Sodium Metabisulfite

1 Nonproprietary Names

BP: Sodium metabisulphite
JP: Sodium metabisulfite
PhEur: Natrii metabisulfis
USPNF: Sodium metabisulfite

2 Synonyms

Disodium disulfite; disodium pyrosulfite; disulfurous acid, disodium salt; E223; natrii disulfis; sodium acid sulfite; sodium pyrosulfite.

3 Chemical Name and CAS Registry Number

Sodium pyrosulfite [7681-57-4]

4 Empirical Formula and Molecular Weight

Empirical Formula	Molecular Weight
$Na_2S_2O_5$	190.1

5 Structural Formula

$Na_2S_2O_5$

6 Functional Category

Antioxidant.

7 Applications in Pharmaceutical Formulation or Technology

Sodium metabisulfite is used as an antioxidant in oral, parenteral, and topical pharmaceutical formulations, at concentrations of 0.01–1.0% w/v. Primarily, sodium metabisulfite is used in acidic preparations; for alkaline preparations, sodium sulfite is usually preferred; *see* Sections 17 and 18. Sodium metabisulfite also has some antimicrobial activity, which is greatest at acid pH, and may be used as a preservative in oral preparations such as syrups.

In the food industry and in wine production, sodium metabisulfite is similarly used as an antioxidant, antimicrobial preservative, and antibrowning agent. However, at concentrations above about 550 ppm it imparts a noticeable flavor to preparations.

Sodium metabisulfite usually contains small amounts of sodium sulfite and sodium sulfate; *see* Section 17.

8 Description

Sodium metabisulfite occurs as colorless, prismatic crystals or as a white to creamy-white crystalline powder that has the odor of sulfur dioxide and an acidic, saline taste. Sodium metabisulfite crystallizes from water as a hydrate containing seven water molecules.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for sodium metabisulfite.

Test	JP 2001	PhEur 2002	USPNF 20
Identification	+	+	+
Characters	—	+	—
Appearance of solution	+	+	—
pH (5% w/v solution)	—	3.5–5.0	—
Chloride	—	—	≤0.05%
Trisulfate	+	+	≤0.05%
Arsenic	≤4 ppm	≤5 ppm	—
Heavy metals	≤20 ppm	≤20 ppm	≤0.002%
Iron	≤20 ppm	≤20 ppm	≤0.002%
Assay (as $Na_2S_2O_5$)	≥95.0%	95.0–100.5%	—
Assay (as SO_2)	—	—	65.0–67.4%

10 Typical Properties

Acidity/alkalinity: pH = 3.5–5.0 for a 5% w/v aqueous solution at 20°C.
Melting point: sodium metabisulfite melts with decomposition at less than 150°C.
Osmolarity: a 1.38% w/v aqueous solution is isoosmotic with serum.
Solubility: *see* Table II.

Table II: Solubility of sodium metabisulfite.

Solvent	Solubility at 20°C unless otherwise stated
Ethanol (95%)	Slightly soluble
Glycerin	Freely soluble
Water	1 in 1.9
	1 in 1.2 at 100°C

11 Stability and Storage Conditions

On exposure to air and moisture, sodium metabisulfite is slowly oxidized to sodium sulfate with disintegration of the crystals.[1] Addition of strong acids to the solid liberates sulfur dioxide.

In water, sodium metabisulfite is immediately converted to sodium (Na^+) and bisulfite (HSO_3^-) ions. Aqueous sodium metabisulfite solutions also decompose in air, especially on heating. Solutions that are to be sterilized by autoclaving should be filled into containers in which the air has been replaced with an inert gas, such as nitrogen. The addition of dextrose to aqueous sodium metabisulfite solutions results in a decrease in the stability of the metabisulfite.[2]

