Acacia

1 Nonproprietary Names

BP: Acacia
JP: Acacia
PhEur: Acacia
USP-NF: Acacia

2 Synonyms

Acaciae gummi; acacia gum; arabic gum; E414; gum acacia; gummi africanum; gum arabic; gummi arabicum; gummi mimosae; talha gum.

3 Chemical Name and CAS Registry Number

Acacia [9000-01-5]

4 Empirical Formula and Molecular Weight

Acacia is a complex, loose aggregate of sugars and hemicelluloses with a molecular weight of approximately 240 000–580 000. The aggregate consists essentially of an arabic acid nucleus to which are connected calcium, magnesium, and potassium along with the sugars arabinose, galactose, and rhamnose.

5 Structural Formula

See Section 4.

6 Functional Category

Emulsifying agent; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Acacia is mainly used in oral and topical pharmaceutical formulations as a suspending and emulsifying agent, often in combination with tragacanth. It is also used in the preparation of pastilles and lozenges, and as a tablet binder, although if used incautiously it can produce tablets with a prolonged disintegration time. Acacia has also been evaluated as a bioadhesive;[1] and has been used in novel tablet formulations,[2] and modified release tablets.[3] *See* Table I.

Acacia is also used in cosmetics, confectionery, food products, and spray-dried flavors.[4]

See also Section 18.

Table I: Uses of acacia.

Use	Concentration (%)
Emulsifying agent	10–20
Pastille base	10–30
Suspending agent	5–10
Tablet binder	1–5

8 Description

Acacia is available as white or yellowish-white thin flakes, spheroidal tears, granules, powder, or spray-dried powder. It is odorless and has a bland taste.

9 Pharmacopeial Specifications

The PhEur 6.3 provides monographs on acacia and spray-dried acacia, while the USP32–NF27 describes acacia in a single monograph that encompasses tears, flakes, granules, powder, and spray-dried powder. The USP32–NF27 also has a monograph on acacia syrup. The JP XV has monographs on acacia and powdered acacia. *See* Table II.

Table II: Pharmacopeial specifications for acacia.

Test	JP XV	PhEur 6.3	USP32–NF27
Identification	+	+	+
Characters	+	+	+
Microbial limit	–	$\leqslant 10^4$ cfu/g	+
Water	⩽17.0% ⩽15.0%[a]	⩽15.0% ⩽10.0%[b]	⩽15.0% –
Total ash	⩽4.0%	⩽4.0%	⩽4.0%
Acid-insoluble ash	⩽0.5%	–	⩽0.5%
Insoluble residue	⩽0.2%	⩽0.5%	⩽50 mg/5g
Arsenic	–	–	⩽3 ppm
Lead	–	–	⩽0.001%
Heavy metals	–	–	⩽0.004%
Starch, dextrin, and agar	–	+	+
Tannin-bearing gums	+	+	+
Tragacanth	–	+	–
Sterculia gum	–	+	–
Glucose and fructose	+	+	–
Solubility and reaction	–	–	+

(a) Powdered acacia.
(b) Spray-dried acacia.

10 Typical Properties

Acidity/alkalinity pH = 4.5–5.0 (5% w/v aqueous solution)

Acid value 2.5

Hygroscopicity At relative humidities of 25–65%, the equilibrium moisture content of powdered acacia at 25°C is 8–13% w/w, but at relative humidities above about 70% it absorbs substantial amounts of water.

NIR spectra *see* Figure 1.

Solubility Soluble 1 in 20 of glycerin, 1 in 20 of propylene glycol, 1 in 2.7 of water; practically insoluble in ethanol (95%). In water, acacia dissolves very slowly, although almost completely after two hours, in twice the mass of water leaving only a very small residue of powder. The solution is colorless or yellowish, viscous, adhesive, and translucent. Spray-dried acacia dissolves more rapidly, in about 20 minutes.

Specific gravity 1.35–1.49

Viscosity (dynamic) 100 mPa s (100 cP) for a 30% w/v aqueous solution at 20°C. The viscosity of aqueous acacia solutions varies depending upon the source of the material, processing, storage conditions, pH, and the presence of salts. Viscosity increases slowly up to about 25% w/v concentration and exhibits Newtonian behavior. Above this concentration, viscosity increases rapidly (non-Newtonian rheology). Increasing temperature or prolonged heating of solutions results in a decrease of viscosity owing to depolymerization or particle agglomeration. *See also* Section 12.

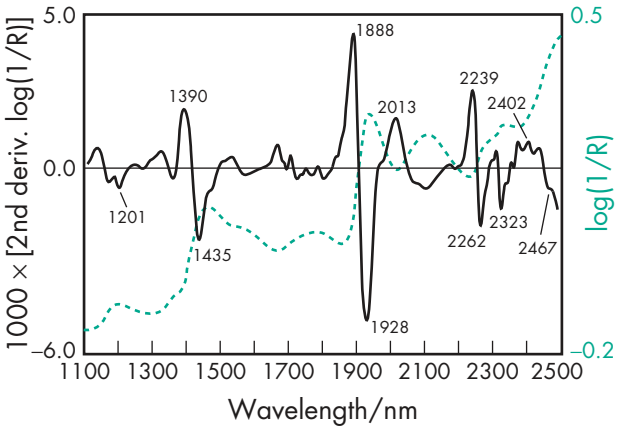

Figure 1: Near-infrared spectrum of acacia measured by reflectance.

11 Stability and Storage Conditions

Aqueous solutions are subject to bacterial or enzymatic degradation but may be preserved by initially boiling the solution for a short time to inactivate any enzymes present; microwave irradiation can also be used.[5] Aqueous solutions may also be preserved by the addition of an antimicrobial preservative such as 0.1% w/v benzoic acid, 0.1% w/v sodium benzoate, or a mixture of 0.17% w/v methylparaben and 0.03% propylparaben. Powdered acacia should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Acacia is incompatible with a number of substances including amidopyrine, apomorphine, cresol, ethanol (95%), ferric salts, morphine, phenol, physostigmine, tannins, thymol, and vanillin.

An oxidizing enzyme present in acacia may affect preparations containing easily oxidizable substances. However, the enzyme may be inactivated by heating at 100°C for a short time; *see* Section 11.

Many salts reduce the viscosity of aqueous acacia solutions, while trivalent salts may initiate coagulation. Aqueous solutions carry a negative charge and will form coacervates with gelatin and other substances. In the preparation of emulsions, solutions of acacia are incompatible with soaps.

13 Method of Manufacture

Acacia is the dried gummy exudate obtained from the stems and branches of *Acacia senegal* (Linné) Willdenow or other related species of *Acacia* (Fam. Leguminosae) that grow mainly in the Sudan and Senegal regions of Africa.

The bark of the tree is incised and the exudate allowed to dry on the bark. The dried exudate is then collected, processed to remove bark, sand, and other particulate matter, and graded. Various acacia grades differing in particle size and other physical properties are thus obtained. A spray-dried powder is also commercially available.

14 Safety

Acacia is used in cosmetics, foods, and oral and topical pharmaceutical formulations. Although it is generally regarded as an essentially nontoxic material, there have been a limited number of reports of hypersensitivity to acacia after inhalation or ingestion.[6,7] Severe anaphylactic reactions have occurred following the parenteral administration of acacia and it is now no longer used for this purpose.[6]

The WHO has not set an acceptable daily intake for acacia as a food additive because the levels necessary to achieve a desired effect were not considered to represent a hazard to health.[8]

LD_{50} (hamster, oral): >18 g/kg[9]

LD_{50} (mouse, oral): >16 g/kg

LD_{50} (rabbit, oral): 8.0 g/kg

LD_{50} (rat, oral): >16 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Acacia can be irritant to the eyes and skin and upon inhalation. Gloves, eye protection, and a dust respirator are recommended.

16 Regulatory Status

GRAS listed. Accepted for use in Europe as a food additive. Included in the FDA Inactive Ingredients Database (oral preparations and buccal or sublingual tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Ceratonia; guar gum; tragacanth.

18 Comments

Concentrated aqueous solutions are used to prepare pastilles since on drying they form solid rubbery or glasslike masses depending upon the concentration used. Foreign policy changes and politically unstable conditions in Sudan, which is the principal supplier of acacia, has created a need to find a suitable replacement.[10] Poloxamer 188 (12–15% w/w) can be used to make an oil/water emulsion with similar rheological characteristics to acacia. Other natural by-products of foods can also be used.[11] Acacia is also used in the food industry as an emulsifier, stabilizer, and thickener. A specification for acacia is contained in the Food Chemicals Codex (FCC).[12]

The EINECS number for acacia is 232-519-5.

19 Specific References

1 Attama AA *et al.* Studies on bioadhesive granules. *STP Pharma Sci* 2003; **13**(3): 177–181.

2 Streubel A *et al.* Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. *Eur J Pharm Sci* 2003; **18**: 37–45.

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4 Buffo R, Reineccius G. Optimization of gum acacia/modified starch/maltodextrin blends for spray drying of flavors. *Perfumer & Flavorist* 2000; **25**: 45–54.

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8 FAO/WHO. Evaluation of certain food additives and contaminants. Thirty-fifth report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1990; No. 789.

9 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 289.

10 Scheindlin S. Acacia – a remarkable excipient: the past, present, and future of gum arabic. *JAMA* 2001; **41**(5): 669–671.

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12 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 425.

20 General References

Anderson DMW, Dea ICM. Recent advances in the chemistry of acacia gums. *J Soc Cosmet Chem* 1971; **22**: 61–76.

Anderson DM *et al*. Specifications for gum arabic (*Acacia Senegal*): analytical data for samples collected between 1904 and 1989. *Food Add Contam* 1990; **7**: 303–321.
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Whistler RL. *Industrial Gums*. New York: Academic Press, 1959.

21 Author

AH Kibbe.

22 Date of Revision

10 February 2009.

Acesulfame Potassium

1 Nonproprietary Names

BP: Acesulfame Potassium

PhEur: Acesulfame Potassium

USP-NF: Acesulfame Potassium

2 Synonyms

Acesulfame K; ace K; acesulfamum kalicum; E950; 6-methyl-3,4-dihydro-1,2,3-oxathiazin-4(3*H*)-one-2,2-dioxide potassium salt; potassium 6-methyl-2,2-dioxo-oxathiazin-4-olate; *Sunett*; *Sweet One*.

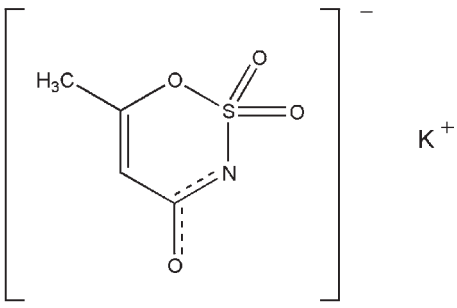
3 Chemical Name and CAS Registry Number

6-Methyl-1,2,3-oxathiazin-4(3*H*)-one-2,2-dioxide potassium salt [55589-62-3]

4 Empirical Formula and Molecular Weight

$C_4H_4KNO_4S$ 201.24

5 Structural Formula



6 Functional Category

Sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Acesulfame potassium is used as an intense sweetening agent in cosmetics, foods, beverage products, table-top sweeteners, vitamin and pharmaceutical preparations, including powder mixes, tablets, and liquid products. It is widely used as a sugar substitute in compounded formulations,[1] and as a toothpaste sweetener.[2]

The approximate sweetening power is 180–200 times that of sucrose, similar to aspartame, about one-third as sweet as sucralose, one-half as sweet as sodium saccharin, and about 4-5 times sweeter than sodium cyclamate.[3] It enhances flavor systems and can be used to mask some unpleasant taste characteristics.

8 Description

Acesulfame potassium occurs as a colorless to white-colored, odorless, crystalline powder with an intensely sweet taste.

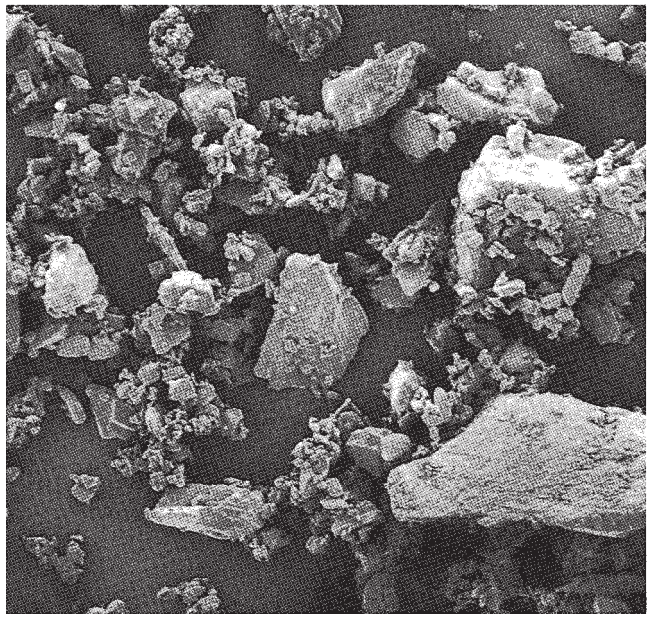
9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity pH = 5.5–7.5 (1% w/v aqueous solution)
Bonding index 0.007[4]
Brittle fracture index 0.08[4]
Density (bulk) 1.04 g/cm^3 [4]
Density (tapped) 1.28 g/cm^3 [4]
Elastic modulus 4000 MPa[4]
Flowability 19% (Carr compressibility index)[4]
Melting point 250°C
NIR spectra *see* Figure 1.
Solubility *see* Table II.

SEM 1: Excipient: acesulfame potassium; magnification: 150×; voltage: 5 kV.



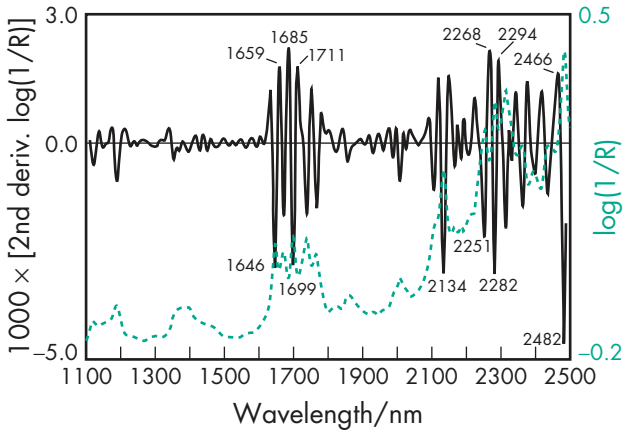


Figure 1: Near-infrared spectrum of acesulfame potassium measured by reflectance.

Table I: Pharmacopeial specifications for acesulfame potassium.

Test	PhEur 6.0	USP32–NF27
Characters	+	–
Identification	+	+
Appearance of solution	+	–
Acidity or alkalinity	+	+
Acetylacetamide	0.125%	–
Impurity B[a]	⩽20 ppm	–
Unspecified impurities	⩽0.1%	⩽0.002%
Total impurities	⩽0.1%	–
Fluorides	⩽3 ppm	⩽0.0003%
Heavy metals	⩽5 ppm	⩽10 µg/g
Loss on drying	⩽1.0%	⩽1.0%
Assay (dried basis)	99.0–101.0%	99.0–101.0%

(a) Impurity B is 5-chloro-6-methyl-1,2,3-oxathiazin-4(3*H*)-one 2,2-dioxide.

Table II: Solubility of acesulfame potassium.[3]

Solvent	Solubility at 20°C unless otherwise stated
Ethanol	1 in 1000
Ethanol (50%)	1 in 10
Ethanol (15%)	1 in 4.5
Water	1 in 6.7 at 0°C 1 in 3.7 at 20°C 1 in 0.77 at 100°C

Specific volume 0.538 cm^3/g[5]
Surface tension 73.2 mN/m[6] (1% w/v aqueous solution at 20°C
Tensile strength 0.5 MPa[4]
Viscoelastic index 2.6[4]

11 Stability and Storage Conditions

Acesulfame potassium possesses good stability. In the bulk form it shows no sign of decomposition at ambient temperature over many years. In aqueous solutions (pH 3.0–3.5 at 20°C) no reduction in sweetness was observed over a period of approximately 2 years. Stability at elevated temperatures is good, although some decomposition was noted following storage at 40°C for several months. Sterilization and pasteurization do not affect the taste of acesulfame potassium.[7]

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

12 Incompatibilities

—

13 Method of Manufacture

Acesulfame potassium is synthesized from acetoacetic acid *tert*-butyl ester and fluorosulfonyl isocyanate. The resulting compound is transformed to fluorosulfonyl acetoacetic acid amide, which is then cyclized in the presence of potassium hydroxide to form the oxathiazinone dioxide ring system. Because of the strong acidity of this compound, the potassium salt is produced directly.[8]

An alternative synthesis route for acesulfame potassium starts with the reaction between diketene and amidosulfonic acid. In the presence of dehydrating agents, and after neutralization with potassium hydroxide, acesulfame potassium is formed.

14 Safety

Acesulfame potassium is widely used in beverages, cosmetics, foods, and pharmaceutical formulations, and is generally regarded as a relatively nontoxic and nonirritant material. Pharmacokinetic studies have shown that acesulfame potassium is not metabolized and is rapidly excreted unchanged in the urine. Long-term feeding studies in rats and dogs showed no evidence to suggest acesulfame potassium is mutagenic or carcinogenic.[9]

The WHO has set an acceptable daily intake for acesulfame potassium of up to 15 mg/kg body-weight.[9] The Scientific Committee for Foods of the European Union has set a daily intake value of up to 9 mg/kg of body-weight.[3]

LD_{50} (rat, IP): 2.2 g/kg[7]
LD_{50} (rat, oral): 6.9–8.0 g/kg

15 Handling Precautions

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

16 Regulatory Status

Included in the FDA Inactive Ingredients Database for oral and sublingual preparations. Included in the Canadian List of Acceptable Non-medicinal Ingredients. Accepted for use in Europe as a food additive. It is also accepted for use in certain food products in the USA and several countries in Central and South America, the Middle East, Africa, Asia, and Australia.

17 Related Substances

Alitame.

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 the bulk, textural, or preservative characteristics of sugar, if sugar is removed from a formulation.

Synergistic effects for combinations of sweeteners have been reported, e.g. acesulfame potassium with aspartame or sodium cyclamate; *see also* Aspartame. A ternary combination of sweeteners that includes acesulfame potassium and sodium saccharin has a greater decrease in sweetness upon repeated tasting than other combinations.[10]

Note that free acesulfame acid is not suitable for use as a sweetener.

A specification for acesulfame potassium is contained in the Food Chemicals Codex (FCC).[11]

19 Specific References

1 Kloesel L. Sugar substitutes. *Int J Pharm Compound* 2000; **4**(2): 86–87.
2 Schmidt R *et al*. Evaluating toothpaste sweetening. *Cosmet Toilet* 2000; **115**: 49–53.

3 Wilson R, ed. *Sweeteners*, 3rd edn. Oxford, UK: Blackwell Publishing, 2007; 3–19.
4 Mullarney MP *et al*. The powder flow and compact mechanical properties of sucrose and three high-intensity sweeteners used in chewable tablets. *Int J Pharm* 2003; **257**: 227–236.
5 Birch GG *et al*. Apparent specific volumes and tastes of cyclamates, other sulfamates, saccharins and acesulfame sweeteners. *Food Chem* 2004; **84**: 429–435.
6 Hutteau F *et al*. Physiochemical and psychophysical characteristics of binary mixtures of bulk and intense sweeteners. *Food Chem* 1998; **63**(1): 9–16.
7 Lipinski G-WvR, Huddart BE. Acesulfame K. *Chem Ind* 1983; **11**: 427–432.
8 Shetty K, ed. *Functional Foods and Biotechnology*. Boca Raton, FL: CRC Press, 2007; 327–344.
9 FAO/WHO. Evaluation of certain food additives and contaminants. Thirty-seventh report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1991; No. 806.
10 Schiffman SS *et al*. Effect of repeated presentation on sweetness intensity of binary and tertiary mixtures of sweetness. *Chem Senses* 2003; **28**: 219–229.
11 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 9.

20 General References

Anonymous. Artificial sweetners. *Can Pharm J* 1996; **129**: 22.
Lipinski G-WvR, Lück E. Acesulfame K: a new sweetener for oral cosmetics. *Manuf Chem* 1981; **52**(5): 37.
Marie S. Sweeteners. Smith J, ed. *Food Additives User's Handbook*. Glasgow: Blackie, 1991; 47–74.
Celanese Corp. Nutrinova technical literature: The *Sunett* guide to sweetness, 2008.

21 Author

BA Johnson.

22 Date of Revision

26 February 2009.

Acetic Acid, Glacial

1 Nonproprietary Names

BP: Glacial Acetic Acid
JP: Glacial Acetic Acid
PhEur: Acetic Acid, Glacial
USP: Glacial Acetic Acid

2 Synonyms

Acidum aceticum glaciale; E260; ethanoic acid; ethylic acid; methane carboxylic acid; vinegar acid.

See also Sections 17 and 18.

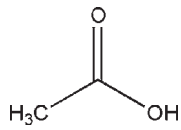
3 Chemical Name and CAS Registry Number

Ethanolic acid [64-19-7]

4 Empirical Formula and Molecular Weight

$C_2H_4O_2$ 60.05

5 Structural Formula



6 Functional Category

Acidifying agent.

7 Applications in Pharmaceutical Formulations or Technology

Glacial and diluted acetic acid solutions are widely used as acidifying agents in a variety of pharmaceutical formulations and food preparations. Acetic acid is used in pharmaceutical products as a buffer system when combined with an acetate salt such as sodium acetate. Acetic acid is also claimed to have some antibacterial and antifungal properties.

8 Description

Glacial acetic acid occurs as a crystalline mass or a clear, colorless volatile solution with a pungent odor.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for glacial acetic acid.

Test	JP XV	PhEur 6.0	USP 32
Identification	+	+	+
Characters	+	+	—
Freezing point	⩾14.5°C	⩾14.8°C	⩾15.6°C
Nonvolatile matter	⩽1.0 mg	⩽0.01%	⩽1.0 mg
Sulfate	+	+	+
Chloride	+	+	+
Heavy metals	⩽10 ppm	⩽5 ppm	⩽5 ppm
Iron	—	⩽5 ppm	—
Readily oxidizable impurities	+	+	+
Assay	⩾99.0%	99.5–100.5%	99.5–100.5%

10 Typical Properties

Acidity/alkalinity
pH = 2.4 (1 M aqueous solution);
pH = 2.9 (0.1 M aqueous solution);
pH = 3.4 (0.01 M aqueous solution).
Boiling point 118°C
Dissociation constant pK_a = 4.76
Flash point 39°C (closed cup); 57°C (open cup).
Melting point 17°C
Refractive index n_D^{20} = 1.3718

A

Solubility Miscible with ethanol, ether, glycerin, water, and other fixed and volatile oils.
Specific gravity 1.045

11 Stability and Storage Conditions

Acetic acid should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Acetic acid reacts with alkaline substances.

13 Method of Manufacture

Acetic acid is usually made by one of three routes: acetaldehyde oxidation, involving direct air or oxygen oxidation of liquid acetaldehyde in the presence of manganese acetate, cobalt acetate, or copper acetate; liquid-phase oxidation of butane or naphtha; methanol carbonylation using a variety of techniques.

14 Safety

Acetic acid is widely used in pharmaceutical applications primarily to adjust the pH of formulations and is thus generally regarded as relatively nontoxic and nonirritant. However, glacial acetic acid or solutions containing over 50% w/w acetic acid in water or organic solvents are considered corrosive and can cause damage to skin, eyes, nose, and mouth. If swallowed glacial acetic acid causes severe gastric irritation similar to that caused by hydrochloric acid.[1]

Dilute acetic acid solutions containing up to 10% w/w of acetic acid have been used topically following jellyfish stings.[2] Dilute acetic acid solutions containing up to 5% w/w of acetic acid have also been applied topically to treat wounds and burns infected with *Pseudomonas aeruginosa*.[3]

The lowest lethal oral dose of glacial acetic acid in humans is reported to be 1470 µg/kg.[4] The lowest lethal concentration on inhalation in humans is reported to be 816 ppm.[4] Humans, are, however, estimated to consume approximately 1 g/day of acetic acid from the diet.

LD_{50} (mouse, IV): 0.525 g/kg[4]
LD_{50} (rabbit, skin): 1.06 g/kg
LD_{50} (rat, oral): 3.31 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Acetic acid, particularly glacial acetic acid, can cause burns on contact with the skin, eyes, and mucous membranes. Splashes should be washed with copious quantities of water. Protective clothing, gloves, and eye protection are recommended.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Database (injections, nasal, ophthalmic, and oral preparations). Included in parenteral and nonparenteral preparations licensed in the UK.

17 Related Substances

Acetic acid; artificial vinegar; dilute acetic acid.

Acetic acid

Comments A diluted solution of glacial acetic acid containing 30–37% w/w of acetic acid. *See* Section 18.

Artificial vinegar

Comments A solution containing 4% w/w of acetic acid.

Dilute acetic acid

Comments A weak solution of acetic acid which may contain between 6–10% w/w of acetic acid. *See* Section 18.

18 Comments

In addition to glacial acetic acid, many pharmacopeias contain monographs for diluted acetic acid solutions of various strengths. For example, the USP32–NF27 has a monograph for acetic acid, which is defined as an acetic acid solution containing 36.0–37.0% w/w of acetic acid. Similarly, the BP 2009 contains separate monographs for glacial acetic acid, acetic acid (33%), and acetic acid (6%). Acetic acid (33%) BP 2009 contains 32.5–33.5% w/w of acetic acid. Acetic acid (6%) BP 2009 contains 5.7–6.3% w/w of acetic acid. The JP XV also contains a monograph for acetic acid that specifies that it contains 30.0–32.0% w/w of acetic acid.

