Handbook of PHARMACEUTICAL EXCIPIENTS

Second Edition

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Alpha Tocopherol

1. Nonproprietary Names
BP: Alpha tocopherol
PhEur: α-Tocopherolum
USP: Vitamin E
See also Sections 3, 9 and 18.

2. Synonyms
(±)-3,4-Dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-ol; E307; synthetic alpha tocopherol; all-rac-α-tocopherol; dl-α-tocopherol; 5,7,8-trimethyltolcol.

3. Chemical Name and CAS Registry Number
(+)-(2RS,4'R,8'S,8'R)-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 (2R,4'R,8'S,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 18 for further information.

4. Empirical Formula Molecular Weight
C₂₉H₄₈O₂ 430.69

5. Structural Formula

\[
\begin{align*}
\text{CH}_3 & \quad \text{HO} & \quad \text{CH}_3 \\
\text{R}_1 & \quad \text{R}_2 & \quad \text{R}_3 & \quad \text{R}_4
\end{align*}
\]

Alpha tocopherol: \( R_1 = R_2 = R_3 = \text{CH}_3 \).
Beta tocopherol: \( R_1 = R_3 = \text{CH}_3; R_2 = \text{H} \).
Delta tocopherol: \( R_1 = \text{CH}_3; R_2 = R_3 = \text{H} \).
Gamma tocopherol: \( R_1 = R_2 = \text{CH}_3; R_3 = \text{H} \).
* Indicates chiral centres.

6. Functional Category
Antioxidant; therapeutic agent.

7. Applications in Pharmaceutical Formulation or Technology
Alpha tocopherol is primarily recognised as a source of vitamin E and the commercially available materials and specifications reflect this purpose. Whilst alpha tocopherol also exhibits antioxidant properties, the beta, delta and gamma tocopherols are considered to be more effective as antioxidants.

Of widespread regulatory acceptability, tocopherols are of value in oil or fat-based pharmaceutical products and are normally used in the concentration range of 0.001-0.05%.

There is frequently an optimum concentration; thus the autoxidation of linoleic acid and methyl linolenate is reduced at low concentrations of alpha tocopherol but accelerated by higher concentrations. Antioxidant effectiveness can be increased by the addition of oil soluble synergists such as lecithin and ascorbyl palmitate.(1)

8. Description
Alpha tocopherol is a practically odorless, clear, colorless, yellow, yellowish-brown or greenish-yellow colored viscous oil. See also Section 18.

9. Pharmacopeial Specifications

<table>
<thead>
<tr>
<th>Test</th>
<th>PhEur 1990</th>
<th>USP XXII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acidity</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>Acid value</td>
<td>≤ 2</td>
<td>—</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>≤ 20 ppm</td>
<td>—</td>
</tr>
<tr>
<td>Sulfated ash</td>
<td>≤ 0.1%</td>
<td>—</td>
</tr>
<tr>
<td>Assay</td>
<td>96.0-102.0%</td>
<td>96.0-102.0%</td>
</tr>
</tbody>
</table>

Note that the USP XXII 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 1990 and the BP 1993 describe alpha tocopherol and alpha tocopheryl acetate in separate monographs.
The diversity of the tocopherols described in the various pharmacopeial monographs makes a comparison of specifications difficult.

10. Typical Properties
**Solubility:** Practically insoluble in water; freely soluble in acetone, ethanol, ether and vegetable oils.

11. Stability and Storage Conditions
Tocopherols are slowly oxidized 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 18.

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.(2)

13. Method of Manufacture
Naturally occurring tocopherols are obtained by the extraction or molecular distillation of steam distillates of vegetable oils, e.g. alpha tocopherol occurs in concentrations of 0.1-0.3% in corn, rapeseed, soybean, sunflower and wheat germ oils(3)
Beta tocopherol 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.(4)

14. Safety
Tocopherols (vitamin E) occur in many food substances that are consumed as part of the normal diet. The daily nutritional

Noven Ex. 1003
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requirement has not been clearly defined but is estimated to be 3-20 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 large oral doses may cause diarrhea or other gastrointestinal disturbances. Topical application of tocopherols may cause 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 mg/kg body-weight. (5)

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. Pharmacopeias

Aust, Br, Braz, Chin, Cz, Egypt, Eur, Fr, Ger, Gr, Hung, Ind, It, Jpn, Neth, Nord, Rom, Rus, Swiss, US and Yug. Also in BP Vet.

Note that the nomenclature for tocopherols and tocopherol derivatives is confusing and many pharmacopeias do not specify clearly the isomer or form of the tocopherol.

18. Related Substances

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

d-Archa tocoherol: C_{29}H_{52}O_{2}

Molecular weight: 430.69

CAS number: [59-02-9]

Synonyms: natural alpha tocopherol; (+)-(2R,4,R,8'R)-2,5,7,8-tetramethyl-2-(4',8',12'-trimethyltridecyl)-6-chromanol; d-alpha-tocopherol; vitamin E.

Appearance: a practically odorless, clear, yellow or greenish-yellow colored viscous oil.

Solubility: practically insoluble in water; soluble in ethanol (95%). Miscible with acetone, chloroform, ether and vegetable oils.

Comments: this is the naturally occurring form of alpha tocopherol.

d-Archa tocopheryl acetate: C_{31}H_{55}O_{3}

Molecular weight: 472.73

CAS number: [58-95-7]

Synonyms: (+)-(2R,4,R,8'R)-2,5,7,8-tetramethyl-2-(4',8',12'-trimethyltridecyl)-6-chromanol acetate; d-alpha-tocopheryl acetate; vitamin E.

