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

Hydroxyzine Oral Solution

General Notices

Action and use

Histamine H_1 receptor antagonist.

DEFINITION

Hydroxyzine Oral Solution contains Hydroxyzine Hydrochloride in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of hydroxyzine hydrochloride, $C_{21}H_{27}ClN_2O_2,2HCl$

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, prepared in a solution containing 1 volume of *dichloromethane* and 1 volume of *methanol* (solution A).
(1) Shake a quantity of the oral solution containing 50 mg of Hydroxyzine Hydrochloride with 10 mL of solution A. Centrifuge, allow to separate and use the lower layer.
(2) 1% w/v of *hydroxyzine hydrochloride BPCRS*.
(3) 0.5% w/v each of *hydroxyzine hydrochloride BPCRS* and *meclozine hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel*.
(b) Use the mobile phase as described below.
(c) Apply 30 µL of solution (1) and 2 µL of each of solutions (2) and (3).
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air, spray with *potassium iodobismuthate solution R2*, heat at 105° for 5 minutes and allow to cool.

MOBILE PHASE

1 volume of 13.5M *ammonia*, 24 volumes of *ethanol* and 75 volumes of *toluene*.

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 retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the peak due to hydroxyzine hydrochloride in the chromatogram obtained with solution (2).

TESTS

Acidity

pH, 2.7 to 3.0, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in a mixture of 1 volume of *acetonitrile* and 4 volumes of *water*.

(1) Dilute a quantity of the oral solution containing 5 mg of Hydroxyzine Hydrochloride to produce 50 mL and filter.
(2) Dilute 1 volume of solution (1) to 50 volumes. Further dilute 1 volume of the resulting solution to 10 volumes.
(3) 0.005% w/v each of *hydroxyzine hydrochloride BPCRS* and *decloxizine hydrochloride*.
(4) 0.00005% w/v of *4-chlorobenzophenone*.
(5) Dilute 1 volume of solution (2) to 4 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (2.7 µm) (Supelco Ascentis Express C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.6 mL per minute.
(d) Use a column temperature of 40°.
(e) Use detection wavelengths of 230 nm and 260 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.01M *potassium dihydrogen phosphate* adjusted to pH 3.0 with *dilute phosphoric acid*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-1	80	20	isocratic
1-10	80→70	20→30	linear gradient
10-25	70→10	30→90	linear gradient
25-27	10→80	90→20	linear gradient
27-30	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention time relative to hydroxyzine (retention time, about 9 minutes) are: impurity 1, about 0.44; impurity 2, about 0.81; impurity 3, about 0.83; impurity 4, about 0.85; impurity B, about 1.05; impurity 5, about 1.72 and impurity 6, about 2.0.

SYSTEM SUITABILITY

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

LIMITS

At 260 nm In the chromatogram obtained with solution (1):

identify any peak corresponding to impurity 6 using solution (4);

the area of any peak due to impurity 6 is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.5%).

At 230 nm In the chromatogram obtained with solution (1):

the area of impurity 1 is not greater than 2.5 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 the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the total impurities are not greater than 2.0%.

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

For formulations containing sugars Identify any peak corresponding to impurities 2, 3 and 4 using the retention time relative to hydroxyzine: impurity 2, about 0.81; impurity 3, about 0.83 and impurity 4, about 0.85.

In the chromatogram obtained with solution (1) at 230 nm:

the sum of the areas of impurity 2, impurity 3 and impurity 4 is not greater than 4.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.9%).

ASSAY

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

(1) To a quantity of the oral solution containing 50 mg of Hydroxyzine Hydrochloride, add 10 mL of *water*, 125 mL of *methanol* and add a sufficient quantity of a 30% v/v solution of *acetonitrile* to produce 250 mL. Dilute 5 mL of the filtrate to 10 mL with a 30% v/v solution of *acetonitrile*.
(2) 0.01% w/v of *hydroxyzine hydrochloride BPCRS* in a 30% v/v solution of *acetonitrile*.
(3) 0.01% w/v of *hydroxyzine hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Luna C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 230 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for 3 times the retention time of hydroxyzine.

MOBILE PHASE

14 volumes of *triethylamine*, 300 volumes of *acetonitrile* and 686 volumes of a 0.075% w/v solution of *sodium methanesulfonate*, adjust the mobile phase to pH 2.7 with *sulfuric acid*.

When the chromatograms are recorded under the prescribed conditions the retention time of hydroxyzine is about 9 min.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *peak-to-valley ratio* is at least 10, where H_p is the height above the baseline of the peak immediately before the peak due to hydroxyzine and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to hydroxyzine.

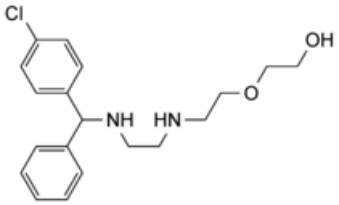
DETERMINATION OF CONTENT

Calculate the content of $C_{21}H_{27}ClN_2O_2,2HCl$ in the oral solution using the declared content of $C_{21}H_{27}ClN_2O_2,2HCl$ in *hydroxyzine hydrochloride BPCRS*.

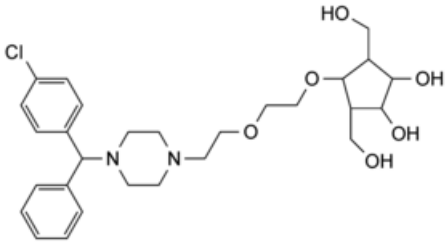
IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Hydroxyzine Hydrochloride and:

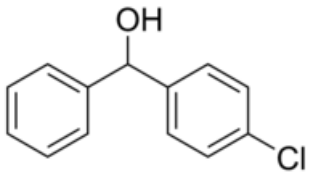
1. (2-(2-2((4-chlorophenyl)(phenyl)methylamino)ethylamino)ethanol);



2, 3 and 4. Isomers of an adduct formed by the interaction of hydroxyzine and fructose;



5. 4-chlorobenzhydrol;



6. 4-chlorobenzophenone