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Benzalkonium Chloride

1. Nonproprietary Names

BP: Benzalkonium chloride
JP: Benzalkonium chloride
PhEur: Benzalkonii chloridum
USP: Benzalkonium chloride

2. Synonyms

Alkylbenzyltrimethylammonium chloride; alkyl dimethyl benzyl ammonium chloride; BKC; *Catigene DC 100*; *Exameen 3580*; *Hyamine 3500*; *Pentonium*; *Roccal*; *Zephiran*.

3. Chemical Name and CAS Registry Number

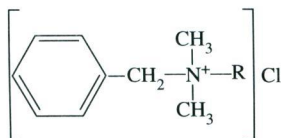
Alkyldimethyl(phenylmethyl)ammonium chloride [8001-54-5]

4. Empirical Formula Molecular Weight

The USP describes benzalkonium chloride as a mixture of alkylbenzyltrimethylammonium chlorides of the general formula $[C_6H_5CH_2N(CH_3)_2R]Cl$, where 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 $n-C_{16}H_{33}$ comprising the major portion.

The average molecular weight of benzalkonium chloride is 360.

5. Structural Formula



R = mixture of alkyls: $n-C_8H_{17}$ to $n-C_{18}H_{37}$; mainly $n-C_{12}H_{25}$ (dodecyl), $n-C_{14}H_{29}$ (tetradecyl), and $n-C_{16}H_{33}$ (hexadecyl).

6. Functional Category

Antimicrobial preservative; antiseptic; disinfectant; solubilizing agent; wetting agent.

7. Applications in Pharmaceutical Formulation or Technology

Benzalkonium chloride is a quaternary ammonium compound used in pharmaceutical formulations as an antimicrobial preservative in applications similar to other cationic surfactants, such as cetrimide.

In ophthalmic preparations, benzalkonium chloride is one of the most widely used preservatives, at a concentration of 0.01-0.02% w/v. Often it is used in combination with other preservatives or excipients, particularly 0.1% w/v disodium

edetate, to enhance its antimicrobial activity against strains of *Pseudomonas*.

In nasal and otic formulations a concentration of 0.002-0.02% is used, sometimes in combination with 0.002-0.005% w/v thimerosal. Benzalkonium chloride 0.01% w/v is also employed as a preservative in small-volume parenteral products.

Benzalkonium chloride is additionally used as a preservative in cosmetics.

8. Description

Benzalkonium chloride occurs as a white or yellowish-white amorphous powder, a thick gel, or gelatinous flakes. It is hygroscopic, soapy to the touch, and has a mild aromatic odor and very bitter taste.

9. Pharmacopeial Specifications

Test	JP	PhEur	USP
Identification	+	+	+
Characters	—	+	—
Acidity or alkalinity	—	+	—
Appearance of solution	+	+	—
Water	≤ 15.0%	≤ 10.0%	≤ 15.0%
Residue on ignition	≤ 0.2%	—	≤ 2.0%
Sulfated ash	—	≤ 0.1%	—
Water-insoluble matter	—	—	+
Foreign amines	—	+	+
Ratio of alkyl components	—	—	+
Assay (dried basis)			
Of $n-C_{12}H_{25}$	—	—	≥ 40.0%
Of $n-C_{14}H_{29}$	—	—	≥ 20.0%
Of $n-C_{12}H_{25}$ & $n-C_{14}H_{29}$	—	—	≥ 70.0%
For total alkyl content	95.0-105.0%	95.0-104.0%	97.0-103.0%

10. Typical Properties

Acidity/alkalinity: pH = 5-8 for a 10% w/v aqueous solution.

