Appearance. The substance to be examined, in liquid form or liquefied by slight heating, is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

pH (*2.2.3*). The pH of solution S is 6.0 to 7.8.

Refractive index (*2.2.6*). 1.524 to 1.526.

Related substances. Examine by thin-layer chromatography (*2.2.27*), using *silica gel* GF_{254} *R* as the coating substance.

Test solution. Dissolve 0.4 g of the substance to be examined in *methanol R* and dilute to 10 ml with the same solvent.

Reference solution (a). Dissolve 40 mg of *ethylnicotinamide CRS* in *methanol R* and dilute to 100 ml with the same solvent.

Reference solution (b). Dilute 1 ml of reference solution (a) to 10 ml with *methanol R*.

Apply separately to the plate 10 µl of each solution. Develop over a path of 15 cm using a mixture of 25 volumes of *propanol R* and 75 volumes of *chloroform R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. In the chromatogram obtained with the test solution, any spot corresponding to ethylnicotinamide is not more intense than the spot in the chromatogram obtained with reference solution (a) (1.0 per cent) and any spot, apart from the principal spot and the spot corresponding to ethylnicotinamide, is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.1 per cent).

Heavy metals (*2.4.8*). Dilute 10 ml of solution S to 25 ml with *water R*. 12 ml of this solution complies with limit test A for heavy metals (10 ppm). Prepare the standard using *lead standard solution (1 ppm Pb) R*.

Water (*2.5.12*). Not more than 0.3 per cent, determined on 2.00 g by the semi-micro determination of water.

Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

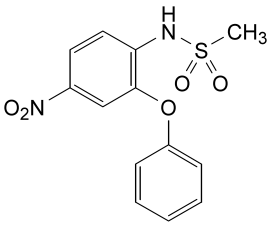
Dissolve 0.150 g in a mixture of 5 ml of *acetic anhydride R* and 20 ml of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M perchloric acid* is equivalent to 17.82 mg of $C_{10}H_{14}N_2O$.

01/2008:1548
corrected 6.0

NIMESULIDE

Nimesulidum



$C_{13}H_{12}N_2O_5S$ M_r 308.3
[51803-78-2]

DEFINITION

N-(4-Nitro-2-phenoxyphenyl)methanesulphonamide.

Content: 98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance: yellowish crystalline powder.

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

mp: about 149 °C.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *nimesulide CRS*.

If the spectra obtained show differences, dissolve the substance to be examined and the reference substance separately in *acetone R*, evaporate to dryness and record new spectra using the residues.

TESTS

Absorbance (*2.2.25*): maximum 0.50 at 450 nm.

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

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 20 mg of the substance to be examined in 8 ml of *acetonitrile R* and dilute to 20.0 ml with *water R*.

Reference solution (a). Dissolve 5 mg of *2-phenoxyaniline R* (impurity C) in 10 ml of *acetonitrile R* and dilute to 25.0 ml with *water R*. Dilute 1.0 ml of the solution to 50.0 ml with the mobile phase. Mix 1.0 ml of this solution with the contents of a vial of *nimesulide impurity D CRS* previously dissolved in 1.0 ml of *acetonitrile R*.

Reference solution (b). Dilute 1.0 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:

– *dimensions*: *l* = 0.125 m, Ø = 4.0 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R*.

Mobile phase: a mixture of 35 volumes of *acetonitrile R* and 65 volumes of a 1.15 g/l solution of *ammonium dihydrogen phosphate R* adjusted to pH 7.0 with *ammonia R*.

Flow rate: 1.3 ml/min.

Detection: spectrophotometer at 230 nm.

Injection: 20 µl.

Run time: 7 times the retention time of nimesulide.

System suitability: reference solution (a):

– *resolution*: minimum 2.0 between the 2 principal peaks.

Limits:

– *any impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);
– *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent);
– *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.01 per cent).

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

1.0 g complies with test D. 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 4 h.

