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BV Kadri.

22 Date of Revision

4 May 2017.

Thymol

1 Nonproprietary Names

BP: Thymol
JP: Thymol
PhEur: Thymol
USP–NF: Thymol

2 Synonyms

Acido trimico; 3-*p*-cymenol; *p*-cymen-3-ol; *Flavinol*; 3-hydroxy-*p*-cymene; 3-hydroxy-1-methyl-4-isopropylbenzene; *Intrasol*; isopropyl cresol; isopropyl-*m*-cresol; 6-isopropyl-*m*-cresol; isopropyl metacresol; 2-isopropyl-5-methylphenol; 1-methyl-3-hydroxy-4-isopropylbenzene; 5-methyl-2-isopropylphenol; 5-methyl-2-(1-methylethyl) phenol; *Medophyll*; *p*-cymen-3-ol; thyme camphor; thymic acid; *m*-thymol; thymolum; timol.

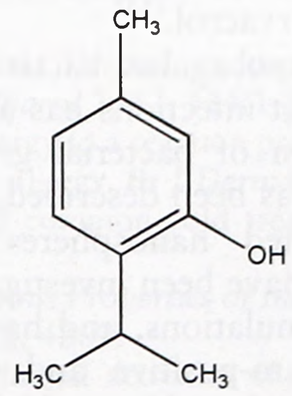
3 Chemical Name and CAS Registry Number

Thymol [89-83-8]
m-Thymol [3228-03-3]

4 Empirical Formula and Molecular Weight

$C_{10}H_{14}O$ 150.24

5 Structural Formula



6 Functional Category

Antioxidant; flavoring agent; penetration enhancer.

7 Applications in Pharmaceutical Formulation or Technology

Thymol is a phenolic antiseptic, which has antibacterial and antifungal activity. *See* Section 10. However, it is not suitable for use as a preservative in pharmaceutical formulations because of its low aqueous solubility.

Thymol is used as a skin penetrant and has been shown to enhance the *in vitro* percutaneous absorption of a number of drugs, including 5-fluorouracil,[1] piroxicam,[2] propranolol,[3] naproxen,[4] and tamoxifen.[5] Studies have also demonstrated that the melting point of lidocaine is significantly lowered when it is mixed with thymol.[6,7]

Thymol is a true antioxidant and has been used at concentrations of 0.01% as an antioxidant for halothane, trichloroethylene, and tetrachloroethylene. The antioxidant activity of thymol[8,9] and thymol analogues[8] has been described.

T

Thymol is also used as a synthetic flavoring agent in pharmaceutical formulations. It has been investigated for use in a copolymer complex with β-cyclodextrin to improve its aqueous solubility, dissolution rate, bioavailability, and palatability.[10]

8 Description

Thymol occurs as colorless or often large translucent crystals, or as a white crystalline powder with a herbal odor (aromatic and thyme-like) and a pungent caustic taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for thymol.

Test	JP XVII	PhEur 9.2	USP 40–NF 35 S1
Identification	+	+	+
Characters	–	+	–
Melting range	49–51°C	48–52°C	48–51°C
Appearance of solution	–	+	–
Acidity	–	+	–
Related substances	–	+	–
Residue on evaporation	≤0.05%	≤0.05%	≤0.05%
Other phenols	+	–	–
Assay	≥98.0%	–	99.0–101.0%

10 Typical Properties

Acidity/alkalinity A 4% solution in ethanol (50%) is neutral to litmus; a 1% solution in water has a pH of 7.

Antimicrobial activity The antimicrobial activity of thymol against eight oral bacteria has been studied *in vitro*. Inhibitory activity was noted against almost all organisms, and a synergistic effect was observed for combinations of thymol and eugenol, and of thymol and carvacrol.[11]

The activity of thymol against bacteria commonly involved in upper respiratory tract infections has also been shown.[12] The continued suppression of bacterial growth following limited exposure to thymol has been described.[13]

Thymol-encapsulated nanospheres at concentrations of 0.078–0.625 mg/mL have been investigated for use as preservatives in cosmetic formulations, and have been shown to be as effective against Gram-positive and Gram-negative bacteria compared with methylparaben, which is routinely used at concentrations of 4.0 mg/mL.[14]

Boiling point . About 233°C

Density 0.97 g/cm^3 at 25°C; has a greater density than water, but when liquefied by fusion is less dense than water.

