Handbook of Pharmaceutical Excipients

SIXTH EDITION

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21 Author

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22 Date of Revision

13 February 2009.

Boric Acid

1 Nonproprietary Names

BP: Boric Acid
JP: Boric Acid
PhEur: Boric Acid
USP-NF: Boric Acid

2 Synonyms

Acidum boricum; boracic acid; boraic acid; *Borofax*; boron trihydroxide; E284; orthoboric acid; trihydroxyborene.

3 Chemical Name and CAS Registry Number

Orthoboric acid [10043-35-3]
Metaboric acid [13460-50-9]

4 Empirical Formula and Molecular Weight

H_3BO_3 61.83 (for trihydrate)
HBO_2 43.82 (for monohydrate)

5 Structural Formula

See Section 4.

6 Functional Category

Antimicrobial preservative; buffering agent.

7 Applications in Pharmaceutical Formulation or Technology

Boric acid is used as an antimicrobial preservative[1] in eye drops, cosmetic products, ointments, and topical creams. It is also used as an antimicrobial preservative in foods.

Boric acid and borate have good buffering capacity and are used to control pH; they have been used for this purpose in external preparations such as eye drops.[2]

Boric acid has also been used therapeutically in the form of suppositories to treat yeast infections.[3,4] In dilute concentrations it is used as a mild antiseptic, with weak bacteriostatic and fungistatic

8 Description

Boric acid occurs as a hygroscopic, white crystalline powder, colorless shiny plates, or white crystals.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for boric acid.

Test	JP XV	PhEur 6.0	USP32–NF27
Identification	+	+	+
Characters	–	+	–
Appearance of solution	+	+	–
Loss on drying	⩽0.50%	–	⩽0.50%
Sulfate	–	⩽450 ppm	–
Heavy metals	⩽10 ppm	⩽15 ppm	⩽0.002%
Organic matter	–	+	–
Arsenic	⩽5 ppm	–	–
pH	3.5–4.1	3.8–4.8	–
Solubility in ethanol (96%)	–	+	+
Completeness of solution	–	–	+
Assay	⩾99.5%	99.0–100.5%	99.5–100.5%

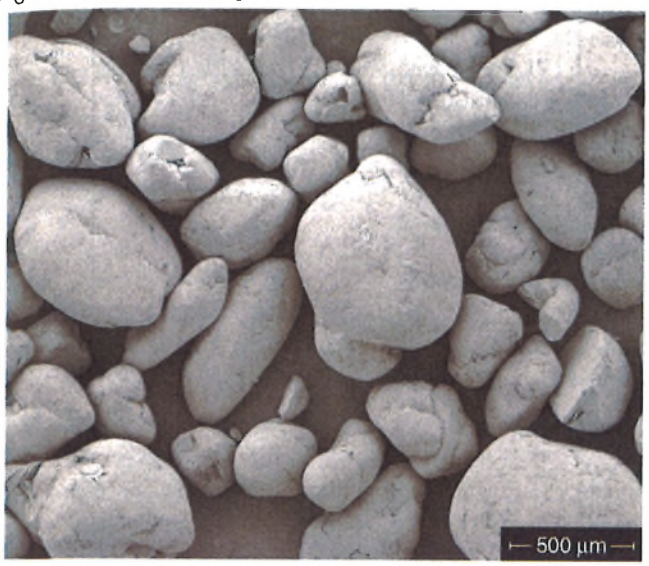
10 Typical Properties

Acidity/alkalinity pH = 3.5–4.1 (5% w/v aqueous solution)
Density 1.435
Melting point 170.9°C. When heated slowly to 181.0°C, boric acid loses water to form metaboric acid (HBO_2); tetraboric acid ($H_2B_4O_7$) and boron trioxide (B_2O_3) are formed at higher temperatures.[6]
Solubility Soluble in ethanol, ether, glycerin, water, and other fixed and volatile oils. Solubility in water is increased by addition of hydrochloric, citric, or tartaric acids.
Specific gravity 1.517

11 Stability and Storage Conditions

Boric acid is hygroscopic and should therefore be stored in an air-

SEM 1: Excipient: boric acid; manufacturer: Alfa Aesar; lot no.: 23672; magnification: 100×; voltage: 5 kV.



SEM 2: Excipient: boric acid; manufacturer: Aldrich Chemical Company Inc.; lot no.: 01559BU; magnification: 100×; voltage: 5 kV.

12 Incompatibilities

Boric acid is incompatible with water, strong bases and alkali metals. It reacts violently with potassium and acid anhydrides. It also forms a complex with glycerin, which is a stronger acid than boric acid.

13 Method of Manufacture

Boric acid occurs naturally as the mineral sassolite. However, the majority of boric acid is produced by reacting inorganic borates with sulfuric acid in an aqueous medium. Sodium borate and partially refined calcium borate (colemanite) are the principal raw materials. When boric acid is made from colemanite, the fine-ground ore is vigorously stirred with mother liquor and sulfuric acid at about 90°C. The by-product calcium sulfate is removed by filtration, and the boric acid is crystallized by cooling the filtrate.

