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# Synthesis and spectral characterization of potential impurities of solifenacin succinate

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## ABSTRACT

During the process development of solifenacin succinate **(5)**. Three stereoisomeric impurities **(1-3)** and one n-oxide impurity **(4)** with respect to solifenacin succinate were detected by reported method of simple reverse phase high-performance liquid chromatograpjy (HPLC). Three 1-3 have been prepared by the known synthetic method. To the best of our knowledge, impurity **(4)** had not been isolated or synthesized as pure substance until now. The new synthesis, characterization of impurity **(4)** was discussed. The $^{1}H$ and $^{13}C$ NMR data of impurity **(4)** and solifenacin succinate **5** were reported in this paper for the first time. Based on the spectral data, the structure of these impurities **(1-4)** were characterized as (3S)-1-Azabicyclo[2.2.2]octan-3-yl(1S)-1-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylate butanedioic acid **(1)**, (3R)-1-Azabicyclo[2.2.2]octan-3-yl(1R)-1-phenyl-3,4-dihydro-1H- isoquinoline-2-carboxylate butanedioic acid 2, (3S)-1-Azabicyclo[2.2.2]octan-3-yl(1R)-1-phenyl-3,4-dihydro-1H- isoquinoline-2-carboxylate butanedioic acid 3 and (3R)-1-Azabicyclo[2.2.2]octan-3-yl(1S)-1-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylate N-oxide **(4)**. The synthesis, characterization of these impuritieswere discussed. 

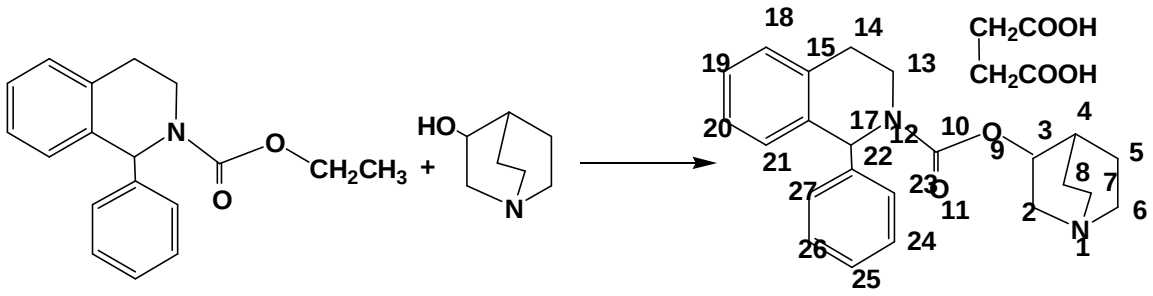
## KEYWORDS

Solifenacin;
Impurities;
N-oxide;
Characterization and synthesis.

## INTRODUCTION

Solifenacin succinate, is a muscarnic receptor antagonist, it is used in the treatment overactive bladder with or without urinary incontinence[1]. Solifenacin succinate is the succinic acid salt of (3R)-1-azabicyclo[2.2.2]oct-3-yl-(IS)-1-phe-nyl-3,4-dihydroisoquinoline-2(1H)-carboxylate having two chiral centers at C1 and C3. Positions, and hence four possible stereoisomers do exist. Chemical structures of solifenacin and its three stereoisomers, namely (SS)-stereoisomer, (RR)-stereoisomer and (SR)-stereoisomer are shown in Figure1. Stereoisomers of racemic drugs often differ in pharmacokinetic behavior or pharmacological action, and among the four stereoisomers, the pharmacological action of (RS)-stereoisomer, that is, solifenacin shows high affinity and selectivity for the M3 receptor and hence has been approved as the drug[2]. Two methods are reported for the sepration of stereoisomers in the solifenacin succinate[3,4] using chiralpak AD-H column (mobile phase comprising n-hexane;isopropylalcohol;diethyl amine (800 : 200 : 1, v/v/v); flow rate 1.0 mL/min; column temperature 20°C; wavelength 220 nm) and Chiralcel OD-H column (mo-

bile phase comprising n-hexane;isopropylalcohol:diethyl amine (500:8:1, v/v/v); flow rate 1.0mL/min; column temperature 40$^0$C; wavelength 230 nm), respectively. In thisarticle. We report synthesis of three stereoisomers (Figure 1)by known method[5]. The new synthesis (Figure 2), characterization of impurity **(4)** was discussed. The $^1$H and $^{13}$C NMR data of impurity **(4)** and solifenacin succinate 5 were reported in this paper for the first time. The **(1-3)** stereoisomers data almost similar to **(5)**.




