Reference solution (a). Dissolve 5 mg of the substance to be examined and 10 µl of *2-pyrrolidone R* in a mixture of 10 volumes of *acetonitrile R1* and 90 volumes of *water R* and dilute to 100.0 ml with the same mixture of solvents.

Reference solution (b). Dilute 1.0 ml of test solution (a) to 100.0 ml with a mixture of 10 volumes of *acetonitrile R1* and 90 volumes of *water R*. Dilute 5.0 ml of this solution to 50.0 ml with a mixture of 10 volumes of *acetonitrile R1* and 90 volumes of *water R*.

Reference solution (c). Dissolve 50.0 mg of *piracetam CRS* in a mixture of 10 volumes of *acetonitrile R1* and 90 volumes of *water R* and dilute to 100.0 ml with the same mixture of solvents. Dilute 10.0 ml of this solution to 50.0 ml with a mixture of 10 volumes of *acetonitrile R1* and 90 volumes of *water R*.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,

– *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 10 volumes of *acetonitrile R1* and 90 volumes of a 1.0 g/l solution of *dipotassium hydrogen phosphate R*; adjust to pH 6.0 with *dilute phosphoric acid R*.

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 205 nm.

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

Run time: 8 times the retention time of piracetam.

Relative retention with reference to piracetam (retention time = about 4 min): impurity D = about 0.8; impurity A = about 1.15; impurity B = about 2.8; impurity C = about 6.3.

System suitability: reference solution (a):

– *resolution*: minimum 3.0 between the peaks due to piracetam and impurity A,

– *symmetry factor*: maximum 2.0 for the peak due to piracetam.

Limits:

– *impurities A, B, C, D*: for each impurity, not more than the area of the principal 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 (b) (0.1 per cent),

– *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent),

– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Heavy metals (*2.4.8*): maximum 10 ppm.

Dissolve 2.0 g in 20 ml of *water R*. 12 ml of the solution complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 1.0 per cent, determined on 1.000 g by drying in an oven at 100-105 °C.

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

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection: test solution (b) and reference solution (c).

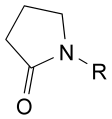
Calculate the percentage content of $C_6H_{10}N_2O_2$ from the areas of the peaks and the declared content of *piracetam CRS*.

STORAGE

Protected from light.

IMPURITIES

Specified impurities: A, B, C, D.



A. R = H: pyrrolidin-2-one (2-pyrrolidone),

B. R = CH_2-CO-O-CH_3: methyl (2-oxopyrrolidin-1-yl)acetate,

C. R = CH_2-CO-O-C_2H_5: ethyl (2-oxopyrrolidin-1-yl)acetate,

D. R = CH_2-CO_2H: (2-oxopyrrolidin-1-yl)acetic acid.

04/2006:0428

POLYSORBATE 80

Polysorbatum 80

DEFINITION

Mixture of partial esters of fatty acids, mainly *Oleic acid (0799)*, with sorbitol and its anhydrides ethoxylated with approximately 20 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydrides.

CHARACTERS

Appearance: oily, yellowish or brownish-yellow, clear or slightly opalescent liquid.

Solubility: dispersible in water, in anhydrous ethanol, in ethyl acetate and in methanol, practically insoluble in fatty oils and in liquid paraffin.

Relative density: about 1.10.

Viscosity: about 400 mPa·s at 25 °C.

IDENTIFICATION

First identication: A, D.

Second identification: B, C, D, E.

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *Ph. Eur. reference spectrum of polysorbate 80*.

B. Hydroxyl value (see Tests).

C. Saponification value (see Tests).

D. Composition of fatty acids (see Tests).

E. Dissolve 0.1 g in 5 ml of *methylene chloride R*. Add 0.1 g of *potassium thiocyanate R* and 0.1 g of *cobalt nitrate R*. Stir with a glass rod. The solution becomes blue.

TESTS

Acid value (*2.5.1*): maximum 2.0.

Dissolve 5.0 g in 50 ml of the prescribed mixture of solvents.

Hydroxyl value (*2.5.3, Method A*): 65 to 80.

Peroxide value: maximum 10.0.