A specification for glacial acetic acid is contained in the Food Chemicals Codex (FCC).[5]

The EINECS number for acetic acid is 200-580-7. The PubChem Compound ID (CID) for glacial acetic acid is 176.

19 Specific References

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2 Fenner PJ, Williamson JA. Worldwide deaths and severe envenomation from jellyfish stings. *Med J Aust* 1996; **165**: 658–661.
3 Milner SM. Acetic acid to treat *Pseudomonas aeruginosa* in superficial wounds and burns. *Lancet* 1992; **340**: 61.
4 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 15–16.
5 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 12.

20 General References

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21 Author

WG Chambliss.

22 Date of Revision

23 March 2009.

Acetone

1 Nonproprietary Names

BP: Acetone
PhEur: Acetone
USP-NF: Acetone

2 Synonyms

Acetonum; dimethylformaldehyde; dimethyl ketone; β-ketopropane; pyroacetic ether.

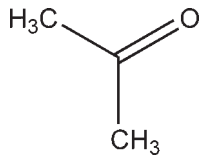
3 Chemical Name and CAS Registry Number

2-Propanone [67-64-1]

4 Empirical Formula and Molecular Weight

C_3H_6O 58.08

5 Structural Formula



6 Functional Category

Solvent.

7 Applications in Pharmaceutical Formulation or Technology

Acetone is used as a solvent or cosolvent in topical preparations, and as an aid in wet granulation.[1,2] It has also been used when formulating tablets with water-sensitive active ingredients, or to solvate poorly water-soluble binders in a wet granulation process. Acetone has also been used in the formulation of microspheres to enhance drug release.[3] Owing to its low boiling point, acetone has been used to extract thermolabile substances from crude drugs.[4]

8 Description

Acetone is a colorless volatile, flammable, transparent liquid, with a sweetish odor and pungent sweetish taste.

9 Pharmacopeial Specifications

See Table I. *See also* Section 18.

Table I: Pharmacopeial specifications for acetone.

Test	PhEur 6.0	USP32–NF27
Identification	+	+
Characters	+	–
Appearance of solution	+	–
Acidity or alkalinity	+	–
Relative density	0.790–0.793	⩽0.789
Related substances	+	–
Matter insoluble in water	+	–
Reducing substances	+	+
Residue on evaporation	⩽50 ppm	⩽0.004%
Water	⩽3 g/L	+
Assay	–	⩾99.0%

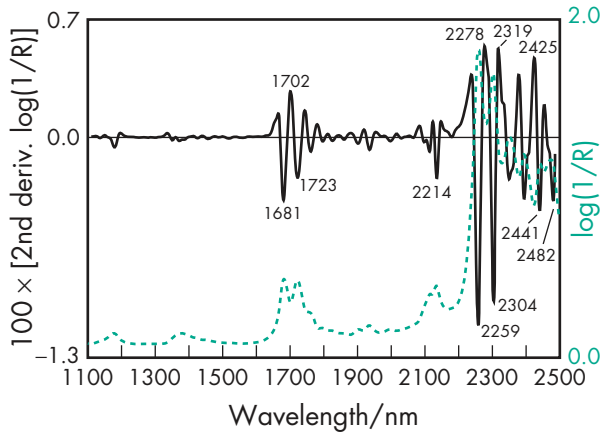


Figure 1: Near-infrared spectrum of acetone measured by transflectance (1 mm path-length).

10 Typical Properties

Boiling point 56.2°C
Flash point –20°C
Melting point 94.3°C
NIR spectra *see* Figure 1.
Refractive index n_D^{20} = 1.359
Solubility Soluble in water; freely soluble in ethanol (95%).
Vapor pressure 185 mmHg at 20°C

11 Stability and Storage Conditions

Acetone should be stored in a cool, dry, well-ventilated place out of direct sunlight.

12 Incompatibilities

Acetone reacts violently with oxidizing agents, chlorinated solvents, and alkali mixtures. It reacts vigorously with sulfur dichloride, potassium *t*-butoxide, and hexachloromelamine. Acetone should not be used as a solvent for iodine, as it forms a volatile compound that is extremely irritating to the eyes.[4]

13 Method of Manufacture

Acetone is obtained by fermentation as a by-product of *n*-butyl alcohol manufacture, or by chemical synthesis from isopropyl alcohol; from cumene as a by-product in phenol manufacture; or from propane as a by-product of oxidation-cracking.

14 Safety

Acetone is considered moderately toxic, and is a skin irritant and severe eye irritant. Skin irritation has been reported due to its defatting action, and prolonged inhalation may result in headaches. Inhalation of acetone can produce systemic effects such as conjunctival irritation, respiratory system effects, nausea, and vomiting.[5]

LD_{50} (mouse, oral): 3.0 g/kg[5]
LD_{50} (mouse, IP): 1.297 g/kg
LD_{50} (rabbit, oral): 5.340 g/kg
LD_{50} (rabbit, skin): 0.2 g/kg

A

LD_{50} (rat, IV): 5.5 g/kg
LD_{50} (rat, oral): 5.8 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Acetone is a skin and eye irritant (*see* Section 14); therefore gloves, eye protection and a respirator are recommended. In the UK, the long-term (8-hour TWA) workplace exposure limit for acetone is 1210 mg/m^3 (500 ppm). The short-term (15-minute) exposure limit is 3620 mg/m^3 (1500 ppm).[6]

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (inhalation solution; oral tablets; topical preparations). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in nonparenteral medicines licensed in the UK.

17 Related Substances

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18 Comments

A specification for acetone is included in the *Japanese Pharmaceutical Excipients* (JPE).[7]

The EINECS number for acetone is 200-662-2. The PubChem Compound ID (CID) for acetone is 180.

19 Specific References

1 Ash M, Ash I. *Handbook of Pharmaceutical Additives*, 3rd edn. Endicott, NY: Synapse Information Resources, 2007; 430.
2 Tang ZG *et al*. Surface properties and biocompatibility of solvent-cast poly[ε-caprolactone] films. *Biomaterials* 2004; **25**(19): 4741–4748.
3 Ruan G, Feng SS. Preparation and characterization of poly(lactic acid)–poly(ethylene glycol)–poly(lactic acid) (PLA-PEG-PLA) microspheres for controlled release of paclitaxel. *Biomaterials* 2003; **24**(27): 5037–5044.
4 Todd RG, Wade A, eds. *The Pharmaceutical Codex*, 11th edn. London: Pharmaceutical Press, 1979; 6.
5 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 22–23.
6 Health and Safety Executive. *EH40/2005: Workplace Exposure Limits*. Sudbury: HSE Books, 2005 (updated 2007). http://www.hse.gov.uk/coshh/table1.pdf (accessed 5 February 2009).
7 Japan Pharmaceutical Excipients Council. *Japanese Pharmaceutical Excipients 2004*. Tokyo: Yakuji Nippo, 2004; 35–36.

20 General References

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21 Author

AH Kibbe.

22 Date of Revision

5 February 2009.

Acetyltributyl Citrate

1 Nonproprietary Names

USP-NF: Acetyltributyl Citrate
PhEur: Tributyl Acetylcitrate

2 Synonyms

Acetylbutyl citrate; acetylcitric acid, tributyl ester; ATBC; *Citroflex A-4*; tributyl acetylcitrate; tributylis acetylcitras; tributyl *O*-acetylcitrate; tributyl citrate acetate.

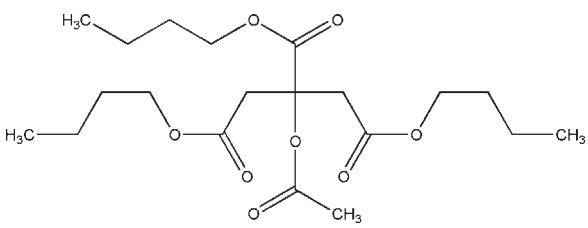
3 Chemical Name and CAS Registry Number

1,2,3-Propanetricarboxylic acid, 2-acetyloxy, tributyl ester [77-90-7]

4 Empirical Formula and Molecular Weight

$C_{20}H_{34}O_8$ 402.5

5 Structural Formula



6 Functional Category

Plasticizer.

7 Applications in Pharmaceutical Formulation or Technology

Acetyltributyl citrate is used to plasticize polymers in formulated pharmaceutical coatings,[1–5] including capsules, tablets, beads, and granules for taste masking, immediate release, sustained-release and enteric formulations.

8 Description

Acetyltributyl citrate is a clear, odorless, practically colorless, oily liquid.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acid value 0.02
Boiling point 326°C (decomposes)
Flash point 204°C
Pour point −59°C
Solubility Miscible with acetone, ethanol, and vegetable oil; practically insoluble in water.
Viscosity (dynamic) 33 mPa s (33 cP) at 25°C

Table I: Pharmacopeial specifications for acetyltributyl citrate.

Test	PhEur 6.3	USP32–NF27
Identification	+	+
Appearance	+	—
Characters	+	—
Specific gravity	—	1.045–1.055
Refractive index	1.442–1.445	1.4410–1.4425
Sulfated ash	⩽0.1%	—
Acidity	+	+
Water	⩽0.25%	⩽0.25%
Heavy metals	⩽10 ppm	⩽0.001%
Related substances	+	—
Assay (anhydrous basis)	99.0–101.0%	⩾99.0%

11 Stability and Storage Conditions

Acetyltributyl citrate should be stored in a well-closed container in a cool, dry location at temperatures not exceeding 38°C. When stored in accordance with these conditions, acetyltributyl citrate is a stable product.

12 Incompatibilities

Acetyltributyl citrate is incompatible with strong alkalis and oxidizing materials.

13 Method of Manufacture

Acetyltributyl citrate is prepared by the esterification of citric acid with butanol followed by acylation with acetic anhydride.

14 Safety

Acetyltributyl citrate is used in oral pharmaceutical formulations and films intended for direct food contact. It is also used in self-adhesive thin films used for topical delivery systems.[6] It is generally regarded as a relatively nontoxic and nonirritating material. However, ingestion of large quantities may be harmful.

LD_{50} (cat, oral): >50 mL/kg[7]
LD_{50} (mouse, IP): >4 g/kg
LD_{50} (rat, oral): >31.5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Acetyltributyl citrate is slightly irritating to the eyes and may be irritating to the respiratory system as a mist or at elevated temperatures. Gloves and eye protection are recommended for normal handling, and a respirator is recommended when using acetyltributyl citrate at elevated temperatures.

16 Regulatory Status

Included in FDA Inactive Ingredients Database (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Approved in the USA for direct food contact in food films.

17 Related Substances

Acetyltriethyl citrate; tributyl citrate; triethyl citrate.

18 Comments

Acetyltributyl citrate is used as a plasticizer in food contact films, although it has been known to migrate from food-grade PVC films into high-fat foods such as olive oil.[8]

Polylactide plasticized with acetyltributyl citrate has been investigated as a biodegradable barrier for use in guided-tissue regeneration therapy.[9]

The EINECS number for acetyltributyl citrate is 201-067-0. The PubChem Compound ID (CID) for acetyltributyl citrate is 6505.

19 Specific References

1 Gutierrez-Rocca JC, McGinity JW. Influence of water soluble and insoluble plasticizer on the physical and mechanical properties of acrylic resin copolymers. *Int J Pharm* 1994; **103**: 293–301.
2 Lehmann K. Chemistry and application properties of polymethacrylate coating systems. McGinity JW, ed. *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*. New York: Marcel Dekker, 1989; 153–245.
3 Steurnagel CR. Latex emulsions for controlled drug delivery. McGinity JW, ed. *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*. New York: Marcel Dekker, 1989; 1–61.
4 Gutierrez-Rocca JC, McGinity JW. Influence of aging on the physical-mechanical properties of acrylic resin films cast from aqueous dispersions and organic solutions. *Drug Dev Ind Pharm* 1993; **19**(3): 315–332.
5 Repka MA *et al*. Influence of plasticisers and drugs on the physical-mechanical properties of hydroxypropylcellulose films prepared by hot melt extrusion. *Drug Dev Ind Pharm* 1999; **25**(5): 625–633.
6 Lieb S *et al*. Self-adhesive thin films for topical delivery of 5-aminolevulinic acid. *Eur J Pharm Biopharm* 2002; **53**(1): 99–106.
7 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 3512.
8 Goulas AE *et al*. Effect of high-dose electron beam irradiation on the migration of DOA and ATBC plasticizers from food-grade PVC and PVDC/PVC films, respectively, into olive oil. *J Food Prot* 1998; **61**(6): 720–724.
9 Dorfer CE *et al*. Regenerative periodontal surgery in interproximal intrabony defects with biodegradable barriers. *J Clin Peridontol* 2000; **27**(3): 162–168.

20 General References

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21 Authors

ME Quinn, PJ Sheskey.

22 Date of Revision

18 February 2009.

Acetyltriethyl Citrate

1 Nonproprietary Names

USP-NF: Acetyltriethyl Citrate

2 Synonyms

ATEC; *Citroflex A-2*; triethyl acetylcitrate; triethyl *O*-acetylcitrate; triethyl citrate acetate.

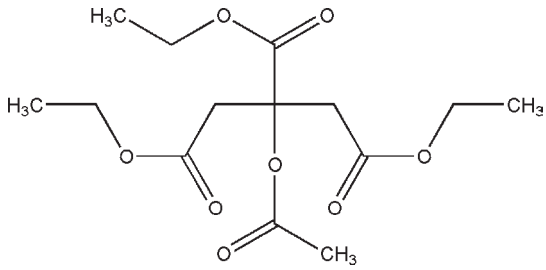
3 Chemical Name and CAS Registry Number

1,2,3-Propanetricarboxylic acid, 2-acetyloxy, triethyl ester [77-89-4]

4 Empirical Formula and Molecular Weight

$C_{14}H_{22}O_8$ 318.3

5 Structural Formula



6 Functional Category

Plasticizer.

7 Applications in Pharmaceutical Formulation or Technology

Acetyltriethyl citrate is used to plasticize polymers in formulated pharmaceutical coatings.[1] The coating applications include capsules, tablets, beads and granules for taste masking, immediate release, sustained-release and enteric formulations.[2–5] It is also used in diffusion-controlled release drug delivery systems.[6]

8 Description

Acetyltriethyl citrate occurs as a clear, odorless, practically colorless oily liquid.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for acetyltriethyl citrate.

Test	USP32–NF27
Identification	+
Specific gravity	1.135–1.139
Refractive index	1.432–1.441
Acidity	+
Water	≤0.3%
Heavy metals	≤0.001%
Assay (anhydrous basis)	≥99.0%

10 Typical Properties

Acid value 0.02
Boiling point 294°C (decomposes)
Flash point 188°C
Pour point −43°C
Solubility Soluble 1 in 140 of water; miscible with acetone, ethanol, and propan-2-ol.
Viscosity (dynamic) 54 mPa s (54 cP) at 25°C.

11 Stability and Storage Conditions

Acetyltriethyl citrate should be stored in dry, closed containers at temperatures not exceeding 38°C. When stored in accordance with these conditions, acetyltriethyl citrate is a stable product.

12 Incompatibilities

Acetyltriethyl citrate is incompatible with strong alkalis and oxidizing materials.

13 Method of Manufacture

Acetyltriethyl citrate is prepared by the esterification of citric acid with ethanol followed by acylation with acetic anhydride.

14 Safety

Acetyltriethyl citrate is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritating material. However, ingestion of large quantities may be harmful.

LD_{50} (cat, oral): 8.5 g/kg[7]
LD_{50} (mouse, IP): 1.15 g/kg
LD_{50} (rat, oral): 7 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Acetyltriethyl citrate may be irritating to the eyes or the respiratory system as a mist or at elevated temperatures. Gloves and eye protection are recommended for normal handling and a respirator is recommended if used at elevated temperatures.

16 Regulatory Status

Approved in the USA for direct food contact in food films.

17 Related Substances

Acetyltributyl citrate; tributyl citrate; triethyl citrate.

18 Comments

The EINECS number for acetyltriethyl citrate is 201-066-5. The PubChem Compound ID (CID) for acetyltriethyl citrate is 6504.

19 Specific References

1 Jensen JL *et al*. Variables that affect the mechanism of drug release from osmotic pumps coated with acrylate/methacrylate copolymer latexes. *J Pharm Sci* 1995; **84**: 530–533.
2 Gutierrez-Rocca JC, McGinity JW. Influence of water soluble and insoluble plasticizer on the physical and mechanical properties of acrylic resin copolymers. *Int J Pharm* 1994; **103**: 293–301.
3 Lehmann K. Chemistry and application properties of polymethacrylate coating systems. McGinity JW, ed. *Aqueous Polymeric Coatings for*

Pharmaceutical Dosage Forms. New York: Marcel Dekker, 1989; 153–245.
4 Steurnagel CR. Latex emulsions for controlled drug delivery. McGinity JW, ed. *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*. New York: Marcel Dekker,1–61.
5 Gutierrez-Rocca JC, McGinity JW. Influence of aging on the physical-mechanical properties of acrylic resin films cast from aqueous dispersions and organic solutions. *Drug Dev Ind Pharm* 1993; **19**(3): 315–332.
6 Siepmann J *et al*. Diffusion-controlled drug delivery systems: calculation of the required composition to achieve desired release profiles. *J Control Release* 1999; **60**(2–3): 379–389.
7 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 58–59.

20 General References

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21 Authors

ME Quinn, PJ Sheskey.

22 Date of Revision

18 February 2009.

Adipic Acid

1 Nonproprietary Names

PhEur: Adipic Acid
USP-NF: Adipic Acid

2 Synonyms

Acidum adipicum; acifloctin; acinetten; adilactetten; asapic; 1,4-butanedicarboxylic acid; E355; 1,6-hexanedioic acid; *Inipol DS*.

3 Chemical Name and CAS Registry Number

Hexanedioic acid [124-04-9]

4 Empirical Formula and Molecular Weight

$C_6H_{10}O_4$ 146.14

5 Structural Formula

6 Functional Category

Acidifying agent; buffering agent; flavoring agent.

7 Applications in Pharmaceutical Formulation or Technology

Adipic acid is used as an acidifying and buffering agent in intramuscular, intravenous and vaginal formulations. It is also used in food products as a leavening, pH-controlling, or flavoring agent.

Adipic acid has been incorporated into controlled-release formulation matrix tablets to obtain pH-independent release for both weakly basic[1,2] and weakly acidic drugs.[3,4] It has also been incorporated into the polymeric coating of hydrophilic monolithic systems to modulate the intragel pH, resulting in zero-order release of a hydrophilic drug.[5] The disintegration at intestinal pH of the enteric polymer shellac has been reported to improve when adipic acid was used as a pore-forming agent without affecting release in the acidic media.[6] Other controlled-release formulations have included adipic acid with the intention of obtaining a late-burst release profile.[7]

8 Description

Adipic acid occurs as a white or almost white, odorless nonhygroscopic crystalline powder. The crystal structure of adipic acid is monoclinic holohedral.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for adipic acid.

Test	PhEur 6.0	USP32–NF27
Identification	+	+
Characters	+	—
Melting range	151–154°C	151–154°C
Appearance of solution	+	—
Loss on drying	⩽0.2%	⩽0.2%
Residue on ignition	—	⩽0.1%
Sulfated ash	⩽0.1%	—
Chlorides	⩽200 ppm	⩽0.02%
Nitrates	⩽30 ppm	⩽0.003%
Sulfates	⩽500 ppm	⩽0.05%
Iron	⩽10 ppm	⩽0.001%
Heavy metals	⩽10 ppm	⩽0.001%
Related substances	+	—
Assay (anhydrous)	99.0–101.0%	99.0–101.0%

10 Typical Properties

Acidity/alkalinity pH = 2.7 (saturated solution at 25°C); pH = 3.2 (0.1% w/v aqueous solution at 25°C)
Boiling point 337.5°C
Dissociation constant
pK_{a1}: 4.418 at 25°C;
pK_{a2}: 5.412 at 25°C.
Density 1.360 g/cm^3
Flash point 196°C (closed cup)

Heat of combustion 17 653.9 kJ/mol (4219.28 kcal/mol) at 25°C
Heat of solution 33.193 kJ/mol (7.9 kcal/mol) at 25°C
Melting point 152.1°C
Solubility *see* Table II.
Vapor pressure 133.3 Pa (1 mmHg) at 159.5°C
Viscosity (dynamic) 4.54 mPa s (4.54 cP) at 160°C for molten adipic acid.

Table II: Solubility of adipic acid.

Solvent	Solubility at 20°C unless otherwise stated
Acetone	Soluble
Benzene	Practically insoluble
Cyclohexane	Slightly soluble
Ethanol (95%)	Freely soluble
Ether	1 in 157.8 at 19°C
Ethyl acetate	Soluble
Methanol	Freely soluble
Petroleum ether	Practically insoluble
Water	1 in 71.4 1 in 0.6 at 100°C

11 Stability and Storage Conditions

Adipic acid is normally stable but decomposes above boiling point. It should be stored in a tightly closed container in a cool, dry place, and should be kept away from heat, sparks, and open flame.

12 Incompatibilities

Adipic acid is incompatible with strong oxidizing agents as well as strong bases and reducing agents. Contact with alcohols, glycols, aldehydes, epoxides, or other polymerizing compounds can result in violent reactions.

13 Method of Manufacture

Adipic acid is prepared by nitric acid oxidation of cyclohexanol or cyclohexanone or a mixture of the two compounds. Recently, oxidation of cyclohexene with 30% aqueous hydrogen peroxide under organic solvent- and halide-free conditions has been proposed as an environmentally friendly alternative for obtaining colorless crystalline adipic acid.[8]

14 Safety

Adipic acid is used in pharmaceutical formulations and food products. The pure form of adipic acid is toxic by the IP route, and moderately toxic by other routes. It is a severe eye irritant, and may cause occupational asthma.

LD_{50} (mouse, IP): 0.28 g/kg[9]
LD_{50} (mouse, IV): 0.68 g/kg
LD_{50} (mouse, oral): 1.9 g/kg
LD_{50} (rat, IP): 0.28 g/kg
LD_{50} (rat, oral): >11 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled.

Adipic acid is combustible and can react with oxidizing materials when exposed to heat and flame. It emits acrid smoke and fumes when heated to decomposition. Dust explosion is possible if in powder or granular form, mixed with air.

Adipic acid irritates the eyes and respiratory tract. Protective equipment such as respirators, safety goggles, and heavy rubber gloves should be worn when handling adipic acid.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Database (IM, IV, and vaginal preparations). Accepted for use as a food additive in Europe. Included in an oral pastille formulation available in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

A specification for adipic acid is contained in the Food Chemicals Codex (FCC).[10]

The EINECS number for adipic acid is 204-673-3. The PubChem Compound ID (CID) for adipic acid is 196.

19 Specific References

1 Guthmann C *et al*. Development of a multiple unit pellet formulation for a weakly basic drug. *Drug Dev Ind Pharm* 2007; **33**(3): 341–349.
2 Streubel A *et al*. pH-independent release of a weakly basic drug from water-insoluble and -soluble matrix tablets. *J Control Release* 2000; **67**(1): 101–110.
3 Pillay V, Fassihi R. In situ electrolyte interactions in a disk-compressed configuration system for up-curving and constant drug delivery. *J Control Release* 2000; **67**(1): 55–65.
4 Merkli A *et al*. The use of acidic and basic excipients in the release of 5-fluorouracil and mitomycin C from a semi-solid bioerodible poly(ortho ester). *J Control Release* 1995; **33**(3): 415–421.
5 Pillay V, Fassihi R. Electrolyte-induced compositional heterogeneity: a novel approach for rate-controlled oral drug delivery. *J Pharm Sci* 1999; **88**(11): 1140–1148.
6 Pearnchob N *et al*. Improvement in the disintegration of shellac-coated soft gelatin capsules in simulated intestinal fluid. *J Control Release* 2004; **94**(2–3): 313–321.
7 Freichel OL, Lippold BC. A new oral erosion controlled drug delivery system with a late burst in the release profile. *Eur J Pharm Biopharm* 2000; **50**(3): 345–351.
8 Sato K *et al*. A 'green' route to adipic acid: direct oxidation of cyclohexenes with 30 percent hydrogen peroxide. *Science* 1998; **281**: 1646–1647.
9 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 83–84.
10 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 26.

20 General References

Grant DJW, York P. A disruption index for quantifying the solid state disorder induced by additives or impurities. II. Evaluation from heat of solution. *Int J Pharm* 1986; **28**(2–3): 103–112.

21 Author

D Law.

22 Date of Revision

27 February 2009.

Agar

1 Nonproprietary Names

JP: Agar
PhEur: Agar
USP-NF: Agar

2 Synonyms

Agar-agar; agar-agar flake; agar-agar gum; Bengal gelatin; Bengal gum; Bengal isinglass; Ceylon isinglass; Chinese isinglass; E406; gelosa; gelose; Japan agar; Japan isinglass; layor carang.

3 Chemical Name and CAS Registry Number

Agar [9002-18-0]

4 Empirical Formula and Molecular Weight

See Section 5.

5 Structural Formula

Agar is a dried, hydrophilic, colloidal polysaccharide complex extracted from the agarocytes of algae of the Rhodophyceae. The structure is believed to be a complex range of polysaccharide chains having alternating α-(1→3) and β-(1→4) linkages. There are three extremes of structure noted: namely neutral agarose; pyruvated agarose having little sulfation; and a sulfated galactan. Agar can be separated into a natural gelling fraction, agarose, and a sulfated nongelling fraction, agaropectin.

