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

ASSAY

Dissolve 2.00 g in *water R* and dilute to 100.0 mL with the same solvent. Transfer 25.0 mL of the solution to a separating funnel, add 25 mL of *methylene chloride R*, 10 mL of *0.1 M sodium hydroxide* and 10.0 mL of a freshly prepared 50 g/L solution of *potassium iodide R*. Shake well, allow to separate and discard the methylene chloride layer. Shake the aqueous layer with 3 quantities, each of 10 mL, of *methylene chloride R* and discard the methylene chloride layers. To the aqueous layer add 40 mL of *hydrochloric acid R*, allow to cool and titrate with *0.05 M potassium iodate* until the deep-brown colour is almost discharged. Add 5 mL of *methylene chloride R* and continue the titration, shaking vigorously, until the methylene chloride layer no longer changes colour. Carry out a blank titration on a mixture of 10.0 mL of the freshly prepared 50 g/L solution of *potassium iodide R*, 20 mL of *water R* and 40 mL of *hydrochloric acid R*.

1 mL of *0.05 M potassium iodate* is equivalent to $\frac{x}{10}$ mg of benzalkonium chloride where x is the average relative molecular mass of the sample.

STORAGE

In an airtight container.

IMPURITIES

Specified impurities: *A, B, C.*

A. R = CH_2OH: benzyl alcohol,

B. R = CHO: benzaldehyde,

C. R = CH_2Cl: (chloromethyl)benzene.

04/2009:0371
corrected 7.0

BENZALKONIUM CHLORIDE SOLUTION

Benzalkonii chloridi solutio

DEFINITION

Aqueous solution of a mixture of alkylbenzyldimethylammonium chlorides, the alkyl groups mainly having chain lengths of C_{12}, C_{14} and C_{16}.

Content: 475 g/L to 525 g/L of alkylbenzyldimethylammonium chlorides, calculated using the average relative molecular mass (see Tests). The solution may contain ethanol (96 per cent).

CHARACTERS

Appearance: clear, colourless or slightly yellowish liquid.

Solubility: miscible with water and with ethanol (96 per cent).

It froths copiously when shaken.

IDENTIFICATION

First identification: *B, E.*

Second identification: *A, C, D, E.*

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

Test solution. Dilute 0.3 mL to 100.0 mL with *water R*.

Spectral range: 220-350 nm.

Absorption maxima: at 257 nm, 263 nm and 269 nm.

Shoulder: at about 250 nm.

B. Examine the chromatograms obtained in the test for average relative molecular mass and ratio of alkyl components.

Results: the principal peaks in the chromatogram obtained with the test solution are similar in retention time to the principal peaks in the chromatogram obtained with the reference solution.

C. To 0.05 mL add 2 mL of *water R*, 0.1 mL of *glacial acetic acid R* and, dropwise, 1 mL of *sodium tetraphenylborate solution R*. A white precipitate is formed. Filter. Dissolve the precipitate in a mixture of 1 mL of *acetone R* and 5 mL of *ethanol (96 per cent) R*, heating to not more than 70 °C. Add *water R* dropwise to the warm solution until a slight opalescence forms. Heat gently until the solution is clear and allow to cool. White crystals separate. Filter, wash with 3 quantities, each of 10 mL, of *water R* and dry *in vacuo* over *diphosphorus pentoxide R* or *anhydrous silica gel R* at a temperature not exceeding 50 °C. The crystals melt (*2.2.14*) at 127 °C to 133 °C.

D. To 5 mL of *dilute sodium hydroxide solution R* add 0.1 mL of *bromophenol blue solution R1* and 5 mL of *methylene chloride R* and shake. The methylene chloride layer is colourless. Add 0.05 mL of the solution to be examined and shake. The methylene chloride layer becomes blue.

E. To 0.05 mL add 1 mL of *dilute nitric acid R*. A white precipitate is formed which dissolves on the addition of 5 mL of *ethanol (96 per cent) R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dilute 2.0 g to 100 mL with *carbon dioxide-free water R*.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Acidity or alkalinity. To 50 mL of solution S add 0.1 mL of *bromocresol purple solution R*. Not more than 0.1 mL of *0.1 M hydrochloric acid* or *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Average relative molecular mass and ratio of alkyl components. Liquid chromatography (*2.2.29*).

Test solution. Determine the density (*2.2.5*) of the solution to be examined. Dilute a quantity of the solution to be examined equivalent to about 0.400 g of benzalkonium chloride to 100.0 mL with *water R*.

