Test solution. Dissolve 50.0 mg in *0.01 M hydrochloric acid* and dilute to 250.0 mL with the same acid. Dilute 25.0 mL of the solution to 100.0 mL with *0.01 M hydrochloric acid.*

Spectral range: 230-350 nm.

Absorption maximum: at 270 nm, 280 nm, 287 nm and 291 nm.

Absorbance ratio:

– A_{270}/A_{280} = 0.82 to 0.86,

– A_{291}/A_{280} = 0.65 to 0.69.

C. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *naphazoline nitrate CRS*.

D. Dissolve 45 mg of the substance to be examined in 2 mL of *water R*. Add 1 mL of *sulfuric acid R*. Shake carefully and allow to cool. Add 1 mL of *ferrous sulfate solution R2* dropwise along the walls of the container. At the junction of the 2 liquids, a brown colour develops.

TESTS

Solution S. Dissolve 0.5 g in *carbon dioxide-free water R*, warming gently, and dilute to 50 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*): 5.0 to 6.5 for solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a). Dissolve 5 mg of *1-naphthylacetic acid R* in the mobile phase, add 5 mL of the test solution and dilute to 100 mL with the mobile phase.

Reference solution (b). Dissolve 5.0 mg of *naphazoline impurity A CRS* in the mobile phase and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (c). Dilute 2.0 mL of the test solution to 10.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.0 mm,

– *stationary phase*: *end-capped base-deactivated octylsilyl silica gel for chromatography R* (4 μm) with a pore size of 6 nm.

Mobile phase: dissolve 1.1 g of *sodium octanesulfonate R* in a mixture of 5 mL of *glacial acetic acid R*, 300 mL of *acetonitrile R* and 700 mL of *water R*.

Flow rate: 1 mL/min.

Detection: spectrophotometer at 280 nm.

Injection: 20 μL.

Run time: 3 times the retention time of naphazoline.

Relative retention with reference to naphazoline (retention time = about 14 min): impurity A = about 0.76; impurity D = about 1.24; impurity B = about 1.27; impurity C = about 2.8.

System suitability: reference solution (a):

– *resolution*: minimum 5.0 between the peaks due to naphazoline and impurity B.

Limits:

– *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent),

– *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.10 per cent),

– *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent),

– *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent); disregard the peak due to the nitrate ion.

Chlorides (*2.4.4*): maximum 330 ppm, determined on solution S.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

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

ASSAY

Dissolve 0.200 g in 30 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 27.33 mg of $C_{14}H_{15}N_3O_3$.

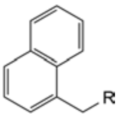
STORAGE

Protected from light.

IMPURITIES

Specified impurities: *A*.

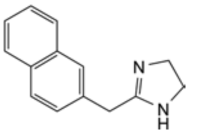
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use (2034).* It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use*): *B, C, D*.



A. R = CO-NH-$[CH_2]_2$-NH_2: *N*-(2-aminoethyl)-2-(naphthalen-1-yl)acetamide (naphthylacetylethylenediamine),

B. R = CO_2H: (naphthalen-1-yl)acetic acid (1-naphthylacetic acid),

C. R = CN: (naphthalen-1-yl)acetonitrile (1-naphthylacetonitrile),

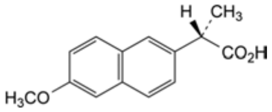


D. 2-(naphthalen-2-ylmethyl)-4,5-dihydro-1*H*-imidazole (β-naphazoline).

07/2008:0731

NAPROXEN

Naproxenum



$C_{14}H_{14}O_3$ M_r 230.3

[22204-53-1]

DEFINITION

(2*S*)-2-(6-Methoxynaphthalen-2-yl)propanoic acid.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, soluble in ethanol (96 per cent) and in methanol.

IDENTIFICATION

First identification: A, D.

Second identification: A, B, C.

A. Specific optical rotation (*2.2.7*): + 59 to + 62 (dried substance).

Dissolve 0.50 g in *ethanol (96 per cent) R* and dilute to 25.0 mL with the same solvent.

B. Melting point (*2.2.14*): 154 °C to 158 °C.

C. Dissolve 40.0 mg in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of this solution to 100.0 mL with *methanol R*. Examined between 230 nm and 350 nm (*2.2.25*), the solution shows 4 absorption maxima, at 262 nm, 271 nm, 316 nm and 331 nm. The specific absorbances at the absorption maxima are 216 to 238, 219 to 241, 61 to 69 and 79 to 87, respectively.

D. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *naproxen CRS*.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

Dissolve 1.25 g in *methanol R* and dilute to 25 mL with the same solvent.

Enantiomeric purity. Liquid chromatography (*2.2.29*). *Protect the solutions from light.*

Test solution. Dissolve 25.0 mg of the substance to be examined in *tetrahydrofuran R* and dilute to 50.0 mL with the same solvent. Dilute 2.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (a). Dilute 2.5 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (b). Dissolve 5 mg of *racemic naproxen CRS* in 10 mL of *tetrahydrofuran R* and dilute to 100 mL with the mobile phase.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *silica gel π-acceptor/π-donor for chiral separations R* (5 μm) (S,S);
- *temperature*: 25 °C.

Mobile phase: *glacial acetic acid R, acetonitrile R, 2-propanol R, hexane R* (5:50:100:845 *V/V/V/V*).

Flow rate: 2 mL/min.

Detection: spectrophotometer at 263 nm.

Injection: 20 μL.

Run time: 1.5 times the retention time of naproxen (retention time = about 5 min).

System suitability: reference solution (b):

- *resolution*: minimum 3 between the peaks due to impurity G and naproxen.

Limit:

- *impurity G*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (2.5 per cent).

Related substances. Liquid chromatography (*2.2.29*). *Protect the solutions from light.*

Test solution. Dissolve 12 mg of the substance to be examined in the mobile phase and dilute to 20 mL with the mobile phase.

Reference solution (a). Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (b). Dissolve 6 mg of *bromomethoxynaphthalene R* (impurity N), 6 mg of *1-(6-methoxynaphthalen-2-yl)ethanone R* (impurity L) and 6 mg of *(1RS)-1-(6-methoxynaphthalen-2-yl)ethanol R* (impurity K) in *acetonitrile R* and dilute to 10 mL with the same solvent. To 1 mL of this solution add 1 mL of the test solution and dilute to 50 mL with the mobile phase. Dilute 1 mL of this solution to 20 mL with the mobile phase.

Column:

- *size*: *l* = 0.10 m, Ø = 4.0 mm;
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (3 μm);
- *temperature*: 50 °C.

Mobile phase: mix 42 volumes of *acetonitrile R* and 58 volumes of a 1.36 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 2.0 with *phosphoric acid R*.

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 230 nm.

Injection: 20 μL.

Run time: 1.5 times the retention time of impurity N.

Relative retention with reference to naproxen (retention time = about 2.5 min): impurity K = about 0.9; impurity L = about 1.4; impurity N = about 5.3.

System suitability: reference solution (b):

- *resolution*: minimum 2.2 between the peaks due to impurity K and naproxen.

Limits:

- *impurity L*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
- *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);
- *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Heavy metals (*2.4.8*): maximum 20 ppm.

1.0 g complies with limit test C. Prepare the reference solution using 2 mL of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 3 h.

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

ASSAY

Dissolve 0.200 g in a mixture of 25 mL of *water R* and 75 mL of *methanol R*. Titrate with *0.1 M sodium hydroxide*, using 1 mL of *phenolphthalein solution R* as indicator.

1 mL of *0.1 M sodium hydroxide* is equivalent to 23.03 mg of $C_{14}H_{14}O_3$.

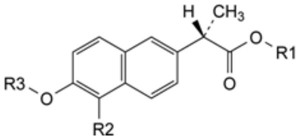
STORAGE

Protected from light.

IMPURITIES

Specified impurities: G, L.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use (2034)*. It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use*): *A, B, C, D, E, F, H, I, J, K, M, N.*



A. R1 = R2 = R3 = H: (2*S*)-2-(6-hydroxynaphthalen-2-yl)propanoic acid,

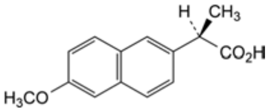
B. R1 = H, R2 = Cl, R3 = CH_3: (2*S*)-2-(5-chloro-6-methoxynaphthalen-2-yl)propanoic acid,

C. R1 = H, R2 = Br, R3 = CH_3: (2*S*)-2-(5-bromo-6-methoxynaphthalen-2-yl)propanoic acid,

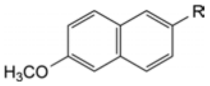
D. R1 = H, R2 = I, R3 = CH_3: (2*S*)-2-(5-iodo-6-methoxynaphthalen-2-yl)propanoic acid,