6 Functional Category

Emulsifying agent; stabilizing agent; suppository base; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Agar is widely used in food applications as a stabilizing agent. In pharmaceutical applications, agar is used in a handful of oral tablet and topical formulations. It has also been investigated in a number of experimental pharmaceutical applications including as a sustained-release agent in gels, beads, microspheres, and tablets.[1-4] It has also been reported to work as a disintegrant in tablets.[5] Agar has been used in a floating controlled-release tablet; the buoyancy in part being attributed to air entrapped in the agar gel network.[6] It can be used as a viscosity-increasing agent in aqueous systems. Agar can also be used as a base for nonmelting, and nondisintegrating suppositories.[7] Agar has an application as a suspending agent in pharmaceutical suspensions.[8]

8 Description

Agar occurs as transparent, odorless, tasteless strips or as a coarse or fine powder. It may be weak yellowish-orange, yellowish-gray to pale-yellow colored, or colorless. Agar is tough when damp, brittle when dry.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for agar.

Test	JP XV	PhEur 6.3	USP32–NF27
Identification	+	+	+
Characters	+	+	—
Swelling index	—	+	—
Arsenic	—	—	⩽3 ppm
Lead	—	—	⩽0.001%
Sulfuric acid	+	—	—
Sulfurous acid and starch	+	—	—
Gelatin	—	+	+
Heavy metals	—	—	⩽0.004%
Insoluble matter	⩽15.0 mg	⩽1.0%	⩽15.0 mg
Water absorption	⩽75 mL	—	⩽75 mL
Loss on drying	⩽22.0%	⩽20.0%	⩽20.0%
Microbial contamination	—	⩽10^3 cfu/g[a]	+
Total ash	⩽4.5%	⩽5.0%	⩽6.5%
Acid-insoluble ash	⩽0.5%	—	⩽0.5%
Foreign organic matter	—	—	⩽1.0%
Limit of foreign starch	—	—	+

(a) Total viable aerobic count, determined by plate-count.

10 Typical Properties

NIR spectra *see* Figure 1.

Solubility Soluble in boiling water to form a viscous solution; practically insoluble in ethanol (95%), and cold water. A 1% w/v aqueous solution forms a stiff jelly on cooling.

11 Stability and Storage Conditions

Agar solutions are most stable at pH 4–10.

Agar should be stored in a cool, dry, place. Containers of this material may be hazardous when empty since they retain product residues (dust, solids).

12 Incompatibilities

Agar is incompatible with strong oxidizing agents. Agar is dehydrated and precipitated from solution by ethanol (95%). Tannic acid causes precipitation; electrolytes cause partial dehydration and decrease in viscosity of sols.[9]

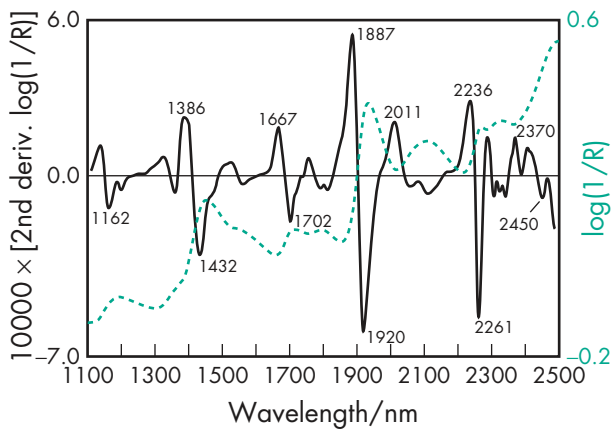

Figure 1: Near-infrared spectrum of agar measured by reflectance.

13 Method of Manufacture

Agar is obtained by freeze-drying a mucilage derived from *Gelidium amansii* Lamouroux, other species of the same family (Gelidiaceae), or other red algae (Rhodophyta).

14 Safety

Agar is widely used in food applications and has been used in oral and topical pharmaceutical applications. It is generally regarded as relatively nontoxic and nonirritant when used as an excipient.

LD_{50} (hamster, oral): 6.1 g/kg[10]
LD_{50} (mouse, oral): 16.0 g/kg
LD_{50} (rabbit, oral): 5.8 g/kg
LD_{50} (rat, oral): 11.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. When heated to decomposition, agar emits acrid smoke and fumes.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (oral tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in nonparenteral medicines licensed in the UK.

17 Related Substances

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18 Comments

The drug release mechanism of agar spherules of felodipine has been studied and found to follow Higuchi kinetics.[11] Agar has also been used to test the bioadhesion potential of various polymers.[12]

The EINECS number for agar is 232-658-1.

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20 General References

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VK Gupta.

22 Date of Revision

10 February 2009.

Albumin

1 Nonproprietary Names

BP: Albumin Solution
PhEur: Human Albumin Solution
USP: Albumin Human

2 Synonyms

Alba; *Albuconn*; *Albuminar*; albumin human solution; albumini humani solutio; *Albumisol*; *Albuspan*; *Albutein*; *Buminate*; human serum albumin; normal human serum albumin; *Octalbin*; *Plasbumin*; plasma albumin; *Pro-Bumin*; *Proserum*; *Zenalb*.

3 Chemical Name and CAS Registry Number

Serum albumin [9048-49-1]

4 Empirical Formula and Molecular Weight

Human serum albumin has a molecular weight of about 66 500 and is a single polypeptide chain consisting of 585 amino acids. Characteristic features are a single tryptophan residue, a relatively low content of methionine (6 residues), and a large number of cysteine (17) and of charged amino acid residues of aspartic acid (36), glutamic acid (61), lysine (59), and arginine (23).

5 Structural Formula

Primary structure Human albumin is a single polypeptide chain of 585 amino acids and contains seven disulfide bridges.

Secondary structure Human albumin is known to have a secondary structure that is about 55% α-helix. The remaining 45% is believed to be divided among turns, disordered, and β structures.[1]

Albumin is the only major plasma protein that does not contain carbohydrate constituents. Assays of crystalline albumin show less than one sugar residue per molecule.

6 Functional Category

Stabilizing agent; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Albumin is primarily used as an excipient in parenteral pharmaceutical formulations, where it is used as a stabilizing agent for formulations containing proteins and enzymes.[2] Albumin has also been used to prepare microspheres and microcapsules for experimental drug-delivery systems.[3–6]

As a stabilizing agent, albumin has been employed in protein formulations at concentrations as low as 0.003%, although concentrations of 1–5% are commonly used. Albumin has also been used as a cosolvent[7] for parenteral drugs, as a cryoprotectant during lyophilization,[8,9] and to prevent adsorption of other proteins to surfaces.

Therapeutically, albumin solutions have been used parenterally for plasma volume replacement and to treat severe acute albumin loss. However, the benefits of using albumin in such applications in critically ill patients has been questioned.[10]

8 Description

The USP 32 describes albumin human as a sterile nonpyrogenic preparation of serum albumin obtained from healthy human donors; *see* Section 13. It is available as a solution containing 4, 5, 20, or 25 g of serum albumin in 100 mL of solution, with not less than 96% of the total protein content as albumin. The solution contains no added antimicrobial preservative but may contain sodium acetyltryptophanate with or without sodium caprylate as a stablizing agent.

The PhEur 6.0 similarly describes albumin solution as an aqueous solution of protein obtained from human plasma; *see* Section 13. It is available as a concentrated solution containing 150–250 g/L of total protein or as an isotonic solution containing 35–50 g/L of total protein. Not less than 95% of the total protein content is albumin. A suitable stabilizer against the effects of heat, such as sodium caprylate (sodium octanoate) or *N*-acetyltryptophan or a combination of these two at a suitable concentration, may be added, but no antimicrobial preservative is added.

Aqueous albumin solutions are slightly viscous and range in color from almost colorless to amber depending upon the protein concentration. In the solid state, albumin appears as brownish amorphous lumps, scales, or powder.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for albumin.

Test	PhEur 6.0	USP 32
Identification	+	–
Characters	+	–
Production	+	–
Protein composition	+	–
Molecular size distribution	+	–
Heat stability	–	+
pH (10 g/L solution)	6.7–7.3	+
Potassium	⩽0.05 mmol/g	–
Sodium	⩽160 mmol/L	130–160 mEq/L
Heme	+	+
Aluminum	⩽200 µg/L	–
Sterility	+	+
Hepatitis B surface antigen	–	+
Pyrogens	+	+
Total protein	95–105%	⩾96%
for 4 g in 100 mL	–	93.75–106.25%
for 5 to 25 g in 100 mL	–	94.0–106.0%
Prekallikrein activator	⩽35 IU/mL	–

10 Typical Properties

Acidity/alkalinity pH = 6.7–7.3 for a 1% w/v solution, in 0.9% w/v sodium chloride solution, at 20°C.

NIR spectra *see* Figure 1.

Osmolarity A 4–5% w/v aqueous solution is isoosmotic with serum.

Solubility Freely soluble in dilute salt solutions and water. Aqueous solutions containing 40% w/v albumin can be readily prepared at pH 7.4. The high net charge of the peptide contributes to its solubility in aqueous media. The seven disulfide bridges contribute to its chemical and spatial conformation. At physiological pH, albumin has a net electrostatic charge of about –17. Aqueous albumin solutions are slightly viscous and range in color from almost colorless to amber depending on the protein concentration.

11 Stability and Storage Conditions

Albumin is a protein and is therefore susceptible to chemical degradation and denaturation by exposure to extremes of pH, high salt concentrations, heat, enzymes, organic solvents, and other chemical agents.

Albumin solutions should be protected from light and stored at a temperature of 2–25°C or as indicated on the label.

12 Incompatibilities

See Section 11.

13 Method of Manufacture

Albumin human (USP 32) Albumin human is a sterile nonpyrogenic preparation of serum albumin that is obtained by fractionating material (source blood, plasma, serum, or placentas) from healthy human donors. The source material is tested for the absence of hepatitis B surface antigen. It is made by a process that yields a product safe for intravenous use.

Human albumin solution (PhEur 6.0) Human albumin solution is an aqueous solution of protein obtained from plasma. Separation of the albumin is carried out under controlled conditions so that the final product contains not less than 95% albumin. Human albumin solution is prepared as a concentrated solution containing 150–250 g/L of total protein or as an isotonic solution containing 35–50 g/L of total protein. A suitable stabilizer against the effects of heat such as sodium caprylate (sodium octanoate) or *N*-acetyltryptophan or a combination of these two at a suitable concentration, may be added, but no antimicrobial preservative is added at any stage during preparation. The solution is passed through a bacteria-retentive filter and distributed aseptically into sterile containers,

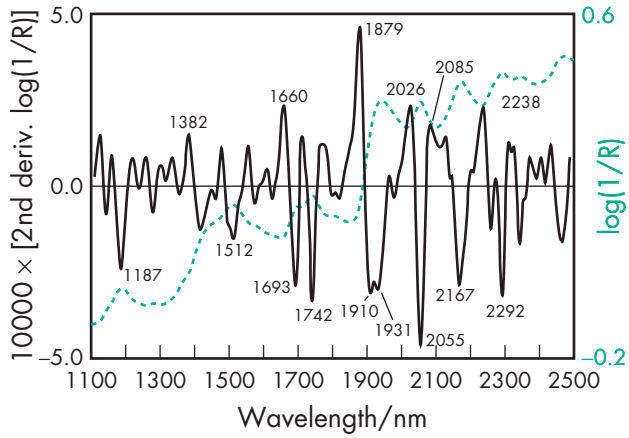

Figure 1: Near-infrared spectrum of albumin measured by reflectance.

which are then closed so as to prevent contamination. The solution in its final container is heated to 60 ± 1.0°C and maintained at this temperature for not less than 10 hours. The containers are then incubated at 30–32°C for not less than 14 days or at 20–25°C for not less than 4 weeks and examined visually for evidence of microbial contamination.

14 Safety

Albumin occurs naturally in the body, comprising about 60% of all the plasma proteins. As an excipient, albumin is used primarily in parenteral formulations and is generally regarded as an essentially nontoxic and nonirritant material. Adverse reactions to albumin infusion rarely occur but include nausea, vomiting, increased salivation, chills, and febrile reactions. Urticaria and skin rash have been reported. Allergic reactions, including anaphylactic shock, can occur. Albumin infusions are contraindicated in patients with severe anemia or cardiac failure. Albumin solutions with aluminum content of less than 200 µg/L should be used in dialysis patients and premature infants.[11]

LD_{50} (monkey, IV): >12.5 g/kg[12]

LD_{50} (rat, IV): >12.5 g/kg

15 Handling Precautions

Observe handling precautions appropriate for a biologically derived blood product.

16 Regulatory Acceptance

Included in the FDA Inactive Ingredients Database (oral, tablets, film-coatings; IV injections, IV infusions and subcutaneous injectables). Included in parenteral products licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Albumins derived from animal sources are also commercially available, e.g. bovine serum albumin.

18 Comments

A 100 mL aqueous solution of albumin containing 25 g of serum albumin is osmotically equivalent to 500 mL of normal human plasma.

The EINECS number for albumin is 310-127-6.

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22 Date of Revision

12 February 2009.

Alcohol

1 Nonproprietary Names

BP: Ethanol (96%)

JP: Ethanol

PhEur: Ethanol (96 per cent)

USP: Alcohol

2 Synonyms

Ethanolum (96 per centum); ethyl alcohol; ethyl hydroxide; grain alcohol; methyl carbinol.

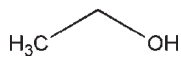
3 Chemical Name and CAS Registry Number

Ethanol [64-17-5]

4 Empirical Formula and Molecular Weight

C_2H_6O 46.07

5 Structural Formula



6 Functional Category

Antimicrobial preservative; disinfectant; skin penetrant; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Ethanol and aqueous ethanol solutions of various concentrations (*see* Sections 8 and 17) are widely used in pharmaceutical formulations and cosmetics; *see* Table I. Although ethanol is primarily used as a solvent, it is also employed as a disinfectant, and in solutions as an antimicrobial preservative.[1,2] Topical ethanol solutions are used in the development of transdermal drug delivery systems as penetration enhancers.[3–10] Ethanol has also been used in the development of transdermal preparations as a co-surfactant.[11–13]

Table I: Uses of alcohol.

Use	Concentration (% v/v)
Antimicrobial preservative	⩾10
Disinfectant	60–90
Extracting solvent in galenical manufacture	Up to 85
Solvent in film coating	Variable
Solvent in injectable solutions	Variable
Solvent in oral liquids	Variable
Solvent in topical products	60–90

8 Description

In the BP 2009, the term 'ethanol' used without other qualification refers to ethanol containing ⩾99.5% v/v of C_2H_6O. The term 'alcohol', without other qualification, refers to ethanol 95.1–96.9% v/v. Where other strengths are intended, the term 'alcohol' or 'ethanol' is used, followed by the statement of the strength.

In the PhEur 6.0, anhydrous ethanol contains not less than 99.5% v/v of C_2H_6O at 20°C. The term ethanol (96%) is used to describe the material containing water and 95.1–96.9% v/v of C_2H_6O at 20°C.

In the USP 32, the term 'dehydrated alcohol' refers to ethanol ⩾99.5% v/v. The term 'alcohol' without other qualification refers to ethanol 94.9–96.0% v/v.

In the JP XV, ethanol (alcohol) contains 95.1–96.9% v/v (by specific gravity) of C_2H_6O at 15°C.

In the *Handbook of Pharmaceutical Excipients*, the term 'alcohol' is used for either ethanol 95% v/v or ethanol 96% v/v.

Alcohol is a clear, colorless, mobile, and volatile liquid with a slight, characteristic odor and burning taste.

See also Section 17.

9 Pharmacopeial Specifications

See Table II. *See also* Sections 17 and 18.

Table II: Pharmacopeial specifications for alcohol.

Test	JP XV	PhEur 6.0	USP 32
Identification	+	+	+
Characters	—	+	—
Specific gravity	0.809–0.816	0.805–0.812	0.812–0.816
Acidity or alkalinity	+	+	+
Clarity and color of solution	+	+	+
Nonvolatile residue	⩽2.5 mg	⩽25 ppm	⩽2.5 mg
Volatile impurities	+	+	+
Absorbance	+	+	+
at 240 nm	⩽0.40	⩽0.40	⩽0.40
at 250–260 nm	⩽0.30	⩽0.30	⩽0.30
at 270–340 nm	⩽0.10	⩽0.10	⩽0.10
Assay	95.1–96.9%	95.1–96.9%	92.3–93.8% by weight 94.9–96.0% by volume

10 Typical Properties

Antimicrobial activity Ethanol is bactericidal in aqueous mixtures at concentrations between 60% and 95% v/v; the optimum concentration is generally considered to be 70% v/v. Antimicrobial activity is enhanced in the presence of edetic acid or edetate salts.[1] Ethanol is inactivated in the presence of nonionic surfactants and is ineffective against bacterial spores.

Boiling point 78.15°C

Flammability Readily flammable, burning with a blue, smokeless flame.

Flash point 14°C (closed cup)

NIR spectra *see* Figures 1 and 2.

Solubility Miscible with chloroform, ether, glycerin, and water (with rise of temperature and contraction of volume).

Specific gravity 0.8119–0.8139 at 20°C

Note The above typical properties are for alcohol (ethanol 95% or 96% v/v). *See* Section 17 for typical properties of dehydrated alcohol.

11 Stability and Storage Conditions

Aqueous ethanol solutions may be sterilized by autoclaving or by filtration and should be stored in airtight containers, in a cool place.

12 Incompatibilities

In acidic conditions, ethanol solutions may react vigorously with oxidizing materials. Mixtures with alkali may darken in color owing to a reaction with residual amounts of aldehyde. Organic

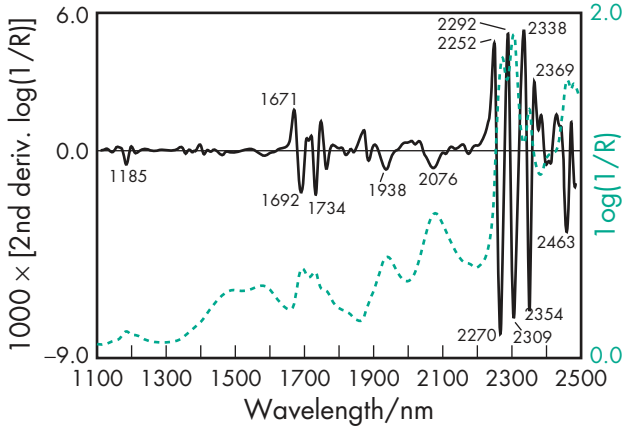


Figure 1: Near-infrared spectrum of alcohol (96%) measured by transflectance (1 mm path-length).

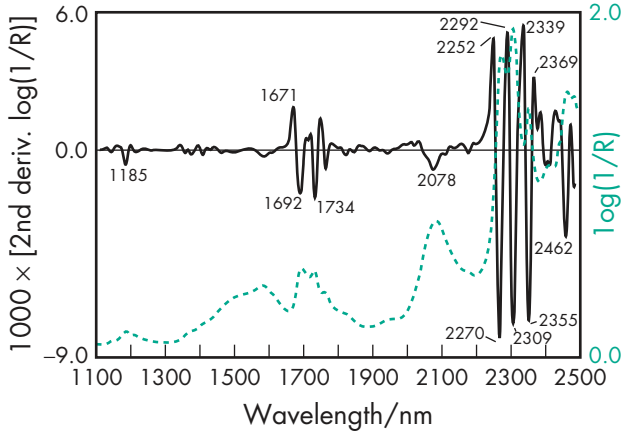


Figure 2: Near-infrared spectrum of alcohol (absolute) measured by transflectance (1 mm path-length).

salts or acacia may be precipitated from aqueous solutions or dispersions. Ethanol solutions are also incompatible with aluminum containers and may interact with some drugs.

13 Method of Manufacture

Ethanol is manufactured by the controlled enzymatic fermentation of starch, sugar, or other carbohydrates. A fermented liquid is produced containing about 15% ethanol; ethanol 95% v/v is then obtained by fractional distillation. Ethanol may also be prepared by a number of synthetic methods.

14 Safety

Ethanol and aqueous ethanol solutions are widely used in a variety of pharmaceutical formulations and cosmetics. It is also consumed in alcoholic beverages.

Ethanol is rapidly absorbed from the gastrointestinal tract and the vapor may be absorbed through the lungs; it is metabolized, mainly in the liver, to acetaldehyde, which is further oxidized to acetate.

Ethanol is a central nervous system depressant and ingestion of low to moderate quantities can lead to symptoms of intoxication including muscle incoordination, visual impairment, slurred speech, etc. Ingestion of higher concentrations may cause depression of medullary action, lethargy, amnesia, hypothermia, hypoglycemia, stupor, coma, respiratory depression, and cardiovascular collapse. The lethal human blood-alcohol concentration is generally estimated to be 400–500 mg/100 mL.

Although symptoms of ethanol intoxication are usually encountered following deliberate consumption of ethanol-containing beverages, many pharmaceutical products contain ethanol as a solvent, which, if ingested in sufficiently large quantities, may cause adverse symptoms of intoxication. In the USA, the maximum quantity of alcohol included in OTC medicines is 10% v/v for products labeled for use by people of 12 years of age and older, 5% v/v for products intended for use by children aged 6–12 years of age, and 0.5% v/v for products for use by children under 6 years of age.[14]

Parenteral products containing up to 50% of alcohol (ethanol 95 or 96% v/v) have been formulated. However, such concentrations can produce pain on intramuscular injection and lower concentrations such as 5–10% v/v are preferred. Subcutaneous injection of alcohol (ethanol 95% v/v) similarly causes considerable pain followed by anesthesia. If injections are made close to nerves, neuritis and nerve degeneration may occur. This effect is used therapeutically to cause anesthesia in cases of severe pain, although the practice of using alcohol in nerve blocks is controversial. Doses of 1 mL of absolute alcohol have been used for this purpose.[15]

Preparations containing more than 50% v/v alcohol may cause skin irritation when applied topically.

LD_{50} (mouse, IP): 0.93 g/kg[16]
LD_{50} (mouse, IV): 1.97 g/kg
LD_{50} (mouse, oral): 3.45 g/kg
LD_{50} (mouse, SC): 8.29 g/kg
LD_{50} (rat, IP): 3.75 g/kg
LD_{50} (rat, IV): 1.44 g/kg
LD_{50} (rat, oral): 7.06 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Ethanol and aqueous ethanol solutions should be handled in a well-ventilated environment. In the UK, the long-term 8-hour TWA workplace exposure limit for ethanol is 1920 mg/m^3 (1000 ppm).[17] Ethanol may be irritant to the eyes and mucous membranes, and eye protection and gloves are recommended. Ethanol is flammable and should be heated with care. Fixed storage tanks should be electrically grounded to avoid ignition from electrostatic discharges when ethanol is transferred.

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (dental preparations; inhalations; IM, IV, and SC injections; nasal and ophthalmic preparations; oral capsules, solutions, suspensions, syrups, and tablets; rectal, topical, and transdermal preparations). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in nonparenteral and parenteral medicines licensed in the UK.

17 Related Substances

Dehydrated alcohol; denatured alcohol; dilute alcohol; isopropyl alcohol.

Dehydrated alcohol

Synonyms Absolute alcohol; anhydrous ethanol; ethanol.
Autoignition temperature 365°C
Boiling point 78.5°C
Explosive limits 3.5–19.0% v/v in air
Flash point 12°C (closed cup)
Melting point −112°C
Moisture content Absorbs water rapidly from the air.
Refractive index n_D^{20} = 1.361
Specific gravity 0.7904–0.7935 at 20°C
Surface tension 22.75 mN/m at 20°C (ethanol/vapor)
Vapor density (relative) 1.59 (air = 1)

Vapor pressure 5.8 Pa at 20°C
Viscosity (dynamic) 1.22 mPa s (1.22 cP) at 20°C
Comments Dehydrated alcohol is ethanol ⩾99.5% v/v. *See* Section 8. Dehydrated alcohol is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

Denatured alcohol

Synonyms Industrial methylated spirit; surgical spirit.
Comments Denatured alcohol is alcohol intended for external use only. It has been rendered unfit for human consumption by the addition of a denaturing agent such as methanol or methyl isobutyl ketone.

Dilute alcohol

Synonyms Dilute ethanol.
Specific gravity *see* Table III.

Table III: Specific gravity of alcohol.

Strength of alcohol (% v/v)	Specific gravity at 20°C
90	0.8289–0.8319
80	0.8599–0.8621
70	0.8860–0.8883
60	0.9103–0.9114
50	0.9314–0.9326
45	0.9407–0.9417
25	0.9694–0.9703
20	0.9748–0.9759

Comments The term 'dilute alcohol' refers to a mixture of ethanol and water of stated concentration. The USP32–NF27 lists diluted alcohol. The BP 2009 lists eight strengths of dilute alcohol (dilute ethanol) containing 90%, 80%, 70%, 60%, 50%, 45%, 25%, and 20% v/v respectively of ethanol.

18 Comments

Alcohol is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

Possession and use of nondenatured alcohols are usually subject to close control by excise authorities.

A specification for alcohol is contained in the Food Chemicals Codex (FCC).[18]

The EINECS number for alcohol is 200-578-6. The PubChem Compound ID (CID) for alcohol is 702.

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22 Date of Revision

5 February 2009.

Alginic Acid

1 Nonproprietary Names

BP: Alginic Acid
PhEur: Alginic Acid
USP-NF: Alginic Acid

2 Synonyms

Acidum alginicum; E400; *Kelacid*; L-gulo-D-mannoglycuronan; polymannuronic acid; *Protacid*; *Satialgine H8*.

3 Chemical Name and CAS Registry Number

Alginic acid [9005-32-7]

4 Empirical Formula and Molecular Weight

Alginic acid is a linear glycuronan polymer consisting of a mixture of β-(1→4)-D-mannosyluronic acid and α-(1→4)-L-gulosyluronic acid residues, of general formula $(C_6H_8O)_n$. The molecular weight is typically 20 000–240 000.

5 Structural Formula

The PhEur 6.3 describes alginic acid as a mixture of polyuronic acids $[(C_6H_8O_6)_n]$ composed of residues of D-mannuronic and L-glucuronic acid, and obtained mainly from algae belonging to the Phaeophyceae. A small proportion of the carboxyl groups may be neutralized.

See also Section 4.

