Chlorobutanol

1 Nonproprietary Names

BP: Chlorobutanol
JP: Chlorobutanol
PhEur: Chlorobutanolum anhydricum
USPNF: Chlorobutanol

2 Synonyms

Acetone chloroform; chlorbutanol; chlorbutol; trichloro-*tert*-butanol; β,β,β-trichloro-*tert*-butyl alcohol.

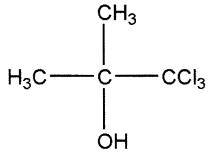
3 Chemical Name and CAS Registry Number

1,1,1-Trichloro-2-methyl-2-propanol [57-15-8]

4 Empirical Formula and Molecular Weight

$C_4H_7Cl_3O$ 177.46

5 Structural Formula



6 Functional Category

Antimicrobial preservative; plasticizer.

7 Applications in Pharmaceutical Formulation or Technology

Chlorobutanol is primarily used in ophthalmic or parenteral dosage forms as an antimicrobial preservative at concentrations up to 0.5% w/v; *see* Section 10. It is commonly used as an antibacterial agent for epinephrine solutions, posterior pituitary extract solutions, and ophthalmic preparations intended for the treatment of miosis. It is especially useful as an antibacterial agent in nonaqueous formulations. Chlorobutanol is also used as a preservative in cosmetics (*see* Section 16) and as a plasticizer for cellulose esters and ethers, and has been used therapeutically as a mild sedative and local analgesic.

8 Description

Volatile, colorless or white crystals with a musty, camphoraceous odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for chlorobutanol.

Test	JP 2001	PhEur 2002	USPNF 20
Identification	+	+	+
Characters	+	+	—
Melting point	≥76°C	+	—
Acidity	+	+	+
Water anhydrous form	≤6.0%	≤1.0%	≤1.0%
hemihydrate		4.5–5.5%	≤6.0%
Chloride	≤0.071%	≤300 ppm	≤0.07%
Residue on ignition	≤0.10%	—	—
Sulfated ash	—	≤0.1%	—
Organic volatile impurities	—	—	+
Assay (anhydrous basis)	≥98.0%	98.0–101.0%	98.0–100.5%

Note: the PhEur 2002 and USPNF 20 allow either the anhydrous form or the hemihydrate; the PhEur 2002 includes them as separate monographs.

10 Typical Properties

Antimicrobial activity: chlorobutanol has both antibacterial and antifungal properties. It is effective against Gram-positive and Gram-negative bacteria and some fungi, e.g., *Candida albicans*, *Pseudomonas aeruginosa*, and *Staphylococcus albus*. Antimicrobial activity is bacteriostatic, rather than bactericidal, and is considerably reduced above pH 5.5. In addition, activity may also be reduced by increasing heat and by incompatibilities between chlorobutanol and other excipients or packaging materials; *see* Sections 11 and 12. However, activity may be increased by combination with other antimicrobial preservatives; *see* Section 18. Typical minimum inhibitory concentrations (MICs) are: Gram-positive bacteria 650 µg/mL; Gram-negative bacteria 1000 µg/mL; yeasts 2500 µg/mL; fungi 5000 µg/mL.
Boiling point: 167°C
Melting point:
76–78°C for the hemihydrate
95–97°C for the anhydrous form.
Refractive index: n_D^{25} = 1.4339
Solubility: *see* Table II.

Table II: Solubility of chlorobutanol.

Solvent	Solubility at 20°C
Chloroform	Freely soluble
Ethanol (95%)	1 in 1
Ether	Freely soluble
Glycerin	1 in 10
Methanol	Freely soluble
Volatile oils	Freely soluble
Water	1 in 125

11 Stability and Storage Conditions

Chlorobutanol is volatile and readily sublimes. In aqueous solution degradation is catalyzed by hydroxide ions. Stability is good at pH 3 but becomes progressively worse with

increasing pH.[1] The half-life at pH 7.5 for a chlorobutanol solution stored at 25°C was determined to be approximately 3 months.[2] In a 0.5% w/v aqueous chlorobutanol solution at room temperature, chlorobutanol is almost saturated and may crystallize out of solution if the temperature is reduced.

Losses of chlorobutanol also occur owing to its volatility, with appreciable amounts being lost during autoclaving; at pH 5 about 30% of chlorobutanol is lost.[3] Porous containers result in losses from solutions, and polyethylene containers result in rapid loss. Losses of chlorobutanol during autoclaving in polyethylene containers may be reduced by pre-autoclaving the containers in a solution of chlorobutanol; the containers should then be used immediately.[4] There is also appreciable loss of chlorobutanol through stoppers in parenteral vials.

The bulk material should be stored in a well-closed container at a temperature of 8–15°C.

12 Incompatibilities

Owing to problems associated with sorption, chlorobutanol is incompatible with plastic vials,[4–8] rubber stoppers, bentonite,[9] magnesium trisilicate,[9] polyethylene, and polyhydroxyethylmethacrylate, which has been used in soft contact lenses.[10] To a lesser extent, carboxymethylcellulose and polysorbate 80 reduce antimicrobial activity by sorption or complex formation.

13 Method of Manufacture

Chlorobutanol is prepared by condensing acetone and chloroform in the presence of solid potassium hydroxide.

14 Safety

Chlorobutanol is widely used as a preservative in a number of pharmaceutical formulations, particularly ophthalmic preparations. Although animal studies have suggested that chlorobutanol may be harmful to the eye, in practice the widespread use of chlorobutanol as a preservative in ophthalmic preparations has been associated with few reports of adverse reactions. A study of the irritation potential of a local anesthetic on the murine cornea indicated significant corneal surface damage in the presence of 0.5% w/v chlorobutanol, which may be related to the preservative's effective concentration.[11] Reported adverse reactions to chlorobutanol include: cardiovascular effects following intravenous administration of heparin sodium injection preserved with chlorobutanol;[12] neurological effects following administration of a large dose of morphine infusion preserved with chlorobutanol;[13] and hypersensitivity reactions, although these are regarded as rare.[14–16]

The lethal human dose of chlorobutanol is estimated to be 50–500 mg/kg.[17]

LD_{50} (dog, oral): 0.24 g/kg[18,19]
LD_{50} (mouse, oral): 0.99 g/kg
LD_{50} (rabbit, oral): 0.21 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Chlorobutanol may be irritant to the skin, eyes, and mucous membranes. Eye protection and gloves are recommended along with a respirator in poorly ventilated environments. There is a slight fire hazard on exposure to heat or flame.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM, IV, and SC injections, inhalations, nasal, otic, ophthalmic, and topical preparations). Labeling must state 'contains chlorobutanol up to 0.5%'. Included in nonparenteral and parenteral medicines licensed in the UK.

In the UK, the maximum concentration of chlorobutanol permitted for use in cosmetics, other than foams, is 0.5%. It is not suitable for use in aerosols.

17 Related Substances

Phenoxyethanol; phenylethyl alcohol.

18 Comments

It has been reported that a combination of chlorobutanol and phenylethanol, both at 0.5% w/v concentration, has shown greater antibacterial activity than either compound alone. An advantage of the use of this combination is that chlorobutanol dissolves in the alcohol; the resulting liquid can then be dissolved in an aqueous pharmaceutical preparation without the application of heat.

The EINECS number for chlorobutanol is 200-317-6.

19 Specific References

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20 General References

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21 Author

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22 Date of Revision

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