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Nitrazepam Tablets

General Notices

Details for the public consultation of this monograph are as follows:

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Notes	Revised monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required. **Related substances** Correction factor for Impurity B and additional system suitability requirement introduced.

Action and use

Benzodiazepine.

DEFINITION

Nitrazepam Tablets contain Nitrazepam.

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

Content of Nitrazepam, $C_{15}H_{11}N_3O_3$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 30 mg of Nitrazepam with 10 mL of *acetone*, filter and evaporate to dryness. The *infrared absorption spectrum* of the dried residue, Appendix II A, is concordant with the *reference spectrum* of nitrazepam (*RS 482*).

TESTS

Carry out the following tests protected from light.

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia 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 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the *absorbance* of a layer of suitable thickness of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 280 nm, Appendix II B using 0.1M *hydrochloric acid* in the reference cell.
(2) Measure the *absorbance* of a suitable solution of *nitrazepam BPCRS* using 0.1M *hydrochloric acid* in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of nitrazepam, $C_{15}H_{11}N_3O_3$, in the medium from the absorbances obtained and using the declared content of $C_{15}H_{11}N_3O_3$ in *nitrazepam BPCRS*.

Related substances

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

(1) Shake a quantity of the powdered tablets containing 25 mg of Nitrazepam with 10 mL of *acetonitrile*, add sufficient *acetonitrile* to produce 20 mL and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with *acetonitrile*.
(3) 0.1% w/v of *nitrazepam BPCRS* and 0.002% w/v of *clonazepam BPCRS* in *acetonitrile*.
(4) Dilute 1 volume of solution (2) to 10 volumes with *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP8 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 270 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.05M *sodium dihydrogen orthophosphate*, adjusted to pH 3.0 with *orthophosphoric acid*.

Mobile phase B 20 volumes of mobile phase A and 80 volumes of *acetonitrile*.

When the chromatograms are recorded under the prescribed conditions the approximate retention time of nitrazepam is about 9 minutes. The retention times relative to nitrazepam are clonazepam, about 1.1; impurity A, about 1.3; impurity B, about 1.6.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0→3	55	45	isocratic
3→10	55→37	45→63	linear gradient
10→20	37	63	isocratic
20→22	37→55	63→45	linear gradient
22→30	55	45	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to nitrazepam and clonazepam is at least 1.3;

in the chromatogram obtained with solution (4), the *signal-to-noise ratio* is at least 20.

LIMITS

Identify any peak corresponding to impurity B in the chromatogram obtained with solution (1) and multiply the area of this peak by a correction factor of 1.8.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 0.5 times 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 0.5 times 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 0.2 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 the area of the principal peak in the chromatogram obtained with solution (2) (1%).

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

Tablets containing the equivalent of less than 2 mg and/or less than 2% w/w of nitrazepam, 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) Disperse one tablet with 30 mL of *acetonitrile* with the aid of ultrasound, add sufficient *acetonitrile* to produce 50 mL and filter. Dilute the filtrate, if necessary, to produce a solution containing 0.01% w/v of Nitrazepam.
(2) 0.01% w/v of *nitrazepam BPCRS* in *acetonitrile*.
(3) 0.01% w/v of *nitrazepam BPCRS* and 0.002% w/v of *clonazepam BPCRS* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Lichrospher RP8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 270 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

35 volumes of *acetonitrile* and 65 volumes of 0.05M *sodium dihydrogen orthophosphate*, previously adjusted to pH 3.0 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to nitrazepam and clonazepam is at least 1.3.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{11}N_3O_3$ in each tablet using the declared content of $C_{15}H_{11}N_3O_3$ in *nitrazepam BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of Nitrazepam

Use the average of the 10 individual results obtained in the test for Uniformity of content.

For tablets containing 2 mg or more and 2% w/w or more of Nitrazepam

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of powdered tablets containing 5 mg of Nitrazepam with 30 mL of *acetonitrile*, add sufficient *acetonitrile* to produce 50 mL and filter.
(2) 0.01% w/v of *nitrazepam BPCRS* in *acetonitrile*.
(3) 0.01% w/v of *nitrazepam BPCRS* and 0.002% w/v of *clonazepam BPCRS* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content 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 nitrazepam and clonazepam is at least 1.3.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{11}N_3O_3$ in the tablets using the declared content of $C_{15}H_{11}N_3O_3$ in *nitrazepam BPCRS*.

STORAGE

Nitrazepam Tablets should be protected from light.

IMPURITIES

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