EUROPEAN PHARMACOPOEIA

E49 : Propyl parahydroxybenzoate (rev. 1)
(Stage 4, CP:EP)

Briefing note

Comments on the stage 3 draft were received from JP. USP indicated that they had no comments. The stage 4 draft has been prepared taking due account of the comments received.

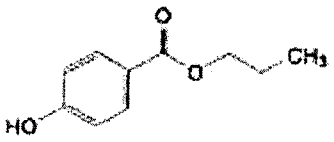
Related substances.
Test solution. The interpretation of « dissolve 50.0 mg… » is defined for EP in the General Notices (sample size 50 mg +- 10%, weighed to nearest 0.05mg). The proposal from JP is in line with their General Notices and in equivalent to EP. It is therefore understood that the text published in JP can be editorially adapted to the JP General Notices without affecting harmonisation.

Reference solution (b). The comment from JP (harmonisation with test solution) has been incorporated in the stage 4 text.

Assay. It is not the editorial policy of EP to include calculation formulae for simple case. It is understood that JP may adapt the text to its editorial policy and that this will not affect harmonisation.

PROPYL PARAHYDROXYBENZOATE

Propylis parahydroxybenzoas



$C_{10}H_{12}O_3$ Mr 180.2

DEFINITION

Propyl 4-hydroxybenzoate.

Content: 98.0 per cent to 102.0 per cent.

IDENTIFICATION

A. *Melting point:* 96 °C to 99 °C.

TESTS

Solution S. Dissolve 1.0 g in *alcohol* and dilute to 10 ml with the same solvent.

Appearance of solution. Solution S is clear and not more intensely coloured than reference solution BY6.

Acidity. To 2 ml of solution S add 3 ml of *alcohol*, 5 ml of *carbon dioxide-free water* and 0.1 ml of *bromocresol green solution*. Not more than 0.1 ml of *0.1 M sodium hydroxide* is required to change the colour of the indicator to blue.

~~**Related substances.** Thin-layer chromatography.~~

~~*Test solution.* Dissolve 0.10 g of the substance to be examined in *acetone* and dilute to 10 ml with the same solvent.~~

~~*Reference solution (a).* Dilute 0.5 ml of test solution to 100 ml with *acetone.*~~

~~*Reference solution (b).* Dissolve 10 mg of *ethyl parahydroxybenzoate* in 1 ml of test solution (a) and dilute to 10 ml *with acetone.*~~

~~*Plate:* suitable octadecylsilyl silica gel with a fluorescent indicator having an optimal intensity at 254 nm as the coating substance.~~

~~*Mobile phase: glacial acetic acid, water, methanol (1:30:70 V/V/V).*~~

~~*Application:* 2 µl.~~

~~*Development:* over a path of 15 cm.~~

~~*Drying:* in air.~~

~~*Detection:* examine in ultraviolet light at 254 nm.~~

~~*System suitability:* the chromatogram obtained with reference solution (b) shows 2 clearly separated principal spots.~~

~~*Limits:*~~

— *any impurity:* any spot in the chromatogram obtained with test solution, apart from the principal spot, is not more intense than the spot in the chromatogram obtained with reference solution (a) (0.5 per cent).

Related substances. Liquid chromatography.

Test solution. Dissolve 50.0 mg of the sample to be examined in 2.5 ml of *methanol* and dilute to 50.0 ml with the mobile phase. Dilute 10.0 ml of this solution to 100.0 ml with the mobile phase.

Reference solution (a). Dissolve 50 mg each of *ethyl parahydroxybenzoate CRS, 4-hydroxybenzoic acid R* and *propyl parahydroxybenzoate CRS* in the mobile phase and dilute to 100 ml with the same solvent. Dilute 1 ml of this solution to 100 ml with the mobile phase.

Reference solution (b). Dissolve 50.0 mg of *propyl parahydroxybenzoate CRS* in 2.5 ml of *methanol* and dilute to 50.0 ml with the mobile phase. Dilute 10.0 ml of this solution to 100.0 ml with the mobile phase.

Reference solution (c). Dilute 1.0 ml of the test solution to 20.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 10.0 ml with the mobile phase.

Column:

— *size: l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase: octadecylsilyl silica gel for chromatography* (5 µm).

Mobile phase: 6.8 g/l solution of *potassium dihydrogen phosphate, methanol* (35:65 *V/V*).

Flow rate: 1.3 ml/min.

Detection: 272 nm.

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

Run time: 2.5 times the retention time of propyl parahydroxybenzoate.

Relative retention with reference to propyl parahydroxybenzoate (retention time = about 4.5 min): 4-hydroxybenzoic acid = about 0.3; methyl parahydroxybenzoate = about 0.5; ethyl parahydroxybenzoate = about 0.7; butyl parahydroxybenzoate = about 1.6.

System suitability:

- *resolution:* minimum of 2.0 between the peaks due to ethyl parahydroxybenzoate and to propyl parahydroxybenzoate in the chromatogram obtained with reference solution (a).

Limits:

- *correction factor*: for the calculation of content, multiply the peak area of 4-hydroxybenzoic acid by 1.4;
- *4-hydroxybenzoic acid*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);
- *total:* not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent);
- *disregard limit:* 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

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

ASSAY

To 1.000 g add 20.0 ml of *1 M sodium hydroxide*. Heat at about 70 °C for 1 h. Cool rapidly in an ice bath. Prepare a blank in the same manner. Carry out the titration on the solutions at room temperature. Titrate the excess sodium hydroxide with *0.5 M sulphuric acid*, continuing the titration until the second point of inflexion and determining the end-point potentiometrically.

1 ml of *1 M sodium hydroxide* is equivalent to 180.2 mg of $C_{10}H_{12}O_3$.

Liquid chromatography as described in the test for related substances with the following modification.

Injection: test solution and reference solution (b).

Calculate the percentage content of propyl parahydroxybenzoate in the sample to be examined from the peak areas in the chromatograms obtained with test solution and reference solution (b) and the declared content of *propyl parahydroxybenzoate CRS.*

REAGENTS

Bromocresol green solution.

Dissolve 50 mg of *bromocresol green* in 0.72 ml of *0.1 M sodium hydroxide* and 20 ml of *alcohol* and dilute to 100 ml with *water*.

Test for sensitivity. To 0.2 ml of the bromocresol green solution add 100 ml of *carbon dioxide-free water*. The solution is blue. Not more than 0.2 ml of *0.02 M hydrochloric acid* is required to change the colour to yellow.

Colour change: pH 3.6 (yellow) to pH 5.2 (blue).