14 Safety

Boric acid is a weak bacteriostatic and antimicrobial agent, and has and gargles. It has also been used in US- and Japanese-approved intravenous products. Solutions of boric acid were formerly used to wash out body cavities, and as applications to wounds and ulcers, although the use of boric acid for these purposes is now regarded as inadvisable owing to the possibility of absorption.[5] Boric acid is not used internally owing to its toxicity. It is poisonous by ingestion and moderately toxic by skin contact. Experimentally it has proved to be toxic by inhalation and subcutaneous routes, and moderately toxic by intraperitoneal and intravenous routes.

Boric acid is absorbed from the gastrointestinal tract and from damaged skin, wounds, and mucous membranes, although it does not readily permeate intact skin. The main symptoms of boric acid poisoning are abdominal pain, diarrhea, erythematous rash involving both skin and mucous membrane, and vomiting. These symptoms may be followed by desquamation, and stimulation or depression of the central nervous system. Convulsions, hyperpyrexia, and renal tubular damage have been known to occur.[7]

Death has occurred from ingestion of less than 5 g in young children, and of 5–20 g in adults. Fatalities have occurred most frequently in young children after the accidental ingestion of solutions of boric acid, or after the application of boric acid powder to abraded skin.

The permissible exposure limit (PEL) of boric acid is 15 mg/m^3 total dust, and 5 mg/m^3 respirable fraction for nuisance dusts.[8]

Ld_{Lo} (man, oral): 429 mg/kg[9]
Ld_{Lo} (woman, oral): 200 mg/kg[9]
Ld_{Lo} (infant, oral): 934 mg/kg[9]
Ld_{Lo} (man, skin): 2.43 g/kg[9]
Ld_{Lo} (infant, skin): 1.20 g/kg[9]
LD_{50} (mouse, oral): 3.45 g/kg[9]
LD_{50} (mouse, IV): 1.24 g/kg
LD_{50} (mouse, SC): 1.74 g/kg
LD_{50} (rat, oral): 2.660 g/kg
LD_{50} (rat, IV): 1.33 g/kg
LD_{50} (rat, SC): 1.4 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Boric acid is irritating to the skin and is potentially toxic by inhalation. Gloves, eye protection, protective clothing, and a respirator are recommended.

16 Regulatory Status

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (IV injections; ophthalmic preparations; (auricular) otic solutions; topical preparations). Reported in the EPA TSCA Inventory. In the UK, the use of boric acid in cosmetics and toiletries is restricted. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Sodium borate.

18 Comments

Boric acid has been used experimentally as a model oxo-acid to retard mannitol crystallization in the solid state.[10]

The EINECS number for boric acid is 233-139-2. The PubChem Compound ID (CID) for boric acid includes 7628 and 24492.

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22 Date of Revision

19 January 2009.

Bronopol

1 Nonproprietary Names

BP: Bronopol

2 Synonyms

2-Bromo-2-nitro-1,3-propanediol; β-bromo-β-nitrotrimethyleneglycol; *Myacide*.

3 Chemical Name and CAS Registry Number

2-Bromo-2-nitropropane-1,3-diol [52-51-7]

4 Empirical Formula and Molecular Weight

$C_3H_6BrNO_4$ 200.00

5 Structural Formula

6 Functional Category

Antimicrobial preservative; antiseptic.

7 Applications in Pharmaceutical Formulation or Technology

Bronopol 0.01–0.1% w/v is used as an antimicrobial preservative either alone or in combination with other preservatives in topical pharmaceutical formulations, cosmetics, and toiletries; the usual concentration is 0.02% w/v.

8 Description

Bronopol is a white or almost white crystalline powder; odorless or with a faint characteristic odor.

10 Typical Properties

Antimicrobial activity Bronopol is active against both Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*, with typical minimum inhibitory concentrations (MICs) between 10–50 μg/mL;[1–8] *see also* Table II. At room temperature, a 0.08% w/v aqueous solution may reduce the viability of culture collection strains of *Escherichia coli* and

Table I: Pharmacopeial specifications for bronopol.

Test	BP 2009
Identification	+
Characters	+
Acidity or alkalinity (1% w/v solution)	5.0–7.0
Related substances	+
Sulfated ash	≤0.1%
Water	≤0.5%
Assay (anhydrous basis)	99.0–101.0%

Table II: Minimum inhibitory concentrations (MICs) of bronopol.[2,9]

Microorganism	MIC (μg/mL)
Aspergillus niger	3200
Bacillus subtilis	12.5
Burkholderia (Pseudomonas) cepacia	25
Candida albicans	1600
Escherichia coli	12.5–50
Klebsiella aerogenes	25
Legionella pneumophilia	50
Penicillium roqueforti	400
Penicillium funiculosum	1600
Pityrosporum ovale	125
Proteus mirabilis	25–50
Proteus vulgaris	12.5–50
Pseudomonas aeruginosa	12.5–50
Saccharomyces cerevisiae	3200
Salmonella gallinarum	25
Staphylococcus aureus	12.5–50
Staphylococcus epidermidis	50
Streptococcus faecalis	50

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