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Phenoxymethylpenicillin Oral Solution

General Notices

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

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Notes:	Revision to monograph Addition of Related Substances procedure and specific impurity limits Revision to Assay procedure.

Action and use

Penicillin antibacterial.

DEFINITION

Phenoxymethylpenicillin Oral Solution is a solution of Phenoxymethylpenicillin Potassium 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 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 phenoxymethylpenicillin, $C_{16}H_{18}N_2O_5S$, calculated as the sum of the contents of phenoxymethylpenicillin and 4-hydroxyphenoxymethylpenicillin

When freshly constituted, not more than 120.0% of the stated amount of phenoxymethylpenicillin. 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 of phenoxymethylpenicillin.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

(1) Dilute a volume of the oral solution containing the equivalent of 0.1 g of phenoxymethylpenicillin to 100 mL with *mixed phosphate buffer pH 5.4*.
(2) 0.11% w/v of *phenoxymethylpenicillin potassium BPCRS* in *mixed phosphate buffer pH 5.4*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a *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) Develop the plate to 15 cm.
(e) After removal of the plate, allow it to dry in air, spray with 0.1M *sodium hydroxide*, heat at 50° for 10 minutes, allow to cool and spray with a mixture of 100 volumes of *starch mucilage*, 6 volumes of *glacial acetic acid* and 2 volumes of a 1% w/v solution of *iodine* in a 4% w/v solution of *potassium iodide*.

MOBILE PHASE

20 volumes of *acetone* and 80 volumes of *mixed phosphate buffer pH 5.4*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. Dilute a volume containing the equivalent of 25 mg of phenoxymethylpenicillin to 20 mL with *water*. To 10 mL add 0.5 mL of *neutral red solution* and sufficient 0.01M *sodium hydroxide* to produce a permanent orange colour and then add 1.0 mL of *penicillinase solution*. The colour changes rapidly to red.

TESTS

Related substances

Carry out the method for liquid chromatography *Appendix III D*, using the following solutions in solution A. Prepare immediately before use.

Solution A To 250 volumes of 0.2 M *potassium dihydrogren phosphate* add 500 volumes of *water*, adjust to pH 6.5 with a 0.84% w/v solution of *sodium hydroxide*, dilute to 1000 volumes with *water*

(1) Dilute a quantity of the oral solution containing the equivalent of 0.4% w/v of phenoxymethylpenicillin.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.4% w.v *phenoxymethylpenicillin for system suitability EPCRS* and 0.04% w/v *Sodium Benzoate* CRS
(4) Dilute 1 volume of solution (2) to 5 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm x 4.6 mm) packed with *end capped octadecylsilyl silica gel for chromatography* (3 µm) (YMC-Pack Pro 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 temparature of 50 °
(e) Use a detection wavelength of 254 nm
(f) Inject 20 µL of each solution

MOBILE PHASE

Mobile Phase A 10 volumes of phosphate buffer solution pH 3.4, 30 volumes of methanol, and 60 volumes of water

Mobile phase B 5 volumes of phosphate buffer solution pH 3.4, 35 volumes of water, and 60 volumes of methanol.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	85	15	isocratic
2-5	85→70	15→30	linear gradient
5-17	70→0	30→100	linear gradient
17-30	0	100	isocratic
30-31	0→85	100→15	linear gradient
31-40	85	15	re-equillibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to phenoxymethylpenicillin (retention time, about 11 minutes) are: impurity B, about 0.3; impurity D, about 0.4; impurity E, about 0.55 and 0.61; impurity F, about 0.88 and 0.95

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to the epimers of impurity F is at least 3.0

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to sodium benzoate and impurity E1 is at least 3.0

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities B, D, E, and F using the chromatogram supplied with *phenoxymethylpenicillin for system suitability EPCRS*, and the chromatogram obtained with solution (3).

Multiply the area of any peak corresponding to impurity B, D, and E by the following correction factors respectively: 0.6, 1.7, and 1.3.

In the chromatogram obtained with solution (1):

the sum of the areas of any peaks corresponding to the isomers of impurity E or the epimers impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0% of each);

the area of any peak corresponding to impurity B 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 peak corresponding to impurity D is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%);

the area of any other secondary peak is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of all the secondary peaks, other than impurity D, is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%).

Disregard any peak with an area less than 0.75 times the area of the principal peak in the chromatogram obtained with solution (4) (0.15%).

Disregard any peak that elutes before impurity B.

Disregard any peak that elutes after Phenoxymethylpenicillin

ASSAY

Carry out the method for liquid chromatography, Appendix III D, using the following solutions in solution A prepared immediately before use.

Solution A: To 250 volumes of 0.2 M *potassium dihydrogen phosphate* add 500 volumes of *water*, adjust to pH 6.5 with a 0.84% w/v solution of *sodium hydroxide*, and dilute to 1000 volumes with *water*

(1) Dilute a weighed quantity of the oral solution containing the equivalent of 0.1% w/v of phenoxymethylpenicillin.
(2) 0.11% w/v of *phenoxymethylpenicillin potassium BPCRS*

CHROMATOGRAPHIC CONDITIONS

Use the chromatographic conditions described under Related substances

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{18}N_2O_5S$ in the oral solution using the declared content of $C_{16}H_{18}N_2O_5S$ in phenoxymethylpenicillin potassium BPCRS.

Calculate the sum of the percentage contents of phenoxymethylpenicillin and 4-hydroxyphenoxymethylpenicillin (impurity D)

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 phenoxymethylpenicillin.