Introduce 10.0 g into a 100 ml beaker, dissolve with *glacial acetic acid R* and dilute to 20 ml with the same solvent. Add 1 ml of *saturated potassium iodide solution R* and allow to stand for 1 min. Add 50 ml of *carbon dioxide-free water R* and a magnetic stirring bar. Titrate with *0.01 M sodium*

thiosulphate, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

Determine the peroxide value using the following expression:

$$\frac{(n_1 - n_2) \times M \times 1000}{m}$$

n_1 = volume of *0.01 M sodium thiosulphate* required for the substance to be examined, in millilitres,

n_2 = volume of *0.01 M sodium thiosulphate* required for the blank, in millilitres,

M = molarity of the sodium thiosulphate solution, in moles per litre,

m = mass of substance to be examined, in grams.

Saponification value (*2.5.6*): 45 to 55, determined on 4.0 g.

Use 30.0 ml of *0.5 M alcoholic potassium hydroxide*, heat under reflux for 60 min and add 50 ml of *anhydrous ethanol R* before carrying out the titration.

Composition of fatty acids. Gas chromatography (*2.4.22, Method C*). Use the mixture of calibrating substances in Table 2.4.22.-3.

Column:

- *material*: fused silica,
- *size*: *l* = 30 m, Ø = 0.32 mm,
- *stationary phase*: *macrogol 20 000 R* (film thickness 0.5 µm).

Carrier gas: *helium for chromatography R*.

Linear velocity: 50 cm/s.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 14	80 → 220
	14 - 54	220
Injection port		250
Detector		250

Detection: flame ionisation.

Injection: 1 µl.

Composition of the fatty acid fraction of the substance:

- *myristic acid*: maximum 5.0 per cent,
- *palmitic acid*: maximum 16.0 per cent,
- *palmitoleic acid*: maximum 8.0 per cent,
- *stearic acid*: maximum 6.0 per cent,
- *oleic acid*: minimum 58.0 per cent,
- *linoleic acid*: maximum 18.0 per cent,
- *linolenic acid*: maximum 4.0 per cent,

Ethylene oxide and dioxan (*2.4.25, Method A*): maximum 1 ppm of ethylene oxide and maximum 10 ppm of dioxan.

Heavy metals (*2.4.8*): maximum 10 ppm.

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

Water (*2.5.12*): maximum 3.0 per cent, determined on 1.00 g.

Total ash (*2.4.16*): maximum 0.25 per cent, determined on 2.0 g.

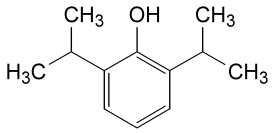
STORAGE

In an airtight container, protected from light.

04/2006:1558

PROPOFOL

Propofolum



$C_{12}H_{18}O$ M_r 178.3

DEFINITION

2,6-Bis(1-methylethyl)phenol.

Content: 98.0 per cent to 102.0 per cent.

This monograph applies to propofol prepared using distillation for purification.

CHARACTERS

Appearance: colourless or very light yellow, clear liquid.

Solubility: very slightly soluble in water, miscible with hexane and with methanol.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *propofol CRS*.

TESTS

Refractive index (*2.2.6*): 1.5125 to 1.5145.

Related substances. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 1.00 g of the substance to be examined in *hexane R* and dilute to 10.0 ml with the same solvent.

Test solution (b). Dissolve 0.240 g of the substance to be examined in *hexane R* and dilute to 100.0 ml with the same solvent.

Reference solution (a). Dissolve 5 µl of the substance to be examined and 15 µl of *propofol impurity J CRS* in *hexane R* and dilute to 50.0 ml with the same solvent.

Reference solution (b). Dilute 0.1 ml of *propofol for peak identification CRS* (containing impurities E and G) to 1.0 ml with *hexane R*.

Reference solution (c). Dilute 1.0 ml of test solution (a) to 100.0 ml with *hexane R*. Dilute 1.0 ml of this solution to 10.0 ml with *hexane R*.

Reference solution (d). Dissolve 0.240 g of *propofol CRS* in *hexane R* and dilute to 100.0 ml with the same solvent.

Column:

- *size*: *l* = 0.20 m, Ø = 4.6 mm;
- *stationary phase*: *silica gel for chromatography R* (5 µm).

Mobile phase: *anhydrous ethanol R, acetonitrile R, hexane R* (1.0:7.5:990 *V/V/V*).

Flow rate: 2.0 ml/min.

Detection: spectrophotometer at 275 nm.

Injection: 10 µl of test solution (a) and reference solutions (a), (b) and (c).

Run time: 7 times the retention time of propofol.