

STORAGE

In a well-filled, airtight container, protected from light and heat.

01/2008:1819

CINNAMON TINCTURE

Cinnamomi corticis tinctura

DEFINITION

Tincture produced from *Cinnamon* (0387).

PRODUCTION

The tincture is produced from 1 part of the drug and 5 parts of ethanol (70 per cent *V/V*) by an appropriate procedure.

CHARACTERS

Appearance: clear, brownish-red liquid, with a characteristic odour.

IDENTIFICATION

Thin-layer chromatography (2.2.27).

Test solution. Place 10 ml of the tincture to be examined, 10 ml of *saturated sodium chloride solution R* and 5 ml of *toluene R* in a ground glass-stoppered tube. Shake for 2 min and centrifuge for 10 min. Use the organic layer.

Reference solution. Dissolve 5 µl of *eugenol R*, 25 µl of *trans-cinnamic aldehyde R* and 5 µl of *trans-2-methoxycinnamaldehyde R* in *toluene R* and dilute to 10 ml with the same solvent.

Plate: TLC silica gel G plate *R*.

Mobile phase: *methylene chloride R*.

Application: 20 µl, as bands.

Development: over a path of 10 cm.

Drying: in air.

Detection A: examine in ultraviolet light at 365 nm.

Results A: see below the sequence of the zones present in the chromatograms obtained with the reference solution and the test solution.

| Top of the plate | |
|---|---|
| <i>Trans-2-methoxycinnamaldehyde</i> : a light blue fluorescent zone | A light blue fluorescent zone (<i>trans-2-methoxycinnamaldehyde</i>) |
| | A greenish fluorescent zone (above the starting line) |
| Reference solution | Test solution |

Detection B: spray with a 200 g/l solution of *phosphomolybdic acid R* in *ethanol R*. Examine in daylight while heating at 100-105 °C for 5-10 min.

Results B: see below the sequence of the zones present in the chromatograms obtained with the reference solution and the test solution. Furthermore, other zones may be present in the chromatogram obtained with the test solution.

| Top of the plate | |
|---|---|
| | 1 blue zone (terpenhydrocarbons) |
| Eugenol: a blue zone | A blue zone (eugenol) |
| <i>Trans-cinnamic aldehyde</i> : a blue zone | A blue zone (<i>trans-cinnamic aldehyde</i>) |
| <i>Trans-2-methoxycinnamaldehyde</i> : an orange-brown zone (the colour fades away) | A weak orange-brown zone (<i>trans-2-methoxycinnamaldehyde</i>) |
| | 2 or 3 blue zones above the starting line |
| Reference solution | Test solution |

TESTS

Ethanol (2.9.10): 64 per cent *V/V* to 70 per cent *V/V*.

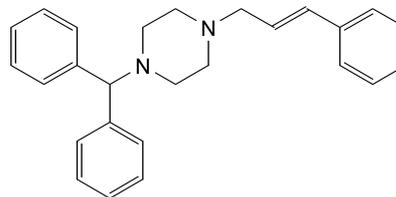
Methanol and 2-propanol (2.9.11): maximum 0.05 per cent *V/V* of methanol and maximum 0.05 per cent *V/V* of 2-propanol.

Dry residue (2.8.16): minimum 1.5 per cent *m/m*, determined on 5.0 g.

01/2008:0816
corrected 6.0

CINNARIZINE

Cinnarizinum



$C_{26}H_{28}N_2$
[298-57-7]

M_r 368.5

DEFINITION

(*E*)-1-(Diphenylmethyl)-4-(3-phenylprop-2-enyl)piperazine.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water, freely soluble in methylene chloride, soluble in acetone, slightly soluble in ethanol (96 per cent) and in methanol.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Melting point (2.2.14): 118 °C to 122 °C.

B. Infrared absorption spectrophotometry (2.2.24).

Preparation: discs.

Comparison: *cinnarizine CRS*.

C. Thin-layer chromatography (2.2.27).

Test solution. Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 20 ml with the same solvent.

Reference solution (a). Dissolve 10 mg of cinnarizine CRS in methanol R and dilute to 20 ml with the same solvent.

Reference solution (b). Dissolve 10 mg of cinnarizine CRS and 10 mg of flunarizine dihydrochloride CRS in methanol R and dilute to 20 ml with the same solvent.

Plate: TLC octadecylsilyl silica gel F₂₅₄ plate R.

Mobile phase: 1 M sodium chloride, methanol R, acetone R (20:30:50 V/V/V).

Application: 5 µl.