Appearance: a practically odorless, clear, yellow or greenish-yellow colored viscous oil which 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]_{D}^{25}: +0.25° (10% w/v solution in chloroform)

Comments: unstable to alkalis.

d-Archa tocopheryl acid succinate: C_{33}H_{54}O_{3}

Molecular weight: 530.8

CAS number: [4345-03-3]

Synonyms: (+)-alpha-tocopherol hydrogen succinate; d-alpha-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.

d-Archa tocopheryl acid succinate: C_{33}H_{54}O_{3}

Molecular weight: 530.8

CAS number: [17407-37-3]

Synonyms: (+)-alpha-tocopherol hydrogen succinate; d-alpha-tocopheryl acid 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: C_{29}H_{52}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)-2H-1-benzopyran-6-ol; 5,8-dimethyltocopherol; neotocopherol; dl-beta-tocopherol; vitamin E; p-xylo tocopherol.

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 [α]_{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: \( \text{C}_{27}\text{H}_{46}\text{O}_2 \)

- Molecular weight: 402.64
- CAS number: [119-13-1]
- Synonyms: \((\pm)-3,4\text{-dihydro}-2,8\text{-dimethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-ol}; \) E309; 8-methyltocol; \( dl-\delta \)-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: \( \text{C}_{28}\text{H}_{48}\text{O}_2 \)

- Molecular weight: 416.66
- CAS number: [7616-22-0]
- Synonyms: \((\pm)-3,4\text{-dihydro}-2,7,8\text{-trimethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-ol}; \) 7,8-dimethyltocol; \( dl-\gamma \)-tocopherol; vitamin E; \( \alpha \)-xylotocopherol.
- Appearance: a pale yellow colored viscous oil.
- Melting point: \(-30^\circ \text{C} \)
- Solubility: practically insoluble in water; freely soluble in acetone, chloroform, ethanol (95%), ether and vegetable oils.
- Specific rotation \( [\alpha]_p^{20} = -2.4^\circ \) (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.
- Pharmacopeias: USPNF.

Comments: tocopherols excipient is described in the USPNF XVII 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 alpha, beta, delta and gamma tocopherols.

19. 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.

20. Specific References


21. General References


22. Authors

UK: JA Stead.
Ascorbic Acid

1. Nonproprietary Names
BP: Ascorbic acid
PhEur: Acidum ascorbicum
USP: Ascorbic acid

2. Synonyms
Cevitamic acid; C-97; 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
C₆H₈O₆
Molecular Weight
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. It is also widely used in foods as an antioxidant.

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

<table>
<thead>
<tr>
<th>Test</th>
<th>PhEur 1984</th>
<th>USP XXII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Specific rotation (10% w/v solution)</td>
<td>+20.5° to +21.5°</td>
<td>+20.5° to +21.5°</td>
</tr>
<tr>
<td>Residue on ignition</td>
<td>--</td>
<td>&lt; 0.1%</td>
</tr>
<tr>
<td>Sulfated ash</td>
<td>&lt; 0.1%</td>
<td>--</td>
</tr>
<tr>
<td>Copper</td>
<td>&lt; 5 ppm</td>
<td>--</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>&lt; 10 ppm</td>
<td>&lt; 0.002%</td>
</tr>
<tr>
<td>Iron</td>
<td>&lt; 2 ppm</td>
<td>--</td>
</tr>
<tr>
<td>Oxalic acid</td>
<td>+</td>
<td>--</td>
</tr>
<tr>
<td>Appearance of solution</td>
<td>+</td>
<td>--</td>
</tr>
<tr>
<td>Assay</td>
<td>99.0-100.5%</td>
<td>99.0-100.5%</td>
</tr>
</tbody>
</table>
SEM: 3
Excipient: Ascorbic acid USP (granular)
Manufacturer: Pfizer Ltd
Lot No.: 9A-1/G01260-CO 140
Magnification: 120x
Voltage: 20 kV

SEM: 5
Excipient: Ascorbic acid USP (fine granular)
Manufacturer: Pfizer Ltd
Lot No.: 9A-2/G01280-CO 148
Magnification: 120x
Voltage: 20 kV

SEM: 4
Excipient: Ascorbic acid USP (granular)
Manufacturer: Pfizer Ltd
Lot No.: 9A-1/G01260-CO 140
Magnification: 600x
Voltage: 20 kV

SEM: 6
Excipient: Ascorbic acid USP (fine granular)
Manufacturer: Pfizer Ltd
Lot No.: 9A-2/G01280-CO 148
Magnification: 600x
Voltage: 20 kV
10. Typical Properties

Acidity/alkalinity: pH = 2.1-2.6 (5% w/v aqueous solution)

Density (bulk): 0.7-0.9 g/cm³ for crystalline material; 0.5-0.7 g/cm³ for powder.

Density (particle): 1.65 g/cm³

Density (tapped): 1.0-1.2 g/cm³ for crystalline material; 0.9-1.1 g/cm³ for powder.

Dissociation constant:

\[ pK_{a1} = 4.17; \]

\[ pK_{a2} = 11.57 \]

Melting point: 190°C (with decomposition)

Moisture content: 0.1% w/w

Particle size distribution: various grades of ascorbic acid with different particle size distributions are commercially available.

See Fig. 1.

Solubility:

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility at 20°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroform</td>
<td>practically insoluble</td>
</tr>
<tr>
<td>Ethanol</td>
<td>1 in 50</td>
</tr>
<tr>
<td>Ethanol (95%)</td>
<td>1 in 25</td>
</tr>
<tr>
<td>Ether</td>
<td>practically insoluble</td>
</tr>
<tr>
<td>Fixed oils</td>
<td>practically insoluble</td>
</tr>
<tr>
<td>Glycerin</td>
<td>1 in 100</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>1 in 20</td>
</tr>
<tr>
<td>Water</td>
<td>1 in 3.5</td>
</tr>
</tbody>
</table>

Fig. 1: Particle size distribution of ascorbic acid.

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. 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 and theobromine salicylate.

