPORTING INFORMATION

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An Improved Process For The Preparation Of Highly Pure Solifenacin Succinate Via Resolution Through Diastereomeric Crystallisation

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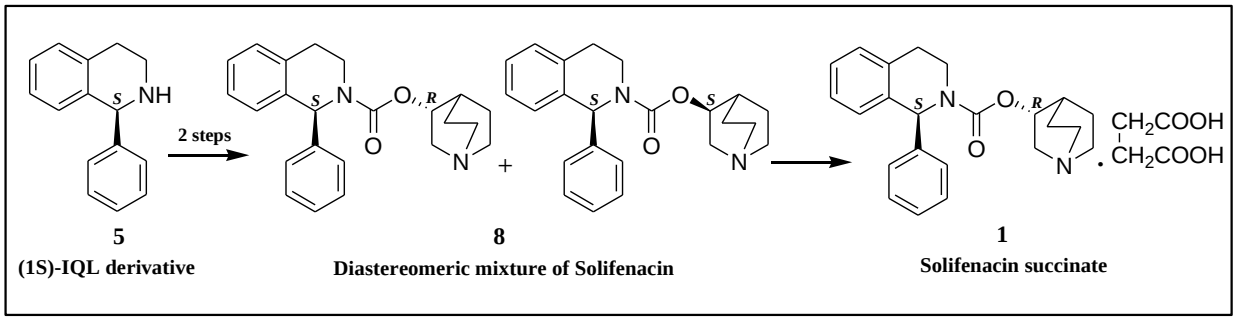
Abstract



An improved process for the preparation of solifenacin succinate (**1**) involving resolution through diastereomeric crystallisation is described. (1S)-IQL derivative (**5**) is esterified to form (1S)-ethoxycarbonyl IQL derivative (**6**) which is condensed with (RS)-3-Quinuclidinol (**7**) to form solifenacin diastereomeric mixture (**8**), this is subjected to resolution through diastereomeric crystallisation to produce solifenacin succinate (**1**), which is used for the treatment of overactive bladder.