Edition: BP 2025 (Ph. Eur. 11.6 update)

Rivastigmine Capsules

General Notices

Action and use

Cholinesterase inhibitor; treatment of dementia in Alzheimer's disease and Parkinson's disease.

DEFINITION

Rivastigmine Capsules contain Rivastigmine Hydrogen Tartrate.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of rivastigmine, $C_{14}H_{22}N_2O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) Shake a quantity of the powdered capsule contents containing the equivalent of 9 mg of rivastigmine with 15 mL of *methanol* and mix with the aid of ultrasound. Add sufficient *methanol* to produce 25 mL and filter (a 0.45-µm Nylon filter is suitable).
(2) 0.058% w/v of *rivastigmine hydrogen tartrate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 10 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

2 volumes of *formic acid*, 5 volumes of *water*, 30 volumes of *methanol* and 70 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 500 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with the dissolution medium if necessary, to produce a solution expected to contain the equivalent of 0.0003% w/v of rivastigmine.
(2) 0.00048% w/v of *rivastigmine hydrogen tartrate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient a column temperature.
(e) Use a detection wavelength of 215 nm.
(f) Inject 100 µL of each solution.

MOBILE PHASE

15 volumes of *acetonitrile R1*, 15 volumes of *methanol* and 70 volumes of a 0.86% w/v solution of *ammonium dihydrogen orthophosphate* that has been previously adjusted to pH 7.0 with *dilute ammonia solution*.

DETERMINATION OF CONTENT

Calculate the total content of rivastigmine, $C_{14}H_{22}N_2O_2$, in the medium from the chromatograms obtained and using the declared content of $C_{18}H_{28}N_2O_8$ in *rivastigmine hydrogen tartrate BPCRS*. Each mg of $C_{18}H_{28}N_2O_8$ is equivalent to 0.6251 mg of $C_{14}H_{22}N_2O_2$.

LIMITS

The amount of rivastigmine released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase and protected from light.

(1) Shake a quantity of the capsule contents containing the equivalent of 50 mg of rivastigmine with 30 mL. Mix with the aid of ultrasound and add sufficient of the mobile phase to produce 50 mL.
(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume of the resulting solution to 5 volumes.
(3) 0.1% w/v of *rivastigmine for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleodur C18 EC Gravity is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 214 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for twice the retention time of rivastigmine.

MOBILE PHASE

42 volumes of a 0.895% w/v solution of *disodium hydrogen orthophosphate dihydrate* previously adjusted to pH 7.0 with *orthophosphoric acid* and 58 volumes of *methanol R1*.

When the chromatograms are recorded under the prescribed conditions the relative retentions with reference to rivastigmine (retention time about 9 minutes) are: impurity A, about 0.4; impurity C, about 0.6 and impurity B, about 0.7.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurities C and B is at least 2.0.

LIMITS

Identify any peak corresponding to impurity C in the chromatogram obtained with solution (1) using the chromatogram obtained with solution (3) and multiply the area of any such peak by a correction factor of 0.6.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Uniformity of content

Capsules containing less than 2 mg and/or less than 2% w/w of Rivastigmine Hydrogen Tartrate comply with the requirements stated under Capsules using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase and protected from light.

(1) Add 5 mL of mobile phase to the contents of one capsule and mix with the aid of ultrasound until completely dispersed. Shake, dilute to produce a solution expected to contain the equivalent of 0.01% w/v of rivastigmine and filter (a 0.45-µm Nylon filter is suitable).
(2) 0.016% w/v of *rivastigmine hydrogen tartrate BPCRS*.
(3) 0.1% w/v of *rivastigmine for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurities C and B is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of rivastigmine, $C_{14}H_{22}N_2O_2$, in the each capsule from the chromatograms obtained and using the declared content of $C_{18}H_{28}N_2O_8$ in *rivastigmine hydrogen tartrate BPCRS*. Each mg of $C_{18}H_{28}N_2O_8$ is equivalent to 0.6251 mg of $C_{14}H_{22}N_2O_2$.

ASSAY

For capsules containing the equivalent of less than 2 mg and/or less than 2% w/w of Rivastigmine Hydrogen Tartrate

Use the average of the individual results determined in the test for Uniformity of content.

For capsules containing the equivalent of 2 mg or more and 2% w/w or more of Rivastigmine Hydrogen Tartrate

Weigh the contents of 20 capsules. Mix and powder if necessary. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase and protected from light.

(1) Shake a quantity of the capsule contents containing the equivalent of 50 mg of rivastigmine with the mobile phase. Mix with the aid of ultrasound, dilute to 50 mL and filter (a 0.45-µm Nylon filter is suitable). Dilute 1 volume of this solution to 10 volumes.
(2) 0.016% w/v of *rivastigmine hydrogen tartrate BPCRS*.
(3) 0.1% w/v of *rivastigmine for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurities C and B is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of rivastigmine, $C_{14}H_{22}N_2O_2$, in the capsules from the chromatograms obtained and using the declared content of $C_{18}H_{28}N_2O_8$ in *rivastigmine hydrogen tartrate BPCRS*. Each mg of $C_{18}H_{28}N_2O_8$ is equivalent to 0.6251 mg of $C_{14}H_{22}N_2O_2$.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and C listed under Rivastigmine Hydrogen Tartrate.