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

Zolpidem Tablets

General Notices

Action and use

Non-benzodiazepine hypnotic.

DEFINITION

Zolpidem Tablets contain Zolpidem Tartrate. They are coated.

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

Content of zolpidem tartrate, $C_{42}H_{48}N_6O_8$

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 tablets containing 30 mg of Zolpidem Tartrate with 5 mL of *water*, centrifuge and filter the supernatant liquid through a 0.45-µm nylon filter. To the filtrate add 0.1 mL of *diethylamine* and dilute to 10 mL with *methanol*.
(2) Dissolve 15 mg of *zolpidem tartate BPCRS* in 2.5 mL of *methanol*, add 0.05 mL of *diethylamine* and dilute to 5 mL with *methanol*.
(3) Dilute 1 volume of solution (2) to 2 volumes with a 0.3% w/v solution of *flunitrazepam BPCRS* in *dichloromethane*.

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 described below.
(c) Apply 5 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

10 volumes of *diethylamine*, 45 volumes of *cyclohexane* and 45 volumes of *ethyl acetate*.

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 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 *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 dissolution 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 0.00055% w/v of Zolpidem Tartrate.
(2) 0.00055% w/v of *zolpidem* tartate *BPCRS* in the medium.
(3) 0.005% w/v each of *zolpidem tartrate BPCRS* and *zolpidem impurity A BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (4 µm) (Novapack C18 column 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 30°.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

18 volumes of *acetonitrile*, 23 volumes of *methanol* and 59 volumes of a solution containing 0.56% w/v of *orthophosphoric acid* adjusted to pH 5.5 with *triethylamine*.

SYSTEM SUITABILITY

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

DETERMINATION OF CONTENT

Calculate the total content of zolpidem tartrate, $C_{42}H_{48}N_6O_8$, in the medium from the chromatograms obtained and using the declared content of $C_{42}H_{48}N_6O_8$ in *zolpidem tartate BPCRS*.

LIMITS

The amount of Zolpidem Tartrate 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.

(1) Shake a quantity of the powdered tablets containing 10 mg of Zolpidem Tartrate with 80 mL of mobile phase A, mix with the aid of ultrasound, add sufficient mobile phase A to produce 100 mL and filter through a 0.45-µm nylon filter.
(2) Dilute 1 volume of solution (1) to 50 volumes with mobile phase A. Dilute 1 volume of this solution to 10 volumes with mobile phase A.

(3) 0.005% w/v each of *zolpidem tartrate BPCRS* and *zolpidem impurity A BPCRS* in mobile phase A.
(4) Dilute 1 volume of solution (2) to 2 volumes with mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.9 mm) packed with *octadecylsilyl silica gel for chromatography* (4 µm) (Novapack C18 column is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 18 volumes of *acetonitrile*, 23 volumes of *methanol* and 59 volumes of a solution containing 0.56% w/v of *phosphoric acid* adjusted to pH 5.5 with *triethylamine*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-20	100	0	isocratic
20-40	100→50	0→50	linear gradient
40-45	50	50	isocratic
45-46	50→100	50→0	linear gradient
46-60	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to zolpidem (retention time about 10.5 minutes) are: tartaric acid, about 0.16 and impurity A, about 0.8.

SYSTEM SUITABILITY

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

LIMITS

In the chromatogram obtained with solution (1):

the area of any *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 area of any *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 the area of the principal peak obtained with solution (4) (0.1%);

due to tartaric acid.

ASSAY

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

(1) Add 80 mL of the mobile phase to a quantity of the powdered tablets containing 10 mg of Zolpidem Tartrate and mix with the aid of ultrasound. Add sufficient mobile phase to produce 100 mL and filter through a 0.45-µm nylon filter. Dilute 1

volume of the filtrate to 10 volumes.
(2) 0.001% w/v of *zolpidem tartrate BPCRS*.
(3) 0.005% w/v each of *zolpidem tartrate BPCRS* and *zolpidem impurity A BPCRS*.

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 the peaks due to impurity A and zolpidem is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{42}H_{48}N_6O_8$ in the tablets using the declared content of $C_{42}H_{48}N_6O_8$ in *zolpidem tartrate BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed in the monograph for Zolpidem Tartrate.