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

Fluvastatin Capsules

General Notices

Action and use

HMG Co-A reductase inhibitor; lipid regulating drug.

DEFINITION

Fluvastatin Capsules contain Fluvastatin Sodium.

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

Content of fluvastatin, $C_{24}H_{26}FNO_4$

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) Mix with the aid of ultrasound a quantity of capsule contents containing the equivalent of 20 mg of fluvastatin with 25 mL of *methanol*. Dilute to 100 mL with *methanol*, filter through a 0.45-µm nylon filter and use the filtrate.
(2) 0.021% w/v of *fluvastatin sodium 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 5 µL of each solution.
(d) Develop the plate to 8 cm.
(e) After removal of the plate, dry in air and examine under *ultraviolet light (366 nm)*.

MOBILE PHASE

1 volume of *glacial acetic acid*, 9 volumes of *toluene*, 15 volumes of *methanol* and 25 volumes of *ethyl acetate*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour 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 principal 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, and rotate the paddle at 50 revolutions per minute.
(b) Use 900 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 30 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with sufficient dissolution medium, if necessary, to produce a solution expected to contain the equivalent of 0.0022% w/v of fluvastatin.
(2) 0.0023% w/v of *fluvastatin sodium BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (YMC Pack Pro S C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 305 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

200 volumes of *acetonitrile*, 300 volumes of *methanol* and 500 volumes of 0.069M *tetramethylammonium hydroxide*, previously adjusted to pH 7.2 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the total content of fluvastatin, $C_{24}H_{26}FNO_4$, in the medium from the chromatograms obtained and using the declared content of $C_{24}H_{25}FNNaO_4$ in *fluvastatin sodium BPCRS*. Each mg of $C_{24}H_{25}FNNaO_4$ is equivalent to 0.950 mg of $C_{24}H_{26}FNO_4$.

LIMITS

The amount of fluvastatin released is not less than 80% (Q) of the stated amount.

Related substances

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

(1) Dissolve a quantity of the contents of the capsules containing the equivalent of 25 mg of fluvastatin in 20 mL of mobile phase B. Add sufficient mobile phase A to produce a solution containing the equivalent of 0.05% w/v of fluvastatin and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with mobile phase A.
(3) Dilute 1 volume of solution (2) to 5 volumes with mobile phase A.
(4) Dissolve the contents of a vial of *fluvastatin for system suitability EPCRS* in 1 mL of a mixture of equal volumes of mobile phase A and mobile phase B.
(5) 0.0005% w/v of *fluvastatin impurity F BPCRS* a mixture of equal volumes of mobile phase A and mobile phase B.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3 µm) (YMC Pack pro C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 40°.

(e) Use detection wavelengths of 305 nm and 365 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A Add 20 volumes of 1.38M *tetramethylammonium hydroxide* to 880 volumes of *water* and adjust to pH 7.2 with *orthophosphoric acid*; mix with 40 volumes of *acetonitrile* and 60 volumes of *methanol*.

Mobile phase B Add 20 volumes of 1.38M *tetramethylammonium hydroxide* to 80 volumes of *water* and adjust to pH 7.2 with *orthophosphoric acid*; mix with 360 volumes of *acetonitrile* and 540 volumes of *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-3	70	30	isocratic
3-23	70→10	30→90	linear gradient
23-28	10	90	isocratic
28-30	10→70	90→30	linear gradient
30-35	70	30	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to fluvastatin (retention time about 14 minutes) are: impurity A, about 1.05; impurity D, about 1.1; impurity F, about 1.2; and impurity B, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3) at 305 nm, the *peak-to-valley ratio* is at least 5 where H_p is the height above the baseline of the peak due to impurity A and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to fluvastatin.

LIMITS

Use the chromatogram supplied with *fluvastatin for system suitability EPCRS* and the chromatogram obtained with solution (4) to identify the peaks due to impurities A, B and D.

Use the chromatogram supplied with *fluvastatin impurity F BPCRS* and the chromatogram obtained with solution (5) to identify the peak due to impurity F in the chromatogram obtained with solution (1).

At a detection wavelength of 305 nm

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (1.0%);

the area of any peak corresponding to impurity A is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.8%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%);

Disregard any peak with an area less than half the area of the principal peak nm in the chromatogram obtained with solution (3) (0.1%).

At a detection wavelength of 365 nm

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D at 365 nm is not greater than half the area of the principal peak at 305 nm in the chromatogram obtained with solution (2) (0.5%).

ASSAY

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

(1) Dissolve a quantity of the mixed contents of 20 capsules containing the equivalent of 25 mg of fluvastatin in 50 mL of mobile phase. Dilute 1 volume to 10 volumes with the mobile phase (to produce a solution containing the equivalent of 0.005% w/v of fluvastatin) and filter.
(2) 0.0053% w/v of *fluvastatin sodium BPCRS* in the mobile phase.
(3) Dissolve the contents of a vial of *fluvastatin for system suitability EPCRS* in 1 mL of the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution 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 fluvastatin and impurity A is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{24}H_{26}FNO_4$, in the capsules using the declared content of $C_{24}H_{25}FNNaO_4$ in *fluvastatin sodium BPCRS*. Each mg of $C_{24}H_{25}FNNaO_4$ is equivalent to 0.950 mg of $C_{24}H_{26}FNO_4$.

STORAGE

Fluvastatin Capsules should be protected from light.

LABELLING

The quantity of the active ingredient is stated in terms of the equivalent amount of fluvastatin.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Fluvastatin Sodium.