6 Functional Category

Release-modifying agent; stabilizing agent; suspending agent; sustained release agent; tablet binder; tablet disintegrant; taste-masking agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Alginic acid is used in a variety of oral and topical pharmaceutical formulations. In tablet and capsule formulations, alginic acid is used as both a binder and disintegrating agent at concentrations of 1–5% w/w.[1,2] Alginic acid is widely used as a thickening and suspending agent in a variety of pastes, creams, and gels; and as a stabilizing agent for oil-in-water emulsions.

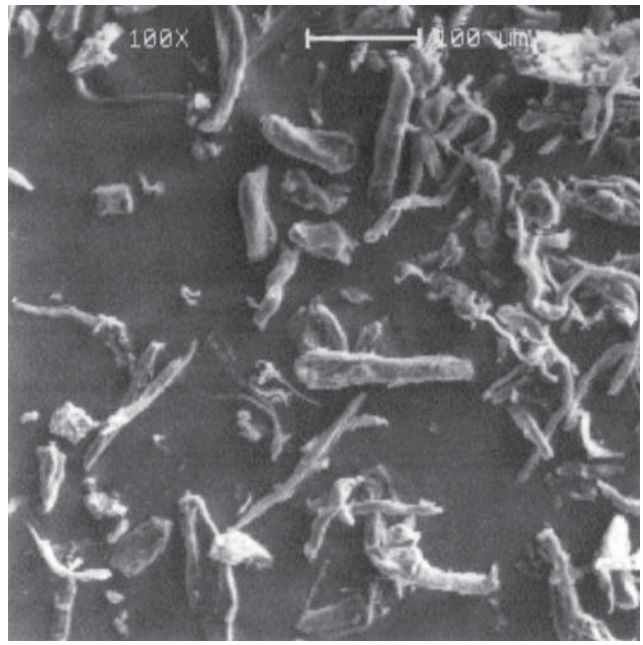
Alginic acid has been used to improve the stability of levosimendan.[3]

Therapeutically, alginic acid has been used as an antacid.[4] In combination with an H_2-receptor antagonist, it has also been utilized for the management of gastroesophageal reflux.[5]

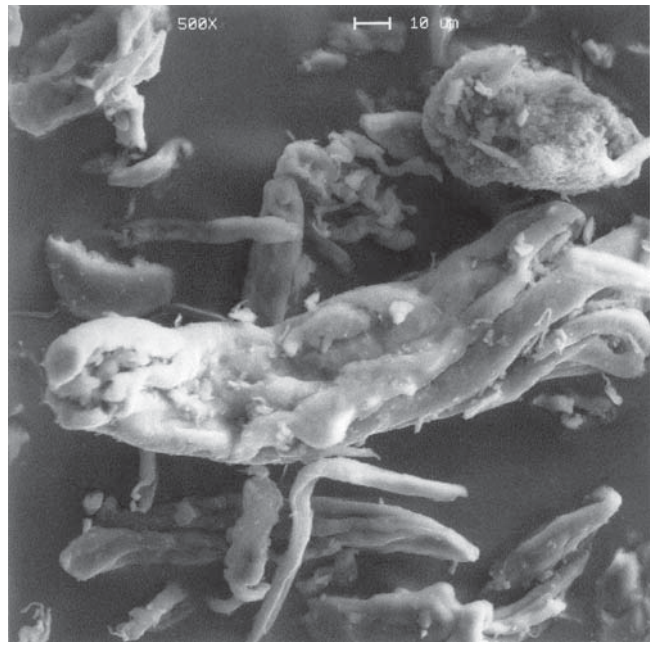
8 Description

Alginic acid is a tasteless, practically odorless, white to yellowish-white, fibrous powder.

SEM 1: Excipient: alginic acid; magnification: 100×; voltage: 25 kV.



SEM 2: Excipient: alginic acid; magnification: 500×; voltage: 25 kV.



9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity pH = 1.5–3.5 for a 3% w/v aqueous dispersion.

Crosslinking Addition of a calcium salt, such as calcium citrate or calcium chloride, causes crosslinking of the alginic acid polymer

Table I: Pharmacopeial specifications for alginic acid

Test	PhEur 6.3	USP32–NF27
Identification	+	+
Characters	+	–
Microbial limits	$\leqslant 10^2$ cfu/g	$\leqslant$200 cfu/g
pH (3% dispersion)	–	1.5–3.5
Loss on drying	$\leqslant$15.0%	$\leqslant$15.0%
Ash	–	$\leqslant$4.0%
Sulfated ash	$\leqslant$8.0%	–
Arsenic	–	$\leqslant$3 ppm
Chloride	$\leqslant$1.0%	–
Lead	–	$\leqslant$0.001%
Heavy metals	$\leqslant$20 ppm	$\leqslant$0.004%
Acid value (dried basis)	–	$\geqslant$230
Assay (of COOH groups)	19.0–25.0%	–

resulting in an apparent increase in molecular weight. Films crosslinked with triphosphate (tripolyphosphate) and calcium chloride were found to be insoluble but permeable to water vapor. Drug permeability varies with pH and the extent of crosslinking.[6]

Density (true) 1.601 g/cm^3

Moisture content 7.01%

NIR spectra *see* Figure 1.

Solubility Soluble in alkali hydroxides, producing viscous solutions; very slightly soluble or practically insoluble in ethanol (95%) and other organic solvents. Alginic acid swells in water but does not dissolve; it is capable of absorbing 200–300 times its own weight of water.

Viscosity (dynamic) Various grades of alginic acid are commercially available that vary in their molecular weight and hence viscosity. Viscosity increases considerably with increasing concentration; typically a 0.5% w/w aqueous dispersion will have a viscosity of approximately 20 mPa s, while a 2.0% w/w aqueous dispersion will have a viscosity of approximately 2000 mPa s. The viscosity of dispersions decreases with increasing temperature. As a general rule, a 1°C increase in temperature results in a 2.5% reduction in viscosity. At low concentrations, the viscosity of an alginic acid dispersion may be increased by the addition of a calcium salt, such as calcium citrate. *See also* Sections 11 and 18.

11 Stability and Storage Conditions

Alginic acid hydrolyzes slowly at warm temperatures producing a material with a lower molecular weight and lower dispersion viscosity.

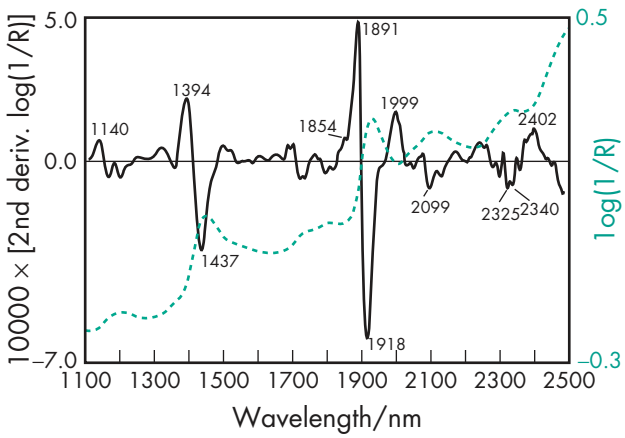


Figure 1: Near-infrared spectrum of alginic acid measured by reflectance.

Alginic acid dispersions are susceptible to microbial spoilage on storage, which may result in some depolymerization and hence a decrease in viscosity. Dispersions should therefore be preserved with an antimicrobial preservative such as benzoic acid; potassium sorbate; sodium benzoate; sorbic acid; or paraben. Concentrations of 0.1–0.2% are usually used.

Alginic acid dispersions may be sterilized by autoclaving or filtration through a 0.22 µm filter. Autoclaving may result in a decrease in viscosity which can vary depending upon the nature of any other substances present.[7]

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

12 Incompatibilities

Incompatible with strong oxidizing agents; alginic acid forms insoluble salts in the presence of alkaline earth metals and group III metals with the exception of magnesium.

13 Method of Manufacture

Alginic acid is a hydrophilic colloid carbohydrate that occurs naturally in the cell walls and intercellular spaces of various species of brown seaweed (Phaeophyceae). The seaweed occurs widely throughout the world and is harvested, crushed, and treated with dilute alkali to extract the alginic acid.

14 Safety

Alginic acid is widely used in food products and topical and oral pharmaceutical formulations. It is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may be harmful. Inhalation of alginate dust may be an irritant and has been associated with industrially related asthma in workers involved in alginate production. However, it appears that the cases of asthma were linked to exposure to unprocessed seaweed dust rather than pure alginate dust.[8] An acceptable daily intake of alginic acid and its ammonium, calcium, potassium, and sodium salts was not set by the WHO because the quantities used, and the background levels in food, did not represent a hazard to health.[9]

LD_{50} (rat, IP): 1.6 g/kg[10]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Alginic acid may be irritant to the eyes or respiratory system if inhaled as dust; *see* Section 14. Eye protection, gloves, and a dust respirator are recommended. Alginic acid should be handled in a well-ventilated environment.

16 Regulatory Status

GRAS listed. Accepted in Europe for use as a food additive. Included in the FDA Inactive Ingredients Database (ophthalmic preparations, oral capsules, and tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Ammonium alginate; calcium alginate; potassium alginate; propylene glycol alginate; sodium alginate.

18 Comments

Alginic acid has been investigated for use in an ocular formulation of carteolol.[11]

In the area of controlled release, the preparation of indomethacin sustained-release microparticles from alginic acid (alginate)–gelatin hydrocolloid coacervate systems has been investigated.[12] In addition, as controlled-release systems for liposome-associated macromolecules, microspheres have been produced encapsulating

liposomes coated with alginic acid and poly-L-lysine membranes.[13] Alginate gel beads capable of floating in the gastric cavity have been prepared, the release properties of which were reported to be applicable for sustained release of drugs, and for targeting the gastric mucosa.[14]

Mechanical properties, water uptake, and permeability properties of a sodium salt of alginic acid have been characterized for controlled-release applications.[6] In addition, sodium alginate has been incorporated into an ophthalmic drug delivery system for pilocarpine nitrate.[15] Sodium alginate has been used to improve pelletization due to polyelectrolyte complex formation between cationic polymers such as chitosan.[16] Alginic acid has also been shown to be beneficial in the development of alginate gel-encapsulated, chitosan-coated nanocores, where the alginates act as a protective agent for sensitive macromolecules such as proteins and peptides for prolonged release.[17] In addition, the crosslinking of dehydrated paracetamol sodium alginate pellets has been shown to successfully mask the drug's unpleasant taste by an extrusion/spheronization technique.[18]

It has also been reported that associated chains of alginic acid complexed with cations can bind to cell surfaces and exert pharmacological effects, which depend on the cell type and the complexed cation. These complexes can be used to treat rheumatic disorders, diseases associated with atopic diathesis and liver diseases.[19]

An alginic oligosaccharide, obtained from a natural edible polysaccharide, has been shown to suppress Th2 responses and IgE production by inducing IL-12 production, and was found to be a useful approach for preventing allergic disorders.[20] Chemically modified alginic acid derivatives have also been researched for their anti-inflammatory, antiviral, and antitumor activities.[21] Alginate/antacid antireflux preparations have been reported to provide symptomatic relief by forming a physical barrier on top of the stomach contents in the form of a raft.[22]

Alginic acid dispersions are best prepared by pouring the alginic acid slowly and steadily into vigorously stirred water. Dispersions should be stirred for approximately 30 minutes. Premixing the alginic acid with another powder, such as sugar, or a water-miscible liquid such as ethanol (95%) or glycerin, aids dispersion.

When using alginic acid in tablet formulations, the alginic acid is best incorporated or blended using a dry granulation process.

Alginic acid gels for use in drug delivery systems may be prepared by adding D-glucono-D-lactone, which hydrolyzes in the presence of water to produce gluconic acid with a continuous lowering of pH.[23]

A specification for alginic acid is contained in the Food Chemicals Codex (FCC).[24]

The EINECS number for alginic acid is 232-680-1.

19 Specific References

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20 General References

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21 Authors

MA Repka, A Singh.

22 Date of Revision

26 February 2009.

Aliphatic Polyesters

1 Nonproprietary Names

None adopted.

2 Synonyms

See Table I.

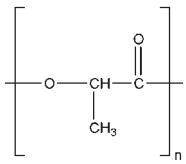
3 Chemical Name and CAS Registry Number

See Table I.

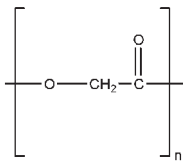
4 Empirical Formula and Molecular Weight

Aliphatic polyesters are synthetic homopolymers or copolymers of lactic acid, glycolic acid, lactide, glycolide and ε-hydroxycaproic acid. Typically, the molecular weights of homopolymers and copolymers range from 2000 to >100 000 Da.

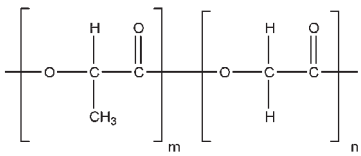
5 Structural Formula



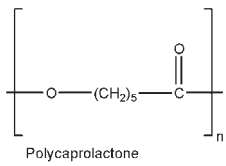
Poly(lactide)



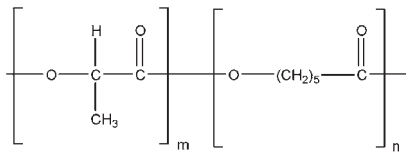
Poly(glycolide)



Poly(lactide-co-glycolide)



Polycaprolactone



Poly(lactide-co-caprolactone)

6 Functional Category

Bioabsorbable material; biocompatible material; biodegradable material.

7 Applications in Pharmaceutical Formulation or Technology

Owing to their reputation as safe materials and their biodegradability, aliphatic polyesters are primarily used as biocompatible and biodegradable carriers in many types of implantable or injectable drug-delivery systems for both human and veterinary use. Examples of implantable drug delivery systems include rods,[1] cylinders, tubing, films,[2] fibers, pellets, and beads.[3] Examples of injectable drug-delivery systems include microcapsules,[4] microspheres,[5] nanoparticles, and liquid injectable controlled-release systems such as gel formulations.[6]

8 Description

Aliphatic polyesters are a group of synthesized homopolymers or copolymers. They are nontoxic and can easily be fabricated into a variety of novel devices, such as rods, screws, nails, and cylinders. The polymers are commercially available in varying molecular weights as both homopolymers and copolymers. Molecular weights of polyesters range from 2000 Da to greater than 100 000 Da.

Co-monomer ratios of lactic acid and glycolic acid (or lactide and glycolide) for poly(DL-lactide-*co*-glycolide) range from 85 : 15 to 50 : 50. Table I shows the chemical and trade names of different commercially available aliphatic polyesters.

9 Pharmacopeial Specifications

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10 Typical Properties

For typical physical and mechanical properties of the aliphatic polyesters, *see* Tables II, III, IV, V, VI, and VII.

Polymer composition and crystallinity play important roles in the solubility of these aliphatic polyesters. The crystalline homopolymers of glycolide or glycolic acid are soluble only in strong solvents, such as hexafluoroisopropanol. The crystalline homopolymers of lactide or lactic acid also do not have good solubility in most organic solvents. However, amorphous polymers of DL-lactide or DL-lactic acid and copolymers of lactide or lactic acid with a low glycolide or glycolic acid content are soluble in many organic solvents (Table II). Aliphatic polyesters are slightly soluble or insoluble in water, methanol, ethylene glycol, heptane, and hexane.

11 Stability and Storage Conditions

The aliphatic polyesters are easily susceptible to hydrolysis in the presence of moisture. Hence, they should be packaged under high-purity dry nitrogen and properly stored in airtight containers, preferably refrigerated at below 0°C. It is necessary to allow the polymers to reach room temperature in a dry environment before opening the container. After the original package has been opened, it is recommended to re-purge the package with high-purity dry nitrogen prior to resealing.

12 Incompatibilities

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13 Method of Manufacture

Generally, aliphatic polyesters can be synthesized via polycondensation of hydroxycarboxylic acids and catalytic ring-opening polymerization of lactones. Ring-opening polymerization is preferred because polyesters with high molecular weights can be

Table I: Chemical names and CAS registry numbers of the aliphatic polyesters.

Generic name	Composition (%)			Synonyms	Trade name	Manufacturer	CAS name	CAS number
	Lactide	Glycolide	Caprolactone					
Poly(L-lactide)	100	0	0	L-PLA	*Lactel L-PLA* *100 L* *Resomer L 206 S, 207 S, 209 S, 210, 210 S*	Durect Lakeshore BI	Poly[oxy[(1*S*)-1-methyl-2-oxo-1,2-ethanediyl]]	[26161-42-2]
Poly(DL-lactide)	100	0	0	DL-PLA	*Lactel DL-PLA* *Purasorb PDL 02A, 02, 04, 05* *Resomer R 202 S, 202 H, 203 S, 203 H* *100 DL 7E*	Durect Purac BI Lakeshore	1,4-Dioxane-2,5-dione, 3,6-dimethyl-, homopolymer	[26680-10-4]
Poly(L-lactide-*co*-glycolide)	85	15	0		*Resomer LG 855 S, 857 S*	BI	1,4-Dioxane-2,5-dione, 3,6-dimethyl-, (3*S*,6*S*)-, polymer with 1,4-dioxane-2,5-dione	[30846-39-0]
Poly(L-lactide-*co*-glycolide)	82	18	0		*Resomer LG 824 S*	BI	1,4-Dioxane-2,5-dione, 3,6-dimethyl-, (3S,6S)-, polymer with 1,4-dioxane-2,5-dione	[30846-39-0]
Poly(L-lactide-*co*-glycolide)	10	90	0		*Resomer GL 903*	BI	1,4-Dioxane-2,5-dione, 3,6-dimethyl-, (3*S*,6*S*)-, polymer with 1,4-dioxane-2,5-dione	[30846-39-0]
Poly(DL-lactide-*co*-glycolide)	85	15	0	Polyglactin;DL-PLGA (85 : 15)	*Lactel 85 : 15 DL-PLG* *8515 DLG 7E* *Resomer RG 858 S*	Durect Lakeshore BI	1,4-Dioxane-2,5-dione, 3,6-dimethyl-, polymer with 1,4-dioxane-2,5-dione	[26780-50-7]
Poly(DL-lactide-*co*-glycolide)	75	25	0	Polyglactin;DL-PLGA (75 : 25)	*Lactel 75:25 DL-PLG* *Purasorb PDLG 7502A, 7502, 7507* *Resomer RG 752 H, 752 S, 753 S, 755 S, 756 S* *7525 DLG 7E*	Durect Purac BI Lakeshore	1,4-Dioxane-2,5-dione, 3,6-dimethyl-, polymer with 1,4-dioxane-2,5-dione	[26780-50-7]
Poly(DL-lactide-*co*-glycolide)	65	35	0	Polyglactin;DL-PLGA (65 : 35)	*Lactel 65:35 DL-PLG* *6535 DLG 7E* *Resomer RG 653 H*	Durect Lakeshore BI	1,4-Dioxane-2,5-dione, 3,6-dimethyl-, polymer with 1,4-dioxane-2,5-dione	[26780-50-7]
Poly(DL-lactide-*co*-glycolide)	50	50	0	Polyglactin;DL-PLGA (50 : 50)	*Lactel 50:50 DL-PLG* *5050 DLG 7E, 5E, 1A, 2A, 3A, 4A, 4.5A* *Purasorb PDLG* 5002A, 5002, 5004A, 5004, 5010 *Resomer RG 502, 502H, 503, 503H, 504, 504H, 509S*	Durect Lakeshore Purac BI	1,4-Dioxane-2,5-dione, 3,6-dimethyl-, polymer with 1,4-dioxane-2,5-dione	[26780-50-7]
Poly-ε-caprolactone	0	0	100	PCL	*Lactel PCL* *100 PCL*	Durect Lakeshore	2-Oxepanone, homopolymer	[24980-41-4]
Poly(DL-lactide-*co*-ε-caprolactone)	85	0	15		*8515 DL/PCL*	Lakeshore	1,4-Dioxane-2,5-dione,3,6-dimethyl-, polymer with 2-oxepanone	[70524-20-8]
Poly(DL-lactide-*co*-ε-caprolactone)	80	0	20	DL-PLCL (80 : 20)	*Lactel 80 : 20 DL-PLCL*	Durect	1,4-Dioxane-2,5-dione, 3,6-dimethyl-, polymer with 2-oxepanone	[70524-20-8]
Poly(DL-lactide-*co*-ε-caprolactone)	25	0	75	DL-PLCL (25 : 75)	*Lactel 25 : 75 DL-PLCL*	Durect	1,4-Dioxane-2,5-dione, 3,6-dimethyl-, polymer with 2-oxepanone	[70524-20-8]
Poly(L-lactide-*co*-ε-caprolactone)	70	0	30		*Resomer LC 703 S*	BI	1,4-Dioxane-2,5-dione, 3,6-dimethyl-, (3*S*,6*S*)-, polymer with 2-oxepanone	[65408-67-5]
Poly(L-lactide-*co*-ε-caprolactone)	85	0	15		*8515 L/PCL*	Lakeshore	1,4-Dioxane-2,5-dione, 3,6-dimethyl-, (3*S*,6*S*)-, polymer with 2-oxepanone	[65408-67-5]
Poly(L-lactide-*co*-ε-caprolactone)	75	0	25		*7525 L/PCL*	Lakeshore	1,4-Dioxane-2,5-dione, 3,6-dimethyl-, (3*S*,6*S*)-, polymer with 2-oxepanone	[65408-67-5]

(a) BI, Boehringer Ingelheim; Durect, Durect Corporation; Lakeshore, Lakeshore Biomaterials; Purac, Purac America.

Table II: Typical physical and mechanical properties of the aliphatic polyesters.[a]

	50/50 DL-PLG	65/35 DL-PLG	75/25 DL-PLG	85/15 DL-PLG	DL-PLA	L-PLA	PGA	PCL
Molecular weight	40 000–100 000	40 000–100 000	40 000–100 000	40 000–100 000	40 000–100 000	>100 000	>100 000	80 000–150 000
Inherent viscosity (dL/g)	0.5–0.8[b]	0.5–0.8[b]	0.5–0.8[c]	0.5–0.8[c]	0.5–0.8[c]	0.9–1.2[c]	1.4–1.8[b]	1.0–1.3[c]
Melting point (°C)	Amorphous	Amorphous	Amorphous	Amorphous	Amorphous	173–178	225–230	58–63
Glass transition temperature (°C)	45–50	45–50	50–55	50–55	50–60	60–65	35–40	–65 to –60
Color	White to light gold	White to light gold	White to light gold	White to light gold	White	White	Light tan	White
Solubility (at 5% w/w)[d]	$MeCl_2$, THF, EtOAc, C_3H_6O, $CHCl_3$, HFIP	$MeCl_2$, THF, EtOAc, C_3H_6O, $CHCl_3$, HFIP	$MeCl_2$, THF, EtOAc, C_3H_6O, $CHCl_3$, HFIP	$MeCl_2$, THF, EtOAc, C_3H_6O, $CHCl_3$, HFIP	$MeCl_2$, THF, EtOAc, C_3H_6O, $CHCl_3$, HFIP	$MeCl_2$, $CHCl_3$, HFIP	HFIP	$MeCl_2$, $CHCl_3$, HFIP
Approx. resorption (months)	1–2	3–4	4–5	5–6	12–16	>24	6–12	>24
Specific gravity	1.34	1.30	1.30	1.27	1.25	1.24	1.53	1.11
Tensile strength (psi)	6000–8000	6000–8000	6000–8000	6000–8000	4000–6000	8000–12 000	10 000+	3000–5000
Elongation (%)	3–10	3–10	3–10	3–10	3–10	5–10	15–20	300–500
Modulus (psi)	$2–4 \times 10^5$	$2–4 \times 10^5$	$2–4 \times 10^5$	$2–4 \times 10^5$	$2–4 \times 10^5$	$4–6 \times 10^5$	1×10^6	$3–5 \times 10^4$

Note: DL-PLG: DL-poly(lactide-co-glycolide); DL-PLA: DL-polylactide; L-PLA: L-polylactide; PGA: polyglycolide; PCL: poly-ε-caprolactone.
(a) Specifications obtained from Durect.
(b) (HFIP) hexafluoroisopropanol.
(c) ($CHCl_3$) chloroform.
(d) Partial listing only: $MeCl_2$, methylene chloride; THF, tetrahydrofuran; EtOAc, ethyl acetate; HFIP, hexafluoroisopropanol; C_3H_6O, acetone.

A

Table III: General mechanical properties of selected aliphatic polyesters.[a]

Property	Polymer			
	5050 DL	100 DL	100 L (Custom)	90/10 L/DL (Custom)
Composition	Poly (DL-lactide-*co*-glycolide) (50 : 50)	Poly (DL-lactide)	Poly (L-lactide)	Poly (L-lactide-*co*-DL-lactide)
Break stress (psi)	8296	6108	7323	7614
Strain at break (%)	5.2	5.0	5.5	5.2
Yield stress (psi)	8371	6666	7678	8414
Strain at yield (%)	5.1	3.7	4.9	4.5
Modulus (psi)	189 340	207 617	182 762	210 680

(a) Specification obtained from Lakeshore Biomaterials.

Table IV: Mechanical properties of poly(L-lactide/caprolactone).[a]

Property	Poly (L-lactide/caprolactone) grade				
	50/50	75/25	85/15	90/10	95/05
Tensile strength (psi)					
At maximum	80	1488	3254	6232	6900
At 100%	79	400	1822	—	—
At 300%	44	950	2615	—	—
Elongation (%)					
To yield	>1000	>400	>6.4	8.1	1.6
To failure	>1000	>400	>500	8.1	1.6
Modulus (kpsi)	0.1	5.3	84	167	185
Shore D-hardness	5	52	87	91	95
Specific gravity	1.2	1.2	1.23	1.25	1.26
Compression molding temperature (°C)	73–130	130 ± 15	140 ± 10	165 ± 5	165 ± 5

(a) Specifications obtained from Lakeshore Biomaterials.

