

Fumaric Acid

1 Nonproprietary Names

USPNF: Fumaric acid

2 Synonyms

Allomaleic acid; allomalenic acid; boletic acid; butenedioic acid; E297; 1,2-ethenedicarboxylic acid; lichenic acid; *trans*-butenedioic acid; NSC-2752; *trans*-1,2-ethylenedicarboxylic acid; U-1149; USAF EK-P-583.

3 Chemical Name and CAS Registry Number

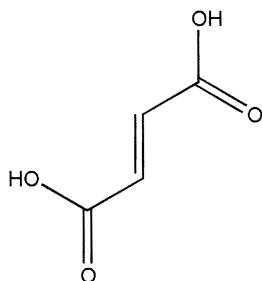
(*E*)-2-Butenedioic acid [110-17-8]

4 Empirical Formula Molecular Weight

C₄H₄O₄

116.07

5 Structural Formula



6 Functional Category

Acidulant; antioxidant; flavoring agent; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Fumaric acid is used primarily in liquid pharmaceutical preparations as an acidulant and flavoring agent. Fumaric acid may be included as the acid part of effervescent tablet formulations, although this use is limited as the compound has an extremely low solubility in water. It is also used as a chelating agent which exhibits synergism when used in combination with other true antioxidants.

In the design of novel pelletized formulations manufactured by extrusion-spheronization, fumaric acid was used to aid spheronization, favoring the production of fine pellets.⁽¹⁾ It has also been investigated as an alternative filler to lactose in pellets.⁽²⁾

Fumaric acid has been investigated as a lubricant for effervescent tablets⁽³⁾ and copolymers of fumaric acid and sebacic acid have been investigated as bioadhesive microspheres.⁽⁴⁾

Fumaric acid is also used as a food additive at concentrations up to 3600 ppm, and as a therapeutic agent in the treatment of psoriasis and other skin disorders.⁽⁵⁾

8 Description

Fumaric acid occurs as white, odorless or nearly odorless, granules or as a crystalline powder that is virtually nonhygroscopic.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for fumaric acid.

Test	USPNF 20
Identification	+
Water	≤0.5%
Residue on ignition	≤0.1%
Heavy metals	≤0.001%
Maleic acid	≤0.1%
Organic volatile impurities	+
Assay (dried basis)	99.5–100.5%

10 Typical Properties

Acidity/alkalinity:

pH = 2.45 (saturated aqueous solution at 20 °C)
pH = 2.58 (0.1% w/v aqueous solution at 25 °C)
pH = 2.25 (0.3% w/v aqueous solution at 25 °C)
pH = 2.15 (0.5% w/v aqueous solution at 25 °C)

Density: 1.635 g/cm³ at 20 °C

Density (bulk): 0.77 g/cm³

Density (tapped): 0.93 g/cm³

Dissociation constant:

pK_{a1} = 3.03 at 25 °C;
pK_{a2} = 4.54 at 25 °C

Melting point: 287 °C (closed capillary, rapid heating); partial carbonization and formation of maleic anhydride occur at 230 °C (open vessel); sublimes at 200 °C.

Boiling point: 290 °C (sealed tube)

Solubility: see Table II.

11 Stability and Storage Conditions

Fumaric acid is stable although it is subject to degradation by both aerobic and anaerobic microorganisms. When heated in sealed vessels with water at 150–170 °C it forms (±)-malic acid.

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

12 Incompatibilities

Fumaric acid undergoes reactions typical of an organic acid.

Table II: Solubility of fumaric acid.

Solvent	Solubility at 20 °C unless otherwise stated
Acetone	1 in 58 at 30 °C
Benzene	Very slightly soluble
Carbon tetrachloride	Very slightly soluble
Chloroform	Very slightly soluble
Ethanol	1 in 28
Ethanol (95%)	1 in 17 at 30 °C
Ether	Slightly soluble 1 in 139 at 25 °C
Olive oil	Very slightly soluble
Propylene glycol	1 in 33
Water	1 in 200 1 in 432 at 0 °C 1 in 303 at 10 °C 1 in 159 at 25 °C 1 in 94 at 40 °C 1 in 42 at 60 °C 1 in 10 at 100 °C

13 Method of Manufacture

Commercially, fumaric acid may be prepared from glucose by the action of fungi such as *Rhizopus nigricans*, as a by-product in the manufacture of maleic and phthalic anhydrides, and by the isomerization of maleic acid using heat or a catalyst.

On the laboratory scale, fumaric acid can be prepared by the oxidation of furfural with sodium chlorate in the presence of vanadium pentoxide.

14 Safety

Fumaric acid is used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material. However, acute renal failure and other adverse reactions have occurred following the topical and systemic therapeutic use of fumaric acid and fumaric acid derivatives in the treatment of psoriasis or other skin disorders.⁽⁵⁾ Other adverse effects of oral therapy have included disturbances of liver function, gastrointestinal effects, and flushing.⁽⁵⁾

The WHO has stated that the establishment of an estimated acceptable daily intake of fumaric acid or its salts was unnecessary since it is a normal constituent of body tissues.⁽⁶⁾

LD₅₀ (mouse, IP): 0.1 g/kg⁽⁷⁾

LD₅₀ (rat, oral): 9.3 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Fumaric acid may be irritating to the skin, eyes, and respiratory system and should

be handled in a well-ventilated environment. Gloves and eye protection are recommended.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (capsules, tablets, and oral liquids).

17 Related Substances

Citric acid monohydrate; malic acid; tartaric acid.

18 Comments

The EINECS number for fumaric acid is 203-743-0.

19 Specific References

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- 4 Chickering DE, Mathiowitz E. Bioadhesive microspheres: I. A novel electrobalance-based method to study adhesive interactions between individual microspheres and intestinal mucosa. *J Control Release* 1995; 34: 251-262.
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20 General References

- Malic and fumaric acids. *Manuf Chem Aerosol News* 1964; 35(12): 56-59.
- Robinson WD, Mount RA. In: *Kirk-Othmer Encyclopedia of Chemical Technology*, vol. 14; 3rd edn. New York: Wiley-Interscience, 1981: 770-793.

21 Author

SC Owen.

22 Date of Revision

21 May 2002.