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 C₃ by air oxidation of the diacetone derivative of L-sorbose and the resulting diacetone-2-keto-L-gulonic acid 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 the recommended daily dose in the UK and 60 mg in the USA. However, these figures are controversial with some advocating doses of 150 mg or 250 mg daily. Megadoses of 10 g daily have also been suggested to prevent illness. 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. However, at the levels employed as an antioxidant in foods and pharmaceuticals no adverse effects have been reported. 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.

\[ \text{LD}_{50} \text{ (mouse, IP): } 0.64 \text{ g/kg} \]

\[ \text{LD}_{50} \text{ (mouse, IV): } 0.52 \text{ g/kg} \]

\[ \text{LD}_{50} \text{ (mouse, oral): } 3.37 \text{ g/kg} \]

\[ \text{LD}_{50} \text{ (rat, oral): } 11.9 \text{ g/kg} \]

15. Handling Precautions

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 as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations, injections, oral capsules, suspensions and tablets). Included in medicines licensed in the UK.

17. Pharmacopeias

Aust, Br, Braz, Chin, Cz, Egypt, Eur, Fr, Ger, Gr, Hung, Ind, Int, It, Jpn, Mex, Neth, Nord, Port, Rom, Rus, Swiss, Turk, US and Yug. Also in BP Vet.

18. Related Substances

Ascorbyl Palmitate; Sodium Ascorbate.
19. Comments

20. Specific References

21. General References

22. Authors
USA: A Abdul-Rahman.
Ascorbyl Palmitate

1. Nonproprietary Names
BP: Ascorbyl palmitate
PhEur: Ascorbylis palmitas
USPNF: Ascorbyl palmitate

2. Synonyms
L-Ascorbic acid 6-palmitate; 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 Molecular Weight
C_{22}H_{36}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. 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

<table>
<thead>
<tr>
<th>Test</th>
<th>PhEur 1993</th>
<th>USPNF XVII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Appearance of solution</td>
<td>+</td>
<td>--</td>
</tr>
<tr>
<td>Melting range</td>
<td>--</td>
<td>107-117°C</td>
</tr>
<tr>
<td>Specific rotation</td>
<td>+21° to +24°</td>
<td>+21° to +24°</td>
</tr>
<tr>
<td>(10% w/v in methanol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss on drying</td>
<td>≤ 1.0%</td>
<td>≤ 2.0%</td>
</tr>
<tr>
<td>Residue on ignition</td>
<td>--</td>
<td>≤ 0.1%</td>
</tr>
<tr>
<td>Sulfated ash</td>
<td>≤ 0.1%</td>
<td>--</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>≤ 10 ppm</td>
<td>≤ 0.001%</td>
</tr>
<tr>
<td>Assay (dried basis)</td>
<td>98.0-100.5%</td>
<td>95.0-100.5%</td>
</tr>
</tbody>
</table>

10. Typical Properties
Solubility:

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility at 20°C (in)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unless otherwise stated</td>
</tr>
<tr>
<td>Acetone</td>
<td>1 in 15</td>
</tr>
<tr>
<td>Chloroform</td>
<td>1 in 3300</td>
</tr>
<tr>
<td></td>
<td>1 in 11 at 60°C</td>
</tr>
<tr>
<td>Ethanol</td>
<td>1 in 8</td>
</tr>
<tr>
<td></td>
<td>1 in 1.7 at 70°C</td>
</tr>
<tr>
<td>Ethanol (95%)</td>
<td>1 in 9.3</td>
</tr>
<tr>
<td>Ethanol (50%)</td>
<td>1 in 2500</td>
</tr>
<tr>
<td>Ether</td>
<td>1 in 132</td>
</tr>
<tr>
<td>Methanol</td>
<td>1 in 5.5</td>
</tr>
<tr>
<td></td>
<td>1 in 1.7 at 60°C</td>
</tr>
<tr>
<td>Olive oil</td>
<td>1 in 3300</td>
</tr>
<tr>
<td>Peanut oil</td>
<td>1 in 3300</td>
</tr>
<tr>
<td>Propan-2-ol</td>
<td>1 in 20</td>
</tr>
<tr>
<td></td>
<td>1 in 5 at 70°C</td>
</tr>
<tr>
<td>Sunflower oil</td>
<td>1 in 3300</td>
</tr>
<tr>
<td>Water</td>
<td>practically insoluble</td>
</tr>
<tr>
<td></td>
<td>1 in 500 at 70°C</td>
</tr>
<tr>
<td></td>
<td>1 in 100 at 100°C</td>
</tr>
</tbody>
</table>

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 twelve months. During processing, temperatures greater than 65°C should be avoided. The bulk material should be stored in an airtight container, in a cool, dry place.

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.\(^{(3)}\)
LD\(_{50}\) (mouse, oral): 25 g/kg \(^{(4)}\)
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 Guide (oral, rectal, topical preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias
Br, Eur, Fr, Ger and USPNF.

18. Related Substances
Ascorbic Acid.

19. 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.

20. Specific References

21. General References

22. Authors
UK: HEC Worthington.
Sodium Metabisulfite

1. Nonproprietary Names
BP: Sodium metabisulphite
PhEur: Natrii metabisulphitum
USPNF: Sodium metabisulfite

2. Synonyms
Disodium disulfite; disodium pyrosulfite; disulfurous acid disodium salt; E223; sodium acid sulfite.

3. Chemical Name and CAS Registry Number
Sodium metabisulfite [7681-57-4]

4. Empirical Formula
\( \text{Na}_2\text{S}_2\text{O}_5 \)

5. Structural Formula
\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{Na}^+ \text{O}^- \text{S-O-S-O}^- \text{Na}^+
\end{array}
\]

6. Functional Category
Antioxidant.

7. Applications in Pharmaceutical Formulation or Technology
Sodium metabisulfite is used as an antioxidant in oral, parenteral and topical pharmaceutical formulations. Primarily, sodium metabisulfite is used in acidic preparations; for alkaline preparations, sodium sulfite is usually preferred, see Sections 18 and 19. Sodium metabisulfite also has some antimicrobial activity, which is greatest at acid pH, and may be used as a preservative in oral preparations such as syrups. In the food industry, and in wine production, sodium metabisulfite is similarly used as an antioxidant, antimicrobial preservative and anti-browning agent. However, at concentrations above about 500 ppm it imparts a noticeable flavor to preparations. Sodium metabisulfite usually contains small amounts of sodium sulfite and sodium sulfate, see Section 18.

