Saccharin

1 Nonproprietary Names

BP: Saccharin
PhEur: Saccharinum
USPNF: Saccharin

2 Synonyms

1,2-Benzisothiazolin-3-one 1,1-dioxide; benzoic sulfimide; benzosulfimide; 1,2-dihydro-2-ketobenzisosulfonazole; 2,3-dihydro-3-oxobenzisosulfonazole; E954; *Garantose*; gluside; *Hermesetas*; sacarina; saccharin insoluble; *o*-sulfobenzimide; *o*-sulfobenzoic acid imide.

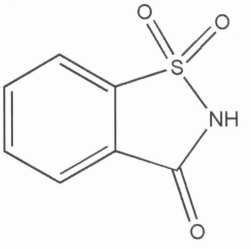
3 Chemical Name and CAS Registry Number

1,2-Benzisothiazol-3(2*H*)-one 1,1-dioxide [81-07-2]

4 Empirical Formula and Molecular Weight

Empirical Formula	Molecular Weight
$C_7H_5NO_3S$	183.18

5 Structural Formula



6 Functional Category

Sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

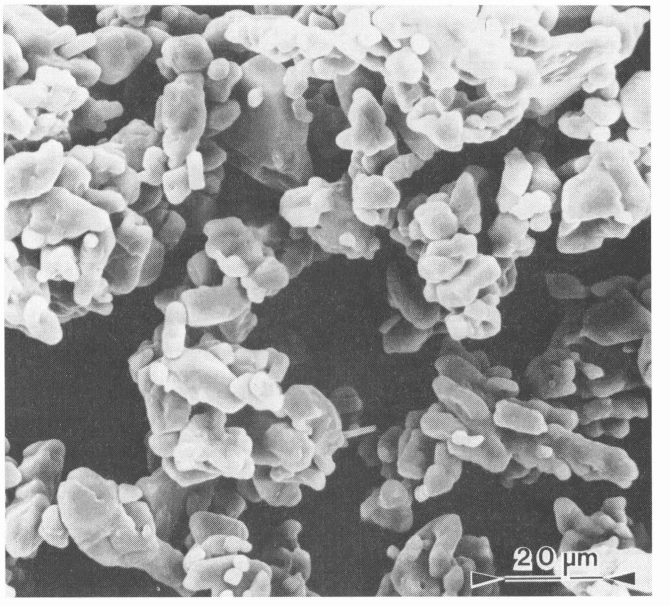
Saccharin is an intense sweetening agent used in beverages, food products, table-top sweeteners, and oral hygiene products such as toothpastes and mouthwashes. In oral pharmaceutical formulations, it is used at a concentration of 0.02–0.5% w/w.

Saccharin can be used to mask some unpleasant taste characteristics or to enhance flavor systems. Its sweetening power is approximately 500 times that of sucrose.

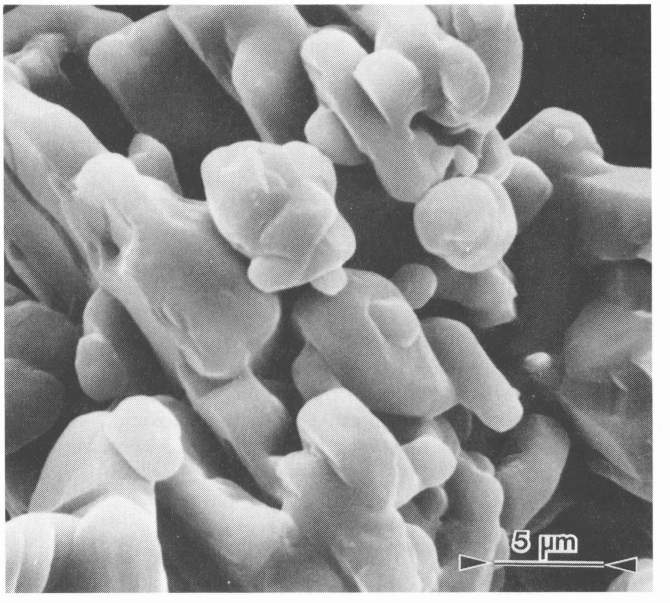
8 Description

Saccharin occurs as odorless white crystals or a white crystalline powder. It has an intensely sweet taste, with a metallic aftertaste that at normal levels of use can be detected by approximately 25% of the population.

SEM: 1
Excipient: Saccharin
Magnification: 600×



SEM: 2
Excipient: Saccharin
Magnification: 2400×



9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for saccharin.

Test	PhEur 2002	USPNF 20
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Melting range	226–230°C	226–230°C
Loss on drying	≤1.0%	≤1.0%
Residue on ignition	—	≤0.2%
Sulfated ash	≤0.1%	—
Toluenesulfonamides	+	≤0.0025%
Selenium	—	≤0.003%
Heavy metals	≤20 ppm	≤0.001%
Readily carbonizable substances	—	+
Benzoic and salicylic acids	—	+
Organic volatile impurities	—	+
Related substances	—	—
Assay (dried basis)	98.0–101.0%	98.0–101.0%

10 Typical Properties

Acidity/alkalinity: pH = 2.0 (0.35% w/v aqueous solution)
Density (bulk): 0.7–1.0 g/cm^3
Density (tapped): 0.9–1.2 g/cm^3
Dissociation constant: pK_a = 1.6 at 25°C
Heat of combustion: 3644.3 kJ/mol (871 kcal/mol)
Moisture content: 0.1%
Solubility: readily dissolved by dilute ammonia solutions, alkali hydroxide solutions, or alkali carbonate solutions (with the evolution of carbon dioxide). *See* Table II.

