Edetic Acid

1 Nonproprietary Names

BP: Edetic acid
PhEur: Acidum edeticum
USPNF: Edetic acid

2 Synonyms

Dissolvine; edathamil; EDTA; ethylenediaminetetraacetic acid; (ethylenedinitrilo)tetraacetic acid; *Questric acid 5286*; *Sequestrene AA*; tetracemic acid; *Versene Acid*.

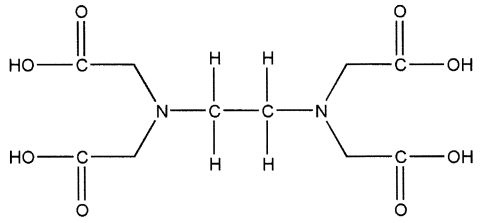
3 Chemical Name and CAS Registry Number

N,*N*-1,2-Ethanediylbis[*N*-(carboxymethyl)glycine] [60-00-4]

4 Empirical Formula and Molecular Weight

$C_{10}H_{16}N_2O_8$ 292.24

5 Structural Formula



6 Functional Category

Chelating agent.

7 Applications in Pharmaceutical Formulation or Technology

Edetic acid and edetate salts are used in pharmaceutical formulations, cosmetics, and foods as chelating agents; that is, they form stable water-soluble complexes (chelates) with alkaline earth and heavy metal ions. The chelated form has few of the properties of the free ion, and for this reason chelating agents are often described as 'removing' ions from solution; this process is also called sequestering. The stability of the metal–edetate complex depends on the metal ion involved and also on the pH. The calcium chelate is relatively weak and will preferentially chelate heavy metals, such as iron, copper, and lead, with the release of calcium ions. For this reason, edetate calcium disodium is used therapeutically in cases of lead poisoning; *see also* Section 18.

Edetic acid and edetates are primarily used as antioxidant synergists, sequestering trace amounts of metal ions, particularly copper, iron, and manganese, that might otherwise catalyze autoxidation reactions. Edetic acid and edetates may be used alone or in combination with true antioxidants, the usual concentration employed being in the range 0.005–0.1% w/v. Edetates have been used to stabilize ascorbic acid; corticosteroids; epinephrine; folic acid; formaldehyde; gums and resins; hyaluronidase; hydrogen peroxide; oxytetracycline; penicillin; salicylic acid, and unsaturated fatty acids. Essential oils may be washed with a 2% w/v solution of edetate to remove trace metal impurities.

Edetic acid and edetates possess some antimicrobial activity but are most frequently used in combination with other antimicrobial preservatives owing to their synergistic effects. Many solutions used for the cleaning, storage, and wetting of contact lenses contain disodium edetate. Typically, edetic acid and edetates are used in concentrations of 0.01–0.1% w/v as antimicrobial preservative synergists; *see* Section 10.

Edetic acid and disodium edetate may also be used as water softeners since they will chelate the calcium and magnesium ions present in hard water; edetate calcium disodium is not effective. Many cosmetic and toiletry products, e.g., soaps, contain edetic acid as a water softener.

Disodium edetate is also used as an anticoagulant since it will chelate calcium and prevent the coagulation of blood *in vitro*. Concentrations of 0.1% w/v are used in small volumes for hematological testing and 0.3% w/v in transfusions.

8 Description

Edetic acid occurs as a white crystalline powder.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for edetic acid.

Test	PhEur 2002	USPNF 20
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Residue on ignition	—	⩽0.2%
Sulfated ash	⩽0.2%	—
Heavy metals	⩽20 ppm	⩽0.003%
Nitrilotriacetic acid	⩽0.1%	⩽0.3%
Iron	⩽80 ppm	⩽0.005%
Chloride	⩽200 ppm	—
Assay	98.0–101.0%	98.0–100.5%

10 Typical Properties

Acidity/alkalinity: pH = 2.2 for a 0.2% w/v aqueous solution.

