Handbook of Pharmaceutical Excipients

FOURTH EDITION

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Alcohol

1 Nonproprietary Names

BP: Ethanol (96%)
JP: Ethanol
PhEur: Ethanolum (96 per centum)
USP: Alcohol

2 Synonyms

Ethyl alcohol; ethyl hydroxide; grain alcohol; methyl carbinol.

3 Chemical Name and CAS Registry Number

Ethanol [64-17-5]

4 Empirical Formula and Molecular Weight

C_2H_6O 46.07

5 Structural Formula

6 Functional Category

Antimicrobial preservative; disinfectant; skin penetrant; solvent.

7 Applications in Pharmaceutical Formulation or Technology

Ethanol and aqueous ethanol solutions of various concentrations (*see* Sections 8 and 17) are widely used in pharmaceutical formulations and cosmetics; *see* Table I. Although ethanol is primarily used as a solvent, it is also employed in solutions as an antimicrobial preservative.[1,2] Topical ethanol solutions are also used as penetration enhancers[3] and as disinfectants.

Table I: Uses of alcohol.

Use	Concentration (% v/v)
Antimicrobial preservative	≥10
Disinfectant	60–90
Extracting solvent in galenical manufacture	Up to 85
Solvent in film coating	Variable
Solvent in injectable solutions	Variable
Solvent in oral liquids	Variable
Solvent in topical products	60–90

8 Description

In the BP 2001, the term 'ethanol' used without other qualification refers to ethanol containing ≥99.5% v/v of C_2H_6O. The term 'alcohol', without other qualification, refers to ethanol 95.1–96.9% v/v. Where other strengths are intended, the term 'alcohol' or 'ethanol' is used, followed by the statement of the strength.

In the PhEur 2002, anhydrous ethanol contains not less than 99.5% v/v of C_2H_6O at 20°C. The term ethanol (96%) is used to describe the material containing water and 95.1–96.9% v/v of C_2H_6O at 20°C.

In the USP 25, the term 'dehydrated alcohol' refers to ethanol ≥99.5% v/v. The term 'alcohol' without other qualification refers to ethanol 94.9–96.0% v/v.

In the JP 2001, ethanol (alcohol) contains 95.1–95.6% v/v (by specific gravity) of C_2H_6O at 15°C.

In the *Handbook of Pharmaceutical Excipients*, the term 'alcohol' is used for either ethanol 95% v/v or ethanol 96% v/v.

Alcohol is a clear, colorless, mobile, and volatile liquid with a slight, characteristic odor and burning taste.

See also Section 17.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for alcohol.

Test	JP 2001	PhEur 2002	USP 25
Identification	+	+	+
Specific gravity	0.814–0.816	0.8051–0.8124	0.812–0.816
Acidity	+	+	+
Clarity of solution	+	+	—
Nonvolatile residue	≤1 mg/40 mL	≤2.5 mg/100 mL	≤1 mg/40 mL
Water-insoluble substances	—	—	+
Aldehydes	+	—	+
Amyl alcohol, etc.	—	—	+
Absorbance	—	+	—
Fusel oil constituents	+	—	—
Acetone and propan-2-ol	—	—	+
Methanol	—	—	+
Reducing substances	+	—	—
Organic volatile impurities	—	—	+
Chloride	+	—	—
Heavy metals	≤1.2 ppm	—	—
Assay	95.1–95.6%	95.1–96.9%	92.3–93.8% by weight 94.9–96.0% by volume

10 Typical Properties

Antimicrobial activity: ethanol is bactericidal in aqueous mixtures at concentrations between 60% and 95% v/v; the optimum concentration is generally considered to be

70% v/v. Antimicrobial activity is enhanced in the presence of edetic acid or edetate salts.[1] Ethanol is inactivated in the presence of nonionic surfactants and is ineffective against bacterial spores.

Boiling point: 78.15°C

Flammability: readily flammable, burning with a blue, smokeless flame.

Flash point: 14°C (closed cup)

Solubility: miscible with chloroform, ether, glycerin, and water (with rise of temperature and contraction of volume).

Specific gravity: 0.8119–0.8139 at 20°C

Note: the above typical properties are for alcohol (ethanol 95% or 96% v/v). *See* Section 17 for typical properties of dehydrated alcohol.

11 Stability and Storage Conditions

Aqueous ethanol solutions may be sterilized by autoclaving or by filtration and should be stored in airtight containers, in a cool place.

12 Incompatibilities

In acidic conditions, ethanol solutions may react vigorously with oxidizing materials. Mixtures with alkali may darken in color owing to a reaction with residual amounts of aldehyde. Organic salts or acacia may be precipitated from aqueous solutions or dispersions. Ethanol solutions are also incompatible with aluminum containers and may interact with some drugs.

13 Method of Manufacture

Ethanol is manufactured by the controlled enzymatic fermentation of starch, sugar, or other carbohydrates. A fermented liquid is produced containing about 15% ethanol; ethanol 95% v/v is then obtained by fractional distillation. Ethanol may also be prepared by a number of synthetic methods.