8. Description
Sodium metabisulfite occurs as colorless, prismatic crystals or as a white to creamy-white crystalline powder which has the odor of sulfur dioxide and an acidic, saline taste. Sodium metabisulfite crystallizes from water as a hydrate containing 7\( \text{H}_2\text{O} \).

9. Pharmacopeial Specifications

<table>
<thead>
<tr>
<th>Test</th>
<th>PhEur 1993</th>
<th>USPNF XVII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Appearance of solution</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

10. Typical Properties

Acidity/alkalinity: pH = 3.5-5.0 for a 5% w/v aqueous solution at 20°C.
Melting point: sodium metabisulfite melts with decomposition at less than 150°C.
Osmolarity: a 1.38% w/v aqueous solution is iso-osmotic with serum.

Solubility:

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol (95%)</td>
<td>slightly soluble</td>
</tr>
<tr>
<td>Glycerin</td>
<td>freely soluble</td>
</tr>
<tr>
<td>Water</td>
<td>1 in 1.9</td>
</tr>
<tr>
<td></td>
<td>1 in 1.2 at 100°C</td>
</tr>
</tbody>
</table>

11. Stability and Storage Conditions
On exposure to air and moisture, sodium metabisulfite is slowly oxidized to sodium sulfate with disintegration of the crystals.\(^1\) Addition of strong acids, to the solid, liberates sulfur dioxide.
In water, sodium metabisulfite is immediately converted to sodium (Na\(^+\)) and bisulfite (HSO\(_3\)\(^-\)) ions. Aqueous sodium metabisulfite solutions also decompose in air, especially on heating, and solutions which are to be sterilized by autoclaving should therefore be filled into containers in which the air has been replaced with an inert gas, such as nitrogen. The addition of dextrose to aqueous sodium metabisulfite solutions results in a decrease in the stability of the metabisulfite.\(^2\) The bulk material should be stored in a well-closed container, protected from light, in a cool, dry, place.

12. Incompatibilities
Sodium metabisulfite reacts with sympathomimetics and other drugs which are ortho- or para-hydroxybenzyl alcohol derivatives to form sulfonic acid derivatives possessing little or no pharmacological activity. The most important drugs subject to this inactivation are adrenaline and its derivatives.\(^3\) In addition, sodium metabisulfite is incompatible with chloramphenicol, due to a more complex reaction,\(^3\) and inactivates cisplatin in solution;\(^4,5\) it is also incompatible with phenylmercuric acetate when autoclaved in eye-drop preparations.\(^6\) Sodium metabisulfite may react with the rubber caps of multidose vials which should therefore be pre-treated with sodium metabisulfite solution.\(^6\)

13. Method of Manufacture
Sodium metabisulfite is prepared by saturating a solution of sodium hydroxide with sulfur dioxide and allowing crystallization to occur; hydrogen is passed through the solution to

---

**Continued**

<table>
<thead>
<tr>
<th>Test</th>
<th>PhEur 1993</th>
<th>USPNF XVII</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH (5% w/v solution)</td>
<td>3.5-5.0</td>
<td>—</td>
</tr>
<tr>
<td>Chloride</td>
<td>—</td>
<td>≤ 0.05%</td>
</tr>
<tr>
<td>Thiosulfate</td>
<td>+</td>
<td>≤ 0.05%</td>
</tr>
<tr>
<td>Arsenic</td>
<td>≤ 5 ppm</td>
<td>≤ 3 ppm</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>≤ 20 ppm</td>
<td>≤ 0.002%</td>
</tr>
<tr>
<td>Iron</td>
<td>≤ 20 ppm</td>
<td>≤ 0.002%</td>
</tr>
<tr>
<td>Assay (as Na(_2)SO(_2))</td>
<td>95-100.5%</td>
<td>—</td>
</tr>
<tr>
<td>Assay (as SO(_3))</td>
<td>—</td>
<td>65-67.4%</td>
</tr>
</tbody>
</table>

---
exclude air. Sodium metabisulfite may also be prepared by saturating a solution of sodium carbonate with sulfur dioxide and allowing crystallization to occur, or by thermally dehydrating sodium bisulfite.

14. Safety
Sodium metabisulfite is widely used as an antioxidant in oral, topical and parenteral pharmaceutical formulations; it is also widely used in food products.

Although it is extensively used in a variety of preparations, sodium metabisulfite, and other sulfites, have been associated with a number of severe, or fatal, adverse reactions. These are usually hypersensitivity type reactions and include bronchospasm and anaphylaxis. Allergy to sulfite antioxidants is estimated to occur in 5-10% of asthmatics although adverse reactions may also occur in non-asthmatics with no history of allergy.

Following oral ingestion, sodium metabisulfite is oxidized to sulfate and is excreted in the urine. Ingestion may result in gastric irritation due to the liberation of sulfurous acid, while ingestion of large amounts of sodium metabisulfite can cause colic, diarrhea, circulatory disturbances, CNS depression and death. In Europe, the acceptable daily intake of sodium metabisulfite, and other sulfites, used in foodstuffs has been set at up to 3.5 mg/kg body-weight, calculated as sulfur dioxide intake of sodium metabisulfite, and other sulfites, at up to 7.0 mg/kg body-weight, calculated as sulfur dioxide (SO2). The WHO has similarly set an acceptable daily intake of sodium metabisulfite, and other sulfites, at up to 7.0 mg/kg body-weight, calculated as sulfur dioxide (SO2).

