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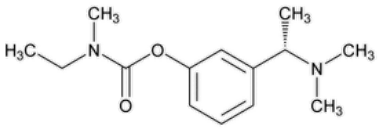
Rivastigmine



$C_{14}H_{22}N_2O_2$ 250.34

Ethylmethylcarbamic acid, 3-[(*S*)-1-(dimethylamino)ethyl]phenyl ester;

(*S*)-3-[1-(Dimethylamino)ethyl]phenyl ethyl(methyl)carbamate CAS RN®: 123441-03-2; UNII: PKI06M3IW0.

DEFINITION

Rivastigmine contains NLT 98.0% and NMT 102.0% of rivastigmine ($C_{14}H_{22}N_2O_2$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197F**▲ (CN 1-May-2020)

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *System suitability solution*, as obtained in the test for *Enantiomeric Purity*.

ASSAY

• **Procedure**

[Note—Protect solutions containing rivastigmine from light.]

Buffer: 8.9 g/L of dibasic sodium phosphate dihydrate in water (0.05 M)

Mobile phase: Methanol and *Buffer* (58:42), adjusted with phosphoric acid to a pH of 8.45. [Note—Let the solution cool to room temperature before pH adjustment.]

System suitability solution: 1 mg/mL of USP Rivastigmine Tartrate RS, and 1 µg/mL each of USP Rivastigmine Related Compound B RS, USP Rivastigmine Related Compound C RS, and USP Rivastigmine Related Compound D RS in *Mobile phase*

Standard solution: 1.0 mg/mL of USP Rivastigmine Tartrate RS in *Mobile phase*

Sample solution: 0.625 mg/mL of Rivastigmine in *Mobile phase*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 214 nm

Column: 4.0-mm × 25-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 1.0 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[Note—The relative retention times for rivastigmine related compound C, rivastigmine related compound D, rivastigmine related compound B, and rivastigmine are 0.37, 0.56, 0.68, and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.5 between rivastigmine related compound D and rivastigmine related compound B, *System suitability solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of rivastigmine ($C_{14}H_{22}N_2O_2$) in the portion of Rivastigmine taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Rivastigmine Tartrate RS in the *Standard solution* (mg/mL)

C_U = concentration of Rivastigmine in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of rivastigmine, 250.34

M_{r2} = molecular weight of rivastigmine tartrate, 400.42

Acceptance criteria: 98.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

• **Organic Impurities**

[Note—Protect solutions containing rivastigmine from light.]

Buffer, Mobile phase, System suitability solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: 0.0025 mg/mL of USP Rivastigmine Tartrate RS in *Mobile phase*

Sensitivity solution: 0.5 µg/mL of USP Rivastigmine Tartrate RS in *Mobile phase* from the *Standard solution*

System suitability

Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*

[Note—The relative retention times for rivastigmine related compound C, rivastigmine related compound D, rivastigmine related compound B, and rivastigmine are 0.37, 0.56, 0.68, and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.5 between rivastigmine related compound D and rivastigmine related compound B, *System suitability solution*

Signal-to-noise ratio: NLT 10 for rivastigmine, *Sensitivity solution*

Relative standard deviation: NMT 10%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any impurity in the portion of Rivastigmine taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of any impurity from the *Sample solution*

r_S = peak response of rivastigmine from the *Standard solution*

C_S = concentration of USP Rivastigmine Tartrate RS in the *Standard solution* (mg/mL)

C_U = concentration of Rivastigmine in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of rivastigmine, 250.34

M_{r2} = molecular weight of rivastigmine tartrate, 400.42

F = relative response factor, see *Table 1*

Acceptance criteria: See *Table 1*. Disregard the system peak eluting at the relative retention time of about 0.45.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Phenol impurity (rivastigmine related compound C)	0.37	1.7	0.3
Nor impurity[a]	0.68	1.0	0.1
Rivastigmine	1.0	—	—
Any other individual impurity	—	1.0	0.10
Total impurities	—	—	0.5

[a] (*S*)-3-[1-(Dimethylamino)ethyl]phenyl dimethylcarbamate (racemic mixture is rivastigmine related compound B).

• **Enantiomeric Purity**

[Note—Protect solutions containing rivastigmine from light.]

Buffer: Dissolve 1.78 g of dibasic sodium phosphate dihydrate and 1.38 g of monobasic sodium phosphate in 1000 mL of water. Adjust with phosphoric acid to a pH of 6.0.

Mobile phase: Transfer 20.0 mL of acetonitrile and 205 µL of *N*,*N*-dimethyloctylamine into a 1000-mL volumetric flask, and dilute with *Buffer* to volume.

System suitability solution: 0.1 mg/mL of USP Rivastigmine Tartrate RS and 0.1 µg/mL of USP Rivastigmine Tartrate R-Isomer RS in *Mobile phase*

Standard solution: 0.1 µg/mL of USP Rivastigmine Tartrate R-Isomer RS in *Mobile phase*

Sample solution: 0.0625 mg/mL of Rivastigmine in *Mobile phase*

Sensitivity solution: 0.05 µg/mL of USP Rivastigmine Tartrate R-Isomer RS in *Mobile phase*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 200 nm

Column: 4.0-mm × 10-cm; 5-µm packing L41

Flow rate: 0.5 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*

[Note—The relative retention times for rivastigmine *R*-isomer and rivastigmine are 0.85 and 1.0, respectively.]

Suitability requirements

Relative standard deviation: NMT 10%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Resolution: NLT 0.8 between rivastigmine *R*-isomer and rivastigmine, *System suitability solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of rivastigmine *R*-isomer in the portion of Rivastigmine taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of rivastigmine *R*-isomer from the *Sample solution*

r_S = peak response of rivastigmine *R*-isomer from the *Standard solution*

C_S = concentration of USP Rivastigmine Tartrate R-Isomer RS in the *Standard solution* (mg/mL)

C_U = concentration of Rivastigmine in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of rivastigmine, 250.34

M_{r2} = molecular weight of rivastigmine tartrate, 400.42

Acceptance criteria: NMT 0.3%

SPECIFIC TESTS

• **Water Determination, *Method Ia* ⟨921⟩:** NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers under inert gas protected from light. Store at 2°–8°.

• **USP Reference Standards ⟨11⟩**

USP Rivastigmine RS

USP Rivastigmine Related Compound B RS

Nor impurity (racemic mixture);
(*RS*)-3-[1-(Dimethylamino)ethyl]phenyl dimethylcarbamate.
$C_{13}H_{20}N_2O_2$ 236.31

USP Rivastigmine Related Compound C RS

Phenol impurity;
(*S*)-3-[1-(Dimethylamino)ethyl]phenol.
$C_{10}H_{15}NO$ 165.23

USP Rivastigmine Related Compound D RS

Acetylphenol impurity;
3-Acetylphenyl ethyl(methyl)carbamate.
$C_{12}H_{15}NO_3$ 221.25

USP Rivastigmine Tartrate RS

USP Rivastigmine Tartrate R-Isomer RS

(*R*)-3-[1-(Dimethylamino)ethyl]phenyl ethyl (methyl)carbamate tartrate.
$C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6$ 400.42

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
RIVASTIGMINE	Documentary Standards Support	SM32020 Small Molecules 3
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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