14 Safety

Ethanol and aqueous ethanol solutions are widely used in a variety of pharmaceutical formulations and cosmetics. It is also consumed in alcoholic beverages.

Ethanol is rapidly absorbed from the gastrointestinal tract and the vapor may be absorbed through the lungs; it is metabolized, mainly in the liver, to acetaldehyde, which is further oxidized to acetate.

Ethanol is a central nervous system depressant and ingestion of low to moderate quantities can lead to symptoms of intoxication including muscle incoordination, visual impairment, slurred speech, etc. Ingestion of higher concentrations may cause depression of medullary action, lethargy, amnesia, hypothermia, hypoglycemia, stupor, coma, respiratory depression, and cardiovascular collapse. The lethal human blood-alcohol concentration is generally estimated to be 400–500 mg/100 mL.

Although symptoms of ethanol intoxication are usually encountered following deliberate consumption of ethanol-containing beverages, many pharmaceutical products contain ethanol as a solvent, which, if ingested in sufficiently large quantities, may cause adverse symptoms of intoxication. In the USA, the maximum quantity of alcohol included in OTC medicines is 10% v/v for products labeled for use by people of 12 years of age and older, 5% v/v for products intended for use by children aged 6–12 years of age, and 0.5% v/v for products for use by children under 6 years of age.[4]

Parenteral products containing up to 50% of alcohol (ethanol 95 or 96% v/v) have been formulated. However, such concentrations can produce pain on intramuscular injection and lower concentrations such as 5–10% v/v are preferred. Subcutaneous injection of alcohol (ethanol 95% v/v) similarly causes considerable pain followed by anesthesia. If injections are made close to nerves, neuritis and nerve degeneration may occur. This effect is used therapeutically to cause anesthesia in cases of severe pain, although the practice of using alcohol in nerve blocks is controversial. Doses of 1 mL of absolute alcohol have been used for this purpose.[5]

Preparations containing more than 50% v/v alcohol may cause skin irritation when applied topically.

LD_{50} (mouse, IP): 0.93 g/kg[6]
LD_{50} (mouse, IV): 1.97 g/kg
LD_{50} (mouse, oral): 3.45 g/kg
LD_{50} (mouse, SC): 8.29 g/kg
LD_{50} (rat, IP): 3.75 g/kg
LD_{50} (rat, IV): 1.44 g/kg
LD_{50} (rat, oral): 7.06 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Ethanol and aqueous ethanol solutions should be handled in a well-ventilated environment. In the UK, the long-term 8-hour TWA exposure limit for ethanol is 1920 mg/m^3 (1000 ppm).[7] Ethanol may be irritant to the eyes and mucous membranes and eye protection and gloves are recommended. Ethanol is flammable and should be heated with care. Fixed storage tanks should be electrically grounded to avoid ignition from electrostatic discharges when ethanol is transferred.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (dental preparations; inhalations; IM and IV injections; nasal and ophthalmic preparations; oral capsules, solutions, suspensions, syrups, and tablets; rectal, topical, and transdermal preparations). Included in nonparenteral and parenteral medicines licensed in the UK.

17 Related Substances

Dehydrated alcohol; denatured alcohol; dilute alcohol; isopropyl alcohol.

Dehydrated alcohol

Synonyms: absolute alcohol; anhydrous ethanol; ethanol.

Autoignition temperature: 365°C

Boiling point: 78.5°C

Explosive limits: 3.5–19.0% v/v in air

Flash point: 12°C (closed cup)

Melting point: −112°C

Moisture content: absorbs water rapidly from the air.

Refractive index: $n_D^{20} = 1.361$

Specific gravity: 0.7904–0.7935 at 20°C

Surface tension: 22.75 mN/m at 20°C (ethanol/vapor)

Vapor density (relative): 1.59 (air = 1)

Vapor pressure: 5.8 Pa at 20°C

Viscosity (dynamic): 1.22 mPa s (1.22 cP) at 20°C

Comments: dehydrated alcohol is ethanol ⩾99.5% v/v. *See* Section 8.

Denatured alcohol
Synonyms: industrial methylated spirit; surgical spirit.
Comments: denatured alcohol is alcohol intended for external use only. It has been rendered unfit for human consumption by the addition of a denaturing agent such as methanol or methyl isobutyl ketone.

Dilute alcohol
Synonyms: dilute ethanol.
Specific gravity: *see* Table III.

Table III: Specific gravity of alcohol.

Strength of alcohol (% v/v)	Specific gravity at 20°C
90	0.8289–0.8319
80	0.8599–0.8621
70	0.8860–0.8883
60	0.9103–0.9114
50	0.9314–0.9326
45	0.9407–0.9417
25	0.9694–0.9703
20	0.9748–0.9759

Comments: the term 'dilute alcohol' refers to a mixture of ethanol and water of stated concentration. The BP 2001 lists eight strengths of dilute alcohol (dilute ethanol) containing 90%, 80%, 70%, 60%, 50%, 45%, 25%, and 20% v/v respectively of ethanol.

18 Comments

Possession and use of nondenatured alcohols are usually subject to close control by excise authorities.

The EINECS number for alcohol is 200-578-6.

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