Table VI: Glass transition temperature and melting point of selected biodegradable polymers.[a]

Polymer	Composition	Glass transition temperature (°C)	Melting point (°C)
100 PGA	Poly (glycolic acid)	35–40	225–230
100 L	Poly (L-lactide)	56–60	173–178
9010 G/L	Poly (L-lactide-*co*-glycolide)(10 : 90)	35–45	180–200
100 DL	Poly (DL-lactide)	50–55	Amorphous[b]
8515 DL/G	Poly (DL-lactide-*co*-glycolide) (85 : 15)	50–55	Amorphous[b]
7525 DL/G	Poly (DL-lactide-*co*-glycolide) (75 : 25)	48–53	Amorphous[b]
6335 DL/G	Poly (DL-lactide-*co*-glycolide) (65 : 35)	45–50	Amorphous[b]
5050 DL/G	Poly (DL-lactide-*co*-glycolide) (50 : 50)	43–48	Amorphous[b]
8515 DL/PCL	Poly (DL-lactide-*co*-caprolactone) (85 : 15)	20–25	Amorphous[b]
8515 L/PCL	Poly (L-lactide-*co*-caprolactone) (85 : 15)	20–25	Amorphous[b]
7525 L/PCL	Poly (L-lactide-*co*-caprolactone) (75 : 25)	13–20	Amorphous[b]
100 PCL	Poly (caprolactone)	(−60) – (−65)	60

(a) Specifications obtained from Lakeshore Biomaterials.
(b) Process temperature range: 140–160°C.

Table VII: Solubility of selected aliphatic polyesters.[a]

Polymer	Solvent						
Polymer	Ethyl acetate	Methylene chloride	Chloroform	Acetone	Dimethyl formamide (DMF)	Tetrahydrofuran (THF)	Hexafluoro-isopropanol (HFIP)
Poly (L-lactide)	NS	S	S	NS	NS	NS	S
Poly (DL-lactide)	S	S	S	S	S	S	S
Poly (DL-lactide-*co*-glycolide) (85 : 15)	S	S	S	S	S	S	S
Poly (DL-lactide-*co*-glycolide) (75 : 25)	S	S	S	S	S	S	S
Poly (DL-lactide-*co*-glycolide) (65 : 35)	S	S	S	S	S	S	S
Poly (DL-lactide-*co*-glycolide) (50 : 50)	SS	S	S	SS	S	SS	S
Poly (caprolactone)	S	S	S	S	S	S	S
Poly (L-lactide-*co*-caprolactone) (75 : 25)	S	S	S	S	S	S	S
Poly (DL-lactide-*co*-caprolactone) (80 : 20)	S	S	S	S	S	S	S
Poly (glycolic acid)	NS	NS	NS	NS	NS	NS	S

(a) Specifications obtained from Lakeshore Biomaterials.
NS, not soluble; SS, slightly soluble (degree of solubility is dependent on molecular weight or inherent viscosity); S, soluble.

Table V: Mechanical properties of poly (DL-lactide/caprolactone).[a]

Property	Poly(DL-lactide/caprolactone) grade				
	60/40	75/25	85/15	90/10	95/05
Tensile strength (psi)					
At maximum	65	1300	1555	4453	5493
At 100%	65	224	1555	—	—
At 300%	43	332	1041	—	—
Elongation (%)					
To yield	—	—	—	5.6	—
To failure	>400	>600	>500	5.6	7.2
Modulus (kpsi)	0.1	1.05	6.04	106	135
Shore D-hardness	0	42	79	88	95
Specific gravity	—	1.20	1.22	1.24	—
Compression molding temperature (°C)	—	82–140	82–140	82–140	120

(a) Specifications obtained from Lakeshore Biomaterials.

produced. Moreover, the dehydration of hydroxycarboxylic acids to form lactones does not have to be carried to a high degree of completion. Lactones can easily be purified owing to the differences of their physical and chemical properties from those of the corresponding hydroxycarboxylic acid. The esterification of the carboxylic acid end group makes polymers more hydrophobic, which decreases the hydrolytic degradation rate of the polymers in the presence of water or moisture.

14 Safety

Poly(lactic acide) or poly(lactide), poly(glycolic acid) or poly(glycolide), poly (lactic-*co*-glycolic acid) or poly(lactide-*co*-glycolide), and polycaprolactone are used in parenteral pharmaceutical formulations and are regarded as biodegradable, biocompatible, and bioabsorbable materials. Their biodegradation products are nontoxic, noncarcinogenic, and nonteratogenic. In general, these polyesters exhibit very little hazard.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Contact with eyes, skin, and clothing, and breathing the dust of the polymers should be avoided. Aliphatic polyesters produce acid materials such as hydroxyacetic and/or lactic acid in the presence of moisture; thus, contact with materials that will react with acids, especially in moist conditions, should be avoided.

16 Regulatory Status

GRAS listed. Included in the Canadian List of Acceptable Non-medicinal Ingredients. Poly(lactide) and poly(lactide-*co*-glycolide) have been used in medical products and medical devices approved by the FDA.

17 Related Substances

Lactic acid.

18 Comments

Aliphatic polyesters are a group of synthesized, nontoxic, biodegradable polymers. In an aqueous environment, the polymer backbone undergoes hydrolytic degradation, through cleavage of the ester linkages, into nontoxic hydroxycarboxylic acids. Aliphatic polyesters are eventually metabolized to carbon dioxide and water, via the citric acid cycle.

The rate of biodegradation and drug-release characteristics from injectable drug-delivery systems formulated with the aliphatic polyesters can be controlled by changing the physicochemical properties of the polymers, such as crystallinity, hydrophobicity, monomer stereochemistry, copolymer ratio, end group, and polymer molecular weight or by changing the porosity and geometry of the formulation.

Due to their ability to form complexes with heavy metal ions, aliphatic polyesters are added to skin-protective ointments.[7]

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21 Authors

RK Chang, W Qu, AJ Shukla, N Trivedi.

22 Date of Revision

16 February 2009.

Alitame

1 Nonproprietary Names

None adopted.

2 Synonyms

Aclame; L-aspartyl-D-alanine-*N*-(2,2,4,4-tetramethylthietan-3-yl)amide; 3-(L-aspartyl-D-alaninamido)-2,2,4,4-tetramethylthietane.

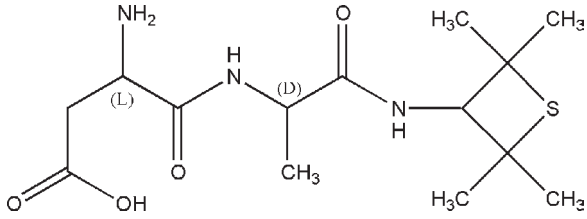
3 Chemical Name and CAS Registry Number

L-α-Aspartyl-*N*-(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide anhydrous [80863-62-3]
L-α-Aspartyl-*N*-(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide hydrate [99016-42-9]

4 Empirical Formula and Molecular Weight

$C_{14}H_{25}N_3O_4S$ 331.44 (for anhydrous)
$C_{14}H_{25}N_3O_4S \cdot 2^1/_2H_2O$ 376.50 (for hydrate)

5 Structural Formula



6 Functional Category

Sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Alitame is an intense sweetening agent developed in the early 1980s and is approximately 2000 times sweeter than sucrose. It has an insignificant energy contribution of 6 kJ (1.4 kcal) per gram of alitame.

Alitame is currently primarily used in a wide range of foods and beverages at a maximum level of 40–300 mg/kg.[1]

8 Description

Alitame is a white nonhygroscopic crystalline powder; odorless or having a slight characteristic odor.

9 Pharmacopeial Specifications

—

10 Typical Properties

Acidity/alkalinity pH = 5–6 (5% w/v aqueous solution)
Isoelectric point pH 5.6
Melting point 136–147°C
Solubility *see* Table I.

Table I: Solubility of alitame.

Solvent	Solubility at 20°C unless otherwise stated
Chloroform	1 in 5000 at 25°C
Ethanol	1 in 1.6 at 25°C
n-Heptane	Practically insoluble
Methanol	1 in 2.4 at 25°C
Propylene glycol	1 in 1.9 at 25°C
Water	1 in 8.3 at 5°C
	1 in 7.6 at 25°C
	1 in 3.3 at 40°C
	1 in 2.0 at 50°C

Specific rotation $[\alpha]_D^{25}$ = +40° to +50° (1% w/v aqueous solution)

11 Stability and Storage Conditions

Alitame is stable in dry, room temperature conditions but undergoes degradation at elevated temperatures or when in solution at low pH. Alitame can degrade in a one-stage process to aspartic acid and alanine amide (under harsh conditions) or in a slow two-stage process by first degrading to its β-aspartic isomer and then to aspartic acid and alanine amide. At pH 5–8, alitame solutions at 23°C have a half-life of approximately 4 years. At pH 2 and 23°C the half-life is 1 year.

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

12 Incompatibilities

Alitame may be incompatible with oxidizing and reducing substances or strong acids and bases.

13 Method of Manufacture

Alitame may be synthesized by a number of routes.[2,3] For example, 3-(D-alaninamido)-2,2,4,4-tetramethylthietane is dissolved in water and L-aspartic acid *N*-thiocarboxyanhydride is then added in portions with vigorous stirring, maintaining the pH of 8.5–9.5. The pH is then adjusted to 5.5 and *p*-toluenesulfonic acid

monohydrate is added over a period of one hour. The precipitated crystalline *p*-toluenesulfonate salt is collected by filtration. To obtain alitame from its salt, a mixture of *Amberlite LA-1* (liquid anion exchange resin), dichloromethane, deionized water, and the salt is stirred for one hour, resulting in two clear layers. The aqueous layer is treated with carbon, clarified by filtration, and cooled to crystallize alitame.

Alternatively, tetramethylthietane amine is condensed with an *N*-protected form of D-alanine to give alanyl amide. This is then coupled to a protected analogue of L-aspartic acid to give a crude form of alitame. The crude product is then purified.

14 Safety

Alitame is a relatively new intense sweetening agent used primarily in foods and confectionary. It is generally regarded as a relatively nontoxic and nonirritant material.

Chronic animal studies in mice, rats, and dogs carried out for a minimum of 18 months at concentrations >100 mg/kg per day exhibited no toxic or carcinogenic effects. In people, no evidence of untoward effects were observed following ingestion of 15 mg/kg per day for two weeks.

Following oral administration 7–22% of alitame is unabsorbed and excreted in the feces. The remaining amount is hydrolyzed to aspartic acid and alanine amide. The aspartic acid is metabolized normally and the alanine amide excreted in the urine as a sulfoxide isomer, as the sulfone, or conjugated with glucuronic acid.

The WHO has set an acceptable daily intake of alitame at up to 0.1 mg/kg body-weight.[4]

LD_{50} (mouse, oral): >5 g/kg

LD_{50} (rabbit, skin): >2 g/kg

LD_{50} (rat, oral): >5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Alitame should be stored in tightly closed containers, and protected from exposure to direct sunlight and higher than normal room temperatures.

16 Regulatory Status

Alitame is approved for use in food applications in a number of countries worldwide including Australia, Chile, China, Mexico, and New Zealand.

17 Related Substances

Acesulfame potassium; aspartame; saccharin; saccharin sodium; sodium cyclamate.

18 Comments

The PubChem Compound ID (CID) for alitame is 64763.

19 Specific References

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22 Date of Revision

5 August 2008.

Almond Oil

1 Nonproprietary Names

BP: Virgin Almond Oil

PhEur: Almond Oil, Virgin

USP-NF: Almond Oil

2 Synonyms

Almond oil, bitter; amygdalae oleum virginale; artificial almond oil; bitter almond oil; expressed almond oil; huile d'amande; oleo de amêndoas; olio di mandorla; sweet almond oil; virgin almond oil.

3 Chemical Name and CAS Registry Number

Almond oil [8007-69-0]

4 Empirical Formula and Molecular Weight

Almond oil consists chiefly of glycerides of oleic acid, with smaller amounts of linoleic and palmitic acids. The PhEur 6.0 describes almond oil as the fatty oil obtained by cold expression from the ripe seeds of *Prunus dulcis* (Miller) DA Webb var. *dulcis* or *Prunus dulcis* (Miller) DA Webb var. *amara* (DC) Buchheim or a mixture of both varieties. A suitable antioxidant may be added.

The USP32–NF27 describes almond oil as the fixed oil obtained by expression from the kernels of varieties of *Prunus dulcis* (Miller) D.A. Webb (formerly known as *Prunus amygdalus* Batsch) (Fam. Rosaceae) except for *Prunus dolcii* (Miller) D.A. Webb var. *amara* (De (Andolle) Focke).

5 Structural Formula

See Section 4.

A

6 Functional Category

Emollient; oleaginous vehicle; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Almond oil is used therapeutically as an emollient[1] and to soften ear wax. As a pharmaceutical excipient it is employed as a vehicle in parenteral preparations,[2] such as oily phenol injection. It is also used in nasal spray,[3] and topical preparations.[4]Almond oil is also consumed as a food substance; *see* Section 18.

8 Description

A clear, colorless, or pale-yellow colored oil with a bland, nutty taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for almond oil.

Test	PhEur 6.0	USP32–NF27
Identification	+	+
Absorbance	+	—
Acid value	⩽2.0	⩽0.5
Characters	+	—
Peroxide value	⩽15.0	⩽5.0
Saponification value	—	—
Specific gravity	—	0.910–0.915
Unsaponifiable matter	⩽0.9%	⩽0.9%
Composition of fatty acids	+	+
Saturated fatty acids < C_{16}	⩽0.1%	⩽0.1%
Arachidic acid	⩽0.2%	⩽0.2%
Behenic acid	⩽0.2%	⩽0.2%
Eicosenoic acid	⩽0.3%	⩽0.3%
Erucic acid	⩽0.1%	⩽0.1%
Linoleic acid	20.0–30.0%	20.0–30.0%
Linolenic acid	⩽0.4%	⩽0.4%
Margaric acid	⩽0.2%	⩽0.2%
Oleic acid	62.0–86.0%	62.0–76.0%
Palmitic acid	4.0–9.0%	4.0–9.0%
Palmitoleic acid	⩽0.8%	⩽0.8%
Stearic acid	⩽3.0%	⩽3.0%
Sterols	+	+
Δ^5-Avenasterol	⩾10.0%	⩾5.0%
Δ^7-Avenasterol	⩽3.0%	⩽3.0%
Brassicasterol	⩽0.3%	⩽0.3%
Cholesterol	⩽0.7%	⩽0.7%
Campesterol	⩽4.0%	⩽5.0%
Stigmasterol	⩽3.0%	⩽4.0%
β-Sitosterol	73.0–87.0%	73.0–87.0%
Δ^7-Stigmasterol	⩽3.0%	⩽3.0%

10 Typical Properties

Flash point 320°C
Melting point −18°C
Refractive index n_D^{40} = 1.4630–1.4650
Smoke point 220°C
Solubility Miscible with chloroform, and ether; slightly soluble in ethanol (95%).

11 Stability and Storage Conditions

Almond oil should be stored in a well-closed container in a cool, dry place away from direct sunlight and odors. It may be sterilized by heating at 150°C for 1 hour. Almond oil does not easily turn rancid.

12 Incompatibilities

—

13 Method of Manufacture

Almond oil is expressed from the seeds of the bitter or sweet almond, *Prunus dulcis (Prunus amygdalus; Amygdalus communis)* var. *amara* or var. *dulcis* (Rosaceae).[5] *See also* Section 4.

14 Safety

Almond oil is widely consumed as a food and is used both therapeutically and as an excipient in topical and parenteral pharmaceutical formulations, where it is generally regarded as a nontoxic and nonirritant material. However, there has been a single case reported of a 5-month-old child developing allergic dermatitis attributed to the application of almond oil for 2 months to the cheeks and buttocks.[6]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16 Regulatory Status

Included in nonparenteral and parenteral medicines licensed in the UK. Widely used as an edible oil.

17 Related Substances

Canola oil; corn oil; cottonseed oil; peanut oil; refined almond oil; sesame oil; soybean oil.

Refined almond oil

Synonyms Amygdalae oleum raffinatum.
Comments Refined almond oil is defined in some pharmacopeias such as the PhEur 6.0. Refined almond oil is a clear, pale yellow colored oil with virtually no taste or odor. It is obtained by expression of almond seeds followed by subsequent refining. It may contain a suitable antioxidant.

18 Comments

A 100 g quantity of almond oil has a nutritional energy value of 3700 kJ (900 kcal) and contains 100 g of fat of which 28% is polyunsaturated, 64% is monounsaturated and 8% is saturated fat.

Studies have suggested that almond consumption is associated with health benefits, including a decreased risk of colon cancer.[7]

A specification for bitter almond oil is contained in the Food Chemicals Codex (FCC).[8]

19 Specific References

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21 Authors

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22 Date of Revision

12 February 2009.

Alpha Tocopherol

1 Nonproprietary Names

BP: *RRR*-Alpha-Tocopherol

JP: Tocopherol

PhEur: *RRR*-α-Tocopherol

USP: Vitamin E

See also Sections 3, 9, and 17.

2 Synonyms

Copherol F1300; (±)-3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-ol; E307; *RRR*-α-tocopherolum; synthetic alpha tocopherol; all-*rac*-α-tocopherol; *dl*-α-tocopherol; 5,7,8-trimethyltocol.

3 Chemical Name and CAS Registry Number

(±)-(2*RS*,4′*RS*,8′*RS*)-2,5,7,8-Tetramethyl-2-(4′,8′,12′-trimethyltridecyl)-6-chromanol [10191-41-0]

Note that alpha tocopherol has three chiral centers, giving rise to eight isomeric forms. The naturally occurring form is known as *d*-alpha tocopherol or (2*R*,4′*R*,8′*R*)-alpha-tocopherol. The synthetic form, *dl*-alpha tocopherol or simply alpha tocopherol, occurs as a racemic mixture containing equimolar quantities of all the isomers.

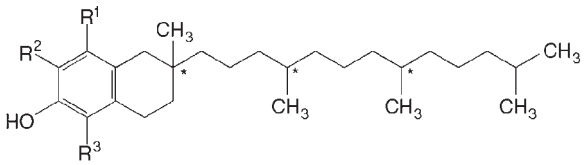
Similar considerations apply to beta, delta, and gamma tocopherol and tocopherol esters.

See Section 17 for further information.

4 Empirical Formula and Molecular Weight

$C_{29}H_{50}O_2$ 430.72

5 Structural Formula



Alpha tocopherol: $R^1 = R^2 = R^3 = CH_3$

Beta tocopherol: $R^1 = R^3 = CH_3$; $R^2 = H$

Delta tocopherol: $R^1 = CH_3$; $R^2 = R^3 = H$

Gamma tocopherol: $R^1 = R^2 = CH_3$; $R^3 = H$

* Indicates chiral centers.

6 Functional Category

Antioxidant; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Alpha tocopherol is primarily recognized as a source of vitamin E, and the commercially available materials and specifications reflect this purpose. While alpha tocopherol also exhibits antioxidant properties, the beta, delta, and gamma tocopherols are considered to be more effective as antioxidants.

Alpha-tocopherol is a highly lipophilic compound, and is an excellent solvent for many poorly soluble drugs.[1–4] Of widespread regulatory acceptability, tocopherols are of value in oil- or fat-based pharmaceutical products and are normally used in the concentration range 0.001–0.05% v/v. There is frequently an optimum concentration; thus the autoxidation of linoleic acid and methyl linolenate is reduced at low concentrations of alpha tocopherol, and is accelerated by higher concentrations. Antioxidant effectiveness can be increased by the addition of oil-soluble synergists such as lecithin and ascorbyl palmitate.[4]

Alpha tocopherol may be used as an efficient plasticizer.[5] It has been used in the development of deformable liposomes as topical formulations.[6]

d-Alpha-tocopherol has also been used as a non-ionic surfactant in oral and injectable formulations.[3]

8 Description

Alpha tocopherol is a natural product. The PhEur 6.0 describes alpha-tocopherol as a clear, colorless or yellowish-brown, viscous, oily liquid. *See also* Section 17.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for alpha tocopherol.

Test	JP XV	PhEur 6.0	USP 32
Identification	+	+	+
Characters	—	+	—
Acidity	—	—	+
Optical rotation	—	+0.05° to +0.10°	+
Heavy metals	⩽20 ppm	—	—
Related substances	—	+	—
Absorbance at 292 nm	+	—	—
Refractive index	71.0–76.0	—	—
Specific gravity	1.503–1.507	—	—
Clarity and color of solution	0.947–0.955	—	—
Assay	+	—	—
	96.0–102.0%	94.5–102.0%	96.0–102.0%

Note that the USP 32 describes vitamin E as comprising *d*- or *dl*-alpha tocopherol, *d*- or *dl*-alpha tocopheryl acetate, or *d*- or *dl*-alpha tocopheryl acid succinate. However, the PhEur 6.0 describes alpha tocopherol and alpha tocopheryl acetate in separate monographs.

The diversity of the tocopherols described in the various pharmacopeial monographs makes the comparison of specifications more complicated; *see* Section 17.

10 Typical Properties

Boiling point 235°C
Density 0.947–0.951 g/cm^3
Flash point 240°C
Ignition point 340°C
Refractive index n_D^{20} = 1.503–1.507
Solubility Practically insoluble in water; freely soluble in acetone, ethanol, ether, and vegetable oils.

11 Stability and Storage Conditions

Tocopherols are oxidized slowly by atmospheric oxygen and rapidly by ferric and silver salts. Oxidation products include tocopheroxide, tocopherylquinone, and tocopherylhydroquinone, as well as dimers and trimers. Tocopherol esters are more stable to oxidation than the free tocopherols but are in consequence less effective antioxidants. *See also* Section 17.

Tocopherols should be stored under an inert gas, in an airtight container in a cool, dry place and protected from light.

12 Incompatibilities

Tocopherols are incompatible with peroxides and metal ions, especially iron, copper, and silver. Tocopherols may be absorbed into plastic.[7]

13 Method of Manufacture

Naturally occurring tocopherols are obtained by the extraction or molecular distillation of steam distillates of vegetable oils; for example, alpha tocopherol occurs in concentrations of 0.1–0.3% in corn, rapeseed, soybean, sunflower, and wheat germ oils.[8] Beta and gamma tocopherol are usually found in natural sources along with alpha tocopherol. Racemic synthetic tocopherols may be prepared by the condensation of the appropriate methylated hydroquinone with racemic isophytol.[9]

14 Safety

Tocopherols (vitamin E) occur in many food substances that are consumed as part of the normal diet. The daily nutritional requirement has not been clearly defined but is estimated to be 3.0–20.0 mg. Absorption from the gastrointestinal tract is dependent upon normal pancreatic function and the presence of bile. Tocopherols are widely distributed throughout the body, with some ingested tocopherol metabolized in the liver; excretion of metabolites is via the urine or bile. Individuals with vitamin E deficiency are usually treated by oral administration of tocopherols, although intramuscular and intravenous administration may sometimes be used.

Tocopherols are well tolerated, although excessive oral intake may cause headache, fatigue, weakness, digestive disturbance, and nausea. Prolonged and intensive skin contact may lead to erythema and contact dermatitis.

The use of tocopherols as antioxidants in pharmaceuticals and food products is unlikely to pose any hazard to human health since the daily intake from such uses is small compared with the intake of naturally occurring tocopherols in the diet.

The WHO has set an acceptable daily intake of tocopherol used as an antioxidant at 0.15–2.0 mg/kg body-weight.[10]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Gloves and eye protection are recommended.

16 Regulatory Status

GRAS listed. Accepted in Europe as a food additive. Included in the FDA Inactive Ingredients Database (IV injections, powder, lyophilized powder for liposomal suspension; oral capsules, tablets, and topical preparations). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in nonparenteral medicines licensed in the UK.