Antimicrobial activity: edetic acid has some antimicrobial activity against Gram-negative microorganisms, *Pseudomonas aeruginosa*, some yeasts, and fungi, although this activity is insufficient for edetic acid to be used effectively as an antimicrobial preservative on its own.[1,2] However, when used with other antimicrobial preservatives, edetic acid demonstrates a marked synergistic effect in its antimicrobial activity. Edetic acid and edetates are therefore frequently used in combination with such preservatives as benzalkonium chloride; bronopol; cetrimide; imidurea;

parabens; and phenols, especially chloroxylenol. Typically, edetic acid is used at a concentration of 0.1–0.15% w/v. In the presence of some divalent metal ions, such as Ca^{2+} or Mg^{2+}, the synergistic effect may be reduced or lost altogether. The addition of disodium edetate to phenylmercuric nitrate[3] and thimerosal[3,4] has also been reported to reduce the antimicrobial efficacy of the preservative. Edetic acid and iodine form a colorless addition compound that is bactericidal.

Dissociation constant:

$pK_{a1} = 2.00$
$pK_{a2} = 2.67$
$pK_{a3} = 6.16$
$pK_{a4} = 10.26$

Melting point: melts above 220 °C, with decomposition.

Solubility: soluble in solutions of alkali hydroxides; soluble 1 in 500 of water.

11 Stability and Storage Conditions

Although edetic acid is fairly stable in the solid state, edetate salts are more stable than the free acid, which decarboxylates if heated above 150 °C. Disodium edetate dihydrate loses water of crystallization when heated to 120 °C. Edetate calcium disodium is slightly hygroscopic and should be protected from moisture.

Aqueous solutions of edetic acid or edetate salts may be sterilized by autoclaving, and should be stored in an alkali-free container.

Edetic acid and edetates should be stored in well-closed containers in a cool, dry place.

12 Incompatibilities

Edetic acid and edetates are incompatible with strong oxidizing agents, strong bases, and polyvalent metal ions such as copper, nickel, and copper alloy.

Edetic acid and disodium edetate behave as weak acids, displacing carbon dioxide from carbonates and reacting with metals to form hydrogen.

Other incompatibilities include the inactivation of certain types of insulin due to the chelation of zinc, and the chelation of trace metals in total parenteral nutrition (TPN) solutions following the addition of TPN additives stabilized with disodium edetate. Calcium disodium edetate has also been reported to be incompatible with amphotericin and with hydralazine hydrochloride in infusion fluids.

13 Method of Manufacture

Edetic acid may be prepared by the condensation of ethylenediamine with sodium monochloroacetate in the presence of sodium carbonate. An aqueous solution of the reactants is heated to about 90 °C for 10 hours, then cooled, and hydrochloric acid is added to precipitate the edetic acid.

Edetic acid may also be prepared by the reaction of ethylenediamine with hydrogen cyanide and formaldehyde with subsequent hydrolysis of the tetranitrile, or under alkaline conditions with continuous extraction of ammonia.

See Section 17 for information on the preparation of edetate salts.

14 Safety

Edetic acid and edetates are widely used in topical, oral, and parenteral pharmaceutical formulations. They are also extensively used in cosmetics and food products.

Edetic acid is generally regarded as an essentially nontoxic and nonirritant material, although it has been associated with dose-related bronchoconstriction when used as a preservative in nebulizer solutions. It has therefore been recommended that nebulizer solutions for bronchodilation should not contain edetic acid.[5]

Edetates, particularly disodium edetate and edetate calcium disodium, are used in a greater number and variety of pharmaceutical formulations than the free acid. Both disodium edetate and edetate calcium disodium are poorly absorbed from the gastrointestinal tract and are associated with few adverse effects when used as excipients in pharmaceutical formulations.

Disodium edetate, trisodium edetate, and edetic acid readily chelate calcium and can, in large doses, cause calcium depletion (hypocalcemia) if used over an extended period or if administered too rapidly by intravenous infusion. If used in preparations for the mouth, they can also leach calcium from the teeth. In contrast, edetate calcium disodium does not chelate calcium.