Antimicrobial activity: benzalkonium chloride solutions are active against a wide range of bacteria, yeasts, and fungi. Activity is more marked against Gram-positive than Gram-negative bacteria and minimal against bacterial endospores and acid-fast bacteria. The antimicrobial activity of benzalkonium chloride is significantly dependent upon the alkyl composition of the homolog mixture.⁽¹⁾ Benzalkonium chloride is ineffective against some *Pseudomonas aeruginosa* strains, *Mycobacterium tuberculosis*, *Trichophyton interdigitale*, and *T. rubrum*. However, combined with disodium edetate (0.01-0.1% w/v), benzyl alcohol, phenylethanol, or phenylpropanol, the activity against *Pseudomonas aeruginosa* is increased.⁽²⁾ Antimicrobial activity may also be enhanced by the addition of phenylmercuric acetate, phenylmercuric borate, chlorhexidine, cetrimide, or *m*-cresol.^(3,4) In the presence of citrate and phosphate buffers (but not borate), activity against *Pseudomonas* can be reduced. *See also* Sections 11 and 12. Benzalkonium chloride is relatively inactive against spores and molds, but is active against some viruses, including HIV.⁽⁵⁾ Inhibitory activity increases with pH although antimicrobial activity occurs between pH 4-10. Typical minimum inhibitory concentrations (MICs) are shown in Table I.

Table I: Minimum inhibitory concentrations (MICs) of benzalkonium chloride.

Microorganism	MIC ($\mu\text{g/mL}$)
<i>Aerobacter aerogenes</i>	64
<i>Clostridium histolyticum</i>	5
<i>Clostridium oedematiens</i>	5
<i>Clostridium tetani</i>	5
<i>Clostridium welchii</i>	5
<i>Escherichia coli</i>	16
<i>Pneumococcus II</i>	5
<i>Proteus vulgaris</i>	64
<i>Pseudomonas aeruginosa</i>	30
<i>Salmonella enteritidis</i>	30
<i>Salmonella paratyphi</i>	16
<i>Salmonella typhosa</i>	4
<i>Shigella dysenteriae</i>	2
<i>Staphylococcus aureus</i>	1.25
<i>Streptococcus pyrogenes</i>	1.25
<i>Vibrio cholerae</i>	2

Density: $\approx 0.98 \text{ g/cm}^3$ at 20°C

Melting point: $\approx 40^\circ\text{C}$

Partition coefficients: the octanol: water partition coefficient varies with the alkyl chain length of the homolog; 9.98 for C_{12} , 32.9 for C_{14} , and 82.5 for C_{16} .

Solubility: practically insoluble in ether; very soluble in acetone, ethanol (95%), methanol, propanol, and water. Aqueous solutions of benzalkonium chloride foam when shaken, have a low surface tension and possess detergent and emulsifying properties.

11. Stability and Storage Conditions

Benzalkonium chloride is hygroscopic and may be affected by light, air, and metals.

Solutions are stable over a wide pH and temperature range and may be sterilized by autoclaving without loss of effectiveness. Solutions may be stored for prolonged periods at room temperature. Dilute solutions stored in polyvinyl chloride or polyurethane foam containers may lose antimicrobial activity.

The bulk material should be stored in an airtight container, protected from light and contact with metals, in a cool, dry, place.

12. Incompatibilities

Incompatible with aluminum, anionic surfactants, citrates, cotton, fluorescein, hydrogen peroxide, hydroxypropyl methylcellulose,⁽⁶⁾ iodides, kaolin, lanolin, nitrates, nonionic surfactants in high concentration, permanganates, protein, salicylates, silver salts, soaps, sulfonamides, tartrates, zinc oxide, zinc sulfate, some rubber mixes, and some plastic mixes.

Benzalkonium chloride has been shown to be adsorbed to various filtering membranes especially those that are hydrophobic or anionic.⁽⁷⁾

13. Method of Manufacture

Benzalkonium chloride is formed by the reaction of a solution of *N*-alkyl-*N*-methyl-benzamine with methyl chloride in an organic solvent suitable for precipitating the quaternary compound as it is formed.

