

Benzyl Alcohol

1 Nonproprietary Names

BP: Benzyl alcohol
JP: Benzyl alcohol
PhEur: Alcohol benzylicus
USPNF: : Benzyl alcohol

2 Synonyms

α -Hydroxytoluene; phenylcarbinol; phenylmethanol; α -toluenol.

3 Chemical Name and CAS Registry Number

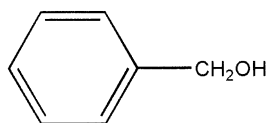
Benzenemethanol [100-51-6]

4 Empirical Formula Molecular Weight

C₇H₈O

108.14

5 Structural Formula



6 Functional Category

Antimicrobial preservative; disinfectant; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Benzyl alcohol is an antimicrobial preservative used in cosmetics, foods, and a wide range of pharmaceutical formulations,⁽¹⁻⁴⁾ including oral and parenteral preparations, at concentrations up to 2.0% v/v. In cosmetics, concentrations up to 3.0% v/v may be used as a preservative. Concentrations of 5% v/v or more are employed as a solubilizer, while a 10% v/v solution is used as a disinfectant.

Benzyl alcohol 10% v/v solutions also have some local anesthetic properties, which are exploited in some parenterals, cough products, ophthalmic solutions, ointments, and dermatological aerosol sprays.

Although widely used as an antimicrobial preservative, benzyl alcohol has been associated with some fatal adverse reactions when administered to neonates. It is now recommended that parenteral products preserved with benzyl alcohol, or other antimicrobial preservatives, should not be used in newborn infants if at all possible; see Section 14.

8 Description

A clear, colorless, oily liquid with a faint aromatic odor and a sharp, burning taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for benzyl alcohol.

Test	JP 2001	PhEur 2002	USPNF 20
Identification	+	+	+
Characters	—	+	—
Solubility	—	+	—
Acidity	+	+	+
Clarity of solution	+	—	—
Specific gravity	1.043–1.053	1.043–1.049	1.042–1.047
Distilling range	202.5–206.5°C	—	—
Refractive index	1.538–1.541	1.538–1.541	1.539–1.541
Residue on ignition	≤0.005%	—	≤0.005%
Nonvolatile matter	—	≤0.05%	≤1 mg
Chlorinated compounds	+	≤300 ppm	≤0.03%
Benzaldehyde	+	≤0.2%	≤0.2%
Peroxide value	—	≤5	—
Organic volatile impurities	—	—	+
Assay	≥98.0%	97.0–100.5%	97.0–100.5%

10 Typical Properties

Acidity/alkalinity: aqueous solutions are neutral to litmus.

Antimicrobial activity: benzyl alcohol is bacteriostatic and is used as an antimicrobial preservative against Gram-positive bacteria, molds, fungi, and yeasts, although it possesses only modest bactericidal properties. Optimum activity occurs at pH below 5; little activity is shown above pH 8. Antimicrobial activity is reduced in the presence of nonionic surfactants, such as polysorbate 80. However, the reduction in activity is less than is the case with either hydroxybenzoate esters or quaternary ammonium compounds. The activity of benzyl alcohol may also be reduced by incompatibilities with some packaging materials, particularly polyethylene; see Section 12.

See Table II for reported minimum inhibitory concentrations (MICs).

Table II: Minimum inhibitory concentrations (MICs) of benzyl alcohol.⁽⁴⁾

Microorganism	MIC (μg/ml)
<i>Aspergillus niger</i>	5000
<i>Candida albicans</i>	2500
<i>Escherichia coli</i>	2000
<i>Pseudomonas aeruginosa</i>	2000
<i>Staphylococcus aureus</i>	25

Bacteria: benzyl alcohol is moderately active against most Gram-positive organisms (typical MICs are 3–5 mg/mL), although some Gram-positive bacteria are very sensitive

(MICs 0.025–0.05 mg/mL). In general, benzyl alcohol is less active against Gram-negative organisms.

Fungi: benzyl alcohol is effective against molds and yeasts; typical MICs are 3–5 mg/mL.

Spores: benzyl alcohol is inactive against spores, but activity may be enhanced by heating. Benzyl alcohol 1% v/v, at pH 5–6, has been claimed to be as effective as phenylmercuric nitrate 0.002% w/v against *Bacillus stearothermophilus* at 100°C for 30 min.

Autoignition temperature: 436.5°C

Boiling point: 204.7°C

Flammability: flammable. Limits in air 1.7–15.0% v/v.

Flash point:

100.6°C (closed cup)

104.5°C (open cup)

Freezing point: –15°C

Partition coefficients:

Liquid paraffin: water = 0.2

Peanut oil: water = 1.3

Refractive index: $n_D^{20} = 1.5404$

Solubility: see Table III.

Table III: Solubility of benzyl alcohol.

