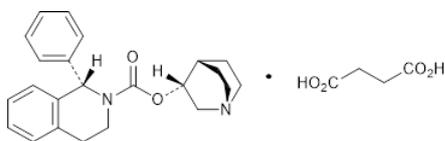


# 1 Solifenacin Succinate

2 ソリフェナシンコハク酸塩



3

4  $C_{23}H_{26}N_2O_2 \cdot C_4H_6O_4$ : 480.55

5 (3*R*)-1-Azabicyclo[2.2.2]octan-3-yl(1*S*)-1-phenyl-3,4-  
6 dihydroisoquinoline-2(1*H*)-carboxylate monosuccinate  
7 [242478-38-2]

8

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

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

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

16 It is practically insoluble in sodium hydroxide TS.

17 Optical rotation  $[\alpha]_D^{20}$ : +79 – +83° (0.25 g, methanol,  
18 25 mL, 100 mm).

19 **Identification (1)** Determine the absorption spectrum of  
20 a solution of Solifenacin Succinate in methanol (1 in 2000)  
21 as directed under Ultraviolet-visible Spectrophotometry  
22 <2.24>, and compare the spectrum with the Reference Spec-  
23 trum or the spectrum of a solution of Solifenacin Succinate  
24 RS prepared in the same manner as the sample solution: both  
25 spectra exhibit similar intensities of absorption at the same  
26 wavelengths.

27 **(2)** Determine the infrared absorption spectrum of Sol-  
28 ifenacin Succinate as directed in the ATR method under In-  
29 frared Spectrophotometry <2.25>, and compare the spectrum  
30 with the spectrum of Solifenacin Succinate RS: both spectra  
31 exhibit similar intensities of absorption at the same wave  
32 numbers.

33 **(3)** Add 2 mL of sodium hydroxide TS to 0.1 g of Sol-  
34 ifenacin Succinate and allow to stand for 10 minutes. Filter  
35 this liquid through a membrane filter with a pore size of 0.2  
36  $\mu\text{m}$ , adjust the filtrate to pH 6 with 1 mol/L hydrochloric acid  
37 TS, and add 2 to 3 drops of iron (III) chloride TS: a light  
38 brown precipitate is formed.

39 **Melting point** <2.60> 144 – 149°C

40 **Purity (1)** Related substances 1—Dissolve 50 mg of Sol-  
41 ifenacin Succinate in the mobile phase in the Assay to make  
42 100 mL, and use this solution as the sample solution. Pipet 1  
43 mL of the sample solution, add the mobile phase in the Assay  
44 to make exactly 100 mL, and use this solution as the standard

45 solution. Perform the test with exactly 10  $\mu\text{L}$  each of the sam-  
46 ple solution and standard solution as directed under Liquid  
47 Chromatography <2.01> according to the conditions de-  
48 scribed below. Determine each peak area by the automatic  
49 integration method. Calculate the amounts of the related sub-  
50 stances by the following equation: the amount of each related  
51 substance is not more than 0.10%.

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

53  $A_S$ : Peak area of solifenacin from the standard solution

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

56 **Operating conditions**—

57 Detector, column, and column temperature: Proceed as di-  
58 rected in the operating conditions in the Assay.

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

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

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

68 **System suitability**—

69 Test for required detectability: Pipet 3 mL of the standard  
70 solution, and add the mobile phase in the Assay to make ex-  
71 actly 100 mL. Confirm that the peak area of solifenacin ob-  
72 tained with 10  $\mu\text{L}$  of this solution is equivalent to 2 to 4% of  
73 that with 10  $\mu\text{L}$  of the standard solution.

74 System performance: Dissolve 50 mg of benzyl parahy-  
75 droxybenzoate in the mobile phase to make 100 mL. To 1 mL  
76 of this solution and 2 mL of the sample solution add the mo-  
77 bile phase to make 100 mL. When the procedure is run with  
78 10  $\mu\text{L}$  of this solution under the above operating conditions,  
79 solifenacin and benzyl parahydroxybenzoate are eluted in  
80 this order with the resolution between these peaks being not  
81 less than 10.