Edetate calcium disodium is nephrotoxic and should be used with caution in patients with renal impairment. Disodium edetate should similarly be used with caution in patients with renal impairment, tuberculosis, and impaired cardiac function.

The WHO has set an estimated acceptable daily intake for disodium edetate in foodstuffs at up to 2.5 mg/kg body-weight.[6]

See also Section 18.

LD_{50} (mouse, IP): 0.25 g/kg[7]
LD_{50} (rat, IP): 0.397 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Edetic acid and edetates are mildly irritant to the skin, eyes, and mucous membranes. Ingestion, inhalation, and contact with the skin and eyes should therefore be avoided. Eye protection, gloves, and a dust mask are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (otic, rectal, and topical preparations). Included in nonparenteral medicines licensed in the UK.

See also Section 17.

17 Related Substances

Dipotassium edetate; disodium edetate; edetate calcium disodium; sodium edetate; trisodium edetate.

Dipotassium edetate

Empirical formula: $C_{10}H_{14}K_2N_2O_8$
Molecular weight: 368.46
CAS number: [2001-94-7]
Synonyms: dipotassium edathamil; dipotassium ethylenediaminetetraacetate; edathamil dipotassium; edetate dipotassium; edetic acid dipotassium salt; EDTA dipotassium; *N*,*N*′-1,2-ethanediylbis[*N*-(carboxymethyl)glycine]

dipotassium salt; ethylenebis(iminodiacetic acid) dipotassium salt; ethylenediaminetetraacetic acid dipotassium salt; (ethylenedinitrilo)tetraacetic acid dipotassium salt; tetracemate dipotassium.
Appearance: white crystalline powder.
Comments: The EINECS number for dipotassium edetate is 217-895-0.

Disodium edetate

Empirical formula: $C_{10}H_{14}N_2Na_2O_8$
Molecular weight: 336.21
CAS number: [139-33-3] for the anhydrous material and [6381-92-6] for the dihydrate
Synonyms: disodium edathamil; disodium ethylenediaminetetraacetate; edathamil disodium; edetate disodium; edetic acid disodium salt; EDTA disodium; *N*,*N*′-1,2-ethanediylbis[*N*-(carboxymethyl)glycine] disodium salt; ethylenebis(iminodiacetic acid) disodium salt; ethylenediaminetetraacetic acid disodium salt; (ethylenedinitrilo)tetraacetic acid disodium salt; *Questal Di*; *Sequestrene NA2*; tetracemate disodium; *Versene disodium*.
Appearance: odorless white crystalline powder with a slightly acid taste.
Acidity/alkalinity: pH = 4.3–4.7 for a 1% w/v solution in carbon dioxide-free water.
Freezing point depression: 0.14 °C (1% w/v aqueous solution)
Melting point: decomposition at 252 °C for the dihydrate.
Refractive index: 1.335 for a 1% w/v aqueous solution.
Solubility: practically insoluble in chloroform and ether; slightly soluble in ethanol (95%); soluble 1 in 11 of water.
Specific gravity: 1.004 for a 1% w/v aqueous solution.
Viscosity (kinematic): 1.03 mm^2/s (1 cSt) for a 1% w/v aqueous solution.
Method of manufacture: disodium edetate may be prepared by the reaction of edetic acid and sodium hydroxide.
Safety: *see also* Section 14.

LD_{50} (mouse, IP): 0.26 g/kg[7]
LD_{50} (mouse, IV): 0.056 g/kg
LD_{50} (mouse, oral): 2.05 g/kg
LD_{50} (rabbit, IV): 0.047 g/kg
LD_{50} (rabbit, oral): 2.3 g/kg
LD_{50} (rat, oral): 2 g/kg

Regulatory status: GRAS listed. Included in the FDA Inactive Ingredients Guide (inhalations, injections, ophthalmic preparations, oral capsules, solutions, suspensions, syrups and tablets, rectal, topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK.
Comments: in pharmaceutical formulations disodium edetate is used as a chelating agent typically at concentrations between 0.005–0.1% w/v. The EINECS number for disodium edetate is 205-358-3.

