

BRIEFING

Rivastigmine Tartrate Oral Solution. This monograph was posted on the USP Website as a Draft USP Pending Monograph and has been available for public comment for more than 90 days. No comments were received. The SM3 Expert Committee has approved the monograph as an Authorized USP Pending Monograph.

The liquid chromatographic procedures in the *Assay* and the test for *Organic Impurities*, although different, are both based on analyses performed with the 5- μ m Inertsil ODS 3V brand of L1 column. The typical retention times for rivastigmine are about 11–13 min for the *Assay* and about 23 min for *Organic Impurities*.

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Rivastigmine Tartrate Oral Solution

v.1 Authorized January 1, 2011

DEFINITION

Rivastigmine Tartrate Oral Solution contains an amount of Rivastigmine Tartrate equivalent to NLT 95.0% and NMT 105.0% of the labeled amount of rivastigmine (C₁₄H₂₂N₂O₂). It contains sodium benzoate or other suitable preservatives.

IDENTIFICATION

- The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

PROCEDURE

Buffer: To 1 L of a 1.15 g/L solution of monobasic ammonium phosphate in water, add 1 mL of triethylamine. Adjust with phosphoric acid to a pH of 5.6, and pass through a suitable filter of 0.45- μ m pore size.

Mobile phase: Acetonitrile and *Buffer* (16:84)

Standard stock solution: 1.6 mg/mL of USP Rivastigmine Tartrate RS in *Mobile phase*. [NOTE—Use sonication if necessary.]

Sodium benzoate stock solution: 0.5 mg/mL of USP Sodium Benzoate RS in *Mobile phase*. [NOTE—Use sonication if necessary.]

Standard solution: Transfer 5 mL each of *Standard stock solution* and *Sodium benzoate stock solution* to a 50-mL volumetric flask, and dilute with *Mobile phase* to volume. This solution contains 0.16 mg/mL of rivastigmine tartrate and 0.05 mg/mL of sodium benzoate.

Sample solution: Transfer a portion of the Oral Solution, equivalent to about 10 mg of rivastigmine, to a 100-mL volumetric flask. Add 60 mL of *Mobile phase*, and sonicate for about 2 min. Dilute with *Mobile phase* to volume, mix well, and pass through a suitable filter of 0.45- μ m pore size.

Chromatographic system

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

Mode: LC

Detector: UV 217 nm

Column: 4.6-mm \times 25-cm; 5- μ m packing L1

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection size: 20 μ L

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for benzoic acid and rivastigmine are 0.3 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 8.0 between benzoic acid and rivastigmine

Column efficiency: NLT 5000 theoretical plates, determined from the rivastigmine peak

Tailing factor: NMT 1.8, determined from the rivastigmine peak

Relative standard deviation: NMT 1.0% for each peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of rivastigmine (C₁₄H₂₂N₂O₂) in the portion of Oral Solution 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 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 = nominal 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: 95.0%–105.0%

OTHER COMPONENTS

CONTENT OF SODIUM BENZOATE (IF PRESENT)

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the quantity, in mg, of sodium benzoate in each mL of the Oral Solution:

$$\text{Result} = (r_u/r_s) \times (C_s/D)$$

r_u = peak response of benzoic acid from the *Sample solution*

r_s = peak response of benzoic acid from the *Standard solution*

C_s = concentration of USP Sodium Benzoate RS in the *Standard solution* (mg/mL)

D = dilution factor of the *Sample solution*

Calculate the percentage of the labeled amount of sodium benzoate in the portion of Oral Solution taken:

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times 100$$

r_u = peak response of benzoic acid from the *Sample solution*

r_s = peak response of benzoic acid from the *Standard solution*

C_s = concentration of USP Sodium Benzoate RS in the *Standard solution* (mg/mL)

C_u = nominal concentration of sodium benzoate in the *Sample solution* (mg/mL)

Acceptance criteria: 0.900–1.100 mg of sodium benzoate in each mL of Oral Solution; 90.0%–110.0% of the labeled amount of sodium benzoate

PERFORMANCE TESTS

- DELIVERABLE VOLUME (698):** Meets the requirements

IMPURITIES

Organic Impurities

PROCEDURE

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

Solution A: Acetonitrile and *Buffer* (8:92)

Solution B: Acetonitrile and *Buffer* (75:25)

Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	100	0
8	100	0
25	80	20
35	80	20
40	30	70

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Time (min)	Solution A (%)	Solution B (%)
45	30	70
47	100	0
55	100	0

Standard solution: 0.008 mg/mL of USP Rivastigmine Tartrate RS in water. [NOTE—Use sonication if necessary.]

Sample solution: Dilute a portion of Oral Solution with water to volume to obtain a solution with a nominal concentration of 0.5 mg/mL of rivastigmine, and pass through a suitable filter of 0.45- μ m pore size.

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Column efficiency: NLT 80,000 theoretical plates

Relative standard deviation: NMT 5%

Analysis

Samples: *Standard solution* and *Sample solution*

[NOTE—Identify the peaks using the relative retention times provided in *Impurity Table 1*.]

Calculate the percentage of each impurity in the portion of Oral Solution 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 each individual 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 = nominal 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 *Impurity Table 1*)

Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Total impurities: NMT 1.0%. [NOTE—If sodium benzoate is present in the formulation, disregard a peak due to benzoic acid eluting at a relative retention time of about 0.3.]

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Tartaric acid	0.08	—	Disregard
Phenol impurity ^a	0.18	1.4	0.6
Rivastigmine	1.0	—	—
Any other individual impurity	—	1.0	0.2

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

SPECIFIC TESTS

- **MICROBIAL ENUMERATION TESTS** (61) and **TESTS FOR SPECIFIED MICROORGANISMS** (62): The total aerobic microbial count does not exceed 100 cfu/mL, and the total combined molds and yeasts count does not exceed 10 cfu/mL. It meets the requirements of the tests for absence of *Escherichia coli*.
- **PH** (791): 3.5–4.5

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers and store at controlled room temperature. Protect from freezing.
- **LABELING:** Label it to indicate the name and quantity of any added preservative.
- **USP REFERENCE STANDARDS** (11)
USP Rivastigmine Tartrate RS
USP Sodium Benzoate RS