82 System repeatability: When the test is repeated 6 times  
83 with 10  $\mu\text{L}$  of the standard solution under the above operating  
84 conditions, the relative standard deviation of the peak area of  
85 solifenacin is not more than 2.0%.

86 **(2)** Related substances 2—Perform the test with exactly  
87 10  $\mu\text{L}$  each of the sample solution and standard solution ob-  
88 tained in (1) as directed under Liquid Chromatography <2.01>  
89 according to the conditions described below. Determine each  
90 peak area by the automatic integration method. Calculate the  
91 amounts of the related substances by the following equation:  
92 the amount of each related substance is not more than 0.10%.

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

94  $A_S$ : Peak area of solifenacin from the standard solution

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

97 *Operating conditions—*

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

101 Time span of measurement: From after the solvent and  
102 succinic acid peaks to immediately before the peak of sol-  
103 ifenacin.

104 *System suitability—*

105 Test for required detectability: Pipet 3 mL of the standard  
106 solution, and add the mobile phase to make exactly 100 mL.  
107 Confirm that the peak area of solifenacin obtained with 10  
108  $\mu\text{L}$  of this solution is equivalent to 2 to 4% of that with 10  $\mu\text{L}$   
109 of the standard solution.

110 System performance: Dissolve 50 mg of ethyl parahy-  
111 droxybenzoate in the mobile phase to make 100 mL. To 1 mL  
112 of this solution and 2 mL of the sample solution add the mo-  
113 bile phase to make 100 mL. When the procedure is run with  
114 10  $\mu\text{L}$  of this solution under the above operating conditions,  
115 ethyl parahydroxybenzoate and solifenacin are eluted in this  
116 order with the resolution between these peaks being not less  
117 than 10.

118 System repeatability: When the test is repeated 6 times  
119 with 10  $\mu\text{L}$  of the standard solution under the above operating  
120 conditions, the relative standard deviation of the peak area of  
121 solifenacin is not more than 3.5%.

122 (3) Related substances 3—Perform the test with exactly  
123 10  $\mu\text{L}$  each of the sample solution and standard solution ob-  
124 tained in (1) as directed under Liquid Chromatography <2.01>  
125 according to the conditions described below. Determine each  
126 peak area by the automatic integration method. Calculate the  
127 amounts of the related substances by the following equation:  
128 the amount of each related substance is not more than 0.10%.

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

130  $A_S$ : Peak area of solifenacin from the standard solution

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

133 *Operating conditions—*

134 Detector, column and column temperature: Proceed as di-  
135 rected in the operating conditions in the Assay.

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

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

143 Time span of measurement: About 2.5 times as long as the  
144 retention time of solifenacin, beginning after the peak of sol-  
145 ifenacin.

146 *System suitability—*

147 Test for required detectability: Pipet 3 mL of the standard  
148 solution, and add the mobile phase in the Assay to make ex-  
149 actly 100 mL. Confirm that the peak area of solifenacin ob-  
150 tained with 10  $\mu\text{L}$  of this solution is equivalent to 2 to 4% of  
151 that with 10  $\mu\text{L}$  of the standard solution.

152 System performance: Dissolve 50 mg of benzyl parahy-  
153 droxybenzoate in the mobile phase in (1) to make 100 mL.  
154 To 1 mL of this solution and 2 mL of the sample solution add  
155 the mobile phase in (1) to make 100 mL. When the procedure  
156 is run with 10  $\mu\text{L}$  of this solution under the above operating  
157 conditions, solifenacin and benzyl parahydroxybenzoate are  
158 eluted in this order with the resolution between these peaks  
159 being not less than 10.

160 System repeatability: When the test is repeated 6 times  
161 with 10  $\mu\text{L}$  of the standard solution under the above operating  
162 conditions, the relative standard deviation of the peak area of  
163 solifenacin is not more than 3.0%.