15. Handling Precautions
Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium metabisulfite may be irritant to the skin and eyes; eye protection and gloves are recommended. In the UK, the long-term (8-hour TWA) occupational exposure limit for sodium metabisulfite is 5 mg/m3.

16. Regulatory Status
GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (epidural, IM and IV injections, ophthalmic solutions and oral preparations). Included in nonparenteral and parenteral medicines licensed in the UK.

17. Pharmacopeias
Aust, Belg, Br, Cz, Egypt, Eur, Fr, Hung, Ind, Jpn, Mex, Neth, Nord, Turk, USPNF and Yug. Also in BP Vet.

18. Related Substances
Potassium bisulfite; potassium metabisulfite; sodium bisulfite; sodium sulfite.

Potassium bisulfite: KHSO3
Molecular weight: 120.20
CAS number: [7775-03-7]
Synonyms: E228; potassium hydrogen sulfite.

Potassium metabisulfite: K2S2O3
Molecular weight: 222.32
CAS number: [16731-55-8]
Synonyms: dipotassium pyrosulfite; E224; potassium pyrosulfite.

Appearance: white crystalline powder.

Pharmaciepas: Fr and USPNF.
Solubility: freely soluble in water; practically insoluble in ethanol (95%).

Sodium bisulfite: NaHSO3
Molecular weight: 104.07
CAS number: [7631-90-5]
Synonyms: E222; sodium hydrogen sulfite.
Appearance: white crystalline powder.
Pharmaciepas: Jpn.
Density: 1.48 g/cm³
Solubility: soluble 1 in 3.5 parts of water at 20°C, 1 in 2 parts of water at 100°C, and 1 in 70 parts of ethanol (95%).

Comments: most substances sold as sodium bisulfite contain significant, variable, amounts of sodium metabisulfite, since the latter is less hygroscopic and more stable during storage and shipment. See Section 19.

Sodium sulfite: Na2SO3
Molecular weight: 126.06
CAS number: [7757-83-7]
Synonyms: anhydrous sodium sulfite; E221; exsiccated sodium sulfite.
Appearance: a white, odorless or almost odorless crystalline powder.
Pharmaciepas: Br, Eur, Fr, Jpn and Mex.
Acidity/alkalinity: pH = 9 for a saturated aqueous solution at 20°C.
Solubility: soluble 1 in 3.2 parts of water; soluble in glycerin; practically insoluble in ethanol (95%).

Comments: see Section 19.

19. Comments
Sodium metabisulfite is used as an antioxidant at low pH, sodium bisulfite at intermediate pH, and sodium sulfite at higher pH values.

20. Specific References


21. General References


22. Authors

USA: JT Stewart.
Butylated Hydroxyanisole

1. Nonproprietary Names
BP: Butylated hydroxyanisole
USPNF: Butylated hydroxyanisole

2. Synonyms
Antrancine 12; BHA; tert-butyl-4-methoxyphenol; 1,1-dimethyl-4-methoxyphenol; E320; Embanox BHA; Nipanox BHA; Nipantiox 1-F; PM 1787; PM 1788; PM 12366; Sustane 1-F; Tenox BHA.

3. Chemical Name and CAS Registry Number
2-tert-Butyl-4-methoxyphenol [25013-16-5]

4. Empirical Formula Molecular Weight
C_{11}H_{16}O_2 180.25
The BP 1993 describes butylated hydroxyanisole as 2-tert-butyl-4-methoxyphenol containing a variable amount of 3-tert-butyl-4-methoxyphenol.

5. Structural Formula

\[
\begin{align*}
\text{CH}_3 & \quad \text{C(CH}_3)_3 \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

6. Functional Category
Antioxidant.

7. Applications in Pharmaceutical Formulation or Technology
Butylated hydroxyanisole is an antioxidant with some antimicrobial properties.\(^1\) It is used in cosmetics, foods and pharmaceuticals particularly to delay or prevent oxidative rancidity of fats and oils and to prevent loss of activity of oil-soluble vitamins.

Butylated hydroxyanisole is frequently used in combination with other antioxidants, particularly butylated hydroxytoluene and alkyl gallates, and with sequestrants or synergists such as citric acid.

8. Description
Butylated hydroxyanisole occurs as a white or almost white crystalline powder or a yellowish-white waxy solid with a faint, characteristic aromatic odor.

9. Pharmacopeial Specifications

<table>
<thead>
<tr>
<th>Test</th>
<th>BP 1993 (Ad 1994)</th>
<th>USPNF XVII (Suppl 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Residue on ignition</td>
<td>—</td>
<td>≤ 0.01%</td>
</tr>
<tr>
<td>Sulfated ash</td>
<td>≤ 0.05%</td>
<td>—</td>
</tr>
<tr>
<td>Related substances</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Arsenic</td>
<td>—</td>
<td>≤ 3 ppm</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>—</td>
<td>≤ 0.001%</td>
</tr>
<tr>
<td>Organic volatile matter</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>Assay</td>
<td>—</td>
<td>≥ 98.5%</td>
</tr>
</tbody>
</table>

10. Typical Properties

Antimicrobial activity: activity is similar to that of the p-hydroxybenzoate esters (parabens). The greatest activity is against molds and Gram-positive bacteria, with less activity against Gram-negative bacteria.

Boiling point: 264°C
Melting point: 47°C (for pure 2-tert-butyl-4-methoxyphenol), see also Section 19.

Solubility: practically insoluble in water; freely soluble in

- ≥ 50% aqueous ethanol, propylene glycol, chloroform, ether, hexane, cottonseed oil, peanut oil, soybean oil and in solutions of alkali hydroxides. See also HPE Data.