Reference solution. Dissolve 40 mg of *benzalkonium chloride for system suitability CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

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

Mobile phase: mix 45 volumes of *acetonitrile R* and 55 volumes of a 13.6 g/L solution of *sodium acetate R* previously adjusted to pH 5.0 with *glacial acetic acid R*.

Flow rate: 2.0 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 10 µL.

Identification of homologues: use the chromatogram supplied with *benzalkonium chloride for system suitability CRS* and the chromatogram obtained with the reference solution to identify the peaks due to homologues C_{12}, C_{14} and C_{16}.

Relative retention with reference to C_{12} homologue (retention time = about 6 min): C_{14} homologue = about 1.1; C_{16} homologue = about 1.3.

System suitability: reference solution:

– *resolution*: minimum 1.5 between the peaks due to the C_{12} and C_{14} homologues.

Calculate the average relative molecular mass of the sample by summing the products for each homologue, using the following expression:

$$W\left(\frac{A}{B}\right)$$

A = area of the peak due to the given homologue in the chromatogram obtained with the test solution;

B = sum of the areas of the peaks due to all homologues in the chromatogram obtained with the test solution;

W = relative molecular mass for the given homologue: 340, 368 and 396 for the C_{12}, C_{14} and C_{16} homologues, respectively.

Calculate the percentage of each homologue, using the following expression:

$$100\left(\frac{C}{D}\right)$$

C = product of the relative molecular mass of the given homologue and the area of the corresponding peak in the chromatogram obtained with the test solution;

D = sum of the C values for all homologues quantified.

Limits:

- *C_{12} homologue*: minimum 40 per cent;
- *C_{14} homologue*: minimum 20 per cent;
- *sum of C_{12} and C_{14} homologues*: minimum 70 per cent.

Impurities A, B and C. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Determine the density (*2.2.5*) of the solution to be examined. Dilute a quantity of the solution to be examined equivalent to 2.5 g of benzalkonium chloride to 50.0 mL with *methanol R1*.

Reference solution (a). Dissolve 25.0 mg of *benzyl alcohol CRS* (impurity A) in *methanol R1* and dilute to 100.0 mL with the same solvent.

Reference solution (b). Dissolve 75.0 mg of *benzaldehyde CRS* (impurity B) in *methanol R1* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R1*.

Reference solution (c). Dilute 1.0 mL of reference solution (a) to 10.0 mL with *methanol R1*.

Column:

- *size*: *l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);
- *temperature*: 30 °C.

Mobile phase:

- *mobile phase A*: dissolve 1.09 g of *sodium hexanesulfonate R* and 6.9 g of *sodium dihydrogen phosphate monohydrate R* in *water R*; adjust to pH 3.5 with *concentrated phosphoric acid R* and dilute to 1000.0 mL with the same solvent;
- *mobile phase B*: *methanol R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	80	20
10 - 14	80 → 50	20 → 50
14 - 35	50	50
35 - 36	50 → 20	50 → 80
36 - 55	20	80

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 210 nm for impurities A and C, and at 257 nm for impurity B.

Injection: 20 µL.

Relative retention with reference to impurity A (retention time = about 10 min): impurity B = about 1.3; impurity C = about 2.4.

System suitability: at 210 nm:

- *signal-to-noise ratio*: minimum 10 for the principal peak in the chromatogram obtained with reference solution (c);
- *symmetry factor*: minimum 0.6 for the peak due to impurity A in the chromatogram obtained with reference solution (a).

Limits:

- *correction factor*: for the calculation of content, multiply the peak area of impurity C by 1.3;
- *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.5 per cent);
- *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.15 per cent);
- *impurity C*: not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Amines and amine salts. Mix 10.0 g, while heating, with 20 mL of a mixture of 3 volumes of *1 M hydrochloric acid* and 97 volumes of *methanol R* and add 100 mL of *2-propanol R*. Pass a stream of *nitrogen R* slowly through the solution. Titrate with up to 12.0 mL of *0.1 M tetrabutylammonium hydroxide* and record the potentiometric titration curve (*2.2.20*). If the curve shows 2 points of inflexion, the volume of titrant added between the 2 points is not greater than 5.0 mL. If the curve shows no point of inflexion, the solution to be examined does not comply with the test. If the curve shows 1 point of inflexion, repeat the test but add 3.0 mL of a 25.0 g/L solution of *dimethyldecylamine R* in *2-propanol R* before the titration. If the titration curve after the addition of 12.0 mL of the titrant shows only 1 point of inflexion, the solution to be examined does not comply with the test.

