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

Haloperidol Capsules

General Notices

Action and use

Dopamine receptor antagonist; neuroleptic.

DEFINITION

Haloperidol Capsules contain Haloperidol.

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

Content of haloperidol, $C_{21}H_{23}ClFNO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

To a quantity of the contents of the capsules containing 10 mg of Haloperidol add 10 mL of *water* and 1 mL of 1M *sodium hydroxide* and extract with 10 mL of *ether*. Filter the ether extract through absorbent cotton, evaporate the filtrate to dryness and dry the residue at 60° at a pressure not exceeding 0.7 kPa. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of haloperidol *(RS 173)*.

TESTS

Dissolution

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

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.
(b) Use 900 mL of a solution containing of 0.2% w/v of *sodium chloride* and 8% v/v of 1M *hydrochloric acid* in *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium, filter and dilute with the dissolution medium if necessary, to produce a solution expected to contain 0.00006% w/v of Haloperidol.
(2) 0.00006% w/v of *haloperidol BPCRS* in dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 5 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 247 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

45 volumes of *acetonitrile* and 55 volumes of a 1% w/v solution of *ammonium acetate*.

DETERMINATION OF CONTENT

Calculate the total content of haloperidol, $C_{21}H_{23}ClFNO_2$, in the medium from the chromatograms obtained and using the declared content of $C_{21}H_{23}ClFNO_2$ in *haloperidol BPCRS*.

LIMITS

The amount of haloperidol released is not less than 70% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 1 volume of mobile phase A and 9 volumes of mobile phase B (solution A). Prepare the solutions immediately before use and protect from light.

(1) Shake a quantity of the contents of the capsules containing 10 mg of Haloperidol with 15 mL of solution A and mix with the aid of ultrasound. Dilute to 20 mL and filter.
(2) Dilute 1 volume of solution (1) to 200 volumes.
(3) 0.05% w/v of *haloperidol for system suitability EPCRS*.
(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *base-deactivated end-capped octadecylsilyl silica gel for chromatography* (3 µm) (Hypersil BDS is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 230 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 1.7% w/v of *tetrabutylammonium hydrogen sulfate*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	90	10	isocratic
2-17	90→50	10→50	linear gradient
17-22	50	50	isocratic
22-23	50→90	50→10	linear gradient
23-28	90	10	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to haloperidol (retention time about 8 minutes) are: impurity B, about 0.9 and impurity D, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and haloperidol is at least 3.0.

LIMITS

Identify any peak corresponding to impurity B in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of this peak by a correction factor of 0.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity B is not greater than 0.6 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 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Capsules containing less than 2 mg and/or less than 2% w/w of Haloperidol 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.

(1) Add sufficient of the mobile phase to the contents of one capsule to produce a solution containing 0.005% w/v of Haloperidol, disperse with the aid of ultrasound for 2 minutes, centrifuge and use the supernatant liquid.
(2) 0.005% w/v of *haloperidol BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Dissolution may be used with an injection volume of 20 µL.

DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{23}ClFNO_2$ in each capsule using the declared content of $C_{21}H_{23}ClFNO_2$ in *haloperidol BPCRS*.

ASSAY

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

IMPURITIES

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