Specific gravity: 1.05 at 20°C
Viscosity (kinematic): 3.3 mm²/s (3.3 cSt) at 99°C

<table>
<thead>
<tr>
<th>HPE Laboratory Project Data Method Lab # Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density</td>
</tr>
<tr>
<td>Solubility</td>
</tr>
<tr>
<td>Ethanol (95%) at 25°C</td>
</tr>
<tr>
<td>Ethanol (95%) at 37°C</td>
</tr>
<tr>
<td>Hexane at 25°C</td>
</tr>
<tr>
<td>Hexane at 37°C</td>
</tr>
<tr>
<td>Propylene glycol at 25°C</td>
</tr>
<tr>
<td>Propylene glycol at 37°C</td>
</tr>
<tr>
<td>Water at 25°C</td>
</tr>
</tbody>
</table>

Supplier: Eastman Fine Chemicals.

11. Stability and Storage Conditions

Exposure to light causes discoloration and loss of activity. Butylated hydroxyanisole should be stored in a well-closed container, protected from light, in a cool, dry, place.

12. Incompatibilities

Butylated hydroxyanisole is phenolic and undergoes reactions characteristic of phenols. It is incompatible with oxidizing agents and ferric salts. Trace quantities of metals, and exposure to light, cause discoloration and loss of activity.

13. Method of Manufacture

Prepared by the reaction of p-methoxyphenol with isobutene.

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Page 17 of 23
14. Safety
Butylated hydroxyanisole is absorbed from the gastrointestinal tract and is metabolized and excreted in the urine with less than 1% unchanged within 24 hours of ingestion. Although there have been some isolated reports of adverse skin reactions to butylated hydroxyanisole, it is generally regarded as nonirritant and nonsensitizing at the levels employed as an antioxidant.

Concern over the use of butylated hydroxyanisole has occurred following long-term animal feeding studies. Although previous studies in rats and mice fed butylated hydroxyanisole at several hundred times the US permitted level in the human diet showed no adverse effects, a study in which rats, hamsters and mice were fed butylated hydroxyanisole at 1-2% of the diet produced benign and malignant tumors of the forestomach, but in no other sites. However, humans do not have any region of the stomach comparable to the rodent forestomach and studies in animals that also do not have a comparable organ (dogs, monkeys and guinea pigs) showed no adverse effects. Thus, the weight of evidence does not support any relevance to the human diet where butylated hydroxyanisole is ingested at much lower levels. The WHO acceptable daily intake of butylated hydroxyanisole has been set at 500 µg/kg body-weight.

LD₅₀ (mouse, oral): 2.0 g/kg
LD₅₀ (rat, oral): 0.88 g/kg
LD₅₀ (rat, oral): 2.2 g/kg

15. Handling Precautions
Observe normal precautions appropriate to the circumstances and quantity of material handled. Butylated hydroxyanisole may be irritant to the eyes, skin, and on inhalation. It should be handled in a well-ventilated environment; gloves and eye protection are recommended.

16. Regulatory Status
GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhaledons, IM and IV injections, oral capsules and tablets, rectal, topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias
Br, Fr, Ind, It, Mex and USPNF.

18. Related Substances
Butylated Hydroxytoluene.

19. Comments
The commercially available material can have a wide melting point range (47-57°C) due to the presence of varying amounts of 3-tert-butyl-4-methoxyphenol. Tenox brands contain 0.1% w/w citric acid as a stabilizer.

20. Specific References

21. General References

22. Authors
USA: MJ Groves.
Butylated Hydroxytoluene

1. Nonproprietary Names
BP: Butylated hydroxytoluene
PhEur: Butylhydroxytoluenum
USPNF: Butylated hydroxytoluene

2. Synonyms
Advastah-401; Agidol; Annulex BHT; Antioxidant 30; Antracine 8; BHT; 2,6-bis(1,1-dimethylethyl)-4-methylphenol; butylhydroxytoluene; Dalpac; dibutylated hydroxytoluene; 2,6-di-tert-butyl-p-cresol; 3,5-di-tert-butyl-4-hydroxytoluene; E321; Embanox BHT; Impruvol; Ionol; OHS28890; Sustane; Tenox BHT; Topanol; Vianol.

3. Chemical Name and CAS Registry Number
2,6-Di-tert-butyl-4-methylphenol [128-37-0]

4. Empirical Formula
C₁₃H₂₄O

5. Structural Formula

6. Functional Category
Antioxidant.

7. Applications in Pharmaceutical Formulation or Technology
Butylated hydroxytoluene is used as an antioxidant in cosmetics, foods and pharmaceuticals. It is mainly used to delay or prevent oxidative rancidity of fats and oils and to prevent loss of activity of oil-soluble vitamins. Butylated hydroxytoluene is also used at 0.5-1% concentration in natural or synthetic rubber to provide enhanced color stability. Butylated hydroxytoluene has some antiviral activity and has been used therapeutically to treat herpes simplex labialis.

8. Description
Butylated hydroxytoluene occurs as a white or pale yellow crystalline solid or powder with a faint characteristic odor.

9. Pharmacopeial Specifications

<table>
<thead>
<tr>
<th>Test</th>
<th>PhEur 1988</th>
<th>USP NF XVII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Appearance of solution</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Congealing temperature</td>
<td>-</td>
<td>≥ 69.2°C</td>
</tr>
<tr>
<td>Freezing-point</td>
<td>69-70°C</td>
<td>-</td>
</tr>
<tr>
<td>Residue on ignition</td>
<td>-</td>
<td>≤ 0.002%</td>
</tr>
<tr>
<td>Sulfated ash</td>
<td>&lt; 0.1%</td>
<td>-</td>
</tr>
<tr>
<td>Arsenic</td>
<td>-</td>
<td>≤ 3 ppm</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>-</td>
<td>≤ 0.001%</td>
</tr>
<tr>
<td>Related substances</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Assay</td>
<td>-</td>
<td>≥ 99.0%</td>
</tr>
</tbody>
</table>