17 Related Substances

d-Alpha tocopherol; *d*-alpha tocopheryl acetate; *dl*-alpha tocopheryl acetate; *d*-alpha tocopheryl acid succinate; *dl*-alpha tocopheryl acid succinate; beta tocopherol; delta tocopherol; gamma tocopherol; tocopherols excipient.

d-Alpha tocopherol

Empirical formula $C_{29}H_{50}O_2$
Molecular weight 430.72
CAS number [59-02-9]
Synonyms Natural alpha tocopherol; (+)-(2*R*,4′*R*,8′*R*)-2,5,7,8-tetramethyl-2-(4′,8′,12′-trimethyltridecyl)-6-chromanol; *d*-α-tocopherol; vitamin E.
Appearance A practically odorless, clear, yellow, or greenish-yellow viscous oil.
Melting point 2.5–3.5°C
Solubility Practically insoluble in water; soluble in ethanol (95%). Miscible with acetone, chloroform, ether, and vegetable oils.
Specific gravity 0.95
Comments *d*-Alpha tocopherol is the naturally occurring form of alpha tocopherol.

d-Alpha tocopheryl acetate

Empirical formula $C_{31}H_{52}O_3$
Molecular weight 472.73
CAS number [58-95-7]
Synonyms (+)-(2*R*,4′*R*,8′*R*)-2,5,7,8-Tetramethyl-2-(4′,8′,12′- trimethyltridecyl)-6-chromanyl acetate; *d*-α-tocopheryl acetate; vitamin E.
Appearance A practically odorless, clear, yellow, or greenish-yellow colored viscous oil that may solidify in the cold.
Melting point 28°C
Solubility Practically insoluble in water; soluble in ethanol (95%). Miscible with acetone, chloroform, ether, and vegetable oils.
Specific rotation $[\alpha]_D^{25}$ = +0.25° (10% w/v solution in chloroform)
Comments Unstable to alkalis.

dl-Alpha tocopheryl acetate

Empirical formula $C_{31}H_{52}O_3$
Molecular weight 472.73
CAS number [7695-91-2]
Synonyms (±)-3,4-Dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-ol acetate; (±)-(2*RS*,4′*RS*,8′*RS*)-2,5,7,8-tetramethyl-2-(4′,8′,12′-trimethyltridecyl)-6-chromanyl acetate; (±)-α-tocopherol acetate; α-tocopheroli acetas; all-*rac*-α-tocopheryl acetate; *dl*-α-tocopheryl acetate; vitamin E.
Appearance A practically odorless, clear, yellow, or greenish-yellow viscous oil.
Density 0.953 g/cm^3
Melting point –27.5°C
Refractive index n_D^{20} = 1.4950–1.4972
Solubility Practically insoluble in water; freely soluble in acetone, chloroform, ethanol, ether, and vegetable oils; soluble in ethanol (95%).
Comments Unstable to alkali. However, unlike alpha tocopherol, the acetate is much less susceptible to the effects of air, light, or

ultraviolet light. Alpha tocopherol acetate concentrate, a powdered form of alpha tocopherol acetate, is described in the PhEur 6.0. The concentrate may be prepared by either dispersing alpha tocopherol acetate in a suitable carrier such as acacia or gelatin, or by adsorbing alpha tocopherol acetate on silicic acid.

d-Alpha tocopheryl acid succinate

Empirical formula $C_{33}H_{54}O_5$
Molecular weight 530.8
CAS number [4345-03-3]
Synonyms (+)-α-Tocopherol hydrogen succinate; *d*-α-tocopheryl acid succinate; vitamin E.
Appearance A practically odorless white powder.
Melting point 76–77°C
Solubility Practically insoluble in water; slightly soluble in alkaline solutions; soluble in acetone, ethanol (95%), ether, and vegetable oils; very soluble in chloroform.
Comments Unstable to alkalis.

dl-Alpha tocopheryl acid succinate

Empirical formula $C_{33}H_{54}O_5$
Molecular weight 530.8
CAS number [17407-37-3]
Synonyms (±)-α-Tocopherol hydrogen succinate; *dl*-α-tocopheryl acid succinate; *dl*-α-tocopherol succinate; vitamin E.
Appearance A practically odorless, white crystalline powder.
Solubility Practically insoluble in water; slightly soluble in alkaline solutions; soluble in acetone, ethanol (95%), ether, and vegetable oils; very soluble in chloroform.
Comments Unstable to alkalis.

Beta tocopherol

Empirical formula $C_{28}H_{48}O_2$
Molecular weight 416.66
CAS number [148-03-8]
Synonyms Cumotocopherol; (±)-3,4-dihydro-2,5,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-β-benzopyran-6-ol; 5,8-dimethyltocol; neotocopherol; *dl*-β-tocopherol; vitamin E; *p*-xylotocopherol.
Appearance A pale yellow-colored viscous oil.
Solubility Practically insoluble in water; freely soluble in acetone, chloroform, ethanol (95%), ether, and vegetable oils.
Specific rotation $[\alpha]_D^{20} = +6.37°$
Comments Less active biologically than alpha tocopherol. Obtained along with alpha tocopherol and gamma tocopherol from natural sources. Beta tocopherol is very stable to heat and alkalis and is slowly oxidized by atmospheric oxygen.

Delta tocopherol

Empirical formula $C_{27}H_{46}O_2$
Molecular weight 402.64
CAS number [119-13-1]
Synonyms (±)-3,4-Dihydro-2,8-dimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-ol; E309; 8-methyltocol; *dl*-δ-tocopherol; vitamin E.
Appearance A pale yellow-colored viscous oil.
Solubility Practically insoluble in water; freely soluble in acetone, chloroform, ethanol (95%), ether, and vegetable oils.
Comments Occurs naturally as 30% of the tocopherol content of soybean oil. Delta tocopherol is said to be the most potent antioxidant of the tocopherols.

Gamma tocopherol

Empirical formula $C_{28}H_{48}O_2$
Molecular weight 416.66
CAS number [7616-22-0]
Synonyms (±)-3,4-Dihydro-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-ol; 7,8-dimethyltocol; E308; *dl*-γ-tocopherol; vitamin E; *o*-xylotocopherol.
Appearance A pale yellow-colored viscous oil.
Melting point –30°C
Solubility Practically insoluble in water; freely soluble in acetone, chloroform, ethanol (95%), ether, and vegetable oils.
Specific rotation $[\alpha]_D^{20} = -2.4°$ (in ethanol (95%))
Comments Occurs in natural sources along with alpha and beta tocopherol. Gamma tocopherol is biologically less active than alpha tocopherol. Very stable to heat and alkalis; slowly oxidized by atmospheric oxygen and gradually darkens on exposure to light.

Tocopherols excipient

Synonyms *Embanox tocopherol*.
Appearance A pale yellow-colored viscous oil.
Comments Tocopherols excipient is described in the USP32–NF27 as a vegetable oil solution containing not less than 50.0% of total tocopherols, of which not less than 80.0% consists of varying amounts of beta, delta, and gamma tocopherols.

18 Comments

Note that most commercially available tocopherols are used as sources of vitamin E, rather than as antioxidants in pharmaceutical formulations.

Various mixtures of tocopherols, and mixtures of tocopherols with other excipients, are commercially available, and individual manufacturers should be consulted for specific information on their products.

Molecularly imprinted polymers for use in the controlled release of alpha tocopherol in gastrointestinal simulating fluids have been investigated.[T1]

The EINECS number for α-tocopherol is 215-798-8. The EINECS number for *d*-α-tocopherol is 200-412-2; and the EINECS number for *dl*-α-tocopherol is 233-466-0. The PubChem Compound ID (CID) for alpha tocopherol includes 14985 and 1548900.

19 Specific References

1 Nielsen PB *et al*. The effect of α-tocopherol on the *in vitro* solubilisation of lipophilic drugs. *Int J Pharm* 2001; **222**: 217–224.
2 Constantinides PP *et al*. Tocol emulsions for drug solubilization and parenteral delivery. *Adv Drug Delivery* 2004; **56**(9): 1243–1255.
3 Strickley RG. Solubilizing excipients in oral and injectable formulations. *Pharm Res* 2004; **21**(2): 201–230.
4 Johnson DM, Gu LC. Autoxidation and antioxidants. Swarbrick J, Boylan JC, eds. *Encyclopedia of Pharmaceutical Technology.*, vol. **1**: New York: Marcel Dekker, 1988; 415–450.
5 Kangarlou S *et al*. Physico-mechanical analysis of free ethyl cellulose films comprised with novel plasticizers of vitamin resources. *Int J Pharm* 2008; **356**: 153–166.
6 Gallarate M *et al*. Deformable liposomes as topical formulations containing alpha-tocopherol. *J Dispers Sci Technol* 2006; **27**: 703–713.
7 Allwood MC. Compatibility and stability of TPN mixtures in big bags. *J Clin Hosp Pharm* 1984; **9**: 181–198.
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9 Rudy BC, Senkowski BZ. *dl*-Alpha-tocopheryl acetate. Florey K, ed. *Analytical Profiles of Drug Substances*., vol. **3**: New York: Academic Press, 1974; 111–126.
10 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.
11 Puoci F *et al*. Molecularly imprinted polymers for alpha-tocopherol delivery. *Drug Deliv* 2008; **15**: 253–258.

20 General References

US National Research Council Food and Nutrition Board. *Recommended Dietary Allowances*, 10th edn. Washington DC: National Academy Press, 1989; 99–105.

21 Author

ME Quinn.

22 Date of Revision

28 January 2009.

Aluminum Hydroxide Adjuvant

1 Nonproprietary Names

PhEur: Aluminium Hydroxide, Hydrated, for Adsorption

2 Synonyms

Alhydrogel; aluminii hydroxidum hydricum ad adsorptionem; aluminium hydroxide adjuvant; aluminium oxyhydroxide; poorly crystalline boehmite; pseudoboehmite; *Rehydragel*.

3 Chemical Name and CAS Registry Number

Aluminum oxyhydroxide [21645-51-2]

4 Empirical Formula and Molecular Weight

AlO(OH) 59.99

5 Structural Formula

Structural hydroxyl groups form hydrogen bonds between AlO(OH) octahedral sheets, where hydroxyl groups are exposed at the surface. The surface hydroxyl groups produce a pH-dependent surface charge by accepting a proton to produce a positive site, or donating a proton to produce a negative site. The pH-dependent surface charge is characterized by the point of zero charge, which is equivalent to the isoelectric point in protein chemistry. The surface hydroxyl groups may also undergo ligand exchange with fluoride, phosphate, carbonate, sulfate, or borate anions.

6 Functional Category

Adsorbent; vaccine adjuvant.

7 Applications in Pharmaceutical Formulation or Technology

Aluminum hydroxide adjuvant is used in parenteral human and veterinary vaccines.[1] It activates Th2 immune responses, including IgG and IgE antibody responses. It is also used for the isolation of certain serum components such as blood clotting factors.[2]

8 Description

Aluminum hydroxide adjuvant is a white hydrogel that sediments slowly and forms a clear supernatant.

9 Pharmacopeial Specifications

See Table I. Note that the USP 32 includes a monograph for aluminum hydroxide gel, which is a form of aluminum hydroxide that is used as an antacid, in which there is a partial substitution of carbonate for hydroxide.

See Section 17.

Table I: Pharmacopeial specifications for aluminum hydroxide adjuvant.

Test	PhEur 6.1
Identification	+
Characters	+
Solution	+
pH	5.5–8.5
Adsorption power	+
Sedimentation	+
Chlorides	⩽0.33%
Nitrates	⩽100 ppm
Sulfates	⩽0.5%
Ammonium	⩽50 ppm
Arsenic	⩽1 ppm
Iron	⩽5 ppm
Heavy metals	⩽20 ppm
Bacterial endotoxins	+
Assay	90.0–110.0%

10 Typical Properties

Acidity/alkalinity pH = 5.5–8.5

Particle size distribution Primary particles are fibrous with average dimensions of 4.5 × 2.2 × 10 nm. The primary particles form aggregates of 1–10 μm.

Point of zero charge pH = 11.4

Protein binding capacity >0.5 mg BSA/mg equivalent Al_2O_3

Solubility Soluble in alkali hydroxides and mineral acids. Heat may be required to dissolve the aluminum hydroxide adjuvant.

Specific surface area 500 m^2/g.[3]

X-ray diffractogram Exhibits characteristic x-ray diffraction pattern having diffraction bands at 6.46, 3.18, 2.35, 1.86, 1.44 and 1.31 Å.

11 Stability and Storage Conditions

Aluminum hydroxide adjuvant is stable for at least 2 years when stored at 4–30°C in well-sealed inert containers. It must not be allowed to freeze as the hydrated colloid structure will be irreversibly damaged.

12 Incompatibilities

When exposed to phosphate, carbonate, sulfate, or borate anions, the point of zero charge for aluminum hydroxide adjuvant decreases.

13 Method of Manufacture

Aluminum hydroxide adjuvant is prepared by the precipitation of a soluble aluminum salt by an alkali hydroxide, or the precipitation of an alkali aluminate by acid.

14 Safety

Aluminum hydroxide adjuvant is intended for use in parenteral vaccines and is generally regarded as nontoxic. It may cause mild irritation, dryness, and dermatitis on skin contact. On eye contact, aluminum hydroxide adjuvant may also cause redness, conjunctivitis, and short-term mild irritation. Ingestion of large amounts may cause gastrointestinal irritation with nausea, vomiting, and constipation. Inhalation of the dried product may cause respiratory irritation and cough. Type I hypersensitivity reactions following parenteral administration have been reported.[4]

15 Handling Precautions

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

16 Regulatory Status

GRAS listed. Accepted for use in human and veterinary parenteral vaccines in Europe and the USA. The limits for use in human vaccines are 0.85 mg aluminum/dose (FDA) and 1.25 mg aluminum/dose (WHO). There are no established limits for use in veterinary vaccines. Reported in the EPA TSCA Inventory.

17 Related Substances

Aluminum phosphate adjuvant.

18 Comments

Different grades of aluminum hydroxide adjuvant with various concentrations, protein binding capacities, and points of zero charge are available.

The impurity limits at 2% equivalent Al_2O_3 are Cl < 0.5%; SO_4 < 0.5%; PO_4 < 0.1%; NO_3 < 0.1%; NH_4 < 0.1%; Fe < 20 ppm; As < 0.6 ppm; and heavy metals < 20 ppm.

The aluminum hydroxide gel referred to in the USP 32 is used in cosmetics as an emollient, filler, humectant, a mild astringent, and viscosity controlling agent. In pharmaceutical preparations it is used as an adsorbent, and as a protein binder.[5] It is also used therapeutically as an antacid, and as an abrasive in dentrifrices. It is not, however, used as a vaccine adjuvant.

19 Specific References

1 Shirodkar S *et al*. Aluminum compounds used as adjuvants in vaccines. *Pharm Res* 1990; **7**: 1282–1288.

2 Prowse CV *et al*. Changes in factor VIII complex activities during the production of a clinical intermediate purity factor VIII concentrate. *Thromb Haemost* 1981; **46**: 597–601.

3 Johnston CT *et al*. Measuring the surface area of aluminum hydroxide adjuvant. *J Pharm Sci* 2002; **91**: 1702–1706.

4 Goldenthal KL *et al*. Safety evaluation of vaccine adjuvants. *AIDS Res Hum Retroviruses* 1993; **9**(Suppl. 1): S47–S51.

5 Ash M, Ash I. *Handbook of Pharmaceutical Additives*, 3rd edn. Endicott, NY: Synapse Information Resources, 2007; 446.

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White JL, Hem SL. Characterization of aluminum-containing adjuvants. Brown F *et al*, ed. *Physico-Chemical Procedures for the Characterization of Vaccines*.IABS Symposia Series, Development in Biologicals, vol. **103**: New York: Karger, 2000; 217–228.

21 Authors

SL Hem, PB Klepak, EB Lindblad.

22 Date of Revision

19 February 2009.

Aluminum Monostearate

1 Nonproprietary Names

JP: Aluminum Monostearate

USP-NF: Aluminum Monostearate

2 Synonyms

Aluminum stearate; aluminum, dihydroxy (octadecanoate-O-); dihydroxyaluminum monostearate; *HyQual*; octadecanoic acid aluminum salt; stearic acid aluminum salt; stearic acid aluminum dihydroxide salt; *Synpro*.

3 Chemical Name and CAS Registry Number

Aluminum monostearate [7047-84-9]

4 Empirical Formula and Molecular Weight

$C_{18}H_{37}AlO_4$ 344.50

5 Structural Formula

$[CH_3(CH_2)_{16}COO]Al(OH)_2$

6 Functional Category

Emollient; emulsion stabilizer; gelling agent; opacifier; stabilizing agent.

7 Applications in Pharmaceutical Formulation or Technology

Aluminum monostearate is mainly used in microencapsulation[1-3] and in the manufacture of ointments. Aluminum monostearate is used as a viscosity-increasing agent in nonaqueous cosmetic and pharmaceutical formulations. In addition, aluminum monostearate can be used as an emulsion stabilizer in cosmetic emulsions and is used in cosmetics such as mascara, moisturizers, and sunscreens.

8 Description

Aluminum monostearate is an aluminum compound of stearic acid and palmitic acid. The USP32–NF27 states that aluminum monostearate contains the equivalent of not less than 14.5% and not more than 16.5% of Al_2O_3, calculated on the dried basis. The JP XV states that it contains not less than 7.2% and not more than 8.9% of aluminium.

Aluminum monostearate occurs as a white, fine, bulky powder with a slight odor of fatty acid. It is a solid material.

9 Pharmacopeial Specifications

See Table I. *See also* Section 18.

Table I: Pharmacopeial specifications for aluminum monostearate.

Test	JP XV	USP32–NF27
Identification	+	+
Description	⩽3.0%	⩽2.0%
Loss on drying	+	—
Arsenic	⩽2 ppm	⩽4 ppm
Heavy metals	⩽50 ppm	⩽50 ppm
Acid value for fatty acid	+	—
Free fatty acid	+	—
Water-soluble salts	⩽10 mg	—
Assay of Al (dried basis)	7.2–8.9%	14.5–16.5%

10 Typical Properties

See Table II.
Melting point 220–225°C
Solubility Practically insoluble in water. Soluble in ethanol (95%) and benzene.
Specific gravity 1.14

Table II: Typical physical properties of slected commercially available aluminum monostearates.

Grade	Assay (as Al_2O_3) (%)	Loss on drying (%)	Median particle size (μm)
Synpro Aluminum Monostearate NF	15.5	0.8	7.0
Synpro Aluminum Monostearate NF Gellant	15.3	1.6	—
HyQual Aluminum Monostearate NF Powder	14.5–16.5	⩽2.0	—
HyQual Aluminum Monostearate NF Fine Powder	14.5–16.5	⩽2.0	—

11 Stability and Storage Conditions

Aluminum monostearate should be stored in a well-closed container in a cool, dry, place. It is stable under ordinary conditions of use and storage.

12 Incompatibilities

—

13 Method of Manufacture

Aluminum monostearate is prepared by reacting aluminum with stearic acid.

14 Safety

Aluminum monostearate is generally regarded as relatively nontoxic and nonirritant when used as an excipient.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. When heated to decomposition, aluminum monostearate emits acrid smoke and irritating vapors.

16 Regulatory Status

Aluminum monostearate and aluminum stearate are included in the FDA Inactive Ingredients Database (oral capsules and tablets, topical creams and ointments). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Aluminum distearate; aluminum tristearate.

Aluminum distearate

Empirical formula $C_{36}H_{37}AlO_5$
Molecular weight 877.39
CAS number [300-92-5]
Synonyms Hydroxyaluminum distearate; aluminum stearate; aluminum monobasic stearate.
Description Aluminum distearate occurs as a fine white to off-white colored powder with a slight odor of fatty acid.
Melting point 150–165°C
Specific gravity 1.01
Solubility Soluble in benzene, and in ethanol (95%); practically insoluble in water.
Comments The EINECS number for aluminum distearate is 206-101-8.

Aluminum tristearate

Empirical formula $C_{54}H_{105}AlO_6$
Molecular weight 610.9
CAS number [637-12-7]
Synonyms Hydroxyaluminum tristearate; aluminum stearate.
Description Aluminum tristearate occurs as a fine white to off-white colored powder with a slight odor of fatty acid.
Melting point 117–120°C
Specific gravity 1.01
Solubility Practically insoluble in water. Soluble in ethanol (95%), benzene, turpentine oil, and mineral oils when freshly prepared.
Comments The EINECS number for aluminum tristearate is 211-279-5.

18 Comments

A specification for aluminum stearate, described as consisting mainly of the distearate, is included in the *Japanese Pharmaceutical Excipients* (JPE).[4]

It should be noted that aluminum stearate can also refer to the distearate (CAS number 300-92-5) and the monostearate (CAS number 7047-84-9) in addition to the tristearate (CAS number 637-12-7). The distearate exhibits the same excipient properties as the tristearate and is used in similar pharmaceutical applications. However, the monostearate is more widely used in both cosmetic and pharmaceutical preparations.

The EINECS number for aluminum monostearate is 230-325-5.

19 Specific References

1 Horoz BB *et al.* Effect of different dispersing agents on the characteristics of *Eudragit* microspheres prepared by a solvent evaporation method. *J Microencapsul* 2004; **21**: 191–202.
2 Wu PC *et al.* Preparation and evaluation of sustained release microspheres of potassium chloride prepared with ethylcellulose. *Int J Pharm* 2003; **260**: 115–121.
3 Wu PC *et al.* Design and evaluation of sustained release microspheres of potassium chloride prepared by *Eudragit*. *Eur J Pharm Sci* 2003; **19**: 115–122.
4 Japan Pharmaceutical Excipients Council. *Japanese Pharmaceutical Excipients 2004*. Tokyo: Yakuji Nippo, 2004; 74–75.

20 General References

Ferro Corporation. Technical literature: *Synpro Aluminum Monostearate NF*, 2008.
Mallinckrodt. Technical literature: *HyQual* Aluminum stearate, 2008.

21 Author

J Shur.

22 Date of Revision

19 February 2009.

Aluminum Oxide

1 Nonproprietary Names

None adopted.

2 Synonyms

Activated alumina; activated aluminum oxide; alpha aluminum oxide; alumina; alumina, calcined; alumina, tabular; aluminum oxide alumite; aluminum trioxide; gamma aluminum oxide.

3 Chemical Name and CAS Registry Number

Aluminum oxide [1344-28-1]

4 Empirical Formula and Molecular Weight

Al_2O_3 101.96

5 Structural Formula

Aluminum oxide occurs naturally as the minerals bauxite, bayerite, boehmite, corundum, diaspore, and gibbsite.

6 Functional Category

Adsorbent; dispersing agent.

7 Applications in Pharmaceutical Formulation or Technology

Aluminum oxide is used mainly in tablet formulations.[1] It is used for decoloring powders and is particularly widely used in antibiotic formulations. It is also used in suppositories, pessaries, and urethral inserts. Hydrated aluminum oxide (*see* Section 18) is used in mordant dyeing to make lake pigments, in cosmetics, and therapeutically as an antacid.

8 Description

Aluminum oxide occurs as a white crystalline powder. Aluminum oxide occurs as two crystalline forms: α-aluminum oxide is composed of colorless hexagonal crystals, and γ-aluminum oxide is composed of minute colorless cubic crystals that are transformed to the α-form at high temperatures.

9 Pharmacopeial Specifications

See Section 18.

10 Typical Properties

Boiling point 2977°C
Density (bulk) 0.9–1.1 g/cm^3
Flammability Nonflammable.
Hardness (Mohs) 8.8
Hygroscopicity Very hygroscopic.
Melting point 2050°C
Solubility Slowly soluble in aqueous alkaline solutions with the formation of hydroxides; practically insoluble in nonpolar organic solvents, diethyl ether, ethanol (95%), and water.
Specific gravity 2.8 (becomes 4.0 at 800°C)
Vapor pressure 133.3 Pa at 2158°C

11 Stability and Storage Conditions

Aluminum oxide should be stored in a well-closed container in a cool, dry, place. It is very hygroscopic.

12 Incompatibilities

Aluminum oxide should be kept well away from water. It is incompatible with strong oxidizers and chlorinated rubber. Aluminum oxide also reacts with chlorine trifluoride, ethylene oxide, sodium nitrate, and vinyl acetate. Exothermic reactions above 200°C with halocarbon vapors produce toxic hydrogen chloride and phosgene fumes.

13 Method of Manufacture

Most of the aluminum oxide produced commercially is obtained by the calcination of aluminum hydroxide.

14 Safety

Aluminum oxide is generally regarded as relatively nontoxic and nonirritant when used as an excipient. Inhalation of finely divided particles may cause lung damage (Shaver's disease).[2]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled.[3] In the UK, the workplace exposure limits for aluminum oxide are 10 mg/m^3 long-term (8-hour TWA) for total inhalable dust and 4 mg/m^3 for respirable dust.[4] In the USA, the OSHA limit is 15 mg/m^3 total dust, 5 mg/m^3 respirable fraction for aluminium oxide.[5]

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (oral tablets and topical sponge). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

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18 Comments

A specification for aluminum oxide is included in the *Japanese Pharmaceutical Excipients* (JPE);[6] *see* Table I. A specification for

light aluminum oxide is also included. The PhEur 6.3 includes a specification for hydrated aluminum oxide that contains the equivalent of 47.0–60.0% of Al_2O_3.

The EINECS number for aluminum oxide is 215-691-6.

Table I: JPE specification for aluminum oxide.[6]

Test	JPE 2004
Identification	+
Water-soluble substances	+
Heavy metals	⩽30 ppm
Lead	⩽30 ppm
Arsenic	⩽5 ppm
Loss on drying	⩽1.5%
Loss on ignition	⩽2.5%
Assay	⩾96.0%

19 Specific References

1 Rupprecht H. Processing of potent substances with inorganic supports by imbedding and coating. *Acta Pharm Technol* 1980; **26**: 13–27.

2 Lewis RJ, ed. *Sax's dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 136.

3 National Poisons Information Service 1997. Aluminium oxide. http://www.intox.org/databank/documents/chemical/alumoxde/ukpid33.htm (accessed 16 January 2009)

4 Health and Safety Executive. *EH40/2005: Workplace Exposure Limits*. Sudbury: HSE Books, 2005 (updated 2007). http://www.hse.gov.uk/coshh/table1.pdf (accessed 5 February 2009).

5 JT Baker (2007). Material safety data sheet: Aluminium oxide. http://www.jtbaker.com/msds/englishhtml/a2844.htm (accessed 5 February 2009).

6 Japan Pharmaceutical Excipients Council. *Japanese Pharmaceutical Excipients 2004*. Tokyo: Yakuji Nippo, 2004; 67–68.

20 General References

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21 Author

T Farrell.

22 Date of Revision

5 February 2009.

Aluminum Phosphate Adjuvant

1 Nonproprietary Names

None adopted.

2 Synonyms

Adju-Phos; aluminum hydroxyphosphate; aluminium hydroxyphosphate; *Rehydraphos*.

3 Chemical Name and CAS Registry Number

Aluminum phosphate [7784-30-7]

4 Empirical Formula and Molecular Weight

$Al(OH)_x(PO_4)_y$

The molecular weight is dependent on the degree of substitution of phosphate groups for hydroxyl groups.

5 Structural Formula

Aluminum phosphate adjuvant occurs as a precipitate of amorphous aluminum hydroxide in which some sites contain phosphate groups instead of hydroxyl. Both hydroxyl and phosphate groups are exposed at the surface. The hydroxyl groups produce a pH-dependent surface charge by accepting a proton to produce a positive site, or donating a proton to produce a negative site. The pH-dependent surface charge is characterized by the point of zero charge, which is equivalent to the isoelectric point in protein chemistry. The surface hydroxyl groups may also undergo ligand exchange with fluoride, phosphate, carbonate, sulfate, or borate anions.

