Benzoic Acid

1 Nonproprietary Names
BP: Benzoic Acid
JP: Benzoic Acid
PhEur: Benzoic Acid
USP: Benzoic Acid

2 Synonyms
Acidum benzoicum; benzenecarboxylic acid; benzeneformic acid; carboxybenzene; dracylic acid; E210; phenylcarboxylic acid; phenylformic acid.

3 Chemical Name and CAS Registry Number
Benzoic acid [65-85-0]

4 Empirical Formula and Molecular Weight
C\(_7\)H\(_6\)O\(_2\) 122.12

5 Structural Formula

6 Functional Category
Antimicrobial preservative; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology
Benzoic acid is widely used in cosmetics, foods, and pharmaceuticals (see Table I), as an antimicrobial preservative. (1–3) Greatest activity is seen at pH values between 2.5–4.5; see Section 10.

Benzoic acid also has a long history of use as an antifungal agent(4) in topical therapeutic preparations such as Whitfield’s ointment (benzoic acid 6% and salicylic acid 3%).

Table I: Uses of benzoic acid.

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM and IV injections</td>
<td>0.17</td>
</tr>
<tr>
<td>Oral solutions</td>
<td>0.01–0.1</td>
</tr>
<tr>
<td>Oral suspensions</td>
<td>0.1</td>
</tr>
<tr>
<td>Oral syrups</td>
<td>0.15</td>
</tr>
<tr>
<td>Topical preparations</td>
<td>0.1–0.2</td>
</tr>
<tr>
<td>Vaginal preparations</td>
<td>0.1–0.2</td>
</tr>
</tbody>
</table>

8 Description
Benzoic acid occurs as feathery, light, white or colorless crystals or powder. It is essentially tasteless and odorless or with a slight characteristic odor suggestive of benzoin.

9 Pharmacopeial Specifications
See Table II.

Table II: Pharmacopeial specifications for benzoic acid.

<table>
<thead>
<tr>
<th>Test</th>
<th>JP XV</th>
<th>PhEur 6.4</th>
<th>USP 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Characters</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Melting point</td>
<td>121–124°C</td>
<td>121–124°C</td>
<td>121–123°C</td>
</tr>
<tr>
<td>Water</td>
<td>≤0.5%</td>
<td>≤0.1%</td>
<td>≤0.05%</td>
</tr>
<tr>
<td>Residue on ignition</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Readily carbonizable</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Substances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Readily oxidizable</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Substances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy metals</td>
<td>≤20 ppm</td>
<td>≤10 ppm</td>
<td>≤10 ppm</td>
</tr>
<tr>
<td>Halogenated compounds</td>
<td>+</td>
<td>≤300 ppm</td>
<td></td>
</tr>
<tr>
<td>and halides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appearance of solution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phthalic acid</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay (anhydrous basis)</td>
<td>≥99.5%</td>
<td>99.0–100.5%</td>
<td>99.5–100.5%</td>
</tr>
</tbody>
</table>

10 Typical Properties

Acidity/alkalinity  pH = 2.8 (saturated aqueous solution at 25°C)

Antimicrobial activity Only the undissociated acid shows antimicrobial properties; the activity therefore depends on the pH of the medium. Optimum activity occurs at pH values below 4.5; at values above pH 5, benzoic acid is almost inactive. (5) It has been reported that antimicrobial activity is enhanced by the addition of protamine, a basic protein. (6)

Bacteria Moderate bacteriostatic activity against most species of Gram-positive bacteria. Typical MIC is 100 μg/mL. Activity is less, in general, against Gram-negative bacteria. MIC for Gram-negative bacteria may be up to 1600 μg/mL.

Molds Moderate activity. Typical MICs are 400–1000 μg/mL at pH 3; 1000–2000 μg/mL at pH 5.

Spores Inactive against spores.

Yeasts Moderate activity. Typical MIC is 1200 μg/mL. The addition of propylene glycol may enhance the fungistatic activity of benzoic acid.