Edetate calcium disodium

Empirical formula: $C_{10}H_{12}CaN_2Na_2O_8$
Molecular weight: 374.28
CAS number: [62-33-9] for the anhydrous material and [23411-34-9] for the dihydrate
Synonyms: calcium disodium edetate; calcium disodium ethylenediaminetetraacetate; calcium disodium (ethylenedinitrilo)tetraacetate; E385; edathamil calcium disodium; edetic acid calcium disodium salt; EDTA calcium; ethylenediaminetetraacetic acid calcium disodium chelate; [(ethylenedinitrilo)tetraacetato]calciate(2-) disodium; sodium calciumedetate; *Versene CA*.
Appearance: white or creamy-white colored, slightly hygroscopic, crystalline powder or granules; odorless, or with a slight odor; tasteless, or with a faint saline taste.
Acidity/alkalinity: pH = 4–5 for a 1% w/v aqueous solution.
Density (bulk): 0.69 g/cm^3
Solubility: practically insoluble in chloroform, ether, and other organic solvents; very slightly soluble in ethanol (95%); soluble 1 in 2 of water.
Method of manufacture: edetate calcium disodium may be prepared by the addition of calcium carbonate to a solution of disodium edetate.
Safety: *see also* Section 14.

LD_{50} (mouse, IP): 4.5 g/kg[7]
LD_{50} (rabbit, IP): 6 g/kg
LD_{50} (rabbit, oral): 7 g/kg
LD_{50} (rat, IP): 3.85 g/kg
LD_{50} (rat, IV): 3.0 g/kg
LD_{50} (rat, oral): 10 g/kg

Regulatory status: GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (injections, oral capsules, solutions, suspensions, syrups, and tablets).
Comments: used in pharmaceutical formulations as a chelating agent in concentrations between 0.01–0.1% w/v. Usually edetate calcium disodium is used in pharmaceutical formulations in preference to disodium edetate or sodium edetate to prevent calcium depletion occurring in the body. In food products, edetate calcium disodium may also be used in flavors and as a color retention agent. Edetate calcium disodium occurs as the dihydrate, trihydrate, and anhydrous material.
Some pharmacopeias specify that edetate calcium disodium is the dihydrate, others that it is the anhydrous material. The USP 25 specifies that edetate calcium disodium is a mixture of the dihydrate and trihydrate but that the dihydrate predominates.
The EINECS number for edetate calcium disodium is 200-529-9.

Sodium edetate

Empirical formula: $C_{10}H_{12}N_2Na_4O_8$
Molecular weight: 380.20
CAS number: [64-02-8]
Synonyms: edetate sodium; edetic acid tetrasodium salt; EDTA tetrasodium; *N*,*N*′-1,2-ethanediylbis[*N*-(carboxymethyl) glycine] tetrasodium salt; ethylenebis(iminodiacetic acid) tetrasodium salt; ethylenediaminetetraacetic acid tetrasodium salt; (ethylenedinitrilo)tetraacetic acid tetrasodium salt; *Sequestrene NA4*; tetracemate tetrasodium; tetracemin; tetrasodium edetate; tetrasodium ethylenebis (iminodiacetate); tetrasodium ethylenediaminetetraacetate; *Versene*.
Appearance: white crystalline powder.
Acidity/alkalinity: pH = 11.3 for a 1% w/v aqueous solution.
Melting point: >300 °C
Solubility: soluble 1 in 1 of water.
Safety: *see also* Section 14.

LD_{50} (mouse, IP): 0.33 g/kg[7]

Regulatory status: included in the FDA Inactive Ingredients Guide (inhalations, injections, ophthalmic preparations, oral capsules and tablets, and topical preparations).
Comments: sodium edetate reacts with most divalent and trivalent metallic ions to form soluble metal chelates and is used in pharmaceutical formulations in concentrations between 0.01–0.1% w/v.

