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

Nicorandil Tablets

General Notices

Action and use

Potassium channel opener; vasodilator.

DEFINITION

Nicorandil Tablets contain Nicorandil.

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

Content of nicorandil, $C_8H_9N_3O_4$

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.
Solvent A: 20 volumes of *methanol* and 80 volumes of *dichloromethane*.
(1) Dissolve a quantity of the powdered tablets containing 10 mg of Nicorandil in solvent A and mix with the aid of ultrasound. Add sufficient solvent A to produce a solution containing 0.1% w/v of Nicorandil and filter.
(2) 0.1% w/v of *nicorandil BPCRS* in *methanol*.
(3) 0.1% w/v each of *nicorandil BPCRS* and *nicotinamide BPCRS* in *methanol*.

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 as described below.
(c) Apply 10 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

1 volume of *methanol*, 4 volumes of *dichloromethane* and 5 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 in position 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 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 1, rotating the basket at 50 revolutions per minute.
(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

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

(1) After 30 minutes, withdraw a sample of the medium and filter (a 0.45-µm PTFE filter is suitable). Use the filtrate, diluted with dissolution medium if necessary, to give a solution expected to contain 0.0011% w/v of Nicorandil.
(2) 0.0011% w/v of *nicorandil BPCRS* in 0.1M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC pack ODS AQ 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 254 nm.
(f) Inject 40 µL of each solution.

MOBILE PHASE

Add 1.5 volumes of *trifluoroacetic acid* to 965 volumes of *water*. Separately mix 2 volumes of *triethylamine*, 10 volumes of *tetrahydrofuran* and 25 volumes of *methanol*. Mix the 2 solutions together.

When the chromatograms are recorded under the prescribed conditions the retention time of nicorandil is about 11 minutes.

DETERMINATION OF CONTENT

Calculate the total content of nicorandil, $C_8H_9N_3O_4$, in the medium from the chromatograms obtained and using the declared content of $C_8H_9N_3O_4$ in *nicorandil BPCRS*.

LIMITS

The amount of nicorandil released is not less than 80% (Q) of the stated amount.

Related substances

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

Solution A: 7 volumes of *methanol* and 93 volumes of *water*.
(1) To a quantity of the powdered tablets containing 0.1 g of Nicorandil, add 4 mL of *water* and 28 mL of *methanol* and shake. Add sufficient *water* to produce 100 mL and filter (a 0.45-µm membrane filter is suitable).
(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.
(3) 0.0004% w/v of *nicorandil impurity standard BPCRS* in solution A.
(4) Heat approximately 40 mg of *nicorandil BPCRS* for 2 hours at 70°. Allow to cool and dissolve a quantity of the material in sufficient solution A to produce a 0.8% w/v solution (generation of impurities 2, D, 4, 5 and 6).

(5) Dilute 1 volume of solution (2) to 5 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (YMC pack ODS AQ 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 254 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

Mobile phase A Add 1.5 volumes of *trifluoroacetic acid* to 965 volumes of *water*. Separately mix 2 volumes of *triethylamine*, 10 volumes of *tetrahydrofuran* and 25 volumes of *methanol*. Mix the 2 solutions together.

Mobile phase B *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-45	100	0	isocratic
45-80	100→75	0→25	linear gradient
80-82	75→100	25→0	linear gradient
82-92	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to nicorandil (retention time about 14 minutes) are: impurity 1, about 0.27; impurity B (nicorandil amide), about 0.31; impurity 2, about 0.36; impurity D (2-(3-pyridyl) 2-oxazoline), about 0.5; impurity 3, about 0.7; impurity 4, about 1.1; impurity 5, about 1.3 and impurity 6, about 1.6.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity 1 (nicotinic acid) and impurity B (nicorandil amide) is at least 1.5;

in the chromatogram obtained with solution (4), the *peak-to-valley ratio* is at least 4.5, where *Hp* is the height above the baseline of the peak due to impurity 4 and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to nicorandil.

LIMITS

Identify any peak in the chromatogram obtained with solution (1) due to impurity 4 using the chromatogram obtained with solution (4). Multiply the area of any peak corresponding to impurity 4 by a correction factor of 1.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D 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 4 is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of any other *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).

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

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

Solution A: 7 volumes of *methanol* and 93 volumes of *water*.
(1) To a quantity of the powdered tablets containing 0.1 g of Nicorandil, add 4 mL of *water* and 28 mL of *methanol* and shake. Add sufficient *water* to produce 100 mL and filter (a 0.45-µm PTFE filter is suitable). Dilute 1 volume to 20 volumes with *water*.
(2) 0.005% w/v of *nicorandil BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

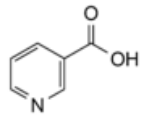
The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

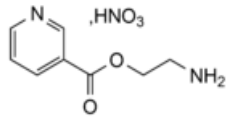
Calculate the content of $C_8H_9N_3O_4$ in the tablets using the declared content of $C_8H_9N_3O_4$ in *nicorandil BPCRS*.

IMPURITIES

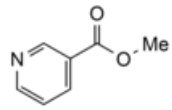
The impurities limited by the requirements of this monograph include impurities A, B and D listed under *Nicorandil* and:



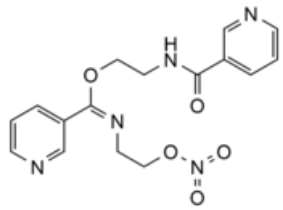
1. pyridine-3-carboxylic acid (nicotinic acid)



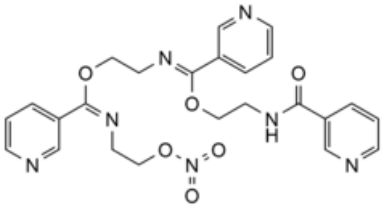
2. 2-aminoethyl pyridine-3-carboxylate nitrate (nicorandil nitrate)



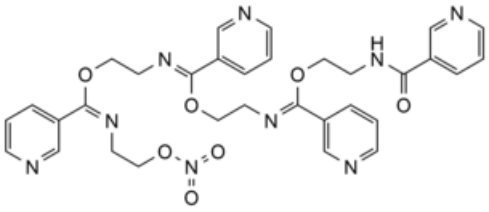
3. methyl pyridine-3-carboxylate (methyl nicotinate)



4. *N*-[2-({*N*-[2-(nitro-oxy)ethyl]pyridin-3-carboximidoyl}oxy)ethyl]pyridine-3-carboxamide (nicorandil dimer)



5. *N*-{2-[{*N*-[2-({*N*-[2-(nitro-oxy)ethyl]pyridin-3-carboximidoyl}oxy)ethyl]pyridin-3-carboximidoyl}oxy]ethyl}pyridine-3-carboxamide (nicorandil trimer)



6. *N*-{2-[(*N*-{2-[{*N*-[2-({*N*-[2-(nitro-oxy)ethyl]pyridin-3-carboximidoyl}oxy)ethyl]pyridin-3-carboximidoyl}oxy]ethyl}pyridin-3-carboximidoyl)oxy]ethyl}pyridine-3-carboxamide (nicorandil tetramer)