

Ethyl Acetate

1 Nonproprietary Names

BP: Ethyl acetate
PhEur: Ethylis acetas
USPNF: Ethyl acetate

2 Synonyms

Acetic acid ethyl ester; acetic ester; acetic ether; acetoxyethane; aethylis acetas; aethylum aceticum; ethyl ethanoate; vinegar naphtha.

3 Chemical Name and CAS Registry Number

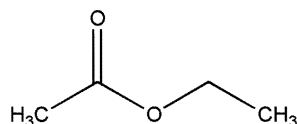
Ethyl acetate [141-78-6]

4 Empirical Formula Molecular Weight

C₄H₈O₂

88.1

5 Structural Formula



6 Functional Category

Flavoring agent; solvent.

7 Applications in Pharmaceutical Formulation or Technology

In pharmaceutical preparations, ethyl acetate is primarily used as a solvent, although it has also been used as a flavoring agent. As a solvent, it is included in topical solutions and gels, and in edible printing inks used for tablets.

Ethyl acetate has also been shown to increase the solubility of chlortalidone⁽¹⁾ and to modify the polymorphic crystal forms obtained for piroxicam pivalate⁽²⁾ and mefenamic acid,⁽³⁾ and has been used in the formulation of microspheres.^(4,5)

In food applications, ethyl acetate is mainly used as a flavoring agent. It is also used in artificial fruit essence and as an extraction solvent in food processing.

8 Description

Ethyl acetate is a clear, colorless, volatile liquid with a pleasant fruity, fragrant, and slightly acetous odor, and has a pleasant taste when diluted. Ethyl acetate is flammable.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for ethyl acetate.

Test	PhEur 2002	USPNF 20
Identification	+	+
Characters	+	—
Boiling point	76–78°C	—
Appearance of solution	+	—
Acidity	+	+
Specific gravity	0.898–0.902	0.894–0.898
Refractive index	1.370–1.373	—
Readily carbonizable substances	+	+
Chromatographic purity	+(a)	+
Residue on evaporation	≤30 ppm	≤0.02%
Water	≤0.1%	—
Limit of methyl compounds	—	+
Organic volatile impurities	—	+
Assay	—	99.0–100.5%

(a) The PhEur 2002 lists impurities in ethyl acetate as methyl acetate, ethanol, and methanol.

10 Typical Properties

Autoignition temperature: 486.1°C

Boiling point: 77°C

Dielectric constant: 6.11

Density: 0.902 g/cm³ at 20°C

Explosive limit: 2.2–11.5% (volume in air)

Flash point:

+7.2°C (open cup)

–5.0°C (closed cup)

Freezing point: –83.6°C

Refractive index: n_D^{20} = 1.3719

Solubility: soluble 1 in 10 of water at 25°C; ethyl acetate is more soluble in water at lower temperatures than at higher temperatures. Miscible with acetone, chloroform, dichloromethane, ethanol (95%), and ether, and with most other organic liquids.

Vapor density: 3.04 (air = 1)

11 Stability and Storage Conditions

Ethyl acetate should be stored in an airtight container, protected from light and at a temperature not exceeding 30°C. Ethyl acetate is slowly decomposed by moisture and becomes acidic; the material can absorb up to 3.3% w/w water.

Ethyl acetate decomposes on heating to produce ethanol and acetic acid, and will emit acrid smoke and irritating fumes. It is flammable and its vapor may travel a considerable distance to an ignition source and cause a 'flashback'.

The alkaline hydrolysis of ethyl acetate has been shown to be inhibited by polyethylene glycol and by mixed micelle systems.⁽⁶⁾

12 Incompatibilities

Ethyl acetate can react vigorously with strong oxidizers, strong alkalis, strong acids, and nitrates to cause fires or explosions. It also reacts vigorously with chlorosulfonic acid, lithium

aluminum hydride, 2-chloromethylfuran, and potassium *tert*-butoxide.

13 Method of Manufacture

Ethyl acetate can be manufactured by the slow distillation of a mixture of ethanol and acetic acid in the presence of concentrated sulfuric acid. It has also been prepared from ethylene using an aluminum alkoxide catalyst.

14 Safety

Ethyl acetate is used in foods and oral and topical pharmaceutical formulations. It is generally regarded as a relatively nontoxic and nonirritant material when used as an excipient.

However, ethyl acetate may be irritant to mucous membranes and high concentrations may cause central nervous system depression. Potential symptoms of over exposure include irritation of the eyes, nose, and throat, narcosis, and dermatitis.

Ethyl acetate has not been shown to be a human carcinogen or a reproductive or developmental toxin.

The WHO has set an estimated acceptable daily intake of ethyl acetate at up to 25 mg/kg body-weight.⁽⁷⁾

In the UK, it has been recommended that ethyl acetate be temporarily permitted for use as a solvent in food and that the maximum concentration consumed in food should be set at 1000 ppm.⁽⁸⁾

LD₅₀ (cat, SC): 3.00 g/kg⁽⁹⁾
 LD₅₀ (guinea-pig, oral): 5.50 g/kg
 LD₅₀ (guinea-pig, SC): 3.00 g/kg
 LD₅₀ (mouse, IP): 0.709 g/kg
 LD₅₀ (mouse, oral): 4.10 g/kg
 LD₅₀ (rabbit, oral): 4.935 g/kg
 LD₅₀ (rat, oral): 5.62 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. In the UK, the occupational exposure limit for ethyl acetate is 400 ppm (short-term) and 200 ppm (long-term).⁽¹⁰⁾

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral tablets and sustained-action tablets). Included in nonparenteral medicines licensed in the UK (tablets, topical solutions, and gels). Ethyl acetate is also accepted for use in food applications in a number of countries including the UK.

17 Related Substances

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18 Comments

The following azeotropic mixtures have been reported:

Ethyl acetate (93.9% w/w)–water (6.1% w/w), boiling point 70.4°C
 Ethyl acetate (83.2% w/w)–water (7.8% w/w)–ethanol (9.0% w/w), boiling point 70.3°C
 Ethyl acetate (69.4%)–ethanol (30.6%), boiling point 71.8°C
 Ethyl acetate (77%)–propan-2-ol (23%), boiling point 74.8°C

The EINECS number for ethyl acetate is 205-500-4.

19 Specific References

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- 2 Giordano F, Gazzaniga A, Moyano JR, *et al*. Crystal forms of piroxicam pivalate: preparation and characterization of two polymorphs. *J Pharm Sci* 1998; 87(3): 333–337.
- 3 Romero S, Escalera B, Bustamante P. Solubility behavior of polymorphs I and II of mefenamic acid in solvent mixtures. *Int J Pharm* 1999; 178: 193–202.
- 4 Abu-Izza K, Garcia-Contreras L, Lu DR. Preparation and evaluation of zidovudine-loaded sustained-release microspheres. 2. Optimization of multiple response variables. *J Pharm Sci* 1996; 85(6): 572–576.
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- 7 FAO/WHO. Specifications for the identity and purity of food additives and their toxicological evaluation: some flavouring substances and non-nutritive sweetening agents. Eleventh report of the Joint FAO/WHO Expert Committee on Food Additives. *World Health Organ Tech Rep Ser* 1968; No. 383.
- 8 Ministry of Agriculture, Fisheries and Food. *Report on the Review of Solvents in Food, FAC/REP/25*. London: HMSO, 1978.
- 9 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 10th edn. New York: Wiley, 2000: 1635–1636.
- 10 Health and Safety Executive. *EH40/2002: Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.

20 General References

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21 Author

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22 Date of Revision

22 November 2002.