Autoignition temperature 570°C

Boiling point 249.2°C

Density 1.311 g/cm\(^3\) for solid at 24°C;
1.075 g/cm\(^3\) for liquid at 130°C

Dissociation constant The dissociation of benzoic acid in mixed solvents is dictated by specific solute–solvent interactions as well as by relative solvent basicity. Increasing the organic solvent fraction favors the free acid form. (7)

pK\(_a\) = 4.19 at 25°C;
pK\(_a\) = 5.54 in methanol 60%.

Flash point 121–131°C

Melting point 122°C (begins to sublime at 100°C)

Moisture content 0.17–0.42% w/w

NIR spectra see Figure 1.

Partition coefficients
Benzene : water = 0.0044;
Cyclohexane : water = 0.30;
Octanol : water = 1.87.


**11 Stability and Storage Conditions**

Aqueous solutions of benzoic acid may be sterilized by autoclaving or by filtration. A 0.1% w/v aqueous solution of benzoic acid has been reported to be stable for at least 8 weeks when stored in polyvinyl chloride bottles, at room temperature.\(^\text{(12)}\)

When added to a suspension, benzoic acid dissociates, with the benzoate anion adsorbing onto the suspended drug particles. This adsorption alters the charge at the surface of the particles, which may in turn affect the physical stability of the suspension.\(^\text{(13–15)}\) The addition of sodium azide has been shown to increase the stability of benzoic acid in skin permeation experiments.\(^\text{(16)}\)

The bulk material should be stored in a well-closed container in a cool, dry place.

**12 Incompatibilities**

Undergoes typical reactions of an organic acid, e.g. with alkalis or heavy metals. Preservative activity may be reduced by interaction with kaolin.\(^\text{(17)}\)

**13 Method of Manufacture**

Although benzoic acid occurs naturally, it is produced commercially by several synthetic methods. One process involves the continuous liquid-phase oxidation of toluene in the presence of a cobalt catalyst at 150–200°C and 0.5–5.0 MPa (5.0–50.0 atm) pressure to give a yield of approximately 90% benzoic acid.

Benzoic acid can also be produced commercially from benzo-trichloride or phthalic anhydride. Benzotrichloride, produced by chlorination of toluene, is reacted with 1 mole of benzoic acid to yield 2 moles of benzoyl chloride. The benzoyl chloride is then converted to 2 moles of benzoic acid by hydrolysis. Yield is 75–80%.

In another commercial process, phthalic anhydride is converted to benzoic acid, in about an 85% yield, by hydrolysis in the presence of heat and chromium and disodium phthalates.

Crude benzoic acid is purified by sublimation or recrystallization.

**14 Safety**

Ingested benzoic acid is conjugated with glycine in the liver to yield hippuric acid, which is then excreted in the urine;\(^\text{(18)}\) care should be taken when administering benzoic acid to patients with chronic liver disease.\(^\text{(19)}\) Benzoic acid is a gastric irritant, and a mild irritant to the skin,\(^\text{(20–23)}\) It is also a mild irritant to the eyes and mucous membranes.\(^\text{(24)}\) Allergic reactions to benzoic acid have been reported, although a controlled study indicated that the incidence of urticaria in patients given benzoic acid is no greater than in those given a lactose placebo.\(^\text{(23)}\) It has been reported that asthmatics may become adversely affected by benzoic acid contained in some antiasthma drugs.\(^\text{(26)}\)

The WHO acceptable daily intake of benzoic acid and other benzoates, calculated as benzoic acid, has been set at up to 5 mg/kg body-weight.\(^\text{(27,28)}\) The minimum lethal human oral dose of benzoic acid is 500 mg/kg body-weight.\(^\text{(29,30)}\)

LD\(_{50}\) (cat, oral): 2 g/kg\(^\text{(29)}\)
LD\(_{50}\) (dog, oral): 2 g/kg
LD\(_{50}\) (mouse, IP): 1.46 g/kg
LD\(_{50}\) (mouse, oral): 1.94 g/kg
LD\(_{50}\) (rat, oral): 1.7 g/kg
See also Sodium benzoate.