Table II: Solubility of saccharin.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	1 in 12
Chloroform	Slightly soluble
Ethanol (95%)	1 in 31
Ether	Slightly soluble
Glycerin	1 in 50
Water	1 in 290
	1 in 25 at 100°C

11 Stability and Storage Conditions

Saccharin is stable under the normal range of conditions employed in formulations. In the bulk form it shows no detectable decomposition and only when it is exposed to a high temperature (125°C) at a low pH (pH 2) for over 1 hour does significant decomposition occur. The decomposition product formed is (ammonium-*o*-sulfo)benzoic acid.[1]

Saccharin should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Saccharin can react with large molecules, resulting in a precipitate being formed.

13 Method of Manufacture

Saccharin is prepared from toluene by a series of reactions known as the Remsen–Fahlberg method. Toluene is first reacted with chlorosulfonic acid to form *o*-toluenesulfonyl chloride, which is reacted with ammonia to form the sulfonamide. The methyl group is then oxidized with dichromate, yielding *o*-sulfamoylbenzoic acid, which forms the cyclic imide saccharin when heated.

An alternative method involves a refined version of the Maumee process. Methyl anthranilate is initially diazotized to form 2-carbomethoxybenzenediazonium chloride; sulfonation followed by oxidation then yields 2-carbomethoxybenzenesulfonyl chloride. Amidation of this material, followed by acidification, forms insoluble acid saccharin.

14 Safety

There has been considerable controversy concerning the safety of saccharin, which has led to extensive studies since the mid-1970s.

Two-generation studies in rats exposed to diets containing 5.0–7.5% total saccharin (equivalent to 175 g daily in humans) suggested that the incidence of bladder tumors was significantly greater in saccharin-treated males of the second generation than in controls.[2,3] Further experiments in rats suggested that a contaminant of commercial saccharin, *o*-toluene sulfonamide, might also account for carcinogenic effects. In view of these studies, a ban on the use of saccharin was proposed in several countries. However, in 1977 a ban by the FDA led to a Congressional moratorium that permitted the continued use of saccharin in the USA.

From the available data it now appears that the development of tumors is a sex-, species-, and organ-specific phenomenon and extensive epidemiological studies have shown that saccharin intake is not related to bladder cancer in humans.[4,5]

The WHO has set a temporary acceptable daily intake for saccharin, including its calcium, potassium, and sodium salts, at up to 2.5 mg/kg body-weight.[6] In the UK, the Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment (COT) has set an acceptable daily intake for saccharin and its calcium, potassium, and sodium salts (expressed as saccharin sodium) at up to 5 mg/kg body-weight.[7]

Adverse reactions to saccharin, although relatively few in relation to its widespread use, include: urticaria with pruritus following ingestion of saccharin-sweetened beverages[8] and photosensitization reactions.[9]

LD_{50} (mouse, oral): 17.5 g/kg[10]
LD_{50} (rat, IP): 7.10 g/kg
LD_{50} (rat, oral): 14.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended.

16 Regulatory Status

Accepted for use as a food additive in Europe. Note that the EU number 'E954' is applied to both saccharin and saccharin salts. Included in the FDA Inactive Ingredients Guide (oral solutions, syrups, tablets, and topical preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Saccharin ammonium; saccharin calcium; saccharin sodium.

Saccharin ammonium
Empirical formula: $C_7H_8N_2O_3S$
Molecular weight: 200.2
CAS number: [6381-61-9]

Saccharin calcium
Empirical formula: $C_{14}H_8CaN_2O_6S_2 \cdot 3H_2O$
Molecular weight: 467.48
CAS number:
[6381-91-5] for the hydrated form
[6485-34-3] for the anhydrous form
Synonyms: *Syncal CAS.*
Appearance: white, odorless crystals or crystalline powder with an intensely sweet taste.
Solubility: 1 in 4.7 ethanol (95%); 1 in 2.6 of water.

18 Comments

The perceived intensity of sweeteners relative to sucrose depends upon their concentration, temperature of tasting, and pH, and on the flavor and texture of the product concerned.

Intense sweetening agents will not replace bulk, textural, or preservative characteristics of sucrose if sucrose is removed from a formulation.

Synergistic effects for combinations of sweeteners have been reported. Saccharin is often used in combination with cyclamates and aspartame since the saccharin content may be reduced to minimize any aftertaste.

The EINECS number for saccharin is 201-321-0.

19 Specific References

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4 Council on Scientific Affairs. Saccharin: review of safety issues. *J Am Med Assoc* 1985; **254**: 2622–2624.
5 Morgan RW, Wong O. A review of epidemiological studies on artificial sweeteners and bladder cancer. *Food Chem Toxicol* 1985; **23**: 529–533.
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9 Gordon HH. Photosensitivity to saccharin. *J Am Acad Dermatol* 1983; **8**: 565.
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20 General References

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21 Authors

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22 Date of Revision

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