Development: in an unsaturated tank, over a path of 15 cm.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

System suitability: reference solution (b):

- the chromatogram shows 2 clearly separated spots.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with reference solution (a).

- D. Dissolve 0.2 g of anhydrous citric acid R in 10 ml of acetic anhydride R in a water-bath at 80 °C and maintain the temperature of the water-bath at 80 °C for 10 min. Add about 20 mg of the substance to be examined. A purple colour develops.

TESTS

Appearance of solution. The solution is clear (2.2.1) and not more intensely coloured than reference solution BY₇ (2.2.2, Method II).

Dissolve 0.5 g in methylene chloride R and dilute to 20 ml with the same solvent.

Acidity or alkalinity. Suspend 0.5 g in 15 ml of water R. Boil for 2 min. Cool and filter. Dilute the filtrate to 20 ml with carbon dioxide-free water R. To 10 ml of this solution add 0.1 ml of phenolphthalein solution R and 0.25 ml of 0.01 M sodium hydroxide. The solution is pink. To 10 ml of the solution add 0.1 ml of methyl red solution R and 0.25 ml of 0.01 M hydrochloric acid. The solution is red.

Related substances. Liquid chromatography (2.2.29).

Test solution. Dissolve 25.0 mg of the substance to be examined in methanol R and dilute to 10.0 ml with the same solvent.

Reference solution (a). Dissolve 12.5 mg of cinnarizine CRS and 15.0 mg of flunarizine dihydrochloride CRS in methanol R and dilute to 100.0 ml with the same solvent. Dilute 1.0 ml of this solution to 20.0 ml with methanol R.

Reference solution (b). Dilute 1.0 ml of the test solution to 100.0 ml with methanol R. Dilute 5.0 ml of this solution to 20.0 ml with methanol R.

Column:

- size: $l = 0.1$ m, $\varnothing = 4.0$ mm;
- stationary phase: base-deactivated octadecylsilyl silica gel for chromatography R (3 µm).

Mobile phase:

- mobile phase A: 10 g/l solution of ammonium acetate R;
- mobile phase B: 0.2 per cent V/V solution of glacial acetic acid R in acetonitrile R1;

| Time (min) | Mobile phase A (per cent V/V) | Mobile phase B (per cent V/V) |
|------------|-------------------------------|-------------------------------|
| 0 - 20 | 75 → 10 | 25 → 90 |
| 20 - 25 | 10 | 90 |

If necessary, adjust the concentration of glacial acetic acid in mobile phase B to obtain a horizontal baseline in the chromatogram.

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 230 nm.

Equilibration: with the mobile phase at the initial composition for at least 30 min.

Injection: 10 µl; inject methanol R as a blank.

Retention time: cinnarizine = about 11 min; flunarizine = about 11.5 min.

System suitability: reference solution (a):

- resolution: minimum 5.0 between the peaks due to cinnarizine and flunarizine; if necessary, adjust the time programme for the gradient elution.

Limits:

- impurities A, B, C, D, E: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent);
- total: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
- disregard limit: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak due to the blank.

Heavy metals (2.4.8): maximum 20 ppm.

Dissolve 1.0 g in a mixture of 15 volumes of water R and 85 volumes of acetone R. Add dilute hydrochloric acid R until dissolution is complete. Dilute to 20 ml with a mixture of 15 volumes of water R and 85 volumes of acetone R. 12 ml of the solution complies with test B. Prepare the reference solution using 10 ml of lead standard solution (1 ppm Pb) obtained by diluting lead standard solution (100 ppm Pb) with a mixture of 15 volumes of water R and 85 volumes of acetone R.

Loss on drying (2.2.32): maximum 0.5 per cent, determined on 1.000 g by drying in an oven *in vacuo* at 60 °C for 4 h.

Sulphated ash (2.4.14): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.150 g in 50 ml of a mixture of 1 volume of anhydrous acetic acid R and 7 volumes of ethyl methyl ketone R. Titrate with 0.1 M perchloric acid, using 0.2 ml of naphtholbenzein solution R as indicator.

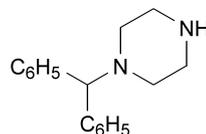
1 ml of 0.1 M perchloric acid is equivalent to 18.43 mg of C₂₆H₂₈N₂.

STORAGE

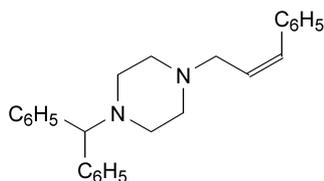
Protected from light.