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

12 Incompatibilities

Sodium metabisulfite reacts with sympathomimetics and other drugs that are *ortho-* or *para*-hydroxybenzyl alcohol derivatives to form sulfonic acid derivatives possessing little or no pharmacological activity. The most important drugs

subject to this inactivation are epinephrine (adrenaline) and its derivatives.[3] In addition, sodium metabisulfite is incompatible with chloramphenicol owing to a more complex reaction;[3] it also inactivates cisplatin in solution.[4,5]

It is incompatible with phenylmercuric acetate when autoclaved in eye drop preparations.[6]

Sodium metabisulfite may react with the rubber caps of multidose vials, which should therefore be pretreated with sodium metabisulfite solution.[7]

13 Method of Manufacture

Sodium metabisulfite is prepared by saturating a solution of sodium hydroxide with sulfur dioxide and allowing crystallization to occur; hydrogen is passed through the solution to exclude air. Sodium metabisulfite may also be prepared by saturating a solution of sodium carbonate with sulfur dioxide and allowing crystallization to occur, or by thermally dehydrating sodium bisulfite.

14 Safety

Sodium metabisulfite is widely used as an antioxidant in oral, topical, and parental pharmaceutical formulations; it is also widely used in food products.

Although it is extensively used in a variety of preparations, sodium metabisulfite and other sulfites have been associated with a number of severe to fatal adverse reactions.[8–19] These are usually hypersensitivity-type reactions and include bronchospasm and anaphylaxis. Allergy to sulfite antioxidants is estimated to occur in 5–10% of asthmatics, although adverse reactions may also occur in nonasthmatics with no history of allergy.

Following oral ingestion, sodium metabisulfite is oxidized to sulfate and is excreted in urine. Ingestion may result in gastric irritation, owing to the liberation of sulfurous acid, while ingestion of large amounts of sodium metabisulfite can cause colic, diarrhea, circulatory disturbances, CNS depression, and death.

In Europe, the acceptable daily intake of sodium metabisulfite and other sulfites used in foodstuffs has been set at up to 3.5 mg/kg body-weight, calculated as sulfur dioxide (SO_2). The WHO has similarly also set an acceptable daily intake of sodium metabisulfite, and other sulfites, at up to 7.0 mg/kg body-weight, calculated as sulfur dioxide (SO_2).[20]

LD_{50} (rat, IV): 0.12 g/kg[21]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium metabisulfite may be irritant to the skin and eyes; eye protection and gloves are recommended. In the UK, the long-term (8-hour TWA) occupational exposure limit for sodium metabisulfite is 5 mg/m^3.[22]

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (epidural, IM, and IV injections; ophthalmic solutions; and oral preparations). Included in nonparenteral and parenteral medicines licensed in the UK.

17 Related Substances

Potassium metabisulfite; sodium bisulfite; sodium sulfite.

Sodium bisulfite

Empirical formula: $NaHSO_3$
Molecular weight: 104.07
CAS number: [7631-90-5]
Synonyms: E222; sodium hydrogen sulfite.
Appearance: white crystalline powder.
Density: 1.48 g/cm^3
Solubility: soluble 1 in 3.5 parts of water at 20°C; 1 in 2 parts of water at 100°C; and 1 in 70 parts of ethanol (95%).
Comments: most substances sold as sodium bisulfite contain significant, variable, amounts of sodium metabisulfite, as the latter is less hygroscopic and more stable during storage and shipment. *See* Section 18.

Sodium sulfite

Empirical formula: Na_2SO_3
Molecular weight: 126.06
CAS number: [7757-83-7]
Synonyms: anhydrous sodium sulfite; E221; exsiccated sodium sulfite.
Appearance: a white, odorless or almost odorless crystalline powder.
Acidity/alkalinity: pH = 9 for a saturated aqueous solution at 20°C.
Solubility: soluble 1 in 3.2 parts of water; soluble in glycerin; practically insoluble in ethanol (95%).
Comments: *see* Section 18. The EINECS number for sodium sulfite is 231-821-4.