Solvent	Solubility at 20°C unless otherwise stated
Chloroform	Miscible in all proportions
Ethanol	Miscible in all proportions
Ethanol (50%)	1 in 2.5
Ether	Miscible in all proportions
Fixed and volatile oils	Miscible in all proportions
Water	1 in 25 at 25°C 1 in 14 at 90°C

Specific gravity: 1.0454 at 20°C

Surface tension: 38.8 mN/m (38.8 dynes/cm)

Vapor density (relative): 3.72 (air = 1)

Vapor pressure:

13.3 Pa (0.1 mmHg) at 30°C

1.769 kPa (13.3 mmHg) at 100°C

Viscosity (dynamic): 6 mPa·s (6 cP) at 20°C

11 Stability and Storage Conditions

Benzyl alcohol oxidizes slowly in air to benzaldehyde and benzoic acid; it does not react with water. Aqueous solutions may be sterilized by filtration or autoclaving; some solutions may generate benzaldehyde during autoclaving.

Benzyl alcohol may be stored in metal or glass containers. Plastic containers should not be used; exceptions to this include polypropylene containers or vessels coated with inert fluorinated polymers such as Teflon; see Section 12.

Benzyl alcohol should be stored in an airtight container, protected from light, in a cool, dry place.

12 Incompatibilities

Benzyl alcohol is incompatible with oxidizing agents and strong acids. It can also accelerate the autoxidation of fats.

Although antimicrobial activity is reduced in the presence of nonionic surfactants, such as polysorbate 80, the reduction is less than is the case with hydroxybenzoate esters or quaternary ammonium compounds.

Benzyl alcohol is incompatible with methylcellulose and is only slowly sorbed by closures composed of natural rubber, neoprene, and butyl rubber closures, the resistance of which can be enhanced by coating with fluorinated polymers.⁽⁵⁾ However, a 2% v/v aqueous solution in a polyethylene container, stored at 20°C, may lose up to 15% of its benzyl alcohol content in 13 weeks.⁽⁶⁾ Losses to polyvinyl chloride and polypropylene containers under similar conditions are usually negligible. Benzyl alcohol can damage polystyrene syringes by extracting some soluble components.⁽⁷⁾

13 Method of Manufacture

Benzyl alcohol is prepared commercially by the distillation of benzyl chloride with potassium or sodium carbonate. It may also be prepared by the Cannizzaro reaction of benzaldehyde and potassium hydroxide.

14 Safety

Benzyl alcohol is used in a wide variety of pharmaceutical formulations. It is metabolized to benzaldehyde and benzoic acid, with benzoic acid being further metabolized in the liver by conjugation with glycine to form hippuric acid, which is excreted in the urine.

Ingestion or inhalation of benzyl alcohol may cause headache, vertigo, nausea, vomiting, and diarrhea. Overexposure may result in CNS depression and respiratory failure. However, the concentrations of benzyl alcohol normally employed as a preservative are not associated with such adverse effects.

Reports of adverse reactions to benzyl alcohol^(8,9) used as an excipient include toxicity following intravenous administration;^(10,11) neurotoxicity in patients administered benzyl alcohol in intrathecal preparations;⁽¹²⁾ hypersensitivity,^(13,14) although relatively rare; and a fatal toxic syndrome in premature infants.^(15–17)

The fatal toxic syndrome in low-birth-weight neonates, which includes symptoms of metabolic acidosis and respiratory depression, was attributed to the use of benzyl alcohol as a preservative in solutions used to flush umbilical catheters. As a result of this, the FDA has recommended that benzyl alcohol should not be used in such flushing solutions and has advised against the use of medicines containing preservatives in the newborn.^(18,19)

The WHO has set the estimated acceptable daily intake of the benzyl/benzoic moiety at up to 5 mg/kg body-weight daily.⁽²⁰⁾

LD₅₀ (mouse, IV): 0.32 g/kg⁽²¹⁾

LD₅₀ (mouse, oral): 1.36 g/kg

LD₅₀ (rat, IP): 0.4 g/kg

LD₅₀ (rat, IV): 0.05 g/kg

LD₅₀ (rat, oral): 1.23 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Benzyl alcohol (liquid and vapor) is irritant to the skin, eyes, and mucous membranes. Eye protection, gloves, and protective clothing are recommended. Benzyl alcohol should be handled in a well-ventilated environment; a self-contained breathing apparatus is recommended in areas of poor ventilation. Benzyl alcohol is flammable.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (injections, oral capsules, solutions and tablets, topical, and vaginal preparations). Included in parenteral and nonparenteral medicines licensed in the UK.

17 Related Substances

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18 Comments

The EINECS number for benzyl alcohol is 202-859-9.

19 Specific References

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20 General References

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21 Author

EL Brunson.

22 Date of Revision

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