Dissociation constant pK_a = 10.6 at 20°C

Melting point 48–51°C, but, once melted, remains liquid at a considerably lower temperature.

Partition coefficient Log *P* (octanol : water) = 3.3

Phenol coefficient About 50

Refractive index

n_D^{25} = 0.15204;

n_D^{20} = 0.15227.

Solubility Soluble 1 in 0.7–1.0 of chloroform; 1 in 1 of ethanol (95%); 1 in 1.5 of ether, glacial acetic acid; 1 in 1.7–2.0 of olive oil; 1 in 1000 of water. Freely soluble in essential oils, fixed oils, and fats. Sparingly soluble in glycerin. Dissolves in dilute solutions of alkali hydroxides, forming salts that have increased solubility but whose solutions darken on standing.

Spectroscopy

IR spectrum *see* Figure 1.

Raman spectrum *see* Figure 2.

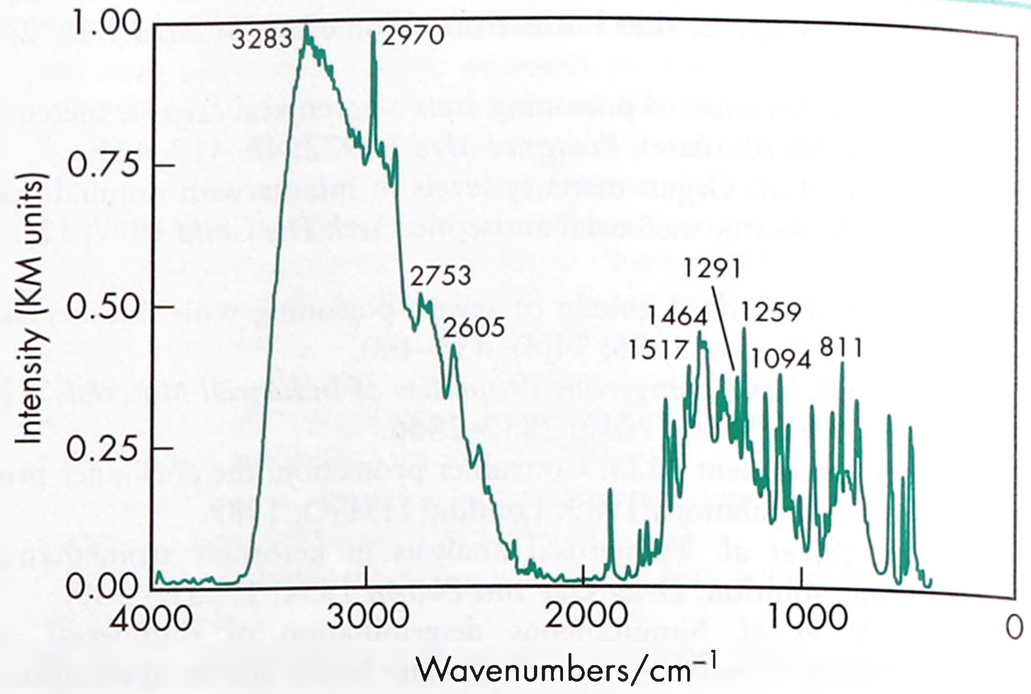


Figure 1: Infrared spectrum of thymol measured by diffuse reflectance. Adapted with permission of Informa Healthcare.

