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

Risperidone Tablets

General Notices

Action and use

Dopamine D_2 receptor antagonist; serotonin $5HT_2$ receptor antagonist; neuroleptic.

DEFINITION

Risperidone Tablets contain Risperidone.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of risperidone, $C_{23}H_{27}FN_4O_2$

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 in *methanol*.
(1) Disperse a quantity of powdered tablets containing 2 mg of Risperidone in 15 mL, mix with the aid of ultrasound and dilute to 20 mL and filter.
(2) 0.01% w/v of *risperidone BPCRS*.
(3) 0.01% w/v each of *risperidone BPCRS* and *trazodone hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.
(b) Use the mobile phase as described below.
(c) Apply 20 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry it in a current of air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

3 volumes of *glacial acetic acid*, 5 volumes of *water* and 12 volumes of *butan-1-ol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

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 principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in 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 0.1M *hydrochloric acid*, 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, suitably diluted with 0.1M *hydrochloric acid* if necessary, expected to contain 0.00005% w/v of Risperidone.
(2) 0.00005% w/v *risperidone BPCRS* in 0.1M *hydrochloric acid*.
(3) 0.005% w/v of *risperidone impurity standard BPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 237 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

0.1 volumes of *trifluoroacetic acid*, 20 volumes of *acetonitrile* and 80 volumes of *water*, adjusting the pH of the mixture to 3.0 with 13.5M *ammonia*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to risperidone (retention time about 10 minutes) are impurity 2, about 0.65, impurity B, about 0.7 and impurity 1, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity 2 and impurity B is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of risperidone, $C_{23}H_{27}FN_4O_2$, in the medium from the chromatograms obtained and using the declared content of $C_{23}H_{27}FN_4O_2$ in *risperidone BPCRS*.

LIMITS

The amount of risperidone 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 immediately before use.

(1) To a quantity of the powdered tablets containing 5 mg of Risperidone add 10 mL of *water* and mix with the aid of ultrasound for 30 minutes. Add 40 mL of *methanol* to the mixture and mix with the aid of ultrasound for a further 15 minutes. Cool and filter through a suitable 0.45-µm filter.

(2) Dilute 1 volume of solution (1) to 200 volumes with 0.1M *hydrochloric acid*.
(3) Dilute 1 volume of solution (2) to 5 volumes with 0.1M *hydrochloric acid*.
(4) 0.01% w/v of *risperidone impurity standard BPCRS* with 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 2.5 mL per minute. Equilibrate the column for at least 30 minutes with *methanol* at the end of each run.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 275 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 0.1 volumes of *trifluoroacetic acid*, 20 volumes of *acetonitrile* and 80 volumes of *water*, adjusting the pH of the mixture to 3.0 with 13.5M *ammonia*.

Mobile phase B 0.1 volumes of *trifluoroacetic acid*, 39 volumes of *methanol* and 61 volumes of *water* adjusting the pH to 3.0 with 13.5M *ammonia*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-8	100	0	isocratic
8-16	100→0	0→100	linear gradient
16-20	0	100	isocratic
20-21	0→100	100→0	linear gradient
21-30	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to risperidone (retention time about 11 minutes) are impurity B, about 0.6; impurity 2, about 0.7 and impurity 1, about 1.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between impurity 2 and impurity B is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* corresponding to impurity 1 is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

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

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

the sum of the areas of any *secondary peaks* is not greater than 2.4 times the area of the principal peak in the chromatogram obtained with solution (2) (1.2%).

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

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Risperidone comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Place 1 tablet in a 50 mL volumetric flask, add 25 mL of 0.1M *hydrochloric acid*, mix with the aid of ultrasound for 30 minutes or until completely dispersed, dilute to volume with 0.1M *hydrochloric acid* and filter through a suitable 0.45-µm filter. Dilute a quantity of the filtrate, if necessary, with sufficient 0.1M *hydrochloric acid* to produce a solution expected to contain 0.0005% w/v of Risperidone.
(2) 0.0005% w/v of *risperidone BPCRS* in 0.1M *hydrochloric acid*.
(3) 0.005% w/v of *risperidone impurity standard BPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic procedure described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity 2 and impurity B is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{27}FN_4O_2$ in each tablet from the chromatograms obtained and from the declared content of $C_{23}H_{27}FN_4O_2$ in *risperidone BPCRS*.

ASSAY

For tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of Risperidone

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

For tablets containing the equivalent of 2 mg or more and 2% w/w or more of Risperidone

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

(1) To a quantity of the powdered tablets containing 10 mg of Risperidone add 50 mL of 0.1M *hydrochloric acid* and mix with the aid of ultrasound for 30 minutes. Dilute the mixture to 100 mL with 0.1M *hydrochloric acid* and filter. Dilute 1 volume of the resulting solution to 10 volumes with 0.1M *hydrochloric acid*.
(2) 0.001% w/v of *risperidone BPCRS* in 0.1M *hydrochloric acid*.
(3) 0.005% w/v of *risperidone impurity standard BPCRS* in 0.1M *hydrochloric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity 2 and impurity B is at least 1.5.

CHROMATOGRAPHIC CONDITIONS

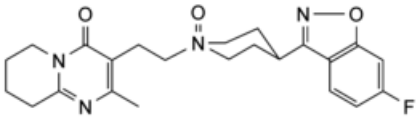
The chromatographic procedure described under Dissolution may be used.

DETERMINATION OF CONTENT

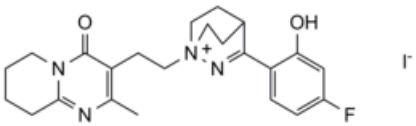
Calculate the total content of Risperidone, $C_{23}H_{27}FN_4O_2$, in the tablets from the chromatograms obtained and using the declared content of $C_{23}H_{27}FN_4O_2$ in *risperidone BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity B, listed under Risperidone and the following:



1. *cis*-4-(6-fluoro-1,2-benzoxazol-3-yl)-1-[2-(2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ethyl]piperidine *N*-oxide hydrate



2. 3-(4-fluoro-2-hydroxyphenyl)-1-[2-(2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)ethyl]-1,2-diazabicyclo[2.2.2]oct-2-en-1-ium iodide