

EUROPEAN PHARMACOPOEIA

Butyl 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.

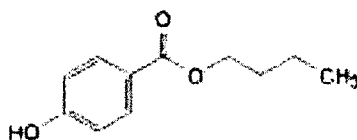
Test solution. The interpretation of « dissolve 50.0 mg... » is defined for EP in the General Notices (sample size 50 mg \pm 10%, weighed to nearest 0.05mg). The proposal from JP is in line with their General Notices and is equivalent to EP. It is therefore understood that the text published in JP can 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.

1
2
3
4 **BUTYL PARAHYDROXYBENZOATE**

5 Butylis parahydroxybenzoas



11 $C_{11}H_{14}O_3$

Mr 194.2

12
13 **DEFINITION**

14 Butyl 4-hydroxybenzoate.

15 *Content:* 98.0 per cent to 102.0 per cent.

16
17 **IDENTIFICATION**

18 A. *Melting point:* 68 °C to 71 °C.

19
20 **TESTS**

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

22
23 **Appearance of solution.** Solution S is clear and not more intensely coloured than reference solution
24 BY6.

25
26 **Acidity.** To 2 ml of solution S add 3 ml of *alcohol*, 5 ml of *carbon dioxide-free water* and 0.1 ml of
27 *bromocresol green solution*. Not more than 0.1 ml of 0.1 M *sodium hydroxide* is required to change the
28 colour of the indicator to blue.

29
30 **Related substances.** ~~Thin-layer chromatography.~~

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

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

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

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

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

39 ~~*Application:* 2 µl.~~

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

41 ~~*Drying:* in air.~~

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

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

45 ~~*Limits:*~~

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

4
5 **Related substances.** Liquid chromatography.

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

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

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

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

16
17 Column:

18 — size: $l = 0.15 \text{ m}$, $\varnothing = 4.6 \text{ mm}$;

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

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

21 Flow rate: 1.3 ml/min.

22 Detection: 272 nm.

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

24 Run time: 1.5 times the retention time of *butyl parahydroxybenzoate*.

25 Relative retention with reference to *butyl parahydroxybenzoate* (retention time = about 7.2 min): *4-*
26 *hydroxybenzoic acid* = about 0.2; *methyl parahydroxybenzoate* = about 0.3; *ethyl parahydroxybenzoate*
27 = about 0.4; *propyl parahydroxybenzoate* = about 0.6; *iso-butyl parahydroxybenzoate* = about 0.9.

28 System suitability:

29 - resolution: reference solution (a):

30 - minimum of 2.0 between the peaks due to *propyl parahydroxybenzoate* and to *butyl*
31 *parahydroxybenzoate*;

32 - minimum of 1.0 between the peaks due to *iso-butyl parahydroxybenzoate* and to *butyl*
33 *parahydroxybenzoate*.

34 Limits:

35 - correction factor: for the calculation of content, multiply the peak area of *4-hydroxybenzoic acid* by
36 1.4;

37 - 4-hydroxybenzoic acid: not more than the area of the principal peak in the chromatogram obtained
38 with reference solution (c) (0.5 per cent);

39 - unspecified impurities: for each impurity, not more than the area of the principal peak in the
40 chromatogram obtained with reference solution (c) (0.5 per cent);

41 - total: not more than twice the area of the principal peak in the chromatogram obtained with reference
42 solution (c) (1.0 per cent);

43 - disregard limit: 0.2 times the area of the principal peak in the chromatogram obtained with reference
44 solution (c) (0.1 per cent).

45
46 **Sulphated ash:** maximum 0.1 per cent, determined on 1.0 g.

47
48 **ASSAY**

49 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
50 bath. Prepare a blank in the same manner. Carry out the titration on the solutions at room temperature.

1 ~~Titrate the excess sodium hydroxide with 0.5 M sulphuric acid, continuing the titration until the second~~
2 ~~point of inflexion and determining the end point potentiometrically.~~

3 ~~1 ml of 1 M sodium hydroxide is equivalent to 194.2 mg of C₁₁H₁₄O₃.~~

4
5 Liquid chromatography as described in the test for related substances with the following modification.

6
7 Injection: test solution and reference solution (b).

8
9 Calculate the percentage content of butyl parahydroxybenzoate in the sample to be examined from the
10 peak areas in the chromatograms obtained with test solution and reference solution (b) and the declared
11 content of butyl parahydroxybenzoate CRS.

12
13
14 **REAGENTS**

15
16 **Bromocresol green solution.**

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

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

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