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

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

169  $A_{S1}$ : Peak area of solifenacin from the standard solution in  
170 (1)

171  $A_{S2}$ : Peak area of solifenacin from the standard solution in  
172 (2)

173  $A_{S3}$ : Peak area of solifenacin from the standard solution in  
174 (3)

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

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

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

181 (5) Enantiomer and diastereomers—Dissolve 0.25 g of  
182 Solifenacin Succinate in a mixture of 2-propanol for liquid  
183 chromatography and hexane for liquid chromatography (1:1)  
184 to make 100 mL, and use this solution as the sample solution.  
185 Pipet 1 mL of the sample solution, add a mixture of 2-propa-  
186 nol for liquid chromatography and hexane for liquid chroma-  
187 tography (1:1) to make exactly 100 mL, and use this solution  
188 as the standard solution. Perform the test with exactly 10  $\mu\text{L}$   
189 each of the sample solution and standard solution as directed  
190 under Liquid Chromatography <2.01> according to the con-  
191 ditions described below. Determine each peak area by the au-  
192 tomatic integration method. Calculate the amounts of enanti-  
193 omer and diastereomers by the following equation: the

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

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

202  $A_S$ : Peak area of solifenacin from the standard solution

203  $A_T$ : Peak area of enantiomer or each diastereomer from the sample solution

205 *Operating conditions*—

206 Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

208 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.

212 Column temperature: A constant temperature of about 20°C.

214 Mobile phase: A mixture of hexane for liquid chromatography, 2-propanol for liquid chromatography and diethylamine (800:200:1).

217 Flow rate: Adjust so that the retention time of solifenacin is about 35 minutes.

219 *System suitability*—

220 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  $\mu$ L of this solution is equivalent to 7 to 13% of that with 10  $\mu$ L of the solution for system suitability test (2).

238 System performance: When the procedure is run with 10  $\mu$ L 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.

244 System repeatability: When the test is repeated 6 times with 10  $\mu$ L of the standard solution under the above operating conditions, the relative standard deviation of the peak area of solifenacin is not more than 5%.

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

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

251 **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  $\mu$ L 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.

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

264  $M_S$ : Amount (mg) of Solifenacin Succinate RS taken

265 *Internal standard solution*—A solution of ethyl parahydroxybenzoate in the mobile phase (1 in 2000).

267 *Operating conditions*—

268 Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

270 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  $\mu$ m in particle diameter).

273 Column temperature: A constant temperature of about 40°C.

275 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.

279 Flow rate: Adjust so that the retention time of solifenacin is about 20 minutes.

281 *System suitability*—

282 System performance: When the procedure is run with 10  $\mu$ L 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.

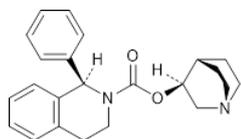
287 System repeatability: When the test is repeated 6 times with 10  $\mu$ L of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of solifenacin to that of the internal standard is not more than 1.0%.

292 **Containers and storage** Containers—Well-closed con-  
 293 tainers.

294 **Others**

295 Related substance F (enantiomer):

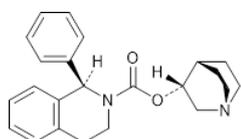
296 (3*S*)-1-Azabicyclo[2.2.2]octan-3-yl(1*R*)-1-phenyl-3,4-  
 297 dihydroisoquinoline-2(1*H*)-carboxylate



298

299 Related substance G (diastereomer):

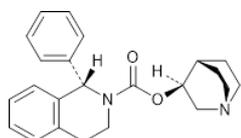
300 (3*R*)-1-Azabicyclo[2.2.2]octan-3-yl(1*R*)-1-phenyl-3,4-  
 301 dihydroisoquinoline-2(1*H*)-carboxylate



302

303 Related substance H (diastereomer):

304 (3*S*)-1-Azabicyclo[2.2.2]octan-3-yl(1*S*)-1-phenyl-3,4-  
 305 dihydroisoquinoline-2(1*H*)-carboxylate



306

307 **Add the following to 9.01 Reference**

308 **Standards (1):**

309 Solifenacin Succinate RS

310 Solifenacin Succinate Related Substance F for System

311 Suitability RS

312 Solifenacin Succinate Related Substance G for System

313 Suitability RS

314 Solifenacin Succinate Related Substance H for System

315 Suitability RS

316