14. Safety

Benzalkonium chloride is usually nonirritating, nonsensitizing, and well tolerated in the dilutions normally employed on the skin and mucous membranes. However, benzalkonium chloride has been associated with adverse effects when used in some pharmaceutical formulations.⁽⁸⁾

Ototoxicity can occur when benzalkonium chloride is applied to the ear⁽⁹⁾ and prolonged contact with the skin can occasionally cause irritation and hypersensitivity. Benzalkonium chloride is also known to cause bronchoconstriction in some asthmatics when used in nebulizer solutions.⁽¹⁰⁻¹⁴⁾

Toxicity experiments with rabbits have shown benzalkonium chloride, in concentrations higher than that normally used as a preservative, to be harmful to the eye. However, the human eye appears to be less affected than the rabbit eye and many ophthalmic products have been formulated with benzalkonium chloride 0.01% w/v as the preservative. Benzalkonium chloride is not suitable for use as a preservative in solutions used for storing and washing hydrophilic soft contact lenses, as the benzalkonium chloride can bind to the lenses and may later produce ocular toxicity when the lenses are worn.⁽¹⁵⁾ Solutions stronger than 0.03% w/v concentration entering the eye require prompt medical attention.

Local irritation of the throat, esophagus, stomach, and intestine can occur following contact with strong solutions ($> 0.1\%$ w/v). The fatal oral dose of benzalkonium chloride in humans is estimated to be 1-3 g. Adverse effects following oral ingestion include vomiting, collapse, and coma. Toxic doses lead to paralysis of the respiratory muscles, dyspnea, and cyanosis.

LD₅₀ (guinea pig, oral): 200 mg/kg⁽¹⁶⁾

LD₅₀ (mouse, IP): 10 mg/kg

LD₅₀ (mouse, IV): 10 mg/kg

LD₅₀ (mouse, oral): 175 mg/kg

LD₅₀ (mouse, SC): 64 mg/kg

LD₅₀ (rat, IP): 14.5 mg/kg

LD₅₀ (rat, IV): 13.9 mg/kg

LD₅₀ (rat, oral): 240 mg/kg

LD₅₀ (rat, SC): 400 mg/kg

LD₅₀ (rat, skin): 1.56 g/kg

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Benzalkonium chloride is irritant to the skin and eyes and repeated exposure to the skin may cause hypersensitivity. Concentrated benzalkonium chloride solutions accidentally spilled on the skin may produce corrosive skin lesions with deep necrosis and scarring, and should be washed immediately with water, followed by soap solutions applied freely. Gloves, eye protection, and suitable protective clothing should be worn.

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (inhalations, IM injections, nasal, ophthalmic, otic, and topical preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias

Eur, Int, Jpn, Pol, and US.

18. Related Substances

Benzethonium chloride; cetrimide.