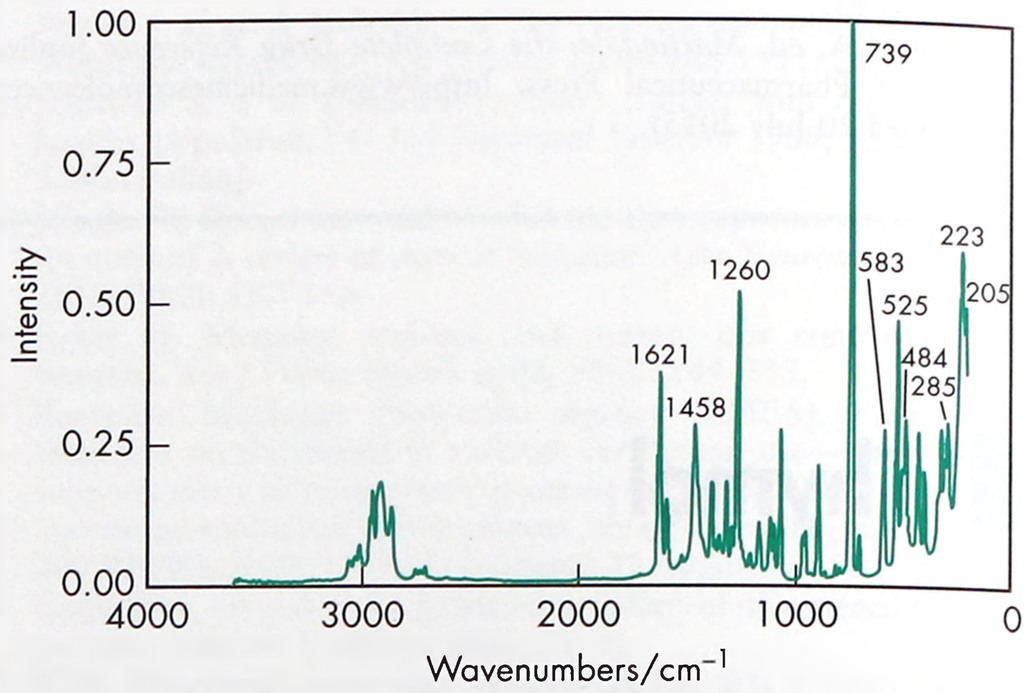


Figure 2: Raman spectrum of thymol measured in the 180° reflectance mode. Adapted with permission of Informa Healthcare.

Vapor pressure 1.0 mmHg at 64°C

Volatility Appreciable volatility at 100°C; volatile in water vapor at 25°C.

11 Stability and Storage Conditions

Thymol should be stored in well-closed, light-resistant containers, in a cool, dry, place. Thymol is affected by light.

12 Incompatibilities

Thymol is incompatible with iodine, alkalis, and oxidizing agents. It liquefies, or forms soft masses, on trituration with acetanilide, antipyrine, camphor, monobromated camphor, chloral hydrate, menthol, phenol, or quinine sulfate. The antimicrobial activity of thymol is reduced in the presence of proteins.

13 Method of Manufacture

Thymol is obtained from the volatile oil of thyme (*Thymus vulgaris* Linné (Fam. Labiatae)) by fractional distillation followed by extraction and recrystallization. Thyme oil yields about 20–30% thymol. Thymol may also be produced synthetically from *p*-cymene, menthone, or piperitone, or by the interaction of *m*-cresol with isopropyl chloride.

14 Safety

Thymol is used in cosmetics, foods, and pharmaceutical applications as an excipient. However, thymol may be irritating when

inhaled or following contact with the skin or eyes, and has been associated with a report of contact allergy.[15] It may also cause abdominal pain and vomiting, and sometimes stimulation followed by depression of the central nervous system following oral consumption; fats and alcohol increase absorption and aggravate symptoms.

Respiratory arrest, attributed to acute nasal congestion and edema, has been reported in a 3-week-old patient due to the erroneous intranasal application of *Karvol*, a combination product that includes thymol. The patient recovered, but it was recommended that inhalation decongestants should not be used in children under the age of 5 years.[16]

LD_{50} (mouse, IV): 0.1 g/kg[17]
LD_{50} (mouse, oral): 0.64 g/kg[17]
LD_{50} (rat, oral): 0.98 g/kg[17]

15 Handling Precautions

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

When thymol is heated to decomposition, carbon dioxide and carbon monoxide are formed. Special precautions should be taken to avoid inhalation, or contact with the skin or eyes. Eye protection and gloves are recommended.

16 Regulatory Status

Although not GRAS listed, thymol is listed as a food additive in the EAFUS list compiled by the FDA. Included in the FDA Inactive Ingredients Database (inhalation, liquid; oral, powder for solution). Included in nonparenteral medicines (oral lozenges; capsules for inhalation, inhalation drops; topical creams and ointments) licensed in the UK. Included in the Canadian Natural Health Products Ingredients Database.