IMPURITIES

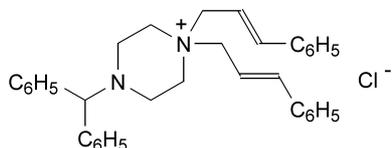
Specified impurities: A, B, C, D, E.



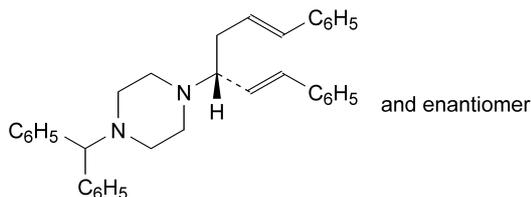
A. 1-(diphenylmethyl)piperazine,



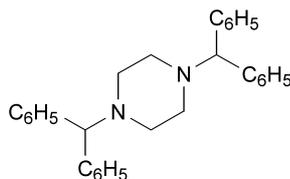
B. (Z)-1-(diphenylmethyl)-4-(3-phenylprop-2-enyl)piperazine,



C. (4-(diphenylmethyl)-1,1-bis[(E)-3-phenylprop-2-enyl]piperazinium chloride,



D. 1-(diphenylmethyl)-4-[(1R,3E)-4-phenyl-1-(E)-2-phenylethenyl]but-3-enyl]piperazine,



E. 1,4-bis(diphenylmethyl)piperazine.

Comparison: ciprofibrate CRS.

TESTS

Appearance of solution. The solution is clear (2.2.1) and not more intensely coloured than reference solution BY₄ (2.2.2, Method II).

Dissolve 1.0 g in *anhydrous ethanol R* and dilute to 10.0 ml with the same solvent.

Related substances. Liquid chromatography (2.2.29).

Test solution. Dissolve 0.125 g of the substance to be examined in a mixture of equal volumes of *acetonitrile R* and *water R* and dilute to 50 ml with the same mixture of solvents.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with a mixture of equal volumes of *acetonitrile R* and *water R*. Dilute 1.0 ml of this solution to 10.0 ml with a mixture of equal volumes of *acetonitrile R* and *water R*.

Reference solution (b). Dissolve the contents of a vial of *ciprofibrate for system suitability CRS* in 2.0 ml of a mixture of equal volumes of *acetonitrile R* and *water R*.

Column:

- size: $l = 0.15$ m, $\varnothing = 4.6$ mm,
- stationary phase: *octylsilyl silica gel for chromatography R* (5 μ m).

Mobile phase:

- mobile phase A: 1.36 g/l solution of *potassium dihydrogen phosphate R* adjusted to pH 2.2 with *phosphoric acid R*,
- mobile phase B: *acetonitrile R*,

| Time (min) | Mobile phase A (per cent V/V) | Mobile phase B (per cent V/V) |
|------------|-------------------------------|-------------------------------|
| 0 - 30 | 75 → 30 | 25 → 70 |
| 30 - 40 | 30 | 70 |
| 40 - 42 | 30 → 75 | 70 → 25 |

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 230 nm.

Injection: 10 μ l.

Identification of impurities: use the chromatogram supplied with *ciprofibrate for system suitability CRS* to identify the peaks due to impurities A, B, C, D and E.

Relative retention with reference to ciprofibrate (retention time = about 18 min): impurity A = about 0.7; impurity B = about 0.8; impurity C = about 0.95; impurity D = about 1.3; impurity E = about 1.5.

System suitability: reference solution (b):

- resolution: baseline separation between the peaks due to impurity C and ciprofibrate.

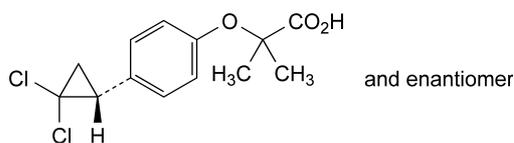
Limits:

- correction factor: for the calculation of content, multiply the peak area of impurity A by 2.3,
- impurities A, C, D: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),
- impurity B: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),
- impurity E: not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent),

01/2008:2013

CIPROFIBRATE

Ciprofibratum



C₁₃H₁₄Cl₂O₃
[52214-84-3]

M_r 289.2

DEFINITION

2-[4-[(1R,3E)-2,2-dichlorocyclopropyl]phenoxy]-2-methylpropanoic acid.

Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or slightly yellow, crystalline powder.

Solubility: practically insoluble in water, freely soluble in anhydrous ethanol, soluble in toluene.

mp: about 115 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).