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Benzalkonium Chloride

Ammonium, alkyldimethyl(phenylmethyl)-, chloride;
Alkylbenzyldimethylammonium chloride
CAS RN®: 8001-54-5.

DEFINITION

Benzalkonium Chloride is a mixture of alkylbenzyldimethylammonium chlorides of the general formula:

$$[C_6H_5CH_2N(CH_3)_2R]Cl$$

in which R represents a mixture of alkyls, including all or some of the group beginning with *n*-C_8H_{17} and extending through higher homologs, with *n*-$C_{12}H_{25}$, *n*-$C_{14}H_{29}$, and *n*-$C_{16}H_{33}$ composing the major portion. On the anhydrous basis, the content of the *n*-$C_{12}H_{25}$ homolog is NLT 40.0%, and the content of the *n*-$C_{14}H_{29}$ homolog is NLT 20.0% of the total alkylbenzyldimethylammonium chloride content. The amount of the *n*-$C_{12}H_{25}$ and *n*-$C_{14}H_{29}$ homolog components together is NLT 70.0% of the total alkylbenzyldimethylammonium chloride content. The total alkylbenzyldimethylammonium chloride content, calculated on the anhydrous basis, with allowance made for the amount of residue on ignition, is NLT 97.0% and NMT 103.0% of $[C_6H_5CH_2N(CH_3)_2R]Cl$.

IDENTIFICATION

• **A.**
Analysis: To 2 mL of a solution (1 in 100) add 1 mL of 2 N nitric acid.
Acceptance criteria: A white precipitate is formed and is dissolved after adding 5 mL of alcohol.

• **B.**
Analysis: Dissolve 200 mg in 1 mL of sulfuric acid, add 100 mg of sodium nitrate, and heat on a steam bath for 5 min. Cool, dilute with water to 10 mL, add 500 mg of zinc dust, and warm for 5 min on a steam bath. To 2 mL of the clear supernatant, add 1 mL of sodium nitrite solution (1 in 20), cool in ice water, and then add 3 mL of a solution of 500 mg of 2-naphthol in 10 mL of 6 N ammonium hydroxide.
Acceptance criteria: An orange-red color is produced.

• **C.** **Identification Tests—General, *Chloride* (191):** The solution in a mixture of equal volumes of water and alcohol meets the requirements.

• **D.** The retention times of the major peaks for benzalkonium chloride of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the test for *Ratio of Alkyl Components*.

ASSAY

• **Ratio of Alkyl Components**
Solution A: Adjust a 0.1 M solution of sodium acetate with glacial acetic acid to a pH of 5.0.
Mobile phase: Acetonitrile and *Solution A* (9:11). Acetonitrile and *Solution A* may be adjusted from (2:3) to (3:2) to meet system suitability requirements.
Standard solution: 4 mg/mL of benzalkonium chloride from USP Benzalkonium Chloride RS and water
Sample solution: 4 mg/mL of Benzalkonium Chloride
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 3.9-mm × 30-cm; packing L10, or 4.6-mm × 25-cm; 10-µm packing L10
Flow rate: 2 mL/min
Injection volume: 20 µL
System suitability
Sample: *Standard solution*
[Note—See *Table 1*. Relative retention times are provided for information only, and the Standard should be used to ensure appropriate peak identification.]

Table 1

Name	Relative Retention Time
C_{10} homolog	0.9
C_{12} homolog	1.0
C_{14} homolog	1.3
C_{16} homolog	1.7

Suitability requirements

Resolution: NLT 1.5 between the C_{12} and C_{14} homologs

Relative standard deviation: NMT 2.0% for the C_{12} homolog

Analysis

Samples: *Standard solution* and *Sample solution*

Identify the homolog peaks by comparison of the retention times of the *Sample solution* with those of the *Standard solution*.

Calculate the percentage of each quaternary ammonium homolog in the portion of Benzalkonium Chloride taken:

$$\text{Result} = \frac{r_U \times M_r}{\sum_i (r_U \times M_r)} \times 100$$

r_U = peak area of each homolog from the *Sample solution*

M_r = molecular weight of each homolog. The molecular weights of C_{10}, C_{12}, C_{14}, and C_{16} homologs are 312, 340, 368, and 396, respectively.

Acceptance criteria: On the anhydrous basis, the content of the *n*-$C_{12}H_{25}$ homolog is NLT 40.0% and the content of the *n*-$C_{14}H_{29}$ homolog is NLT 20.0% of the total alkylbenzyldimethylammonium chloride content. The amount of the *n*-$C_{12}H_{25}$ and *n*-$C_{14}H_{29}$ homolog components together is NLT 70.0% of the total alkylbenzyldimethylammonium chloride content.

• **Total Alkylbenzyldimethylammonium Chlorides**

Sample: Weigh a quantity of Benzalkonium Chloride equivalent to 500 mg of anhydrous benzalkonium chloride.