17 Related Substances

Menthol.

18 Comments

Thymol is a more powerful disinfectant than phenol, but its low water solubility, its irritancy to tissues, and its inactivation by organic material, such as proteins, limit its use as a disinfectant. Thymol is chiefly used as a deodorant in antiseptic mouthwashes, gargles, and toothpastes, such as in Compound Thymol Glycerin BP, in which it has no antiseptic action. It is included in food, perfume, and cosmetic products.

The inhalation of thymol, in combination with other volatile substances, is used to alleviate the symptoms of colds, coughs, and associated respiratory disorders. Externally, thymol has been used in dusting powders for the treatment of fungal skin infections; thymol has been shown to have synergistic antifungal effects when combined with ketoconazole.[18] Thymol was formerly used in the treatment of hookworm infections but has now been superseded by less toxic substances.

In dentistry, thymol has been mixed with phenol and camphor to prepare cavities before filling, and mixed with zinc oxide to form a protective cap for dentine. Thymol has also been used as a pesticide and fungicide.

A specification for thymol is included in the *Food Chemicals Codex* (FCC).[19]

The EINECS number for thymol is 201-944-8. The PubChem Compound ID (CID) for thymol is 6989.

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20 General References

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21 Author

ME Quinn.

22 Date of Revision

4 May 2017.

Titanium Dioxide

1 Nonproprietary Names

BP: Titanium Dioxide

JP: Titanium Oxide

PhEur: Titanium Dioxide

USP–NF: Titanium Dioxide

2 Synonyms

Anatase titanium dioxide; brookite titanium dioxide; E171; *Hombitan AFDC*; *Hombitan FF-Pharma*; *Kronos 1171*; pigment white 6; *Pretiox AV-01-FG*; rutile titanium dioxide; *Tioxide*; *TiPure*; titanic anhydride; titanii dioxidum; *Tronox*.

3 Chemical Name and CAS Registry Number

Dioxotitanium [13463-67-7]

4 Empirical Formula and Molecular Weight

TiO_2 79.88

5 Structural Formula

See Section 4.

6 Functional Category

Coating agent; opacifier; pigment.

7 Applications in Pharmaceutical Formulation or Technology

Titanium dioxide is widely used in confectionery, cosmetics, and foods, in the plastics industry, and in topical and oral pharmaceutical formulations as a white pigment.

Owing to its high refractive index, titanium dioxide has light-scattering properties that may be exploited in its use as a white pigment and opacifier. The range of light that is scattered can be altered by varying the particle size of the titanium dioxide powder. For example, titanium dioxide with an average particle size of 230 nm scatters visible light, while titanium dioxide with an average particle size of 60 nm scatters ultraviolet light and reflects visible light.[1]

In pharmaceutical formulations, titanium dioxide is used as a white pigment in film-coating suspensions,[2,3] sugar-coated tablets, and gelatin capsules. Titanium dioxide may also be admixed with other pigments.

