

Alpha Tocopherol

1 Nonproprietary Names

BP: Alpha tocopherol
JP: Tocopherol
PhEur: α -Tocopherolum
USP: Vitamin E
See also Sections 3, 9, and 17.

2 Synonyms

Copherol F1300; (\pm)-3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-ol; E307; *Eastman Vitamin E TPGS*; synthetic alpha tocopherol; all-*rac*- α -tocopherol; *dl*- α -tocopherol; 5,7,8-trimethyltolcol.

3 Chemical Name and CAS Registry Number

(\pm)-(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 centres, 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.

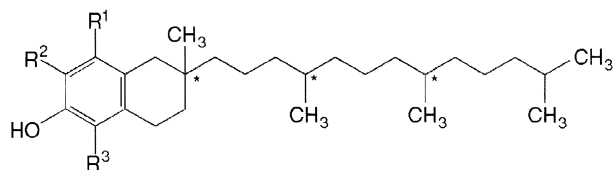
See Section 17 for further information.

4 Empirical Formula Molecular Weight

C₂₉H₅₀O₂

430.72

5 Structural Formula



Alpha tocopherol: R¹ = R² = R³ = CH₃
Beta tocopherol: R¹ = R³ = CH₃; R² = H
Delta tocopherol: R¹ = CH₃; R² = R³ = H
Gamma tocopherol: R¹ = R² = CH₃; R³ = 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⁾ 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.⁽²⁾

8 Description

Alpha tocopherol is a natural product. Therefore, it is available either as a practically odorless, clear, colorless, yellow, yellowish-brown, or greenish-yellow viscous oil. See also Section 17.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for alpha tocopherol.

Test	JP 2001	PhEur 2002	USP 25
Identification	+	+	+
Acidity	—	—	—
Acid value	—	≤2	—
Optical rotation	—	-0.01° to +0.01°	+
Heavy metals	≤20 ppm	≤10 ppm	—
Sulfated ash	—	≤0.1%	—
Organic volatile impurities	—	—	+
Absorbance	+	+	—
Refractive index	1.503–1.507	—	—
Specific gravity	0.947–0.955	—	—
Clarity and color of solution	+	—	—
Assay	96.0–102.0%	96.0–102.0%	96.0–102.0%

Note that the USP 25 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 2002 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/cm³

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.⁽³⁾

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.⁽⁴⁾ 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.⁽⁵⁾

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 to 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.⁽⁶⁾

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 Guide (oral capsules, tablets, and topical preparations). 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: C₂₉H₅₀O₂

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: C₃₁H₅₂O₃

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-chroman-1-yl 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 [α]_D²⁵: +0.25° (10% w/v solution in chloroform)

Comments: unstable to alkalis.

dl-Alpha tocopheryl acetate

Empirical formula: C₃₁H₅₂O₃

Molecular weight: 472.73

CAS number: [7695-91-2]

Synonyms: (\pm)-3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-ol acetate; (\pm)-(2*RS*,4'*RS*,8'*RS*)-2,5,7,8-tetramethyl-2-(4',8',12'-trimethyltridecyl)-6-chroman-1-yl acetate; (\pm)- α -tocopherol acetate; α -tocopheroli acetate; *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/cm³

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 2002. 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: (\pm)- 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; (\pm)-3,4-dihydro-2,5,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1- β -benzopyran-6-ol; 5,8-dimethyltolcol; 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: (\pm)-3,4-dihydro-2,8-dimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-ol; E309; 8-methyltolcol; *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: (\pm)-3,4-dihydro-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-2*H*-1-benzopyran-6-ol; 7,8-dimethyltolcol; 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 USP/NF 20 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.

19 Specific References

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20 General References

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21 Author

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22 Date of Revision

29 July 2002.