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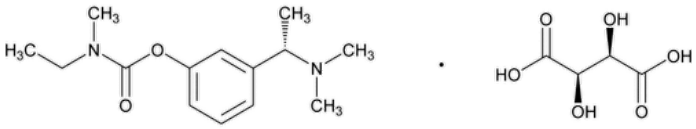
Rivastigmine Tartrate



$C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6$ 400.42

Ethylmethylcarbamic acid, 3-[(*S*)-1-(dimethylamino)ethyl]phenyl ester, (2*R*,3*R*)-2,3-dihydroxybutanedioate;

(*S*)-3-[1-(Dimethylamino)ethyl]phenyl ethylmethylcarbamate, hydrogen tartrate CAS RN®: 129101-54-8; UNII: 9IY2357JPE.

Rivastigmine 250.34 CAS RN®: 123441-03-2; UNII: PKI06M3IW0.

DEFINITION

Rivastigmine Tartrate contains NLT 98.0% and NMT 102.0% of the labeled amount of $C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6$, calculated on the anhydrous basis.

IDENTIFICATION

• **A.** **Spectroscopic Identification Tests** ⟨197⟩, *Infrared Spectroscopy*: **197K**

• **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 *Organic Impurities, Procedure 2: Enantiomeric Purity*.

ASSAY

• **Procedure**

Buffer: 8.6 mg/mL of monobasic ammonium phosphate. Adjust with ammonia solution to a pH of 7.0.

Mobile phase: Methanol, acetonitrile, and *Buffer* (15:15:70)

System suitability solution: 0.05 mg/mL each of USP Rivastigmine Related Compound A RS and USP Rivastigmine Related Compound B RS in *Mobile phase*

Standard solution: 0.2 mg/mL of USP Rivastigmine Tartrate RS in *Mobile phase*

Sample solution: 0.2 mg/mL of Rivastigmine Tartrate in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Flow rate: 1.2 mL/min

Injection size: 20 µL

[Note—The flow rate may be adjusted to 1.5 mL/min, if needed, to achieve a recommended retention time of rivastigmine at about 10 min.]

System suitability

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

Suitability requirements

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

Column efficiency: NLT 5000 theoretical plates, *Standard solution*

Tailing factor: NMT 3.0, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6$ in the portion of Rivastigmine Tartrate taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

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

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

Inorganic Impurities

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

Change to read:

Organic Impurities

- **Procedure 1**

Mobile phase and **System suitability solution:** Proceed as directed in the *Assay*.

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

Sample solution: 1.0 mg/mL of Rivastigmine Tartrate in *Mobile phase*

Chromatographic system: Proceed as directed in the *Assay*.

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

System suitability

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

Suitability requirements

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

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

Analysis [Note—The run time is 8 times the retention time of the rivastigmine peak.]

Samples: *Standard solution* and *Sample solution*

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

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

r_U = peak response for each impurity 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 Tartrate in the *Sample solution* (mg/mL)

F = relative response factor (see *Impurity Table 1*)

Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Total impurities: NMT 0.5%

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Tartrate	0.18	—	Disregard
Phenol impurity[a]	0.28	1.6	0.3
DPTTA[b]	0.46	0.83	0.15
Nor impurity[c]	0.57	1.2	0.15

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Rivastigmine	1.0	1.0	—
Carbamate impurity[d]	4.1	1.3	0.15
Ether impurity[e]	6.5	1.4	0.15
Any other impurity	—	1.0	0.1

[a] (*S*)-3-[1-(Dimethylamino)ethyl]phenol.

[b] (+)-Di-(*p*-toluoyl)-D-tartaric acid (rivastigmine related compound A).

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

[d] ▲4-Nitrophenyl ethyl(methyl)carbamate.▲ (ERR 1-May-2024)

[e] (*S*)-*N*,*N*-Dimethyl-1-[3-(4-nitrophenoxy)phenyl]ethanamine.

• **Procedure 2: Enantiomeric Purity**

Buffer: Transfer 1.78 g of dibasic sodium phosphate dihydrate and 1.38 g of monobasic sodium phosphate into a 1000-mL volumetric flask. Dissolve in and dilute with water to volume. Adjust with phosphoric acid to a pH of 6.0.

Mobile phase: Transfer 20 mL of acetonitrile and 205 µL of *N*,*N*-dimethyloctylamine to a 1000-mL volumetric flask, and dilute with *Buffer* to volume.

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

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

System suitability solution: 100 µg/mL of USP Rivastigmine Tartrate RS and 0.1 µg/mL of USP Rivastigmine Tartrate R-Isomer RS in *Mobile phase*

Sample solution: 100 µg/mL of Rivastigmine Tartrate in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 200 nm

Column: 4.0-mm × 10-cm; packing L41

Flow rate: 0.5 mL/min

Injection size: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 0.8 between the enantiomer peaks, *System suitability solution*

[Note—The elution order is the *R*-enantiomer, followed by the rivastigmine peak, which is the *S*-enantiomer.]

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

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the *R*-enantiomer in the portion of Rivastigmine Tartrate taken:

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

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

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

C_S = concentration of *R*-enantiomer in the *Standard solution* (µg/mL)

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

Acceptance criteria: NMT 0.3% of the *R*-enantiomer

SPECIFIC TESTS

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

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers, and store at room temperature.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Rivastigmine Tartrate RS

USP Rivastigmine Related Compound A RS

(+)-Di-(*p*-toluoyl)-D-tartaric acid.

$C_{20}H_{18}O_8$ 386.35

USP Rivastigmine Related Compound B RS

(*RS*)-3-[1-(Dimethylamino)ethyl]phenyl dimethylcarbamate.

$C_{13}H_{20}N_2O_2$ 236.32

USP Rivastigmine Tartrate R-Isomer RS

▲(*R*)-3-[1-(Dimethylamino)ethyl]phenyl ethylmethylcarbamate, hydrogen tartrate.

$C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6$ 400.42▲ (ERR 1-May-2024)

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

Topic/Question	Contact	Expert Committee
RIVASTIGMINE TARTRATE	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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