

Menthol

1 Nonproprietary Names

BP: Racementhol
JP: *dl*-Menthol
PhEur: Mentholum racemicum
USP: Menthol

2 Synonyms

Hexahydrothymol; 2-isopropyl-5-methylcyclohexanol; 4-isopropyl-1-methylcyclohexan-3-ol; 3-*p*-menthanol; *p*-menthan-3-ol; *dl*-menthol; peppermint camphor; racemic menthol.

3 Chemical Name and CAS Registry Number

(1*RS*,2*RS*,5*RS*)-(±)-5-Methyl-2-(1-methylethyl)cyclohexanol
[15356-70-4]

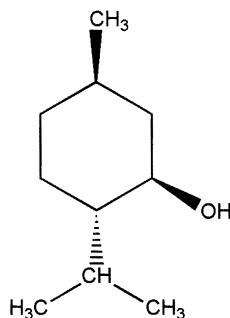
Note that the following CAS numbers have also been used: [1490-04-6] and [89-78-1].

4 Empirical Formula Molecular Weight

C₁₀H₂₀O

156.27

5 Structural Formula



6 Functional Category

Flavoring agent; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Menthol is widely used in pharmaceuticals, confectionery, and toiletry products as a flavoring agent or odor enhancer. In addition to its characteristic peppermint flavor, *l*-menthol, which occurs naturally, also exerts a cooling or refreshing sensation that is exploited in many topical preparations. Unlike mannitol, which exerts a similar effect due to a negative heat of solution, *l*-menthol interacts directly with the body's coldness receptors. *d*-Menthol has no cooling effect, while racemic menthol exerts an effect approximately half that of *l*-menthol.

When used to flavor tablets, menthol is generally dissolved in ethanol (95%) and sprayed onto tablet granules and not used as a solid excipient.

Menthol has been investigated as a skin-penetration enhancer and is also used in perfumery, tobacco products, and as a therapeutic agent. See Table I.

Table I: Uses of menthol.

Use	Concentration (%)
Pharmaceutical products	
Inhalation	0.02–0.05
Oral suspension	0.003
Oral syrup	0.005–0.015
Tablets	0.2–0.4
Topical formulations	0.05–10.0
Cosmetic products	
Toothpaste	0.4
Mouthwash	0.1–2.0
Oral spray	0.3

8 Description

Racemic menthol is a mixture of equal parts of the (1*R*,2*S*,5*R*)- and (1*S*,2*R*,5*S*)-isomers of menthol. It is a free-flowing or agglomerated crystalline powder, or colorless, prismatic, or acicular shiny crystals, with a strong characteristic odor and taste. The crystalline form may change with time owing to sublimation within a closed vessel. The USP 25 specifies that menthol may be either naturally occurring *l*-menthol or synthetically prepared racemic or *dl*-menthol. However, the JP 2001 and PhEur 2001, along with other pharmacopeias, include two separate monographs for racemic and *l*-menthol.

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Boiling point: 212 °C

Flash point: 93 °C

Melting point: 34–36 °C

Refractive index: $n_D^{20} = 1.4615$

Solubility: very soluble in ethanol (95%), chloroform, and ether; very slightly soluble in glycerin; practically insoluble in water.

Specific rotation $[\alpha]_D^{20}$: –2 to +2° (10% w/v alcoholic solution)
See also Section 17.

11 Stability and Storage Conditions

A formulation containing menthol 1% w/w in aqueous cream has been reported to be stable for up to 18 months when stored at room temperature.⁽¹⁾

Menthol should be stored in a well-closed container at a temperature not exceeding 25 °C, since it sublimates readily.

Table II: Pharmacopeial specifications for menthol.

Test	JP 2001	PhEur 2001	USP 25
Identification	+	+	+
Acidity or alkalinity	—	+	—
Congeeing range	27–28 °C	—	+
Melting point			
<i>d</i> -menthol	—	≈ 34 °C	—
<i>l</i> -menthol	42–44 °C	≈ 43 °C	41–44 °C
Specific optical rotation			
<i>d</i> -menthol	–2 to +2 °	–0.2 to +0.2 °	–2 to +2 °
<i>l</i> -menthol	–45 to –51 °	–48 to –51 °	–45 to –51 °
Readily oxidizable substances	—	—	+
Chromatographic purity	—	—	+
Related substances	—	+	—
Appearance of solution	—	+	—
Nonvolatile residue	+	—	≤0.05%
Residue on evaporation	—	≤0.05%	—
Organic volatile impurities	—	—	+
Thymol	+	—	—
Nitromethane or nitroethane	+	—	—
Assay	≥98.0%	—	—

12 Incompatibilities

Incompatible with: butylchloral hydrate; camphor; chloral hydrate; chromium trioxide; β-naphthol; phenol; potassium permanganate; pyrogallol; resorcinol; and thymol.