Aluminum phosphate adjuvant is not a stoichiometric compound. Rather, the degree of phosphate group substitution for hydroxyl groups depends on the precipitation recipe and conditions.

6 Functional Category

Adsorbent; vaccine adjuvant.

7 Applications in Pharmaceutical Formulation or Technology

Aluminum phosphate adjuvant is used in parenteral human and veterinary vaccines.[1] It activates Th2 immune responses, including IgG and IgE antibody responses.

8 Description

Aluminum phosphate adjuvant is a white hydrogel that sediments slowly and forms a clear supernatant.

9 Pharmacopeial Specifications

—

10 Typical Properties

Acidity/alkalinity pH = 6.0–8.0
Al : P atomic ratio 1.0–1.4 : 1.0
Aluminum (%) 0.5–0.75
Particle size distribution Primary particles are platy with an average diameter of 50 nm. The primary particles form aggregates of 1–10 µm.
Point of zero charge pH = 4.6–5.6, depending on the Al : P atomic ratio.
Protein binding capacity >0.6 mg lysozyme/mg equivalent Al_2O_3
Solubility Soluble in mineral acids and alkali hydroxides.
X-ray diffractogram Amorphous to x-rays.

11 Stability and Storage Conditions

Aluminum phosphate adjuvant is stable for at least 2 years when stored at 4–30°C in well-sealed inert containers. It must not be

allowed to freeze as the hydrated colloid structure will be irreversibly damaged.

12 Incompatibilities

The point of zero charge is related directly to the Al : P atomic ratio. Therefore, the substitution of additional phosphate groups for hydroxyl groups will lower the point of zero charge. Substitution of carbonate, sulfate, or borate ions for hydroxyl groups will also lower the point of zero charge.

13 Method of Manufacture

Aluminum phosphate adjuvant is formed by the reaction of a solution of aluminum chloride and phosphoric acid with alkali hydroxide.

14 Safety

Aluminum phosphate adjuvant is intended for use in parenteral vaccines and is generally regarded as safe. It may cause mild irritation, dryness, and dermatitis on skin contact. It may also cause redness, conjunctivitis, and short-term mild irritation on eye contact. Ingestion of large amounts of aluminum phosphate adjuvant may cause respiratory irritation with nausea, vomiting, and constipation. Inhalation is unlikely, although the dried product may cause respiratory irritation and cough. Type I hypersensitivity reactions following parenteral administration have also been reported.[(2)]

15 Handling Precautions

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

16 Regulatory Status

GRAS listed. Accepted for use in human and veterinary vaccines in Europe and the USA. The limits for use in human vaccines are 0.85 mg aluminum/dose (FDA) and 1.25 mg aluminum/dose (WHO). There are no established limits for use in veterinary vaccines. Reported in the EPA TSCA Inventory.

17 Related Substances

Aluminum hydroxide adjuvant.

18 Comments

The USP 32 monograph for aluminum phosphate ($AlPO_4$) gel describes aluminum phosphate, which is used as an antacid, not as a vaccine adjuvant.

19 Specific References

1 Shirodkar S *et al*. Aluminum compounds used as adjuvants in vaccines. *Pharm Res* 1990; **7**: 1282–1288.

2 Goldenthal KL *et al*. Safety evaluation of vaccine adjuvants. *AIDS Res Hum Retroviruses* 1993; **9**: S47–S51.

20 General References

Hem SL, Hogenesch H. Aluminum-containing adjuvants: properties, formulation, and use. Singh M, ed. *Vaccine Adjuvants and Delivery Systems*. New York: Wiley, 2007; 81–114.

Gupta RK *et al*. Adjuvant properties of aluminum and calcium compounds. Powell MF, Newman MJ, eds. *Vaccine Design*. New York: Plenum, 1995; 229–248.

Lindblad EB. Aluminum adjuvants – in retrospect and prospect. *Vaccine* 2004; **22**: 3658–3668.

Lindblad EB. Aluminum adjuvants. Stewart-Tull DES, ed. *The Theory and Practical Application of Adjuvants*. New York: Wiley, 1995; 21–35.

Vogel FR, Hem SL. Immunogenic adjuvants. Plotkin SA *et al*, ed. *Vaccines*, 5th edn. New York: W.B. Saunders, 2008; 59–71.

Vogel FR, Powell MF. A compendium of vaccine adjuvants and excipients. Powell MF, Newman MJ, eds. *Vaccine Design*. New York: Plenum, 1995; 142.

White JL, Hem SL. Characterization of aluminum-containing adjuvants. Brown F *et al*, ed. *Physico-Chemical Procedures for the Characterization of Vaccines*.IABS Symposia Series: Developments in Biologicals, vol. **103**: New York: Karger, 2000; 217–228.

21 Authors

SL Hem, PB Klepak, EB Lindblad.

22 Date of Revision

19 February 2009.

Ammonia Solution

1 Nonproprietary Names

BP: Strong Ammonia Solution

PhEur: Ammonia Solution, Concentrated

USP-NF: Strong Ammonia Solution

2 Synonyms

Ammoniaca; ammoniacum; ammoniae solution concentrata; aqua ammonia; concentrated ammonia solution; spirit of hartshorn; stronger ammonia water.

3 Chemical Name and CAS Registry Number

Ammonia [7664-41-7]

4 Empirical Formula and Molecular Weight

NH_3 17.03

5 Structural Formula

See Section 4.

6 Functional Category

Alkalizing agent.

7 Applications in Pharmaceutical Formulation or Technology

Ammonia solution is typically not used undiluted in pharmaceutical applications. Generally, it is used as a buffering agent or to adjust the pH of solutions. Most commonly, ammonia solution (the

concentrated form) is used to produce more dilute ammonia solutions.

Therapeutically, dilute ammonia solution is used as a reflex stimulant in 'smelling salts', as a rubefacient, and as a counter-irritant to neutralize insect bites or stings.[1]

8 Description

Strong ammonia solution occurs as a clear, colorless liquid having an exceedingly pungent, characteristic odor. The PhEur 6.0 states that concentrated ammonia solution contains not less than 25.0% and not more than 30.0% w/w of ammonia (NH_3). The USP32–NF27 states that strong ammonia solution contains not less than 27.0% and not more than 31.0% w/w of ammonia (NH_3).

See also Section 17.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for ammonia solution.

Test	PhEur 6.0	USP32–NF27
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Oxidizable substances	+	+
Pyridine and related substances	⩽2 ppm	—
Carbonates	⩽60 ppm	—
Chlorides	⩽1 ppm	—
Sulfates	⩽5 ppm	—
Iron	⩽0.25 ppm	—
Heavy metals	⩽1 ppm	⩽0.0013%
Residue on evaporation	⩽20 mg/L	—
Limit of nonvolatile residue	—	⩽0.05%
Assay (of NH_3)	25.0–30.0%	27.0–31.0%

10 Typical Properties

Solubility Miscible with ethanol (95%) and water.
Specific gravity 0.892–0.910

11 Stability and Storage Conditions

On exposure to the air, ammonia solution rapidly loses ammonia. Ammonia solution should be stored in a well-closed container, protected from the air, in a cool, dry place. The storage temperature should not exceed 20°C.

12 Incompatibilities

Ammonia solution reacts vigorously with sulfuric acid or other strong mineral acids and the reaction generates considerable heat; the mixture boils.

13 Method of Manufacture

Ammonia is obtained commercially chiefly by synthesis from its constituent elements, nitrogen and hydrogen, which are combined under high pressure and temperature in the presence of a catalyst. Ammonia solution is produced by dissolving ammonia gas in water.

14 Safety

Ingestion of strong solutions of ammonia is very harmful and causes severe pain in the mouth, throat, and gastrointestinal tract as well as severe local edema with cough, vomiting, and shock. Burns to the esophagus and stomach may result in perforation. Inhalation of the vapor causes sneezing, coughing, and, in high concentration, pulmonary edema. Asphyxia has been reported. The vapor is irritant to the eyes. Strong solutions are harmful when applied to the conjunctiva and mucous membranes. Topical application of even dilute ammonia solutions, used to treat insect bites, has caused burns, particularly when used with a subsequent dressing.[2–4]

When used as an excipient, ammonia solution is generally present in a formulation in a highly diluted form.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Care should be used in handling strong or concentrated ammonia solutions because of the caustic nature of the solution and the irritating properties of its vapor. Before containers are opened, they should be well cooled. The closure should be covered with a cloth or similar material while opening. Ammonia solution should not be tasted and inhalation of the vapor should be avoided. Ammonia solution should be handled in a fume cupboard. Eye protection, gloves, and a respirator are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Database (oral suspensions, topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Dilute ammonia solution.

Dilute ammonia solution
Synonyms Ammonia water
Specific gravity 0.95–0.96
Comments Several pharmacopeias include monographs for dilute ammonia solution. The JP XV, for example, states that ammonia water contains not less than 9.5% and not more than 10.5% w/v of ammonia (NH_3).

18 Comments

Where 'ammonia solution' is prescribed therapeutically, dilute ammonia solution should be dispensed or supplied.

The EINECS number for ammonia solution is 231-635-3.

19 Specific References

1 Frohman IG. Treatment of physalia stings. *J Am Med Assoc* 1996; **197**: 733.
2 Beare JD *et al*. Ammonia burns of the eye: an old weapon in new hands. *Br Med J* 1988; **296**: 590.
3 Payne MP, Delic JI. Ammonia.*Toxicity Review 24*. London: HMSO, 1991; 1–12.
4 Leduc D *et al*. Acute and long term respiratory damage following inhalation of ammonia. *Thorax* 1992; **47**: 755–757.

20 General References

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21 Author

PJ Sheskey.

22 Date of Revision

10 January 2009.

Ammonium Alginate

1 Nonproprietary Names

None adopted.

2 Synonyms

Alginic acid, ammonium salt; ammonium polymannuronate; E404; *Keltose*.

3 Chemical Name and CAS Registry Number

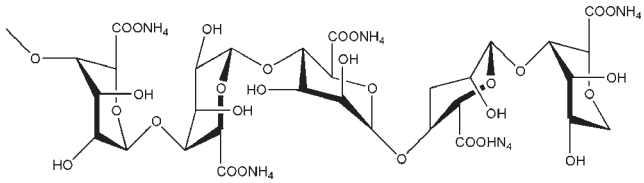
Ammonium alginate [9005-34-9]

4 Empirical Formula and Molecular Weight

$(C_6H_{11}NO_6)_n$ 193.16 (calculated)
217 (actual, average)

Ammonium alginate is the ammonium salt of alginic acid.

5 Structural Formula



The number and sequence of the mannuronate and glucuronate residues shown above vary in the naturally occurring alginate. The associated water molecules are not shown.

6 Functional Category

Diluent; emulsifying agent; film-forming agent; humectant; stabilizing agent; thickening agent.

7 Applications in Pharmaceutical Formulation or Technology

Ammonium alginate is widely used in foods as a stabilizer, thickener and emulsifier. It is also used in pharmaceutical preparations as a color-diluent, emulsifier, film-former, and humectant.

8 Description

Ammonium alginate occurs as white to yellowish brown filamentous, grainy, granular, or powdered forms.

9 Pharmacopeial Specifications

See Section 18.

10 Typical Properties

Moisture content Not more than 15% at 105°C for 4 hours.
Solubility Dissolves slowly in water to form a viscous solution; insoluble in ethanol and in ether.

11 Stability and Storage Conditions

Ammonium alginate is a hygroscopic material, although it is stable if stored at low relative humidities and cool temperatures.

12 Incompatibilities

Incompatible with oxidizing agents and strong acids and alkalis.

13 Method of Manufacture

—

14 Safety

Ammonium alginate is widely used in cosmetics and food products, and also in pharmaceutical formulations such as tablets. It is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may be harmful.

15 Handling Precautions

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

16 Regulatory Status

GRAS listed. Accepted in Europe for use as a food additive. Included in the FDA Inactive Ingredients Database (oral, tablets).

17 Related Substances

Alginic acid; calcium alginate; potassium alginate; propylene glycol alginate; sodium alginate.

18 Comments

Alginates are commonly used in wound dressings.[1] Chitosan and alginates have been used together to produce sponges for use as wound dressings, or matrices for tissue engineering.[2] Alginate microspheres have been produced by internal gelation using emulsification methods.[3]

Although not included in any pharmacopeias, a specification for ammonium alginate is contained in the Food Chemicals Codex (FCC), *see* Table I.

Table I: FCC specification for ammonium alginate.[4]

Test	FCC 6[4]
Identification	+
Arsenic	≤3 mg/kg
Ash	≤7.0% after drying
Lead	≤5 mg/kg
Loss on drying	≤15.0%
Assay	18.0–21.0% of CO_2, corresponding to 88.7–103.6% ammonium alginate

19 Specific References

1 Morgan D. Wounds—what should a dressing formulary include? *Hosp Pharm* 2002; **9**(9): 261–266.
2 Lai HL *et al*. The preparation and characterization of drug-loaded alginate and chitosan sponges. *Int J Pharm* 2003; **251**(1–2): 175–181.
3 Chan LW *et al*. Production of alginate microspheres by internal gelation using an emulsification method. *Int J Pharm* 2002; **242**(1–2): 259–262.
4 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 44.

20 General References

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21 Authors

SA Shah, D Thassu.

22 Date of Revision

30 June 2008.

Ammonium Chloride

1 Nonproprietary Names

BP: Ammonium Chloride
PhEur: Ammonium Chloride
USP: Ammonium chloride

2 Synonyms

Ammonii chloridum; ammonium muriate; E510; sal ammoniac; salmiac.

3 Chemical Name and CAS Registry Number

Ammonium chloride [12125-02-9]

4 Empirical Formula and Molecular Weight

NH_4Cl 53.49

5 Structural Formula

See Section 4.

6 Functional Category

Acidifying agent; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Ammonium chloride is used as an acidifying agent in oral formulations. It is also used as a food additive and antiseptic agent.[1]

Ammonium chloride is used in the treatment of severe metabolic alkalosis to maintain the urine at an acid pH in the treatment of some urinary tract disorders or in forced acid diuresis.[2–4] It is also used as an expectorant in cough medicines.[5]

8 Description

Ammonium chloride occurs as colorless, odorless crystals or crystal masses. It is a white, granular powder with a cooling, saline taste. It is hygroscopic and has a tendency to cake.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for ammonium chloride.

Test	PhEur 6.0	USP 32
Identification	+	+
Characters	+	—
Appearance of solution	+	—
Acidity or alkalinity	+	+
Loss on drying	⩽1.0%	⩽0.5%
Residue on ignition	—	⩽0.1%
Thiocyanate	—	+
Bromides and iodides	+	—
Sulfates	⩽150 ppm	—
Sulfated ash	⩽0.1%	—
Calcium	⩽200 ppm	—
Iron	⩽20 ppm	—
Heavy metals	⩽10 ppm	⩽0.001%
Assay (dried basis)	99.0–100.5%	99.5–100.5%

10 Typical Properties

Acidity/alkalinity pH = 4.5–5.5 (5.5% w/w aqueous solutions at 25°C)
Density (bulk) 0.6–0.9 g/cm^3
Hygroscopicity Hygroscopic with potential to cake.
Melting point Decomposes at 338°C; sublimes without melting.[6]
Solubility Soluble in water; hydrochloric acid and sodium chloride decrease its solubility in water. Also soluble in glycerin; sparingly soluble in methanol and ethanol. Almost insoluble in acetone, ether, and ethyl acetate.
Specific gravity 1.527 g/cm^3
Vapor pressure 133.3 Pa (1 mmHg) at 160°C

11 Stability and Storage Conditions

Ammonium chloride is chemically stable. It decomposes completely at 338°C to form ammonia and hydrochloric acid. Store in airtight containers in a cool, dry place.

12 Incompatibilities

Ammonium chloride is incompatible with strong acids and strong bases. It reacts violently with ammonium nitrate and potassium chlorate, causing fire and explosion hazards. It also attacks copper and its compounds.

13 Method of Manufacture

Ammonium chloride is prepared commercially by reacting ammonia with hydrochloric acid.

14 Safety

Ammonium chloride is used in oral pharmaceutical formulations. The pure form of ammonium chloride is toxic by SC, IV, and IM routes, and moderately toxic by other routes. Potential symptoms of overexposure to fumes are irritation of eyes, skin, respiratory system: cough, dyspnea, and pulmonary sensitization.[7] Ammonium salts are an irritant to the gastric mucosa and may induce nausea and vomiting.

LD_{50} (mouse, IP): 1.44 g/kg[8]
LD_{50} (mouse, oral): 1.3 g/kg
LD_{50} (rat, IM): 0.03 g/kg[9]
LD_{50} (rat, oral): 1.65 g/kg[10]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled.

All grades of ammonium chloride must be kept well away from nitrites and nitrates during transport and storage. They must be stored in a dry place, and effluent must not be discharged into the drains without prior treatment.

Ammonium chloride decomposes on heating, producing toxic and irritating fumes (nitrogen oxides, ammonia, and hydrogen chloride).

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Database (oral syrup, tablets). Accepted for use as a food additive in Europe. Included in medicines licensed in the UK (eye drops; oral syrup).

17 Related Substances

Ammonia solution.

18 Comments

Ammonium chloride has the ability to cross the red blood cell membrane, and a solution that is isotonic to blood will still cause hemolytic rupture because it acts as a hypotonic solution.

A specification for ammonium chloride is contained in the Food Chemicals Codex (FCC).[11]

The EINECS number for ammonium chloride is 235-186-4. The PubChem Compound ID (CID) for ammonium chloride is 25517.

19 Specific References

1 Gottardi W *et al*. *N*-Chlorotaurine and ammonium chloride: an antiseptic preparation with strong bactericidal activity. *Int J Pharm* 2007; **335**: 32–40.
2 Mainzer F. Acid therapy with neutral salts. *Klin Wochenschr* 1927; **6**: 1689–1691.
3 Portnoff JB *et al*. Control of urine pH and its effect on drug excretion in humans. *J Pharm Sci* 1961; **50**: 890.
4 Davies HE. Rise in urine pH and in ammonium excretion during a water diuresis. *J Physiol* 1968; **194**: 79–80P.
5 Coleman W. Expectorant action of ammonium chloride. *Am J Med Sci* 1916; **152**: 569–574.
6 Zhu RS *et al*. Sublimation of ammonium salts: a mechanism revealed by a first-principles study of the NH_4Cl system. *J Phys Chem* 2007; **111**: 13831–13838.
7 *NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140) 1997: **16**.
8 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 231.
9 Boyd EM, Seymour KGW. Ethylene diamine dihydrochloride. II. Untoward toxic reactions. *Exp Med Surg* 1946; **4**: 223–227.
10 Smeets P. Ammonium chloride [and water treatment]. *Tribune de l'Eau* 1994; **47**(570): 26–29.
11 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 46.

20 General References

Ingham JW. The apparent hydration of ions. III. The densities and viscosities of saturated solutions of ammonium chloride in hydrochloric acid. *J Chem Soc* 1929; 2059–2067.

Kumaresan R *et al*. Simultaneous heat and mass transfer studies in drying of ammonium chloride in fluidized bed dryer. *Process Plant Eng* 2007; **25**(3): 60–66.

21 Author

X He.

22 Date of Revision

27 February 2009.

Ascorbic Acid

1 Nonproprietary Names

BP: Ascorbic Acid
JP: Ascorbic Acid
PhEur: Ascorbic Acid
USP: Ascorbic Acid

2 Synonyms

Acidum ascorbicum; C-97; cevitamic acid; 2,3-didehydro-L-*threo*-hexono-1,4-lactone; E300; 3-oxo-L-gulofuranolactone, enol form; vitamin C.

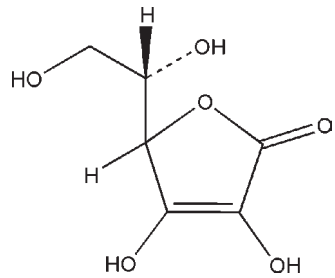
3 Chemical Name and CAS Registry Number

L-(+)-Ascorbic acid [50-81-7]

4 Empirical Formula and Molecular Weight

$C_6H_8O_6$ 176.13

5 Structural Formula



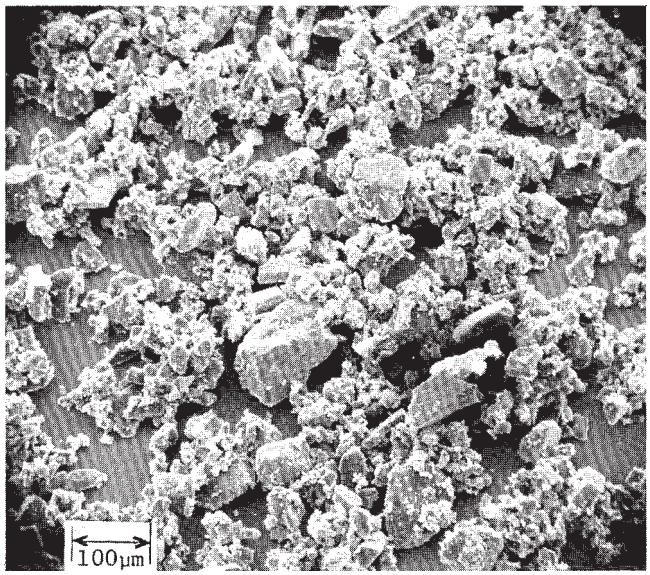
6 Functional Category

Antioxidant; therapeutic agent.

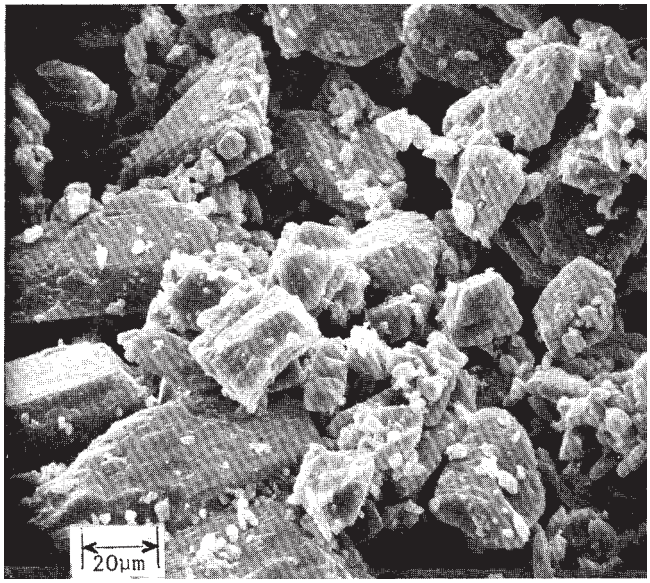
7 Applications in Pharmaceutical Formulation or Technology

Ascorbic acid is used as an antioxidant in aqueous pharmaceutical formulations at a concentration of 0.01–0.1% w/v. Ascorbic acid has been used to adjust the pH of solutions for injection, and as an adjunct for oral liquids. It is also widely used in foods as an antioxidant. Ascorbic acid has also proven useful as a stabilizing agent in mixed micelles containing tetrazepam.[1]

SEM 1: Excipient: ascorbic acid usp (fine powder); manufacturer: Pfizer Ltd; lot no.: 9A-3/G92040-CO 146; magnification: 120×; voltage: 20 kV.



SEM 2: Excipient: ascorbic acid usp (fine powder); manufacturer: Pfizer Ltd; lot no.: 9A-3/G92040-CO 146; magnification: 600×; voltage: 20 kV.



SEM 3: Excipient: ascorbic acid usp (fine granular); manufacturer: Pfizer Ltd; lot no.: 9A-2/G01280-CO 148; magnification: 120×; voltage: 20 kV.

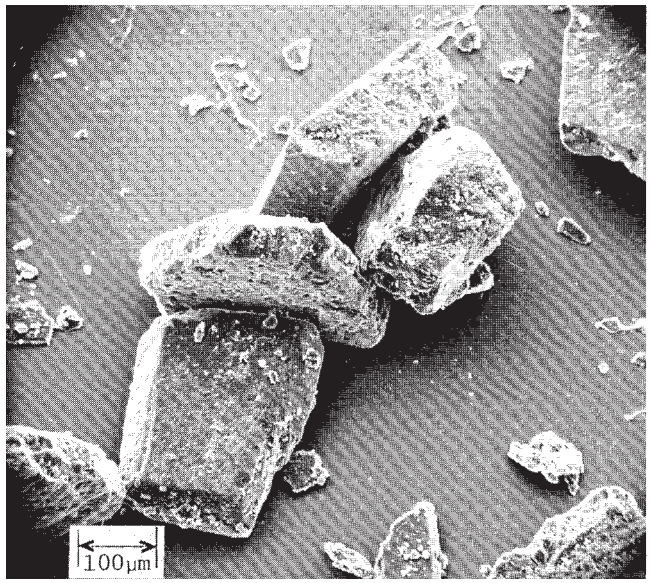


Table I: Pharmacopeial specifications for ascorbic acid.

Test	JP XV	PhEur 6.3	USP 32
Identification	+	+	+
Characters	—	+	—
Specific rotation (10% w/v solution)	+ 20.5° to + 21.5°	+ 20.5° to + 21.5°	+ 20.5° to + 21.5°
Residue on ignition	⩽0.1%	—	⩽0.1%
pH	2.2–2.5	2.1–2.6	—
Sulfated ash	—	⩽0.1%	—
Copper	—	⩽5 ppm	—
Heavy metals	⩽20 ppm	⩽10 ppm	⩽0.002%
Loss on drying	⩽0.20%	—	—
Iron	—	⩽2 ppm	—
Oxalic acid	—	+	—
Related substances	—	+	—
Appearance of solution	+	+	—
Assay	⩾99.0%	99.0–100.5%	99.0–100.5%

Table II: Solubility of ascorbic acid.