18 Comments

Sodium metabisulfite is used as an antioxidant at low pH, sodium bisulfite at intermediate pH, and sodium sulfite at higher pH values.

The EINECS number for sodium metabisulfite is 231-673-0.

19 Specific References

1 Schroeter LC. Oxidation of sulfurous acid salts in pharmaceutical systems. *J Pharm Sci* 1963; **52**: 888–892.
2 Schumacher GE, Hull RL. Some factors influencing the degradation of sodium bisulfite in dextrose solutions. *Am J Hosp Pharm* 1966; **23**: 245–249.
3 Higuchi T, Schroeter LC. Reactivity of bisulfite with a number of pharmaceuticals. *J Am Pharm Assoc (Sci)* 1959; **48**: 535–540.
4 Hussain AA, Haddadin M, Iga K. Reaction of cis-platinum with sodium bisulfite. *J Pharm Sci* 1980; **69**(3): 364–365.
5 Garren KW, Repta AJ. Incompatibility of cisplatin and Reglan injectable. *Int J Pharm* 1985; **24**: 91–99.
6 Collins AJ, Lingham P, Burbridge TA, Bain R. Incompatibility of phenylmercuric acetate with sodium metabisulphite in eye drop formulations. *J Pharm Pharmacol* 1985; **37**(Suppl.): 123P.
7 Schroeter LC. Sulfurous acid salts as pharmaceutical antioxidants. *J Pharm Sci* 1961; **50**(11): 891–901.
8 Jamieson DM, Guill MF, Wray BB, May JR. Metabisulfite sensitivity: case report and literature review. *Ann Allergy* 1985; **54**(4): 115–121.
9 Anonymous. Possible allergic-type reactions. *FDA Drug Bull* 1987; **17**: 2.
10 Tsevat J, Gross GN, Dowling GP. Fatal asthma after ingestion of sulfite-containing wine [letter]. *Ann Intern Med* 1987; **107**(2): 263.
11 Weiner M, Bernstein IL. *Adverse Reactions to Drug Formulation Agents: a Handbook of Excipients*. New York: Marcel Dekker, 1989: 314–320.

12 Fitzharris P. What advances if any, have been made in treating sulfite allergy? *Br Med J* 1992; **305**: 1478.
13 Smolinske SC. *Handbook of Food, Drug and Cosmetic Excipients*. Boca Raton, FL: CRC Press Inc, 1992: 393–406.
14 Anonymous. Sulfites in drugs and food. *Med Lett Drugs Ther* 1986; **28**: 74–75.
15 Baker GJ. Bronchospasm induced by bisulfite containing food and drugs. *Med J Aust* 1981; **ii**: 614–617.
16 Fwarog FJ, Leung DYM. Anaphylaxis to a component of isoethane. *J Am Med Assoc* 1982; **248**: 2030–2031.
17 Koephe JW. Dose dependent bronchospasm from sulfites in isoethane. *J Am Med Assoc* 1984; **251**: 2982–2983.
18 Mikolich DJ, McCloskey WW. Suspected gentamicin allergy could be sulfite sensitivity. *Clin Pharm* 1988; **7**: 269.
19 Deziel-Evans LM, Hussey WJ. Possible sulfite sensitivity with gentamicin infusion. *DICP Ann Pharmacother* 1989; **23**: 1032–1033.
20 FAO/WHO. Evaluation of certain food additives and contaminants. Thirtieth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1987: No. 751.
21 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 10th edn. New York: Wiley, 2000: 3260.
22 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.

20 General References

Halsby SF, Mattocks AM. Absorption of sodium bisulfite from peritoneal dialysis solutions. *J Pharm Sci* 1965; **54**: 52–55.
Wilkins JW, Greene JA, Weller JM. Toxicity of intraperitoneal bisulfite. *Clin Pharmacol Ther* 1968; **9**: 328–332.

21 Author

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22 Date of Revision

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