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

Nadolol Oral Suspension

General Notices

NOTE: *This monograph has been developed to cover unlicensed formulations.*

Action and use

Beta-adrenoceptor antagonist.

DEFINITION

Nadolol Oral Suspension is a suspension of Nadolol in a suitable vehicle.

The oral suspension complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral suspension also complies with the requirements stated under Unlicensed Medicines.

Content of nadolol, $C_{17}H_{27}NO_4$

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 in 0.1M *hydrochloric acid*.
(1) Dilute a quantity of the oral suspension containing 10 mg of Nadolol to 10 mL, centrifuge at 3500 rpm for 25 minutes and filter the supernatant liquid through a 0.45-µm nylon filter.
(2) 0.1% w/v of *nadolol BPCRS*.
(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a *silica gel* precoated plate (Merck silica gel 60 F_{254} plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 25 µL of each solution.
(d) Develop the plate to 10 cm.
(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of 2M *ammonium hydroxide*, 1 volume of *dichloromethane* and 8 volumes of *acetone*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) appears as a single compact spot.

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 retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Complies with the requirements stated under Unlicensed Medicines, Oral Suspensions. Use a volume of the oral suspension containing one dose.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use in a mixture of 1 volume of *acetonitrile R1* and 3 volumes of *water*.

(1) Disperse a quantity of the oral suspension containing 20 mg of Nadolol in 10 mL and shake for 10 minutes; dilute to contain 0.1% w/v of Nadolol and filter through a 0.45-µm nylon filter.
(2) Dilute 1 volume of solution (1) to 50 volumes and further dilute 1 volume to 20 volumes.
(3) Dissolve the contents of a vial of *nadolol impurity mixture EPCRS* in 1 mL of solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Lichrospher 100 RP 18 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 206 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.56% w/v of *sodium octanesulfonate*, adjusted to pH 3.5 with a 30% w/v solution of *orthophosphoric acid*.

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-7	84	16	isocratic
7-30	84→72	16→28	linear gradient
30-35	72→62	28→38	linear gradient
35-55	62	38	isocratic
55-56	62→84	38→16	linear gradient
56-60	84	16	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention time of nadolol is about 30 minutes and the relative retentions with respect to nadolol are: impurity A, about 0.14; impurity C (doublet), about 0.71 and 0.77; impurity D, about 1.2.

Use the chromatogram supplied with *nadolol impurity mixture EPCRS* and the chromatogram obtained with solution (3) to identify the peaks due to impurities A and D.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to nadolol and impurity D is at least 8.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurity C (doublet) and multiply the sum of the areas of the two peaks by the following correction factor: 0.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A, C or D is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2% of each);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of all the *secondary peaks* is not greater than five times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

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

(1) Disperse a weighed quantity of the oral suspension containing 20 mg of Nadolol in 75 mL of mobile phase A and shake for 15 minutes. Add sufficient mobile phase A to produce 100 mL and filter through a 0.45-µm nylon filter.
(2) 0.02% w/v of *nadolol BPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with spherical particles of silica the surface of which has been modified with chemically bonded dimethylsilyl groups (7 µm) (Nucleosil C2 is suitable).
(b) Use gradient 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 220 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 25 volumes of *methanol* and 75 volumes of mobile phase B.

Mobile phase B Dissolve 23.36 g of *sodium chloride* in 5200 mL of water, add 4 mL of 0.1M *hydrochloric acid* and mix.

Mobile phase C *methanol.*

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Mobile phase C (% v/v)	Comment
0-15	100	0	0	isocratic
15-16	100→0	0→50	0→50	linear gradient
16-25	0	50	50	isocratic wash step
25-26	0→100	0	0	linear gradient
26-35	100	0	0	re-equilibration

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{17}H_{27}NO_4$, weight in volume, using the declared content of $C_{17}H_{27}NO_4$ in *nadolol BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, C and D listed under Nadolol.