Solvent	Solubility at 20°C
Chloroform	Practically insoluble
Ethanol	1 in 50
Ethanol (95%)	1 in 25
Ether	Practically insoluble
Fixed oils	Practically insoluble
Glycerin	1 in 1000
Propylene glycol	1 in 20
Water	1 in 3.5

8 Description

Ascorbic acid occurs as a white to light-yellow-colored, nonhygroscopic, odorless, crystalline powder or colorless crystals with a sharp, acidic taste. It gradually darkens in color upon exposure to light.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity pH = 2.1–2.6 (5% w/v aqueous solution)
Density (bulk)
0.7–0.9 g/cm^3 for crystalline material;
0.5–0.7 g/cm^3 for powder.
Density (particle) 1.65 g/cm^3
Density (tapped)
1.0–1.2 g/cm^3 for crystalline material;
0.9–1.1 g/cm^3 for powder.
Density (true) 1.688 g/cm^3
Dissociation constant
pK_{a1} = 4.17;
pK_{a2} = 11.57.
Melting point 190°C (with decomposition)
Moisture content 0.1% w/w

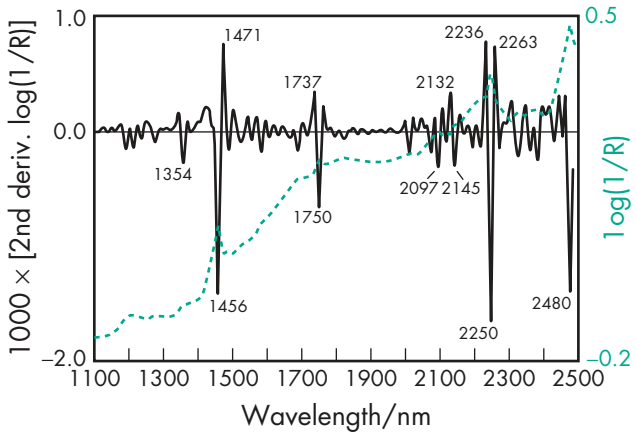


Figure 1: Near-infrared spectrum of ascorbic acid measured by reflectance.

NIR spectra *see* Figure 1.
Solubility *see* Table II.

11 Stability and Storage Conditions

In powder form, ascorbic acid is relatively stable in air. In the absence of oxygen and other oxidizing agents it is also heat stable. Ascorbic acid is unstable in solution, especially alkaline solution, readily undergoing oxidation on exposure to the air.[2,3] The oxidation process is accelerated by light and heat and is catalyzed by traces of copper and iron. Ascorbic acid solutions exhibit maximum stability at about pH 5.4. Solutions may be sterilized by filtration.

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

12 Incompatibilities

Incompatible with alkalis, heavy metal ions, especially copper and iron, oxidizing materials, methenamine, phenylephrine hydrochloride, pyrilamine maleate, salicylamide, sodium nitrite, sodium salicylate, theobromine salicylate, and picotamide.[4,5] Additionally, ascorbic acid has been found to interfere with certain colorimetric assays by reducing the intensity of the color produced.[6]

13 Method of Manufacture

Ascorbic acid is prepared synthetically or extracted from various vegetable sources in which it occurs naturally, such as rose hips, blackcurrants, the juice of citrus fruits, and the ripe fruit of *Capsicum annuum* L. A common synthetic procedure involves the hydrogenation of D-glucose to D-sorbitol, followed by oxidation using *Acetobacter suboxydans* to form L-sorbose. A carboxyl group is then added at C1 by air oxidation of the diacetone derivative of L-sorbose and the resulting diacetone-2-keto-L-gulonic acid is converted to L-ascorbic acid by heating with hydrochloric acid.

14 Safety

Ascorbic acid is an essential part of the human diet, with 40 mg being the recommended daily dose in the UK[7] and 60 mg in the USA.[8] However, these figures are controversial, with some advocating doses of 150 or 250 mg daily. Megadoses of 10 g daily have also been suggested to prevent illness although such large doses are now generally considered to be potentially harmful.[9–11]

The body can absorb about 500 mg of ascorbic acid daily with any excess immediately excreted by the kidneys. Large doses may cause diarrhea or other gastrointestinal disturbances. Damage to the teeth has also been reported.[12] However, no adverse effects have been reported at the levels employed as an antioxidant in foods, beverages,[13] and pharmaceuticals. The WHO has set an acceptable daily intake of ascorbic acid, potassium ascorbate, and sodium ascorbate, as antioxidants in food, at up to 15 mg/kg body-weight in addition to that naturally present in food.[14]

LD_{50} (mouse, IV): 0.52 g/kg[15]
LD_{50} (mouse, oral): 3.37 g/kg
LD_{50} (rat, oral): 11.9 g/kg

15 Handling Precautions

Ascorbic acid may be harmful if ingested in large quantities and may be irritating to the eyes. Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and rubber or plastic gloves are recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (inhalations, injections, oral capsules, suspensions, tablets, topical preparations, and suppositories). Included in medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Ascorbyl palmitate; erythorbic acid; sodium ascorbate.

18 Comments

Many dosage forms for ascorbic acid have been developed for its administration to patients, including microencapsulation.[16]

A specification for ascorbic acid is contained in the Food Chemicals Codex (FCC).[17]

The EINECS number for ascorbic acid is 200-066-2. The PubChem Compound ID (CID) for ascorbic acid is 5785.

19 Specific References

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12 Giunta JL. Dental erosion resulting from chewable vitamin C tablets. *J Am Dent Assoc* 1983; **107**: 253–256.
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21 Author

AH Kibbe.

22 Date of Revision

10 February 2009.

Ascorbyl Palmitate

1 Nonproprietary Names

BP: Ascorbyl Palmitate
PhEur: Ascorbyl Palmitate
USP-NF: Ascorbyl Palmitate

2 Synonyms

L-Ascorbic acid 6-palmitate; ascorbylis palmitas; E304; 3-oxo-L-gulofuranolactone 6-palmitate; vitamin C palmitate.

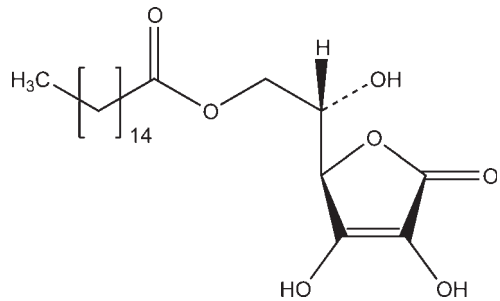
3 Chemical Name and CAS Registry Number

L-Ascorbic acid 6-hexadecanoate [137-66-6]

4 Empirical Formula and Molecular Weight

$C_{22}H_{38}O_7$ 414.54

5 Structural Formula



6 Functional Category

Antioxidant.

7 Applications in Pharmaceutical Formulation or Technology

Ascorbyl palmitate is primarily used either alone or in combination with alpha tocopherol as a stabilizer for oils in oral pharmaceutical formulations and food products; generally 0.05% w/v is used. It may also be used in oral and topical preparations as an antioxidant for drugs unstable to oxygen. The combination of ascorbyl palmitate with alpha tocopherol shows marked synergism, which increases the effect of the components and allows the amount used to be reduced.

The solubility of ascorbyl palmitate in alcohol permits it to be used in nonaqueous and aqueous systems and emulsions.

8 Description

Ascorbyl palmitate is a practically odorless, white to yellowish powder.

9 Pharmacopeial Specifications

See Table I .

Table I: Pharmacopeial specifications for ascorbyl palmitate.

Test	PhEur 6.0	USP32–NF27
Identification	+	+
Appearance of solution	+	—
Melting range	—	107–117°C
Specific rotation (10% w/v in methanol)	+21° to +24°	+21° to +24°
Loss on drying	⩽1.0%	⩽2.0%
Residue on ignition	—	⩽0.1%
Sulfated ash	⩽0.1%	—
Heavy metals	⩽10 ppm	⩽0.001%
Assay (dried basis)	98.0–100.5%	95.0–100.5%

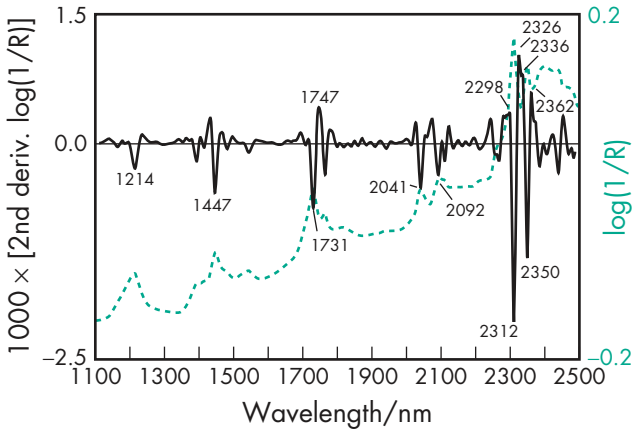


Figure 1: Near-infrared spectrum of ascorbyl palmitate measured by reflectance.

10 Typical Properties

NIR spectra *see* Figure 1.
Solubility *see* Table II.

Table II: Solubility of ascorbyl palmitate.

Solvent	Solubility at 20°C unless otherwise stated[1]
Acetone	1 in 15
Chloroform	1 in 3300
	1 in 11 at 60°C
Cottonseed oil	1 in 1670
Ethanol	1 in 8
	1 in 1.7 at 70°C
Ethanol (95%)	1 in 9.3
Ethanol (50%)	1 in 2500
Ether	1 in 132
Methanol	1 in 5.5
	1 in 1.7 at 60°C
Olive oil	1 in 3300
Peanut oil	1 in 3300
Propan-2-ol	1 in 20
	1 in 5 at 70°C
Sunflower oil	1 in 3300
Water	Practically insoluble
	1 in 500 at 70°C
	1 in 100 at 100°C

11 Stability and Storage Conditions

Ascorbyl palmitate is stable in the dry state, but is gradually oxidized and becomes discolored when exposed to light and high humidity. In an unopened container, stored in a cool place, it has a shelf life of at least 12 months. During processing, temperatures greater than 65°C should be avoided.

The bulk material should be stored in an airtight container at 8–15°C, protected from light.

12 Incompatibilities

Incompatibilities are known with oxidizing agents; e.g. in solution oxidation is catalyzed by trace metal ions such as Cu^{2+} and Fe^{3+}.

13 Method of Manufacture

Ascorbyl palmitate is prepared synthetically by the reaction of ascorbic acid with sulfuric acid followed by reesterification with palmitic acid.

14 Safety

Ascorbyl palmitate is used in oral pharmaceutical formulations and food products, and is generally regarded as an essentially nontoxic and nonirritant material. The WHO has set an estimated acceptable daily intake for ascorbyl palmitate at up to 1.25 mg/kg body-weight.[2]

LD_{50} (mouse, oral): 25 g/kg[3]
LD_{50} (rat, oral): 10 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Ascorbyl palmitate dust may cause irritation to the eyes and respiratory tract. Eye protection is recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (oral, rectal, topical preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Ascorbic acid; sodium ascorbate.

18 Comments

In order to maximize the stability and efficacy of ascorbyl palmitate the following precautions are recommended: stainless steel, enamel, or glass should be used; deaeration (vacuum) procedures and inert gas treatment are recommended where feasible; protect from light and radiant energy.

The formation of ascorbyl palmitate vesicles (Aspasomes) and their pharmaceutical applications has been investigated.[4]

The EINECS number for ascorbyl palmitate is 205-305-4. The PubChem Compound ID (CID) for ascorbyl palmitate is 5282566.

19 Specific References

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21 Author

PJ Weller.

22 Date of Revision

9 January 2009.

Aspartame

1 Nonproprietary Names

BP: Aspartame
PhEur: Aspartame
USP-NF: Aspartame

2 Synonyms

(3*S*)-3-Amino-4-[[(1*S*)-1-benzyl-2-methoxy-2-oxoethyl]amino]-4-oxobutanoic acid; 3-amino-*N*-(α-carboxyphenethyl)succinamic acid *N*-methyl ester; 3-amino-*N*-(α-methoxycarbonylphenethyl)-succinamic acid; APM; aspartamum; aspartyl phenylamine methyl ester; *Canderel*; E951; *Equal*; methyl *N*-L-α-aspartyl-L-phenylalaninate; *NatraTaste*; *NutraSweet*; *Pal Sweet*; *Pal Sweet Diet*; *Sanecta*; SC-18862; *Tri-Sweet*.

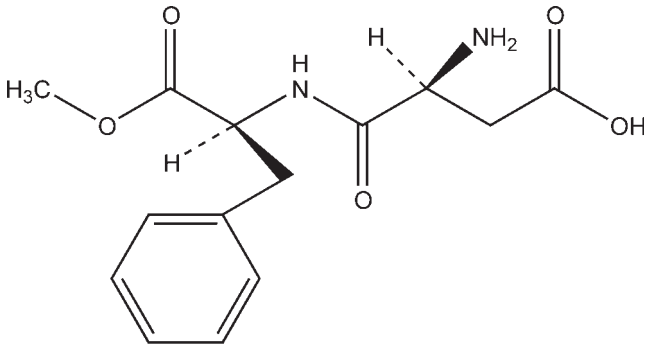
3 Chemical Name and CAS Registry Number

N-L-α-Aspartyl-L-phenylalanine 1-methyl ester [22839-47-0]

4 Empirical Formula and Molecular Weight

$C_{14}H_{18}N_2O_5$ 294.30

5 Structural Formula



6 Functional Category

Sweetening agent.

7 Applications in Pharmaceutical Formulation or Technology

Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets,[1,2] powder mixes, and vitamin preparations. It enhances flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose.

Unlike some other intense sweeteners, aspartame is metabolized in the body and consequently has some nutritive value: 1 g provides approximately 17 kJ (4 kcal). However, in practice, the small quantity of aspartame consumed provides a minimal nutritive effect.

8 Description

Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.

SEM 1: Excipient: aspartame; magnification: 70×; voltage: 3 kV.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for aspartame.

Test	PhEur 6.0	USP32–NF27
Identification	+	+
Characters	+	–
Appearance of solution	+	–
Conductivity	⩽30 µS/cm	–
Specific optical rotation	+14.5° to +16.5°	+14.5° to +16.5°
Related substances	+	–
Heavy metals	⩽10 ppm	⩽0.001%
Loss on drying	⩽4.5%	⩽4.5%
Residue on ignition	–	⩽0.2%
Sulfated ash	⩽0.2%	–
Impurities	+	–
Transmittance	–	+
Limit of 5-benzyl-3,6-dioxo-2-piperazineacetic acid	–	⩽1.5%
Chromatographic purity	–	+
Assay	98.0–102.0%	98.0–102.0%

10 Typical Properties

Acidity/alkalinity pH = 4.5–6.0 (0.8% w/v aqueous solution)
Brittle fracture index 1.05[3]
Bonding index
0.8×10^2 (worst case)[3]
2.3×10^2 (best case)[3]
Flowability 44% (Carr compressibility index)[3]
Density (bulk)
0.5–0.7 g/cm^3 for granular grade;
0.2–0.4 g/cm^3 for powder grade;
0.17 g/cm^3 (Spectrum Quality Products).[3]
Density (tapped) 0.29 g/cm^3 (Spectrum Quality Products)[3]

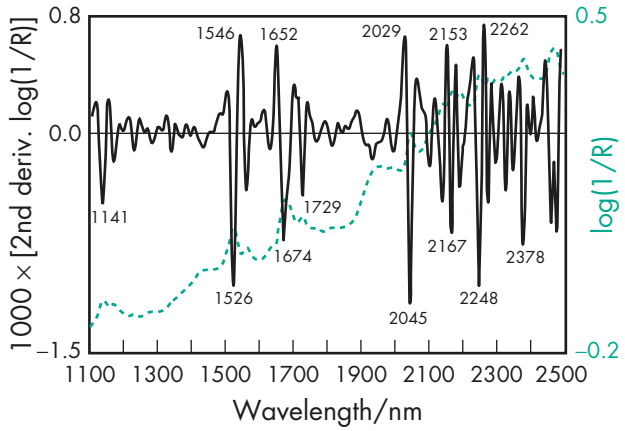


Figure 1: Near-infrared spectrum of aspartame measured by reflectance.

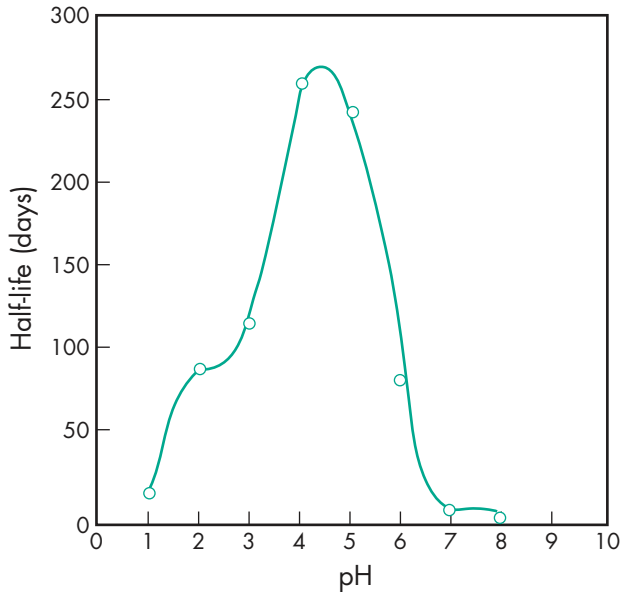


Figure 2: Stability profile of aspartame in aqueous buffers at 25°C.[8]

Density (true) 1.347 g/cm^3
Effective angle of internal friction 43.0°[3]
Melting point 246–247°C
NIR spectra *see* Figure 1.
Solubility Slightly soluble in ethanol (95%); sparingly soluble in water. At 20°C the solubility is 1% w/v at the isoelectric point (pH 5.2). Solubility increases at higher temperature and at more acidic pH, e.g., at pH 2 and 20°C solubility is 10% w/v.
Specific rotation $[\alpha]_D^{22} = -2.3°$ in 1 N HCl

11 Stability and Storage Conditions

Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form the degradation products L -aspartyl-L-phenylalanine and 3-benzyl-6-carboxymethyl-2,5-diketopiperazine with a resulting loss of sweetness. A third-degradation product is also known, β-L-aspartyl-L-phenylalanine methyl ester. For the stability profile at 25°C in aqueous buffers, *see* Figure 2.

Stability in aqueous solutions has been enhanced by the addition of cyclodextrins,[4,5] and by the addition of polyethylene glycol 400 at pH 2.[6] However, at pH 3.5–4.5 stability is not enhanced by the replacement of water with organic solvents.[7]

Aspartame degradation also occurs during prolonged heat treatment; losses of aspartame may be minimized by using processes that employ high temperatures for a short time followed by rapid cooling.

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

12 Incompatibilities

Differential scanning calorimetry experiments with some directly compressible tablet excipients suggests that aspartame is incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate.[9] Reactions between aspartame and sugar alcohols are also known.

13 Method of Manufacture

Aspartame is produced by coupling together L-phenylalanine (or L-phenylalanine methyl ester) and L-aspartic acid, either chemically or enzymatically. The former procedure yields both the sweet α-aspartame and nonsweet β-aspartame from which the α-aspartame has to be separated and purified. The enzymatic process yields only α-aspartame.

14 Safety

Aspartame is widely used in oral pharmaceutical formulations, beverages, and food products as an intense sweetener, and is generally regarded as a nontoxic material. However, the use of aspartame has been of some concern owing to the formation of the potentially toxic metabolites methanol, aspartic acid, and phenylalanine. Of these materials, only phenylalanine is produced in sufficient quantities, at normal aspartame intake levels, to cause concern. In the normal healthy individual any phenylalanine produced is harmless; however, it is recommended that aspartame be avoided or its intake restricted by those persons with phenylketonuria.[10]

The WHO has set an acceptable daily intake for aspartame at up to 40 mg/kg body-weight.[11] Additionally, the acceptable daily intake of diketopiperazine (an impurity found in aspartame) has been set by the WHO at up to 7.5 mg/kg body-weight.[12]

A number of adverse effects have been reported following the consumption of aspartame,[10,12] particularly in individuals who drink large quantities (up to 8 liters per day in one case) of aspartame-sweetened beverages. Reported adverse effects include: headaches;[13] grand mal seizure;[14] memory loss;[15] gastrointestinal symptoms; and dermatological symptoms. However, scientifically controlled peer-reviewed studies have consistently failed to produce evidence of a causal effect between aspartame consumption and adverse health events.[16,17] Controlled and thorough studies have confirmed aspartame's safety and found no credible link between consumption of aspartame at levels found in the human diet and conditions related to the nervous system and behavior, nor any other symptom or illness. Aspartame is well documented to be nongenotoxic and there is no credible evidence that aspartame is carcinogenic.[18]

Although aspartame has been reported to cause hyperactivity and behavioral problems in children, a double-blind controlled trial of 48 preschool-age children fed diets containing a daily intake of 38 ± 13 mg/kg body-weight of aspartame for 3 weeks showed no adverse effects attributable to aspartame, or dietary sucrose, on children's behavior or cognitive function.[19]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Measures should be taken to minimize the potential for dust explosion. Eye protection is recommended.

A

16 Regulatory Status

Accepted for use as a food additive in Europe and in the USA. Included in the FDA Inactive Ingredients Database (oral powder for reconstitution, buccal patch, granules, syrups, and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Alitame; aspartame acesulfame; neotame.

Aspartame acesulfame

Empirical formula $C_{18}H_{23}O_9N_3S$
Molecular weight 457.46
CAS number 106372-55-8
Comments A compound of aspartame and acesulfame approx. 350 times sweeter than sucrose. Aspartame acesulfame is listed in the USP32–NF27.

18 Comments

The 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 the bulk, textural, or preservative characteristics of sugar, if sugar is removed from a formulation.

Synergistic effects for combinations of sweeteners have been reported, e.g. aspartame with acesulfame potassium.

Aspartame can cause browning when used at high temperatures.

A specification for aspartame is contained in the Food Chemicals Codex (FCC).[20]

The PubChem Compound ID (CID) for aspartame includes 2242 and 21462246.

19 Specific References

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Marie S. Sweeteners. Smith J, ed. *Food Additives User's Handbook*. Glasgow: Blackie, 1991; 47–74.
Roy GM. Taste masking in oral pharmaceuticals. *Pharm Technol Eur* 1994; **6**(6): 24, 26–2830–3234, 35.
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21 Author

A Cram.

22 Date of Revision

18 February 2009.

Attapulgite

1 Nonproprietary Names

BP: Attapulgite

2 Synonyms

Actapulgite; *Attaclay*; *Attacote*; *Attagel*; attapulgus; palygorscite; palygorskite; *Pharmsorb Regular*.

3 Chemical Name and CAS Registry Number

Attapulgite [12174-11-7]

4 Empirical Formula and Molecular Weight

Attapulgite is a purified native hydrated magnesium aluminum silicate consisting of the clay mineral palygorskite, with the empirical formula $Mg(Al_{0.5–1}Fe_{0–0.5})Si_4O_{10}(OH)·4H_2O$.

5 Structural Formula

See Section 4.

6 Functional Category

Adsorbent.

7 Applications in Pharmaceutical Formulation or Technology

Attapulgite is widely used as an adsorbent in solid dosage forms. Colloidal clays (such as attapulgite) absorb considerable amounts of water to form gels and in concentrations of 2–5% w/v usually form oil-in-water emulsions. Activated attapulgite, which is attapulgite that has been carefully heated to increase its absorptive capacity, is used therapeutically as an adjunct in the management of diarrhea.

8 Description

Attapulgite occurs as a light cream colored, very fine powder. Particle size ranges depend on the grade and manufacturer.

9 Pharmacopeial Specifications

See Table I. *See also* Section 17.

Table I: Pharmacopeial specifications for attapulgite.

Test	BP 2009
Identification	+
Characters	+
Acidity or alkalinity (5% w/v aqueous suspension)	7.0–9.5
Adsorptive capacity	5–14%
Arsenic	⩽8 ppm
Heavy metals	⩽20 ppm
Acid-insoluble matter	⩽12.5%
Water-soluble matter	⩽0.5%
Loss on drying	⩽17.0%
Loss on ignition	15.0–27.0%

10 Typical Properties

Acidity/alkalinity pH = 9.5 (5% w/v aqueous suspension)
Angle of repose 37.2–45.2°[1]
Density 2.2 g/cm^3
Density (tapped) 0.33 g/cm^3 [1]
Flowability 20.9–29.6% (Carr compressibility index)[1]

Particle size distribution

<2 μm in size for powder;
2–5 μm in size for aggregate.[1]

11 Stability and Storage Conditions

Attapulgite can adsorb water. It should be stored in an airtight container in a cool, dry, location.

12 Incompatibilities

Attapulgite may decrease the bioavailability of some drugs such as loperamide[2] and riboflavin.[3] Oxidation of hydrocortisone is increased in the presence of attapulgite.[4]

13 Method of Manufacture

Attapulgite occurs naturally as the mineral palygorskite.

14 Safety

Attapulgite is widely used in pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. It is not absorbed following oral administration. In oral preparations, activated attapulgite up to 9 g is used in daily divided doses as an adjunct in the management of diarrhea.[5]

LD_{50} (rat, IP): 0.34 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended. Attapulgite should be handled in a well-ventilated environment and dust generation should be minimized. When heated to decomposition, attapulgite emits acrid smoke and irritating fumes.

16 Regulatory Status

Included in nonparenteral medicines licensed in a number of countries worldwide including the UK and USA.

17 Related Substances

Activated attapulgite; magnesium aluminum silicate.

Activated attapulgite

Comments Activated attapulgite is a processed native magnesium aluminum silicate that has been carefully heated to increase its adsorptive capacity. Monographs for activated attapulgite are included in the BP 2009, USP 32, and other pharmacopeias. The USP 32 also includes a monograph for colloidal activated attapulgite.

18 Comments

The EINECS number for attapulgite is 302-243-0.

19 Specific References

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22 Date of Revision

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