(6) (7) (5)

| | | |
|---|---|---|
| S-isomer | R-isomer | Solifenacin succinate(5) |
| S-isomer | S-isomer | SS-isomer succinate(1) |
| R-isomer | R-isomer | RR-isomer succinate(2) |
| R-isomer | S-isomer | RS-isomer succinate(3) |

**Figure 1: Synthesis of impurities (1-3)**

## EXPERIMENTAL

### Samples and chemicals

HPLC grade acetonitrile and acetic acid were obtained from merck, Mumbai, india. Chloroform-d and dimethylsulfoxide-d6 wre purchased form Aldrich Chemicals co., USA.

### High-performance liquid chromatography (HPLC)

An in house LC Isogradient method was developed for the separation of all possible stereoisomers of solifenacinsuccenate. Waters make HPLC system equipped with 515 pump and UV detector was used for better separation and quantification of impurities. Used for the preparation of mobile phase was in the ratio of n-Hexane: Isopropyl alcohol: Ethanol: Diethylamine (85:7.5:7.5:0.02), particle 5 µm size,Chiraipak AD-H,250X4.6mm column was used with a time 60min isogradient program column over temperature was 25 º C and column eluent was monitored by UV detector at 215nm. This LC method was able to separate all the process-related chiral substances with good resolution.

An in house LC Isogradient method was developed for the separation of N-oxide impurity and solifenacin succenate. SHIMADZU make HPLC system equipped with 436 pump and UV detector was used for better separation and quantification of impurities. Used for the preparation of mobile phase was in the buffer (1.36 gm of potassium dihydrogen orthophosphate in 1000ml water containing 1.0 ml of triethylamine), particle5 µm size,kromasil 100-5C$_8$,250X4.6mm column was used with a time 30min isogradient program.column over temperature was 30 º C and column eluent was monitored by UV detector at 210nm. This LC method was able to separate N-oxide and solifenacin with good resolution.

### Mass spectrometry

The electrospray ionization and MS-MS studies were performed on a triple quadruple mass spectrometer PE sciex model API 3000.

### NMRspecroscopy

The $^1$H, $^{13}$C, DEPT and 2D experiments for solifenacin succinate, impurity 1-4 were done on Varian mercury plus 400 MHz FT NMR spectrometer. The solvents used for solifenacin succinate, impurity-1-4 were in $CDCl_3$.

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### FT-IR spectroscopy

The IR spectra were recorded in the solid state as KBr dispersion medium using PerkinElmer 1600 series FT-IR spectophorometer.

### Synthesis of impurities

### General procedure for synthesis of solifenacin succinate and three stereoisomeric impurities

Solifenacin succinate **(5)** and other stereoisomers **(1-3)** were synthesized (Figure 1) by known procedure[5].

Preparation of (3R)-1-azabicyclo[2.2.2]oct-3-yl-(IS)-1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate-N-oxide 4 (solifenacin–N-oxide)(Figure 2)

A mixture of solifenacin succinate (20 g), sodium tungstate (0.2g) and methanesulfonic acid (0.2ml) in 40 ml of acetic acid was stirred at RT for 15min and 5.0 grams of 45% hydrogen peroxide was added to it for 1 hr. The reaction mixture was heated to 80°C and maintained at 80-85°C for 20 hrs. The reaction mixture was cooled to 25°C and diluted with water (200ml) and methylene dichloride (200ml). The diluted reaction mass was adjusted to pH 5.8 (range 5.5-6.0) with solid sodium carbonate (40 gr). The aqueous and organic layers were separated. The organic layer was washed with water. The organic layer was distilled off under reduced pressure to provide a residue. The residue was dissolved in 40 ml of ethyl acetate. The ethyl acetate layer was heated to 60°C. The ethyl acetate layer was treated with activated carbon, stirred at 60°C for 15 min and filtered through hyflow bed. The solvent was distilled off under reduced pressure to provide a residue (10 g, HPLC purity 96.2%). The residue was on cooling to afford low melting solid.

