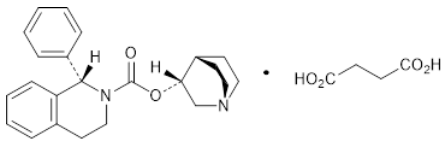
Solifenacin Succinate

ソリフェナシンコハク酸塩



$C_{23}H_{26}N_2O_2.C_4H_6O_4$: 480.55

(3*R*)-1-Azabicyclo[2.2.2]octan-3-yl(1*S*)-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate monosuccinate

[*242478-38-2*]

Solifenacin Succinate contains not less than 98.0% and not more than 102.0% of solifenacin succinate ($C_{23}H_{26}N_2O_2.C_4H_6O_4$: 480.55).

Description Solifenacin Succinate occurs as white, crystals or crystalline powder.

It is freely soluble in water, in dimethyl sulfoxide and in methanol, and sparingly soluble in ethanol (99.5).

It is practically insoluble in sodium hydroxide TS.

Optical rotation $[\alpha]_D^{20}$: +79 – +83° (0.25 g, methanol, 25 mL, 100 mm).

Identification **(1)** Determine the absorption spectrum of a solution of Solifenacin Succinate in methanol (1 in 2000) as directed under Ultraviolet-visible Spectrophotometry *<2.24>*, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Solifenacin Succinate RS prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Solifenacin Succinate as directed in the ATR method under Infrared Spectrophotometry *<2.25>*, and compare the spectrum with the spectrum of Solifenacin Succinate RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

(3) Add 2 mL of sodium hydroxide TS to 0.1 g of Solifenacin Succinate and allow to stand for 10 minutes. Filter this liquid through a membrane filter with a pore size of 0.2 μm, adjust the filtrate to pH 6 with 1 mol/L hydrochloric acid TS, and add 2 to 3 drops of iron (III) chloride TS: a light brown precipitate is formed.

Melting point *<2.60>* 144 – 149°C

Purity **(1)** Related substances 1—Dissolve 50 mg of Solifenacin Succinate in the mobile phase in the Assay to make 100 mL, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add the mobile phase in the Assay to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the conditions described below. Determine each peak area by the automatic integration method. Calculate the amounts of the related substances by the following equation: the amount of each related substance is not more than 0.10%.

Amount (%) of each related substance = A_T / A_S

A_S: Peak area of solifenacin from the standard solution

A_T: Peak area of each related substance from the sample solution

Operating conditions—

Detector, column, and column temperature: Proceed as directed in the operating conditions in the Assay.

Mobile phase: Dissolve 8.7 g of dipotassium hydrogen phosphate in water to make 1000 mL, and adjust to pH 6.0 with phosphoric acid. To 500 mL of this solution add 500 mL of acetonitrile for liquid chromatography.

Flow rate: Adjust so that the retention time of solifenacin is about 3 minutes.

Time span of measurement: About 10 times as long as the retention time of solifenacin, beginning from about 1.5 times as long as the retention time of solifenacin.

System suitability—

Test for required detectability: Pipet 3 mL of the standard solution, and add the mobile phase in the Assay to make exactly 100 mL. Confirm that the peak area of solifenacin obtained with 10 μL of this solution is equivalent to 2 to 4% of that with 10 μL of the standard solution.

System performance: Dissolve 50 mg of benzyl parahydroxybenzoate in the mobile phase to make 100 mL. To 1 mL of this solution and 2 mL of the sample solution add the mobile phase to make 100 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, solifenacin and benzyl parahydroxybenzoate are eluted in this order with the resolution between these peaks being not less than 10.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of solifenacin is not more than 2.0%.

(2) Related substances 2—Perform the test with exactly 10 μL each of the sample solution and standard solution obtained in (1) as directed under Liquid Chromatography *<2.01>* according to the conditions described below. Determine each peak area by the automatic integration method. Calculate the amounts of the related substances by the following equation: the amount of each related substance is not more than 0.10%.

Amount (%) of each related substance = A_T / A_S

A_S: Peak area of solifenacin from the standard solution

A_T: Peak area of each related substance from the sample solution

Operating conditions—

Detector, column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: From after the solvent and succinic acid peaks to immediately before the peak of solifenacin.

