Rivastigmine Tartrate Capsules

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Expert Committee	Chemical Medicines Monographs 3
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 3 Expert Committee has revised the Rivastigmine Tartrate Capsules monograph. The purpose of the revision is to add *Dissolution Test 2* for a drug product approved by the FDA.

Dissolution Test 2 was validated using a BDS Hypersil C-8, 25 cm x 4.6 mm, 5µm brand L7 column. The typical retention time for rivastigmine is about 10.4 min.

The Rivastigmine Tartrate Capsules Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *Second Supplement* to *USP 41–NF 36*.

Should you have any questions, please contact Andrea F. Carney, Associate Scientific Liaison, (301-816-8155 or afc@usp.org).

*This Revision Bulletin was originally posted on January 26, 2018. It was revised to correct a typographical error.

Rivastigmine Tartrate Capsules

DEFINITION

Rivastigmine Tartrate Capsules contain an amount of Rivastigmine Tartrate equivalent to NLT 94.0% and NMT 105.0% of the labeled amount of rivastigmine ($C_{14}H_{22}N_2O_2$).

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

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

Standard solution: 0.064 mg/mL of USP Rivastigmine Tartrate RS in *Mobile phase*. [NOTE—Use a small amount of methanol (about 2% of the final volume) to facilitate dissolution before diluting with *Mobile phase* to volume, and use sonication if necessary.]

System suitability solution: 0.01 mg/mL each of USP Rivastigmine Related Compound A RS and USP Rivastigmine Related Compound B RS in *Mobile phase*

Sample solution: Remove as completely as possible the contents of NLT 20 Capsules, and mix. Transfer a weighed portion of the combined contents, equivalent to about 48 mg of rivastigmine, to a 250-mL volumetric flask. Add 25 mL of methanol and 60 mL of *Mobile phase*, and sonicate for 15 min to disperse the contents. Dilute with *Mobile phase* to volume, mix well, and centrifuge. Dilute a portion of the supernatant with *Mobile phase* to obtain a solution having a concentration of 0.038 mg/mL of rivastigmine, based on the label claim.

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: 1.5 mL/min

Injection size: 20 µL

System suitability

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

[NOTE—The relative retention times for rivastigmine related compound A, rivastigmine related compound B, and rivastigmine are 0.46, 0.57, and 1.0, respectively.]

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 2.3, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{14}H_{22}N_2O_2$ in the portion of Capsules 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: 94.0%–105.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

•**Test 1**• (RB 1-Feb-2018)

Medium: Water; 500 mL, deaerated

Apparatus 2: 50 rpm, with sinkers, if necessary

Time: 30 min

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

Standard solution: 0.192 mg/mL of USP Rivastigmine Tartrate RS in *Mobile phase*. Further dilute with *Medium* to obtain a solution having a concentration similar to that expected in the *Sample solution*.

Sample solutions: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first few mL.

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

[NOTE—Use an injection size of 100 µL.]

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{14}H_{22}N_2O_2$ dissolved:

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

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)
M_{r1} = molecular weight of rivastigmine, 250.34
M_{r2} = molecular weight of rivastigmine tartrate, 400.42
V = volume of *Medium* (mL), 500
L = Capsule label claim (mg)

Tolerances: NLT 75% (*Q*) of the labeled amount of $C_{14}H_{22}N_2O_2$ is dissolved.

•**Test 2:** If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

Medium: Deaerated water; 500 mL

Apparatus 2: 75 rpm

Time: 15 min

Buffer and **Mobile phase:** Proceed as directed in the *Assay*.

Standard solution: 0.192 mg/mL of USP Rivastigmine Tartrate RS in *Mobile phase*. Further dilute with *Medium* to obtain a solution having a concentration similar to that expected in the *Sample solution*.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first few milliliters.

Chromatographic system: Proceed as directed in the *Assay*. [NOTE—Use an injection volume of 100 µL.]
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0%
Tailing factor: NMT 2.3
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of rivastigmine ($C_{14}H_{22}N_2O_2$) dissolved:

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

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)
M_{r1} = molecular weight of rivastigmine, 250.34
M_{r2} = molecular weight of rivastigmine tartrate, 400.42
V = volume of *Medium* (mL), 500
L = label claim (mg/Capsule)

Tolerances: NLT 80% (Q) of the labeled amount of rivastigmine ($C_{14}H_{22}N_2O_2$) is dissolved.● (RB 1-Feb-2018)

- **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

IMPURITIES

Organic Impurities

- **PROCEDURE**

Buffer, Mobile phase, and **System suitability solution:** Prepare as directed in the *Assay*.
Standard solution: 1.6 µg/mL of USP Rivastigmine Tartrate RS in *Mobile phase*
Sample solution: Remove as completely as possible the contents of NLT 20 Capsules, and mix. Transfer a weighed portion of the combined contents, equivalent to 25 mg of rivastigmine, to a 25-mL volumetric flask. Disperse in 10 mL of *Mobile phase*, and sonicate for 15 min. Dilute with *Mobile phase* to volume, mix well, and centrifuge. Use the supernatant.
Chromatographic system: Proceed as directed in the *Assay*.
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 10.0%, *Standard solution*
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 Capsules 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%

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Phenol impurity[a]	0.28	1.6	0.6
Rivastigmine	1.0	1.0	—
Any other individual impurity	—	1.0	0.2
Total impurities	—	—	1.0

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

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.

Add the following:

●• **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.● (RB 1-Feb-2018)

- **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