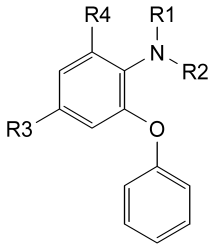
Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.240 g in 30 ml of previously neutralised *acetone R* and add 20 ml of *water R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*).

1 ml of *0.1 M sodium hydroxide* is equivalent to 30.83 mg of $C_{13}H_{12}N_2O_5S$.

IMPURITIES



A. R1 = SO_2-CH_3, R2 = H, R3 = R4 = NO_2: *N*-(2,4-dinitro-6-phenoxyphenyl)methanesulphonamide,

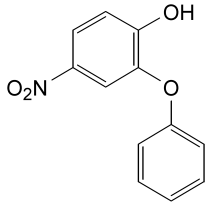
B. R1 = SO_2-CH_3, R2 = R3 = R4 = H: *N*-(2-phenoxyphenyl)methanesulphonamide,

C. R1 = R2 = R3 = R4 = H: 2-phenoxyaniline,

D. R1 = R2 = R4 = H, R3 = NO_2: 4-nitro-2-phenoxyaniline,

E. R1 = R2 = SO_2-CH_3, R3 = R4 = H: *N*,*N*-bis(methylsulphonyl)-2-phenoxyaniline,

F. R1 = R2 = SO_2-CH_3, R3 = NO_2, R4 = H: *N*,*N*-bis(methylsulphonyl)-4-nitro-2-phenoxyaniline,

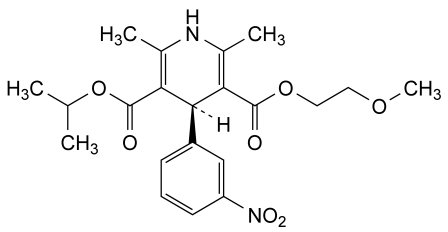


G. 4-nitro-2-phenoxyphenol.

01/2008:1245
corrected 6.0

NIMODIPINE

Nimodipinum



and enantiomer

$C_{21}H_{26}N_2O_7$ M_r 418.4
[66085-59-4]

DEFINITION

2-Methoxyethyl 1-methylethyl (4*RS*)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate.

Content: 98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance: light yellow or yellow, crystalline powder.

Solubility: practically insoluble in water, freely soluble in ethyl acetate, sparingly soluble in anhydrous ethanol.

It shows polymorphism (*5.9*).

Exposure to ultraviolet light leads to the formation of a nitrophenylpyridine derivative.

Prepare solutions immediately before use either protected from light or under long-wavelength light (> 420 nm).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *nimodipine CRS*.

If the spectra obtained in the solid state show differences, record new spectra using 20 g/l solutions in *methylene chloride R* and a 0.2 mm cell.

TESTS

Solution S. Dissolve 1.0 g in *acetone R* and dilute to 20.0 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*).

Optical rotation (*2.2.7*): – 0.10° to + 0.10°, determined on solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 40.0 mg of the substance to be examined in 2.5 ml of *tetrahydrofuran R* and dilute to 25.0 ml with the mobile phase.

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

Reference solution (b). Nimodipine impurity A CRS.

Reference solution (c). Dilute the test solution as described in the leaflet accompanying *nimodipine impurity A CRS.*

Reference solution (d). Mix reference solution (b) and reference solution (c) as described in the leaflet accompanying *nimodipine impurity A CRS.*

Column:

– *size*: *l* = 0.125 m, Ø = 4.6 mm;

– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

– *temperature*: 40 °C.

Mobile phase: *methanol R, tetrahydrofuran R, water R* (20:20:60 *V/V/V*).

Flow rate: 2.0 ml/min.

Detection: spectrophotometer at 235 nm.

Injection: 20 µl of the test solution and reference solutions (a) and (d).

Run time: 4 times the retention time of nimodipine.

Retention time: impurity A = about 7 min; nimodipine = about 8 min.

System suitability: reference solution (d):

– *resolution*: minimum 1.5 between the peaks due to impurity A and nimodipine.