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

ASSAY

Determine the density (*2.2.5*) of the solution to be examined. Dilute 4.00 g to 100.0 mL with *water R*. Transfer 25.0 mL of the solution to a separating funnel, add 25 mL of *methylene chloride R*, 10 mL of *0.1 M sodium hydroxide* and 10.0 mL of a freshly prepared 50 g/L solution of *potassium iodide R*. Shake well, allow to separate and discard the methylene chloride layer. Shake the aqueous layer with 3 quantities, each of 10 mL, of *methylene chloride R* and discard the methylene chloride layers. To the aqueous layer add 40 mL of *hydrochloric acid R*, allow to cool and titrate with *0.05 M potassium iodate* until the deep-brown colour is almost discharged. Add 5 mL of *methylene chloride R* and continue the titration, shaking vigorously, until the methylene chloride layer no longer changes colour. Carry out a blank titration on a mixture of 10.0 mL of the freshly prepared 50 g/L solution of *potassium iodide R*, 20 mL of *water R* and 40 mL of *hydrochloric acid R*.

1 mL of *0.05 M potassium iodate* is equivalent to $\frac{x}{10}$ mg of benzalkonium chloride where x is the average relative molecular mass of the sample.

LABELLING

The label states the content of ethanol (96 per cent), if any.

IMPURITIES

Specified impurities: A, B, C.

A. R = CH_2OH: benzyl alcohol,

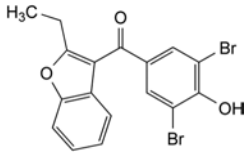
B. R = CHO: benzaldehyde,

C. R = CH_2Cl: (chloromethyl)benzene.

01/2008:1393

BENZBROMARONE

Benzbromaronum



$C_{17}H_{12}Br_2O_3$ M_r 424.1
[3562-84-3]

DEFINITION

(3,5-Dibromo-4-hydroxyphenyl)(2-ethylbenzofuran-3-yl)-methanone.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, freely soluble in acetone and in methylene chloride, sparingly soluble in ethanol (96 per cent).

mp: about 152 °C.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *benzbromarone CRS*.

B. By means of a copper wire, previously ignited, introduce a small amount of the substance to be examined into the non-luminous part of a flame. The colour of the flame becomes green.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

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

Acidity or alkalinity. Shake 0.5 g with 10 mL of *carbon dioxide-free water R* for 1 min and filter. To 2.0 mL of the filtrate add 0.1 mL of *methyl red solution R* and 0.1 mL of *0.01 M hydrochloric acid*. The solution is red. Add 0.3 mL of *0.01 M sodium hydroxide*. The solution is yellow.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.125 g of the substance to be examined in 30 mL of *methanol R* and dilute to 50.0 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 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b). Dissolve 10 mg of *benzarone CRS* (impurity C) in the mobile phase and dilute to 20 mL with the mobile phase. To 5 mL of this solution add 1 mL of the test solution and dilute to 100 mL with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *glacial acetic acid R, acetonitrile R, water R, methanol R* (5:25:300:990 *V/V/V/V*).

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 231 nm.

Injection: 20 µL.

Run time: 2.5 times the retention time of benzbromarone.

Relative retention with reference to benzbromarone: impurity A = about 0.6; impurity B = about 2.

System suitability: reference solution (b):

– *resolution*: minimum 10.0 between the peaks due to impurity C (1st peak) and benzbromarone (2nd peak).

Limits:

– *impurity A*: not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent);
– *impurity B*: not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 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);
– *sum of impurities other than A and B*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
– *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.02 per cent).

Halides expressed as chlorides (*2.4.4*): maximum 400 ppm.

Shake 1.25 g with a mixture of 5 mL of *dilute nitric acid R* and 15 mL of *water R*. Filter. Rinse the filter with *water R* and dilute the filtrate to 25 mL with the same solvent. Dilute 2.5 mL of this solution to 15 mL with *water R*.

Iron (*2.4.9*): maximum 125 ppm.

Moisten the residue obtained in the test for sulfated ash with 2 mL of *hydrochloric acid R* and evaporate to dryness on a water-bath. Add 0.05 mL of *hydrochloric acid R* and 10 mL of *water R*, heat to boiling and maintain boiling for 1 min. Allow to cool. Rinse the crucible with *water R*, collect the rinsings and dilute to 25 mL with *water R*. Dilute 2 mL of this solution to 10 mL with *water R*.

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

0.5 g complies with test C. Prepare the reference solution using 1 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 vacuo* at 50 °C for 4 h.

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

ASSAY

Dissolve 0.300 g in 60 mL of *methanol R*. Stir until completely dissolved and add 10 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 42.41 mg of $C_{17}H_{12}Br_2O_3$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities: *A, B*.

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*