13 Method of Manufacture

Menthol occurs widely in nature as *l*-menthol and is the principal component of peppermint and cornmint oils obtained from the *Mentha piperita* and *Mentha arvensis* species. Commercially, *l*-menthol is mainly produced by extraction from these volatile oils. It may also be prepared by partial or total synthetic methods.

Racemic menthol is prepared synthetically via a number of routes, e.g. by hydrogenation of thymol.

14 Safety

Almost all toxicological data for menthol relate to its use as a therapeutic agent rather than as an excipient. Inhalation or ingestion of large quantities can result in serious adverse reactions such as ataxia⁽²⁾ and CNS depression.⁽³⁾ Although menthol is essentially nonirritant there have been some reports of hypersensitivity following topical application.^(4,5) In a Polish study approximately 1% of individuals were determined as being sensitive to menthol.⁽⁶⁾

The WHO has set an acceptable daily intake of menthol at up to 0.4 mg/kg body-weight.⁽⁷⁾

LD₅₀ (rat, IM): 10.0 g/kg⁽⁸⁾
LD₅₀ (rat, oral): 3.18 g/kg

15 Handling Precautions

May be harmful by inhalation or ingestion in large quantities; may be irritant to the skin, eyes, and mucous membranes. Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (dental preparations, inhalations, oral aerosols, capsules, solutions, suspensions, syrups, and tablets, also topical preparations). Included in nonparenteral medicines licensed in the UK. Accepted for use in foods and confectionery as a flavoring agent of natural origin.

17 Related Substances

d-Menthol; *l*-menthol.

d-Menthol

Empirical formula: C₁₀H₂₀O

Molecular weight: 156.27

CAS number: [15356-60-2]

Synonyms: (1*S*,2*R*,5*S*)-(+)-5-methyl-2-(1-methylethyl)cyclohexanol.

Appearance: colorless, prismatic or acicular, shiny crystals, without the characteristic odor, taste, and cooling effect of *l*-menthol. The crystalline form may change with time owing to sublimation within a closed vessel.

Flash point: 91 °C

Melting point: 43–44 °C

Specific rotation [α]_D²³: +48° (10% w/v alcoholic solution)

l-Menthol

Empirical formula: C₁₀H₂₀O

Molecular weight: 156.27

CAS number: [2216-51-5]

Synonyms: levomenthol; levomentholum; (1*R*,2*S*,5*R*)-(–)-5-methyl-2-(1-methylethyl)cyclohexanol.

Appearance: colorless, prismatic, or acicular, shiny crystals, with a strong, characteristic odor, taste, and cooling effect. The crystalline form may change with time owing to sublimation within a closed vessel.

Flash point: >100 °C

Melting point: 41–44 °C

Refractive index: n_D^{20} = 1.4600

Specific rotation [α]_D²⁰: –50° (10% w/v alcoholic solution)

Safety:

LD₅₀ (mouse, IP): 6.6 g/kg⁽⁸⁾

LD₅₀ (mouse, oral): 3.4 g/kg

LD₅₀ (rat, IP): 0.7 g/kg

LD₅₀ (rat, oral): 3.3 g/kg

18 Comments

It should be noted that considerable variation in the chemical composition of natural menthol oils can occur depending upon their country of origin. The EINECS number for menthol is 201-939-0.

19 Specific References

- Gallagher P, Jones S. A stability and validation study of 1% w/w menthol in aqueous cream. *Int J Pharm Pract* 1997; 5: 101–104.
- Luke E. Addiction to mentholated cigarettes [letter]. *Lancet* 1962; i: 110–111.
- O'Mullane NM, Joyce P, Kamath SV, *et al.* Adverse CNS effects of menthol-containing olabas oil [letter]. *Lancet* 1982; i: 1121.
- Papa CM, Shelley WB. Menthol hypersensitivity. *J Am Med Assoc* 1964; 189: 546–548.
- Hayakawa R, Yamamura M, Sugiura M. Contact dermatitis from *l*-menthol. *Cosmet Toilet* 1996; 111(7): 28–29.

- 6 Rudzki E, Kleniewska D. The epidemiology of contact dermatitis in Poland. *Br J Dermatol* 1970; **83**: 543–545.
- 7 FAO/WHO. Evaluation of certain food additives: Fifty-first report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 2000; No. 891.
- 8 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 10th edn. New York: Wiley, 2000: 2296.

20 General References

Bauer K, Garbe D, Surburg H. *Common Fragrance and Flavor Materials*. Weinheim: VCH, 1990: 43–46.

Eccles R. Menthol and related cooling compounds. *J Pharm Pharmacol* 1994; **46**: 618–630.

21 Author

PJ Weller.

22 Date of Revision

13 May 2002.