10. Typical Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boiling point</td>
<td>265°C</td>
</tr>
<tr>
<td>Density (bulk)</td>
<td>0.48-0.60 g/cm³</td>
</tr>
<tr>
<td>Flash point</td>
<td>127°C (open cup)</td>
</tr>
<tr>
<td>Latent heat of fusion</td>
<td>23.4 J/g (16.5 cal/g)</td>
</tr>
<tr>
<td>Melting point</td>
<td>70°C</td>
</tr>
<tr>
<td>Partition coefficients</td>
<td>Octanol: water = 4.17-5.80</td>
</tr>
<tr>
<td>Refractive index</td>
<td>nD²⁵ = 1.4859</td>
</tr>
<tr>
<td>Solubility</td>
<td>Practically insoluble in water, glycerin, propylene glycol, solutions of alkali hydroxides and dilute aqueous mineral acids. Freely soluble in acetone, benzene, ethanol (95%), ether, methanol, toluene, fixed oils and liquid paraffin. More soluble in food oils and fats than butylated hydroxyanisole. See also HPE Data.</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1.006 at 20°C; 0.890 at 80°C; 0.885 at 90°C; 0.800 at 100°C.</td>
</tr>
<tr>
<td>Specific heat</td>
<td>1.63 J/g°C (0.39 cal/g°C) for solid; 2.05 J/g°C (0.49 cal/g°C) for liquid.</td>
</tr>
<tr>
<td>Vapor density (relative)</td>
<td>7.6 (air = 1)</td>
</tr>
<tr>
<td>Vapor pressure</td>
<td>1.33 Pa (0.01 mmHg) at 20°C; 266.6 Pa (2 mmHg) at 100°C.</td>
</tr>
<tr>
<td>Viscosity (kinematic)</td>
<td>3.47 mm²/s (3.47 cSt) at 80°C</td>
</tr>
</tbody>
</table>

11. Stability and Storage Conditions
Exposure to light, moisture and heat cause discoloration and a loss of activity. Butylated hydroxytoluene should be stored in a...
well-closed container, protected from light, in a cool, dry, place.

12. Incompatibilities
Butylated hydroxytoluene is phenolic and undergoes reactions characteristic of phenols. It is incompatible with strong oxidizing agents such as peroxides and permanganates. Iron salts cause discoloration with loss of activity. Heating with catalytic amounts of acids causes rapid decomposition with the release of the flammable gas isobutylene.

13. Method of Manufacture
Prepared by the reaction of p-cresol with isobutylene.

14. Safety
Butylated hydroxytoluene is readily absorbed from the gastrointestinal tract and is metabolized and excreted in the urine mainly as glucuronide conjugates of oxidation products. Although there have been some isolated reports of adverse skin reactions, butylated hydroxytoluene is generally regarded as nonirritant and nonsensitizing at the levels employed as an antioxidant.(3,6)

The WHO has set a temporary estimated acceptable daily intake for butylated hydroxytoluene at up to 125 μg/kg body weight.(5)

Ingestion of 4 g of butylated hydroxytoluene, although causing severe nausea and vomiting, has been reported to be nonfatal.(6)

LD₅₀ (guinea pig, oral): 6.4-12.8 g/kg(7)
LD₅₀ (mouse, IP): 0.14 g/kg
LD₅₀ (mouse, IV): 0.18 g/kg
LD₅₀ (mouse, oral): 0.8-1.6 g/kg
LD₅₀ (rat, oral): 0.89 g/kg

15. Handling Precautions
Observe normal precautions appropriate to the circumstances and quantity of material handled. Butylated hydroxyanisole may be irritant to the eyes, skin, and on inhalation. It should be handled in a well-ventilated environment; gloves and eye protection are recommended.

16. Regulatory Status
GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations, IM and IV injections, oral capsules and tablets, rectal, topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias
Br, Eur, Fr, Ger, Ind, Mex, Neth, Nord, Swiss and USPNF.

18. Related Substances
Butylated Hydroxyanisole.

19. Comments

20. Specific References

21. General References
Verhagen H. Toxicology of the food additives BHA and BHT. Pharm Weekbl (Sci) 1990; 12: 164-166.

22. Authors
USA: MJ Groves.
Propyl Gallate

1. Nonproprietary Names
BP: Propyl gallate
USPNF: Propyl gallate

2. Synonyms
E310; gallic acid propyl ester; Progallin P; n-propyl gallate; propyl 3,4,5-trihydroxybenzoate; Tenox PG.

3. Chemical Name and CAS Registry Number
3,4,5-Trihydroxybenzoic acid propyl ester [121-79-9]

4. Empirical Formula Molecular Weight
C₁₀H₁₂O₅ 212.20

5. Structural Formula

6. Functional Category
Antioxidant.

7. Applications in Pharmaceutical Formulation or Technology
Propyl gallate has become widely used as an antioxidant in cosmetics, perfumes, foods and pharmaceuticals since its use in preventing autoxidation of oils was first described in 1943.¹ ²
It is primarily used, in concentrations up to 0.1% w/v, to prevent the rancidity of oils and fats; it may also be used at concentrations of 0.002% w/v to prevent peroxide formation in ether and at 0.01% w/v to prevent the oxidation of paraldehyde. Synergistic effects with other antioxidants such as butylated hydroxyanisole and butylated hydroxytoluene have been reported. Propyl gallate is also said to possess some antimicrobial properties, see Section 10.
Other alkyl gallates are also used as antioxidants and have approximately equivalent antioxidant properties when used in equimolar concentration; solubilities however vary, see Section 18.

8. Description
Propyl gallate is a white, odorless or almost odorless crystalline powder, with a bitter astringent taste which is not normally noticeable at the concentrations employed as an antioxidant.