System suitability—

Test for required detectability: Pipet 3 mL of the standard solution, and add the mobile phase to make exactly 100 mL. Confirm that the peak area of solifenacin obtained with 10 μL of this solution is equivalent to 2 to 4% of that with 10 μL of the standard solution.

System performance: Dissolve 50 mg of ethyl parahydroxybenzoate in the mobile phase to make 100 mL. To 1 mL of this solution and 2 mL of the sample solution add the mobile phase to make 100 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, ethyl parahydroxybenzoate and solifenacin are eluted in this order with the resolution between these peaks being not less than 10.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of solifenacin is not more than 3.5%.

(3) Related substances 3—Perform the test with exactly 10 μL each of the sample solution and standard solution obtained in (1) as directed under Liquid Chromatography *<2.01>* according to the conditions described below. Determine each peak area by the automatic integration method. Calculate the amounts of the related substances by the following equation: the amount of each related substance is not more than 0.10%.

$$\text{Amount (\%) of each related substance} = A_T / A_S$$

A_S: Peak area of solifenacin from the standard solution

A_T: Peak area of each related substance from the sample solution

Operating conditions—

Detector, column and column temperature: Proceed as directed in the operating conditions in the Assay.

Mobile phase: Dissolve 8.7 g of dipotassium hydrogen phosphate in water to make 1000 mL, and adjust to pH 6.0 with phosphoric acid. To 650 mL of this solution add 200 mL of acetonitrile for liquid chromatography, 100 mL of 2-propanol for liquid chromatography and 50 mL of methanol.

Flow rate: Adjust so that the retention time of solifenacin is about 12 minutes.

Time span of measurement: About 2.5 times as long as the retention time of solifenacin, beginning after the peak of solifenacin.

System suitability—

Test for required detectability: Pipet 3 mL of the standard solution, and add the mobile phase in the Assay to make exactly 100 mL. Confirm that the peak area of solifenacin obtained with 10 μL of this solution is equivalent to 2 to 4% of that with 10 μL of the standard solution.

System performance: Dissolve 50 mg of benzyl parahydroxybenzoate in the mobile phase in (1) to make 100 mL. To1 mL of this solution and 2 mL of the sample solution add the mobile phase in (1) to make 100 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, solifenacin and benzyl parahydroxybenzoate are eluted in this order with the resolution between these peaks being not less than 10.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of solifenacin is not more than 3.0%.

(4) Total amount of related substances—Calculate the total amount of related substances by the following equation: not more than 0.3%.

$$\text{Total amount (\%) of related substances} = S_{T1} / A_{S1} + S_{T2} / A_{S2} + S_{T3} / A_{S3}$$

A_{S1}: Peak area of solifenacin from the standard solution in (1)

A_{S2}: Peak area of solifenacin from the standard solution in (2)

A_{S3}: Peak area of solifenacin from the standard solution in (3)

S_{T1}: Total peak area of each related substance from the sample solution in (1)

S_{T2}: Total peak area of each related substance from the sample solution in (2)

S_{T3}: Total peak area of each related substance from the sample solution in (3)

(5) Enantiomer and diastereomers—Dissolve 0.25 g of Solifenacin Succinate in a mixture of 2-propanol for liquid chromatography and hexane for liquid chromatography (1:1) to make 100 mL, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add a mixture of 2-propanol for liquid chromatography and hexane for liquid chromatography (1:1) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the conditions described below. Determine each peak area by the automatic integration method. Calculate the amounts of enantiomer and diastereomers by the following equation: the

amount of related substance G (diastereomer), having the relative retention time of about 0.47 to solifenacin, obtained from the sample solution is not more than 0.2%, the amount of related substance H (diastereomer), having the relative retention time of about 0.58, is not more than 0.2%, and the amount of related substance F (enantiomer), having the relative retention time of about 0.52, is not more than 0.1%.