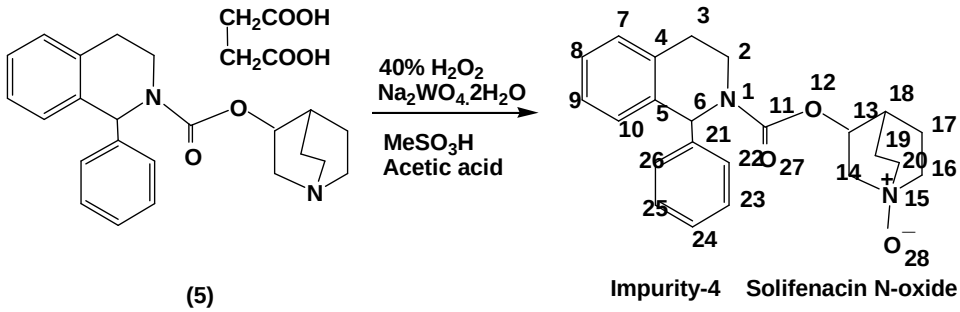


**Figure 2 : Synthesis of impurity-4 solifenacin N-oxid**

## RESULTS AND DISCUSSIONS

### Detection of impurities 1, 2, 3, and 4

A typical analytical LC chromatogram of a laboratory batch of solifenacin succinate **(5)** bulk drug recorded using the LC method as described in section 2.2 is shown in Figure 3a. The target impurities under study are marked as IMP-1, IMP-2, and IMP-3 are stereoisomers recorded using the LC method as described in section 2.2 is shown in Figure 3b. N-oxide (IMP-4)recorded using the LC method as described in section 2.2 is shown in Figure 3c.

### Structural eludcidation of solifenacin succinate and impurity N-oxide

### Structural eludcidation of solifenacin succinate (5)

Sample was analyzed by HPLC and its purity was found to be 99.68%, molecular weight of solifenacin base is 362.48. The EI mass spectrum of solifenacin gave a protonated molecular ion at *m/z* 364 and, IR spectrum displayed characteristic absorptions at 3398.89 & 2982.02,2934.06 cm-1 corresponding to >CH and aromatic >CH stretching. The peaks at 1509.95 & 1452.92 cm-1 in IR spectrum is indicative of >C=C< ring stretching,The $^{13}C$ NMR spectrum displayed signals due to the presence of twenty three carbons. The DEPT spectrum displayed seven negative signals due to seven methylene groups and twelve positive signals due to the presence of twelve methine groups (three in the aliphatic and the rest in aromatic region). The FT-IR spectrum displayed a characteristic absorption band at 1685 $cm^{-1}$ indicating the presence of carbonyl functional group, which was supported by the appearance of quaternary carbon signal due to carbonyl functional group in $^{13}C$ NMR spectrum. Based on the above spectral data (TABLE 1) and molecular for-

mula of solifenacin could be $C_{23}H_{16}N2O_2$. This molecular formula matched well with the molecular ion observed at 364amu in the EI mass spectrum. Molecular Formula: $C_{23}H_{26}N_2O_2.C_4H_6O_4$Molecular Weight: 480.55.