9. Pharmacopeial Specifications

<table>
<thead>
<tr>
<th>Test</th>
<th>BP 1993</th>
<th>USPNF XVII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Melting range</td>
<td>148-151°C</td>
<td>146-150°C</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>≤ 1.0%</td>
<td>≤ 0.5%</td>
</tr>
<tr>
<td>Residue on ignition</td>
<td>—</td>
<td>≤ 0.1%</td>
</tr>
<tr>
<td>Sulfated ash</td>
<td>≤ 0.1%</td>
<td>—</td>
</tr>
<tr>
<td>Chloride</td>
<td>≤ 330 ppm</td>
<td>—</td>
</tr>
<tr>
<td>Sulfate</td>
<td>≤ 0.12%</td>
<td>—</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>—</td>
<td>≤ 0.001%</td>
</tr>
<tr>
<td>Assay (dried basis)</td>
<td>—</td>
<td>98.0-102.0%</td>
</tr>
</tbody>
</table>

10. Typical Properties

Antimicrobial activity: propyl gallate has been reported to possess some antimicrobial activity against Gram-negative, Gram-positive and fungal species.³ Its effectiveness as a preservative may be improved when used in combination with zinc salts, such as zinc sulfate, due to synergistic effects.⁴
Reported minimum inhibitory concentrations (MICs) for aqueous solutions containing 4% v/v ethanol as cosolvent are shown below:³

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida albicans</td>
<td>1500</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>330</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>600</td>
</tr>
</tbody>
</table>

Melting point: 150°C
Solubility:

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility at 20°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almond oil</td>
<td>1 in 44</td>
</tr>
<tr>
<td>Castor oil</td>
<td>1 in 4.5</td>
</tr>
<tr>
<td>Cottonseed oil</td>
<td>1 in 81 at 30°C</td>
</tr>
<tr>
<td>Ethanol (95%)</td>
<td>1 in 3</td>
</tr>
<tr>
<td>Ether</td>
<td>1 in 3</td>
</tr>
<tr>
<td></td>
<td>1 in 1.2 at 25°C</td>
</tr>
<tr>
<td>Lanolin</td>
<td>1 in 16.7 at 25°C</td>
</tr>
<tr>
<td>Lard</td>
<td>1 in 88 at 45°C</td>
</tr>
<tr>
<td>Mineral oil</td>
<td>1 in 200</td>
</tr>
<tr>
<td>Peanut oil</td>
<td>1 in 2000</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>1 in 2.5 at 25°C</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>1 in 100 at 25°C</td>
</tr>
<tr>
<td>Water</td>
<td>1 in 1000</td>
</tr>
<tr>
<td></td>
<td>1 in 286 at 25°C</td>
</tr>
</tbody>
</table>

11. Stability and Storage Conditions
Propyl gallate is unstable at high temperatures and is rapidly destroyed in oils that are used for frying purposes.
The bulk material should be stored in a well-closed, nonmetallic container, protected from light, in a cool, dry, place.
12. Incompatibilities
The alkyl gallates, are incompatible with metals, e.g. sodium, potassium and iron, forming intensely colored complexes. Complex formation may be prevented, under some circumstances, by the addition of a sequestering agent, typically citric acid. Propyl gallate may also react with oxidizing materials.

13. Method of Manufacture
Propyl gallate is prepared by the esterification of 3,4,5-trihydroxybenzoic acid (gallic acid) with n-propanol. Other alkyl gallates are similarly prepared using an appropriate alcohol of the desired alkyl chain length.

14. Safety
It has been reported, following animal studies, that propyl gallate has a strong contact sensitization potential. However, despite this, there have been few reports of adverse reactions. Those that have been described include: contact dermatitis; allergic contact dermatitis; and methemoglobinemia in neonates.

The WHO has set an estimated acceptable daily intake for propyl gallate at up to 2.5 mg/kg body-weight. LD₅₀ (cat, oral): 0.4 g/kg; LD₅₀ (mouse, oral): 1.7 g/kg; LD₅₀ (rat, oral): 3.8 g/kg; LD₅₀ (rat, IP): 0.38 g/kg

15. Handling Precautions
Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. When heated to decomposition propyl gallate may emit toxic fumes and smoke.

16. Regulatory Status
GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM. injections and topical preparations). Included in nonparenteral medicines licensed in the UK.

17. Pharmacopeias
Aust, Br, Cz, Egypt, Fr, Ind, Nord and USPNF.

18. Related Substances
Dodecyl gallate; ethyl gallate; octyl gallate.

Dodecyl gallate: C₁₉H₃₉O₅
Molecular weight: 338.44
CAS number: [1166-52-5]
Synonyms: dodecyl 3,4,5-trihydroxybenzoate; E312; lauryl gallate.
Pharmacopeia: Aust, Br and Fr.
Appearance: white, odorless or almost odorless crystalline powder.
Melting point: 96-97.5°C

Octyl gallate: C₁₅H₃₁O₅
Molecular weight: 282.34
CAS number: [1034-01-1]
Synonyms: E311; octyl 3,4,5-trihydroxybenzoate.
Pharmacopeia: Br and Fr.
Appearance: white, odorless or almost odorless crystalline powder.
Melting point: 100-102°C

19. Comments
Propyl gallate has been reported to impart an 'off' flavor to corn and cottonseed oils when used as an antioxidant. An acceptable daily intake for dodecyl gallate and octyl gallate was not set by the WHO due to insufficient data. The use of octyl gallate in beer and other widely consumed beverages was however not recommended by the WHO due to the possibility of adverse reactions in the buccal mucosa of individuals previously sensitized by cutaneous contact with this compound.

20. Specific References
2. Boehm E, Williams R. A study of the inhibiting actions of propyl gallate (normal propyl trihydroxy benzoeate) and certain other trihydroxy phenols on the autoxidation of animal and vegetable oils. Chemist Drugg 1943; 140: 146-147.

21. General References

22. Authors
UK: PJ Weller.