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

Flucloxacillin Oral Solution

General Notices

Action and use

Penicillin antibacterial.

DEFINITION

Flucloxacillin Oral Solution is a solution of Flucloxacillin Sodium Monohydrate in a suitable flavoured vehicle. It is prepared by dissolving the dry ingredients in the specified volume of water just before issue for use.

The dry ingredients comply with the requirements for Powders and Granules for Oral Solutions and Oral Suspensions stated under Oral Liquids.

For the following tests prepare the oral solution as directed on the label. The solution, examined immediately after preparation unless otherwise indicated, complies with the requirements stated under Oral Liquids and with the following requirements.

Content of flucloxacillin, $C_{19}H_{17}ClFN_3O_5S$

When freshly constituted, not more than 120.0% of the stated amount. When stored at the temperature and for the period stated on the label during which the oral solution may be expected to be satisfactory for use, not less than 80.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) Dilute a quantity of the oral solution containing the equivalent of 50 mg of Flucloxacillin to 20 mL with *phosphate buffer pH 7.0*.
(2) 0.25% w/v of *flucloxacillin sodium BPCRS* in *phosphate buffer pH 7.0*.
(3) 0.25% w/v of each of *cloxacillin sodium BPCRS*, *dicloxacillin sodium BPCRS* and *flucloxacillin sodium BPCRS* in *phosphate buffer pH 7.0*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *TLC silica gel silanised plate* (Merck silanised silica gel 60 plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 1 µL of each solution.
(d) After removal of the plate, allow it to dry in air, expose to iodine vapour until the spots appear and examine in daylight.

MOBILE PHASE

30 volumes of *acetone* and 70 volumes of a 15.4% w/v solution of *ammonium acetate* adjusted to pH 5.0 with *glacial acetic acid*.

SYSTEM SUITABILITY

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

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position, colour and size 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 peak in the chromatogram obtained with solution (2).

TESTS

Acidity or alkalinity

pH, 4.0 to 7.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in 50% v/v of *acetonitrile*, protected from light.

(1) Dilute a volume of the oral solution containing the equivalent of 0.1 g of flucloxacillin to 100 mL with 50% v/v of *acetonitrile* and filter (a 0.45-µm filter is suitable).
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.001% w/v of *flucloxacillin impurity D EPCRS* and 0.1% w/v of *flucloxacillin sodium BPCRS*.
(4) 0.1% w/v of *flucloxacillin for peak identification EPCRS*.
(5) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *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 1.5 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 225 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.118% w/v *sodium hexanesulfonate monohydrate for ion-pair chromatography* in a mixture of 0.8 volumes of *concentrated ammonia* and 1000 volumes of *water for chromatography*. Adjust the pH of the resulting solution to pH 2.9 ± 0.1 with *orthophosphoric acid*.

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-30	80→45	20→55	linear gradient
30-35	45→35	55→65	linear gradient
35-40	35→80	65→20	linear gradient
40-45	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to flucloxacillin (retention time about 18 minutes) are: impurity C, about 0.1; impurity A (isomer 1), about 0.48; impurity A (isomer 2), about 0.50; impurity F, about 0.55; impurity G, about 0.65; impurity B (isomer 1), about 0.75; impurity B (isomer 2), about 0.8; impurity D, about 0.9; impurity H, about 1.2; impurity E, about 1.25; impurity I, about 1.35; impurity J, about 1.55 and impurity K, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between impurity D and flucloxacillin is at least 1.5.

in the chromatogram obtained with solution (5), the *signal-to-noise ratio* of the principal peak is at least 40.

LIMITS

Identify any peak corresponding to impurities B and C in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (4), and multiply the area of these peaks by a correction factor of 1.3 and 4.2 respectively.

In the chromatogram obtained with solution (1):

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

the sum of the areas of any peaks corresponding to impurity B is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

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

the area of any peak corresponding to impurity H 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 peaks corresponding to impurity F, I, J or K is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any peaks corresponding to impurity D or G is not greater than 0.3 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 0.2 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 10 times the area of the principal peak in the chromatogram obtained with solution (2) (10%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in 50% v/v of acetonitrile.

(1) Disperse a weighed quantity of the oral solution containing the equivalent of 0.5 g of flucloxacillin in 50% v/v of acetonitrile and dilute to 200 mL. Dilute 1 volume of the resulting solution to 25 volumes.
(2) 0.011% w/v of *flucloxacillin sodium BPCRS*.
(3) 0.0001% w/v of *flucloxacillin impurity D EPCRS* and 0.01% w/v of *flucloxacillin sodium BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *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 1.8 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 225 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A 0.118% w/v sodium hexanesulfonate monohydrate for ion-pair chromatography in a mixture of 0.8 volumes of *concentrated ammonia* and 1000 volumes of *water*. Adjust the pH of the resulting solution to pH 3.1 ± 0.1 with *orthophosphoric acid*.

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-8	65→41	35→59	linear gradient
8-12	41→65	59→35	linear gradient
12-18	65	35	re-equilibration

SYSTEM SUITABILITY

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

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, *Appendix V G*, and calculate the content of $C_{19}H_{17}ClFN_3O_5S$ weight in volume, using the declared content of $C_{19}H_{16}ClFN_3NaO_5S$ in *flucloxacillin sodium BPCRS*. Each mg of $C_{19}H_{16}ClFN_3NaO_5S$ is equivalent to 0.9538 mg of $C_{19}H_{17}ClFN_3O_5S$.

Repeat the procedure using a portion of the oral solution that has been stored at the temperature and for the period stated on the label during which it may be expected to be satisfactory for use.

STORAGE

The oral solution should be stored at the temperature and used within the period stated on the label.

LABELLING

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

IMPURITIES

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