**TABLE 1 : $^1$H NMR assignments of solifenacin succinate 5**

| Poition | Multiplicity | ppm | $^{13}$C | DEPT |
|---|---|---|---|---|
| 4 | | | 28.3 | CH |
| 5 | 5H | 1.7-2.2, m | 26.2 | CH2 |
| 8 | | | 26.2 | CH2 |
| Succinic acid | 4H | 2.55, brs | 29.7,29.7 | CH2,CH2 |
| 2 | | | 58.5 | CH2 |
| 13 | | | 44.3 | CH2 |
| 14 | | | 26.8 | CH2 |
| 6 | 10H | 2.8-3.6, m | 54.3 | CH2 |
| 7 | | | 54.3 | CH2 |
| 3 | 1H | 4.0, brd | 68.3 | CH |
| 17 | 1H | 5.1-5.2, brs | 54.3 | CH |
| 10 | | | 154.1 | |
| Aromatic | | | | |
| 15 | | | 142.6 | |
| 16 | | | 134.3 | |
| 18 | | | 128.9 | CH |
| 19 | | | 126.1 | CH |
| 20 | | | 127.2 | CH |
| 21 | 9H | 7.13-7.42, m | 127.9 | CH |
| 22 | | | 141.6 | |
| 23 | | | 128.2 | CH |
| 24 | | | 128.8 | CH |
| 25 | | | 125.5 | CH |
| 26 | | | 128.8 | CH |
| 27 | | | 128.2 | CH |
| Succinic acid 2 COOH | 2H | 11.0, m | | |
| Succinic acid | | | 177.7 | |
| 2 COOH | | | 177.7 | |

## Structural eludcidation of solifenacin N-oxide (4)

Sample was analyzed by HPLC and its purity was found to be 96.48%, molecular weight of solifenacin N-oxide is 378.46. The EI mass spectrum of solifenacin gave a protonated molecular ion at *m/z* 379.3 and, IR spectrum displayed characteristic absorptions at 3399 & 2978,2936 cm-1 corresponding to >CH and aromatic >CH stretching. The peaks at 1512 & 1462 cm-1 in IR spectrum is indicative of >C=C< ring stretching,The $^{13}$C NMR spectrum displayed signals due to the presence of twenty three carbons. The DEPT spectrum displayed seven negative signals due to seven methylene groups and twelve positive signals due to the presence of twelve methine groups (three in the aliphatic and the rest in aromatic region). The FT-IR spectrum displayed a characteristic absorption band at 1685 cm$^{-1}$ indicating the presence of carbonyl functional group, which was supported by the appearance of quaternary carbon signal due to carbonyl functional group in $^{13}$C NMR spectrum. Based on the above spectral data (TABLE 2) and molecular formula of solifenacin could be $C_{23}H_{16}N_2O_3$. This molecular formula matched well with the molecular ion observed at 379amu in the EI mass spectrum.

**TABLE 2 : $^1$H NMR assignments of solifenacin N-oxide 4**

| Poition | Multiplicity | ppm | $^{13}$C | DEPT |
|---|---|---|---|---|
| 18 | | | 28.2 | CH |
| 17 | 5H | 1.6-2.2, m | 26.3 | CH2 |
| 19 | | | 26.3 | CH2 |
| 14 | | | 58.6 | CH2 |
| 2 | | | 44.6 | CH2 |
| 3 | 10H | 2.7-3.6, m | 26.6 | CH2 |
| 16 | | | 54.5 | CH2 |
| 20 | | | 54.5 | CH2 |
| 13 | 1H | 4.1, brd | 68.4 | CH |
| 6 | 1H | 5.1-5.2, brs | 54.7 | CH |
| 11 | | | 154.8 | |
| Aromatic | | | | |
| 4 | | | 141.2 | |
| 5 | | | 134.5 | |
| 7 | | | 128.7 | CH |
| 8 | | | 126.2 | CH |
| 9 | | | 127.3 | CH |
| 10 | 9H | 7.2-7.45, m | 127.9 | CH |
| 21 | | | 141.6 | |
| 22 | | | 128.2 | CH |
| 23 | | | 128.8 | CH |
| 24 | | | 125.5 | CH |
| 25 | | | 128.8 | CH |
| 26 | | | 128.2 | CH |

## CONCLUSION

This research paper describes the synthesis, and structure elucidation of process related impurities in solifenacin succinate. The impurities were separated by reverse phasechromatographic technique. The synthesized impurities were characterized using spectroscopic techniques. To the best of our knowledge, impurity **(4)** had not been isolated or synthesized as pure substance until now. The new synthesis, characterization of impurity **(4)** was discussed. The$^1$H and $^{13}$C NMR data of

impurity 4 and solifenacin succinate **(5)** were reported in this paper for the first time.

## ACKNOWLEDGEMENT

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