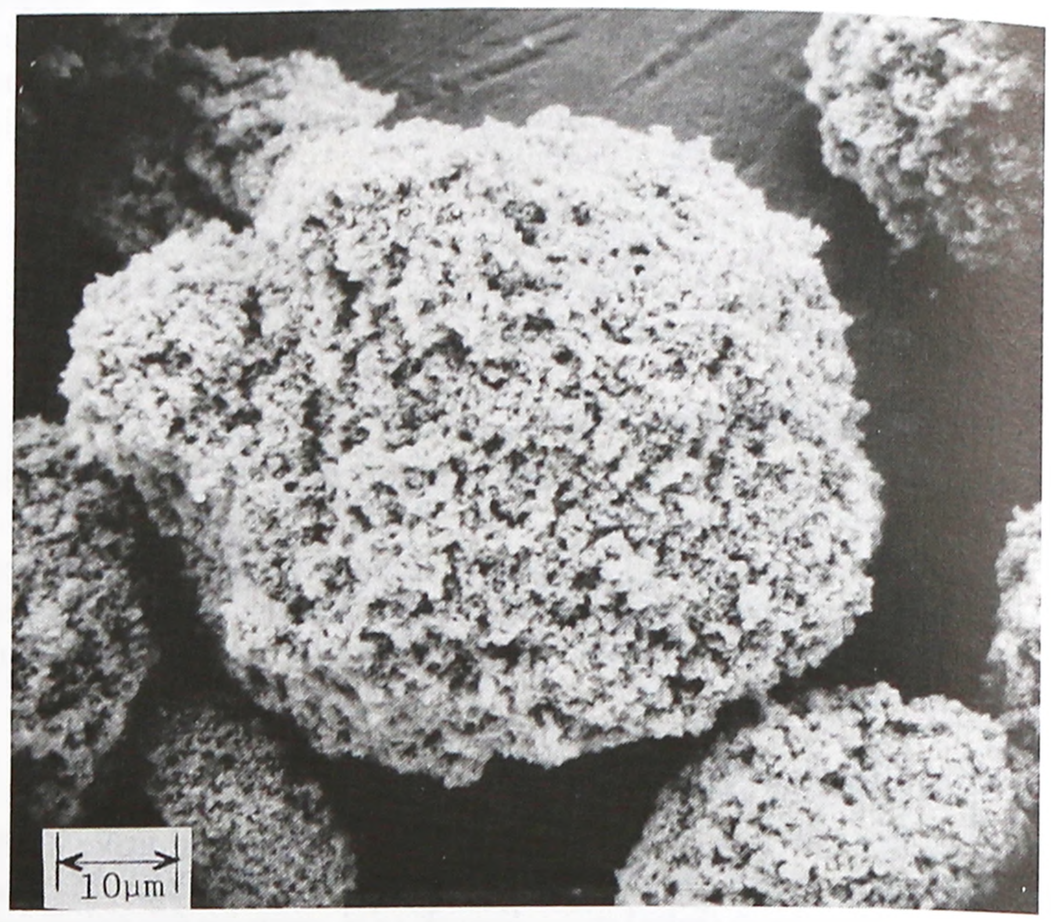
Titanium dioxide is also used in dermatological preparations and cosmetics, such as sunscreens.[1,4]

8 Description

Titanium dioxide occurs as a white, amorphous, odorless, and tasteless nonhygroscopic powder. Although the average particle size of titanium dioxide powder is less than 1 µm, commercial titanium dioxide generally occurs as aggregated particles of approximately 100 µm diameter.

Titanium dioxide may occur in several different crystalline forms: rutile; anatase; and brookite. Of these, rutile and anatase are the only forms of commercial importance. Rutile is the more thermodynamically stable crystalline form, but anatase is the form most commonly used in pharmaceutical applications.

SEM 1: Excipient: titanium dioxide; magnification: 1200×; voltage: 10 kV.



9 Pharmacopeial Specifications

See Table I. The PhEur includes a nonmandatory functionality related characteristics section in the monograph for titanium dioxide. This section applies when the material is being used as an opacifier in solid oral dosage forms and in preparations for cutaneous application. The appropriate test is for particle size distribution, but as this is a nonmandatory test no limits are given.

Table I: Pharmacopeial specifications for titanium dioxide.

Test	JP XVII	PhEur 9.2	USP 40–NF 35 S1
Identification	+	+	+
Characters	—	+	—
Appearance of solution	—	+	—
Acidity or alkalinity	—	+	—
Water-soluble substances	≤5.0 mg	≤0.5%	≤0.25%
Antimony	—	≤100 ppm	—
Arsenic	≤10 ppm	≤5 ppm	≤1 ppm
Barium	—	+	—
Iron	—	≤200 ppm	—
Loss on drying	≤0.5%	—	≤0.5%
Loss on ignition	—	—	≤13%
Acid-soluble substances	—	—	≤0.5%
Lead	≤60 ppm	—	—
Assay	≥98.5%	98.0–100.5%	99.0–100.5%

10 Typical Properties

Density (bulk) 0.4–0.62 g/cm^3 [5]

Density (tapped) 0.625–0.830 g/cm^3 [6]

Density (true)

3.8–4.1 g/cm^3 for anatase;

≈3.9 g/cm^3 for *Hombitan FF-Pharma*;

3.9–4.2 g/cm^3 for rutile.