E. R1 = R3 = CH_3, R2 = H: methyl (2*S*)-2-(6-methoxynaphthalen-2-yl)propanoate,

F. R1 = C_2H_5, R2 = H, R3 = CH_3: ethyl (2*S*)-2-(6-methoxynaphthalen-2-yl)propanoate,



G. (2*R*)-2-(6-methoxynaphthalen-2-yl)propanoic acid ((*R*)-enantiomer),



H. R = OH: 6-methoxynaphthalen-2-ol,

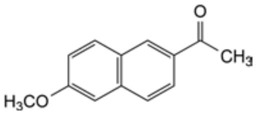
I. R = CH_2-CO_2H: (6-methoxynaphthalen-2-yl)acetic acid,

J. R = C_2H_5: 2-ethyl-6-methoxynaphthalene,

K. R = CHOH-CH_3: (1*RS*)-1-(6-methoxynaphthalen-2-yl)ethanol,

M. R = H: 2-methoxynaphthalene (nerolin),

N. R = Br: 2-bromo-6-methoxynaphthalene,

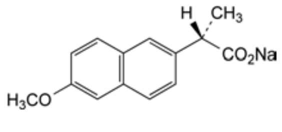


L. 1-(6-methoxynaphthalen-2-yl)ethanone.

01/2008:1702
corrected 7.0

NAPROXEN SODIUM

Naproxenum natricum



$C_{14}H_{13}O_3Na$ M_r 252.2
[26159-34-2]

DEFINITION

Sodium (2*S*)-2-(6-methoxynaphthalen-2-yl)propanoate.

Content: 98.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, hygroscopic, crystalline powder.

Solubility: freely soluble in water, freely soluble or soluble in methanol, sparingly soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, C, D.

Second identification: A, B, D.

A. Specific optical rotation (*2.2.7*): – 14.7 to – 17.0 (dried substance).

Dissolve 0.50 g in a 4.2 g/L solution of *sodium hydroxide R* and dilute to 25.0 mL with the same solution.

B. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution. Dissolve 40.0 mg in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of this solution to 100.0 mL with *methanol R*.

Spectral range: 230-350 nm.

Absorption maxima: at 262 nm, 271 nm, 316 nm and 331 nm.

Specific absorbance at the absorption maxima:

– at 262 nm: 207 to 227;
– at 271 nm: 200 to 220;
– at 316 nm: 56 to 68;
– at 331 nm: 72 to 84.

C. Infrared absorption spectrophotometry (*2.2.24*).

Preparation. Dissolve 50 mg in 5 mL of *water R*. Add 1 mL of *dilute sulfuric acid R* and 5 mL of *ethyl acetate R*. Shake vigorously. Allow the 2 layers to separate. Evaporate the upper layer to dryness and subsequently dry at 60 °C for 15 min. Record the spectrum using the residue.

Comparison: *naproxen CRS*.

D. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

Dissolve 1.25 g in *water R* and dilute to 25 mL with the same solvent.

pH (*2.2.3*): 7.0 to 9.8.

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Enantiomeric purity. Liquid chromatography (*2.2.29*). *Protect the solutions from light.*

Test solution. Dissolve 25.0 mg of the substance to be examined in 15 mL of *water R* and add 1 mL of *hydrochloric acid R*. Shake with 2 quantities, each of 10 mL, of *ethyl acetate R*, combine the upper layers and evaporate to dryness under reduced pressure. Dissolve the residue in 50.0 mL of *tetrahydrofuran R*. Dilute 2.0 mL of this solution to 20.0 mL with the mobile phase.

Reference solution (a). Dilute 2.5 mL of the test solution to 100.0 mL with the mobile phase.

Reference solution (b). Dissolve 5 mg of *racemic naproxen CRS* in 10 mL of *tetrahydrofuran R* and dilute to 100 mL with the mobile phase.

Column:

– *size*: l = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *silica gel π-acceptor/π-donor for chiral separations R* (5 µm) (*S,S*);
– *temperature*: 25 °C.

Mobile phase: *glacial acetic acid R, acetonitrile R, 2-propanol R, hexane R* (5:50:100:845 *V/V/V/V*).

Flow rate: 2 mL/min.

Detection: spectrophotometer at 263 nm.

Injection: 20 µL.

Run time: 1.5 times the retention time of naproxen (retention time = about 5 min).

System suitability: reference solution (b):

– *resolution*: minimum 3 between the peaks due to impurity G and naproxen.