Trisodium edetate
Empirical formula: $C_{10}H_{13}N_2Na_3O_8$
Molecular weight: 358.20
CAS number: [150-38-9]
Synonyms: edetate trisodium; edetic acid trisodium salt; EDTA trisodium; *N*,*N*′-1,2-ethanediylbis[*N*-(carboxymethyl) glycine] trisodium salt; ethylenediaminetetraacetic acid trisodium salt; (ethylenedinitrilo)tetraacetic acid trisodium salt; *Sequestrene NA3*; trisodium ethylenediaminetetraacetate; *Versene-9*.
Appearance: white crystalline powder.
Acidity/alkalinity: pH = 9.3 for a 1% w/v aqueous solution.
Melting point: >300 °C
Method of manufacture: trisodium edetate may be prepared by adding a solution of sodium hydroxide to disodium edetate.
Safety: *see also* Section 14.
LD_{50} (mouse, IP): 0.3 g/kg[7]
LD_{50} (mouse, oral): 2.15 g/kg
LD_{50} (rat, oral): 2.15 g/kg
Regulatory status: included in the FDA Inactive Ingredients Guide (topical preparations).
Comments: more soluble in water than either the disodium salt or the free acid. Trisodium edetate also occurs as the monohydrate and is used in pharmaceutical formulations as a chelating agent. The EINECS number for trisodium edetate is 205-758-8.

18 Comments

Other salts of edetic acid that are commercially available include diammonium, dimagnesium, ferric sodium, and magnesium disodium edetatesTherapeutically, a dose of 50 mg/kg body-weight of disodium edetate, as a slow infusion over a 24-hour period, with a maximum daily dose of 3 g, has been used as a treatment for hypercalcemia. For the treatment of lead poisoning, a dose of 60–80 mg/kg of edetate calcium disodium, as a slow infusion in two daily doses, for 5 days, has been used.

Chelation therapy using edetic acid has been widely used for the treatment of ischemic heart disease. However, it has been suggested that the therapeutic benefits of this treatment may be due to the changes in lifestyle of the patient rather than the administration of edetic acid (40 mg/kg by infusion over a 3-hour period).[8]

The EINECS number for edetic acid is 200-449-4.

19 Specific References

1 Richards RME, Cavill RH. Electron microscope study of effect of benzalkonium chloride and edetate disodium on cell envelope of *Pseudomonas aeruginosa*. *J Pharm Sci* 1976; **65**: 76–80.
2 Whalley G. Preservative properties of EDTA. *Manuf Chem* 1991; **62**(9): 22–23.
3 Richards RME, Reary JME. Changes in antibacterial activity of thiomersal and PMN on autoclaving with certain adjuvants. *J Pharm Pharmacol* 1972; **24**(Suppl.): 84P–89P.
4 Morton DJ. EDTA reduces antimicrobial efficacy of thiomerosal. *Int J Pharm* 1985; **23**: 357–358.
5 Beasley CRW, Rafferty P, Holgate ST. Bronchoconstrictor properties of preservatives in ipratropium bromide (Atrovent) nebuliser solution. *Br Med J* 1987; **294**: 1197–1198.
6 FAO/WHO. Toxicological evaluation of certain food additives with a review of general principles and of specifications. Seventeenth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1974; No. 539.
7 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 10th edn. New York: Wiley, 2000: 1669.
8 Knudtson ML, Wyse DG, Galbraith PD *et al.* Chelation therapy for ischemic heart disease: a randomized controlled trial. *J Am Med Assoc* 2002; **287**(4): 481–486.

20 General References

Chalmers L. The uses of EDTA and other chelates in industry. *Manuf Chem* 1978; **49**(3): 79–80, 83.
Hart JR. Chelating agents in cosmetic and toiletry products. *Cosmet Toilet* 1978; **93**(12): 28–30.
Hart JR. EDTA-type chelating agents in personal care products. *Cosmet Toilet* 1983; **98**(4): 54–58.
Lachman L. Antioxidants and chelating agents as stabilizers in liquid dosage forms. *Drug Cosmet Ind* 1968; **102**(2): 43–45, 146–149.

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22 Date of Revision

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