Amount (%) of enantiomer or each diastereomer $= A_T / A_S$

A_S: Peak area of solifenacin from the standard solution
A_T: Peak area of enantiomer or each diastereomer from the sample solution

Operating conditions—
Detector: An ultraviolet absorption photometer (wavelength: 220 nm).
Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with amylose tris-(3,5-dimethylphenylcarbamate)-coated silica gel for liquid chromatography.
Column temperature: A constant temperature of about 20°C.
Mobile phase: A mixture of hexane for liquid chromatography, 2-propanol for liquid chromatography and diethylamine (800:200:1).
Flow rate: Adjust so that the retention time of solifenacin is about 35 minutes.
System suitability—
Test for required detectability: Dissolve 5 mg each of Solifenacin Succinate, Solifenacin Succinate Related Substance G for System Suitability RS, Solifenacin Succinate Related Substance H for System Suitability RS, and Solifenacin Succinate Related Substance F for System Suitability RS in a mixture of 2-propanol for liquid chromatography and hexane for liquid chromatography (1:1) to make exactly 50 mL, and use this solution as the solution for system suitability test (1). Pipet 2.5 mL of this solution, add a mixture of 2-propanol for liquid chromatography and hexane for liquid chromatography (1:1) to make exactly 10 mL, and use this solution as the solution for system suitability test (2). Pipet 2.5 mL of this solution, and add a mixture of 2-propanol for liquid chromatography and hexane for liquid chromatography (1:1) to make exactly 25 mL. Confirm that the peak area of related substance F obtained with 10 μL of this solution is equivalent to 7 to 13% of that with 10 μL of the solution for system suitability test (2).
System performance: When the procedure is run with 10 μL of the solution for the system suitability test (1) under the above operating conditions, related substance G, related substance F, related substance H, and solifenacin are eluted in this order with the resolutions between adjacent peaks being not less than 1.5.
System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of solifenacin is not more than 5%.

(6) Residual solvent—Being specified separately when the drug is granted approval based on the Law.

Residue on ignition <*2.44*> Not more than 0.1% (1 g).

Assay Weigh accurately about 50 mg each of Solifenacin Succinate and Solifenacin Succinate RS, and dissolve each in the mobile phase to make exactly 50 mL. Pipet 10 mL each of these solutions, add exactly 10 mL of the internal standard solution, add the mobile phase to make 50 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the conditions described below, and calculate the ratios, Q_T and Q_S, of the peak area of solifenacin to that of the internal standard.

Amount (mg) of solifenacin succinate ($C_{23}H_{26}N_2O_2.C_4H_6O_4$) $= M_S \times Q_T / Q_S$

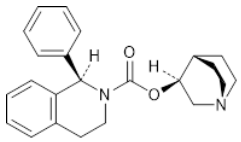
M_S: Amount (mg) of Solifenacin Succinate RS taken

Internal standard solution—A solution of ethyl parahydroxybenzoate in the mobile phase (1 in 2000).
Operating conditions—
Detector: An ultraviolet absorption photometer (wavelength: 210 nm).
Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).
Column temperature: A constant temperature of about 40°C.
Mobile phase: Dissolve 8.7 g of dipotassium hydrogen phosphate in water to make 1000 mL, and adjust to pH 6.0 with phosphoric acid. To 700 mL of this solution add 300 mL of acetonitrile for liquid chromatography.
Flow rate: Adjust so that the retention time of solifenacin is about 20 minutes.
System suitability—
System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the internal standard and solifenacin are eluted in this order with the resolution between these peaks being not less than 10.
System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of solifenacin to that of the internal standard is not more than 1.0%.

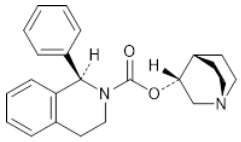
Containers and storage Containers—Well-closed containers.

Others

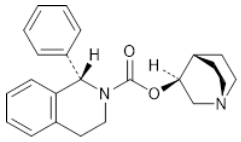
Related substance F (enantiomer):
(3*S*)-1-Azabicyclo[2.2.2]octan-3-yl(1*R*)-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate



Related substance G (diastereomer):
(3*R*)-1-Azabicyclo[2.2.2]octan-3-yl(1*R*)-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate



Related substance H (diastereomer):
(3*S*)-1-Azabicyclo[2.2.2]octan-3-yl(1*S*)-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate



Add the following to 9.01 Reference Standards (1):

Solifenacin Succinate RS
Solifenacin Succinate Related Substance F for System Suitability RS
Solifenacin Succinate Related Substance G for System Suitability RS
Solifenacin Succinate Related Substance H for System Suitability RS