**15 Handling Precautions**

Observe normal precautions appropriate to the circumstances and quantity of material handled. Benzoic acid may be harmful by inhalation, ingestion, or skin absorption and may be irritant to the eyes, skin, and mucous membranes. Benzoic acid should be handled in a well-ventilated environment; eye protection, gloves, and a dust mask or respirator are recommended. Benzoic acid is flammable.

**16 Regulatory Status**

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Database (IM and IV injections, irrigation solutions, oral solutions, suspensions, syrups and tablets, rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

**17 Related Substances**

Potassium benzoate; sodium benzoate.

**18 Comments**

Benzoic acid is known to dimerize in many nonpolar solvents. This property, coupled with pH-dependent dissociation in aqueous media, comprises a classic textbook example of the effects of
dissociation and molecular association on apparent partitioning behavior. The principles involved may be practically applied in determination of the total concentration of benzoate necessary to provide a bacteriostatic level of benzoic acid in the aqueous phase of an oil-in-water emulsion. A specification for benzoic acid is contained in the Food Chemicals Codex (FCC). The EINECS number for benzoic acid is 200-618-2. The PubChem Compound ID (CID) for benzoic acid is 243.

19 Specific References

21 Lahti A et al. Immediate irritant reactions to benzoic acid are enhanced in washed skin areas. Contact Dermatitis 1996; 35(1): 51.
# Benzyl Alcohol

1 **Nonproprietary Names**
- BP: Benzyl Alcohol
- JP: Benzyl Alcohol
- PhEur: Benzyl Alcohol
- USP-NF: Benzyl Alcohol

2 **Synonyms**
Alcohol benzylicus; benzenemethanol; \( \alpha \)-hydroxytoluene; phenyl-carbinol; phenylmethanol; \( \alpha \)-toluenol.

3 **Chemical Name and CAS Registry Number**
Benzenemethanol [100-51-6]

4 **Empirical Formula and Molecular Weight**
\( \text{C}_7\text{H}_8\text{O} \)
108.14

5 **Structural Formulation**

![Structural formula of benzyl alcohol](image)

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, including oral and parenteral preparations, at concentrations up to 2.0\% v/v. The typical concentration used is 1\% v/v, and it has been reported to be used in protein, peptide and small molecule products, although its frequency of use has fallen from 48 products in 1996, 30 products in 2001, to 15 products in 2006.\(^{15}\) 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 parenteral products, 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. See also Section 18.

<table>
<thead>
<tr>
<th>Test</th>
<th>JP XV</th>
<th>PhEur 6.5</th>
<th>USP32–NF27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
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<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Characters</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Solubility</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Acidity</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clarity and color of solution</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1.043–1.049</td>
<td>1.043–1.049</td>
<td>–</td>
</tr>
<tr>
<td>Refractive index</td>
<td>1.538–1.541</td>
<td>1.538–1.541</td>
<td>1.538–1.541</td>
</tr>
<tr>
<td>Residue on evaporation</td>
<td>≤0.05%</td>
<td>≤0.05%</td>
<td>≤0.05%</td>
</tr>
<tr>
<td>Related substances</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Benzaldehyde</td>
<td>+</td>
<td>+</td>
<td>0.05–0.15</td>
</tr>
<tr>
<td>Peroxide value</td>
<td>≤0.5</td>
<td>≤0.5</td>
<td>≤5</td>
</tr>
<tr>
<td>Assay</td>
<td>98.0–100.5%</td>
<td>98.0–100.5%</td>
<td>98.0–100.5%</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Microorganism</th>
<th>MIC ((\mu)g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus niger</td>
<td>5000</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>2500</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>2000</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>2000</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>25</td>
</tr>
</tbody>
</table>

**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 \textit{Bacillus stearothermophilus} at 100°C for 30 min.