Analysis: Transfer the *Sample*, with the aid of 35 mL of water, to a glass-stoppered, 250-mL conical separator containing 25 mL of methylene chloride. Add 10 mL of 0.1 N sodium hydroxide, and 10.0 mL of freshly prepared potassium iodide solution (1 in 20). Insert the stopper into the separator, shake, allow the layers to separate, and discard the methylene chloride layer. Wash the aqueous layer with three 10-mL portions of methylene chloride, and discard the washings. Transfer the aqueous layer to a glass-stoppered, 250-mL conical flask, and rinse the separator with three 5-mL portions of water, adding the washings to the flask. Add 40 mL of cold hydrochloric acid to the flask, mix, and titrate with 0.05 M potassium iodate VS until the solution becomes light brown in color. Add 5 mL of methylene chloride, insert the stopper into the flask, and shake vigorously. Continue the titration, dropwise, with shaking after each addition, until the methylene chloride layer no longer changes color and the aqueous layer is clear yellow. Record the titrant volume, V_t, in mL. Perform a blank determination, using 20 mL of water as the sample, and record the titrant volume, V_b, in mL. [Note—$V_b > V_t$.] The difference between the two titrations represents the amount of potassium iodate equivalent to the weight of benzalkonium chloride in the sample. Each mL of 0.05 M potassium iodate is equivalent to x/10 mg of benzalkonium chloride, where x represents the average molecular weight of the sample, derived by summing, for all homologs, the products:

$$\text{Result } (x) = \sum_i [(r_U / r_T) \times M_r]$$

r_U = peak area of each homolog from the *Ratio of Alkyl Components* test

r_T = sum of all the peak areas of the homologs from the *Ratio of Alkyl Components* test

M_r = molecular weight of each homolog. The molecular weights of the C_{10}, C_{12}, C_{14}, and C_{16} homologs are 312, 340, 368, and 396, respectively.

Acceptance criteria: 97.0%–103.0% on the anhydrous basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 2.0%

• **Limit of Amines and Amine Salts**

Sample: 5.0 g of Benzalkonium Chloride

Analysis: Dissolve the *Sample* by heating carefully (e.g., on top of a steam bath with water as the steam source) in 20 mL of a mixture of methanol and 1 N hydrochloric acid VS (97:3). [Note—The mixed solution, however, must not reach the boiling point.] Add 100 mL of isopropyl alcohol, and pass a stream of nitrogen slowly through the solution. Gradually add 12.0 mL of 0.1 N tetrabutylammonium hydroxide VS while recording the potentiometric titration curve.

Acceptance criteria: If the curve shows two inflection points, the volume of titrant added between the two points is NMT 5.0 mL, corresponding to NMT 0.1 mmol/g of amines and amine salts. If the curve shows no point of inflection, the substance being examined does not comply with the test. If the curve shows one point of inflection, repeat the test, but add 3.0 mL of a 25.0 mg/mL solution of dimethyldecylamine in isopropyl alcohol before the titration. If after addition of 12.0 mL of the titrant, the titration curve shows only one point of inflection, the substance being examined does not comply with the test.

• **Limit of Benzyl Alcohol, Benzaldehyde, and (Chloromethyl)benzene**

[Note—Prepare the solutions immediately before use.]

Solution A: Dissolve 1.09 g of sodium 1-hexanesulfonate and 6.9 g of monobasic sodium phosphate in water in a 1000-mL volumetric flask, adjust with phosphoric acid to a pH of 3.5, and dilute with water to volume.

Solution B: Methanol

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	80	20
10	80	20
14	50	50
35	50	50
36	20	80
55	20	80
56	80	20
65	80	20

Standard solution A: 0.25 mg/mL of USP Benzyl Alcohol RS in methanol

Standard solution B: 0.075 mg/mL of USP Benzaldehyde RS in methanol

Standard solution C: 0.025 mg/mL of USP Benzyl Alcohol RS in methanol, prepared from *Standard solution A* and methanol

Sample solution: 50 mg/mL of Benzalkonium Chloride in methanol

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 210 nm for benzyl alcohol and (chloromethyl)benzene; UV 257 nm for benzaldehyde

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1.0 mL/min

Injection volume: 20 µL

System suitability

Samples: *Standard solution A*, *Standard solution B*, *Standard solution C*, and *Sample solution*

[Note—See *Table 3* for relative retention times.]

Table 3

Name	Relative Retention Time
Benzyl alcohol	1.0

Name	Relative Retention Time
Benzaldehyde	1.3
(Chloromethyl)benzene	2.4

Suitability requirements

Relative standard deviation: NMT 5.0% for benzyl alcohol, *Standard solution A*

Signal-to-noise ratio: NLT 10 for the principal peak, *Standard solution C*

Analysis

Samples: *Standard solution A*, *Standard solution B*, *Standard solution C*, and *Sample solution*

Calculate the content of (chloromethyl)benzene by multiplying the peak area of (chloromethyl)benzene by 1.3. [Note—The correction factor is used to adjust for baseline shift.]

Acceptance criteria

Benzyl alcohol: The response of the benzyl alcohol peak from the *Sample solution* is NMT that of the benzyl alcohol peak from *Standard solution A*, corresponding to NMT 0.5%.

Benzaldehyde: The response of the benzaldehyde peak from the *Sample solution* is NMT that of the benzaldehyde peak from *Standard solution B*, corresponding to NMT 0.15%.

(Chloromethyl)benzene: The response of the (chloromethyl)benzene peak from the *Sample solution* is NMT 0.1 times that of the principal peak from *Standard solution A*, corresponding to NMT 0.05%.

SPECIFIC TESTS

- **Acidity or Alkalinity**

Sample: 0.5 g of Benzalkonium Chloride

Analysis: Dissolve the *Sample* in water, dilute with water to 50 mL, and mix. Add 0.1 mL of bromocresol purple TS.

Acceptance criteria: NMT 0.5 mL of 0.1 N hydrochloric acid or 0.1 N sodium hydroxide is required to change the color of the indicator.

- **Water Determination, *Method I* ⟨921⟩:** NMT 15.0%
- **Water-Insoluble Matter:** A solution (1 in 10) is free from turbidity and insoluble matter.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers. No storage requirements specified.
- **USP Reference Standards ⟨11⟩**

USP Benzaldehyde RS
USP Benzalkonium Chloride RS
USP Benzyl Alcohol RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
BENZALKONIUM CHLORIDE	Documentary Standards Support	SE2020 Simple Excipients

Chromatographic Database Information: Chromatographic Database

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