19. Comments

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20. Specific References

1. Euerby MR. High performance liquid chromatography of benzalkonium chlorides - variation in commercial preparations. *J Clin Hosp Pharm* 1985; 10: 73-77.
2. Richards RME, McBride RJ. Enhancement of benzalkonium chloride and chlorhexidine acetate activity against *Pseudomonas aeruginosa* by aromatic alcohols. *J Pharm Sci* 1973; 62: 2035-2037.
3. Hugbo PG. Additivity and synergism *in vitro* as displayed by mixtures of some commonly employed antibacterial preservatives. *Can J Pharm Sci* 1976; 11: 17-20.
4. McCarthy TJ, Myburgh JA, Butler N. Further studies on the influence of formulation on preservative activity. *Cosmet Toilet* 1977; 92(3): 33-36.
5. Chermann JC, Barre-Sinoussi F, Henin Y, Marechal V. HIV inactivation by a spermicide containing benzalkonium. *AIDS Forsch* 1987; 2: 85-86.
6. Richards RME. Effect of hypromellose on the antibacterial activity of benzalkonium chloride. *J Pharm Pharmacol* 1976; 28: 264.
7. Bin T, Kulshreshtha AK, Al-Shakhshir R, Hem SL. Adsorption of benzalkonium chloride by filter membranes: mechanisms and effect of formulation and processing parameters. *Pharm Dev Technol* 1999; 4(2), 151-165.
8. Smolinske SC. *Handbook of Food, Drug, and Cosmetic Excipients*. Boca Raton, FL, CRC Press Inc, 1992; 31-39.
9. Honigman JL. Disinfectant ototoxicity [letter]. *Pharm J* 1975; 215: 523.
10. Beasley CRW, Rafferty P, Holgate ST. Bronchoconstrictor properties of preservatives in ipratropium bromide (Atrovent) nebuliser solution. *Br Med J* 1987; 294: 1197-1198.
11. Miszkial KA, Beasley R, Rafferty P, Holgate ST. The contribution of histamine release to bronchoconstriction provoked by inhaled benzalkonium chloride in asthma. *Br J Clin Pharmacol* 1988; 25: 157-163.
12. Miszkial KA, Beasley R, Holgate ST. The influence of ipratropium bromide and sodium cromoglycate on benzalkonium chloride-induced bronchoconstriction in asthma. *Br J Clin Pharmacol* 1988; 26: 295-301.

13. Worthington I. Bronchoconstriction due to benzalkonium chloride in nebulizer solutions. *Can J Hosp Pharm* 1989; 42: 165-166.
14. Boucher M, Roy MT, Henderson J. Possible association of benzalkonium chloride in nebulizer solutions with respiratory arrest. *Ann Pharmacother* 1992; 26: 772-774.
15. Gasset AR. Benzalkonium chloride toxicity to the human cornea. *Am J Ophthalmol* 1977; 84: 169-171.
16. Sweet DV, editor. Registry of Toxic Effects of Chemical Substances. Cincinnati, US Department of Health, 1987

21. General References

- Cowen RA, Steiger B. Why a preservative system must be tailored to a specific product. *Cosmet Toilet* 1977; 92(3): 15-20.
- El-Falaha BMA, Rogers DT, Furr JR, Russell AD. Surface changes in *Pseudomonas aeruginosa* exposed to chlorhexidine diacetate and benzalkonium chloride. *Int J Pharmaceutics* 1985; 23: 239-243.
- El-Falaha BMA, Russell AD, Furr JR, Rogers DT. Activity of benzalkonium chloride and chlorhexidine diacetate against wild-type and envelope mutants of *Escherichia coli* and *Pseudomonas aeruginosa*. *Int J Pharmaceutics* 1985; 23: 239-243.
- Karabit MS, Juneskans OT, Lundgren P. Studies on the evaluation of preservative efficacy III: the determination of antimicrobial characteristics of benzalkonium chloride. *Int J Pharmaceutics* 1988; 46: 141-147.
- Lien EJ, Perrin JH. Effect of chain length on critical micelle formation and protein binding of quaternary ammonium compounds. *J Med Chem* 1976; 19: 849-850.
- Martin AR. Anti-infective agents. In: Doerge RF, editor. *Wilson and Gisvold's Textbook of Organic, Medicinal and Pharmaceutical Chemistry*. Philadelphia, J.B. Lippincott Company, 1982; 141-142.
- Pensé AM, Vauthier C, Puisieux F, Benoit JP. Microencapsulation of benzalkonium chloride. *Int J Pharmaceutics* 1992; 81: 111-117.
- Prince HN, Nonemaker WS, Norgard RC, Prince DL. Drug resistance studies with topical antiseptics. *J Pharm Sci* 1978; 67: 1629-1631.
- Wallhäuser KH. Benzalkonium chloride. In: Kabara JJ, editor. *Cosmetic and Drug Preservation Principles and Practice*. New York, Marcel Dekker Inc, 1984; 731-734.

22. Authors

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