
**Handbook of
PHARMACEUTICAL
EXCIPIENTS**

Second Edition

Edited by
Ainley Wade and Paul J Weller

**American Pharmaceutical Association
Washington**

**The Pharmaceutical Press
London**

1994

R00267 97489

© Copyright 1986, 1994 by the American Pharmaceutical Association, 2215 Constitution Avenue NW, Washington, DC 20037-2985, USA, and The Pharmaceutical Press, Royal Pharmaceutical Society of Great Britain, 1 Lambeth High Street, London, SE1 7JN, England.

A catalogue record for this book is available from the British Library.

Library of Congress Catalog Card Number: 94-79492.

International Standard Book Number (ISBN) in the UK: 0 85369 305 6
International Standard Book Number (ISBN) in the USA: 0 91730 66 8

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage or retrieval system, without prior written permission from the joint publishers.

Typeset in Great Britain by Alden Multimedia, Northampton.
Printed and bound in Great Britain by

Alcohol

1. Nonproprietary Names

BP: Ethanol (96%)
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 Molecular Weight

C₂H₆O 46.07

5. Structural Formula

C₂H₅OH

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 18) are widely used in pharmaceutical formulations and cosmetics. 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.

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 1993, the term 'ethanol' used without other qualification refers to ethanol ≥ 99.5% v/v. The term 'alcohol', without other qualification, refers to ethanol 96.0-96.6% v/v. Where other strengths are intended, the term 'alcohol' or 'ethanol' is used, followed by the statement of the strength.

In the USP XXII, 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 *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 18.

9. Pharmacopeial Specifications

Test	BP 1993	USP XXII
Identification	+	+
Specific gravity	0.8038-0.8063	0.812-0.816
Acidity	+	—
Clarity of solution	+	—
Nonvolatile residue	≤ 5 mg/100 mL	≤ 1 mg/40 mL
Water-insoluble substances	—	+
Aldehydes	≤ 10 ppm	+
Amyl alcohol, etc	—	+
Benzene	≤ 2 ppm	—
Fusel oil constituents	—	+
Acetone and propan-2-ol	—	+
Methanol	—	+
Reducing substances	+	—
Volatile impurities	+	—

10. Typical Properties

Antimicrobial activity: ethanol is bactericidal in aqueous mixtures at concentrations between 60-95% 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 18 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 due 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. Ethanol is also consumed in alcoholic beverages.

Ethanol is rapidly absorbed from the gastrointestinal tract and vapor may be absorbed through the lungs. Ethanol 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.

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.⁽⁴⁾

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

LD₅₀ (guinea pig, IP): 3.41 g/kg⁽⁵⁾

LD₅₀ (guinea pig, IV): 2.3 g/kg

LD₅₀ (guinea pig, oral): 5.56 g/kg

LD₅₀ (hamster, IP): 5.07 g/kg

LD₅₀ (mouse, IP): 0.93 g/kg

LD₅₀ (mouse, IV): 1.97 g/kg

LD₅₀ (mouse, oral): 7.5 g/kg

LD₅₀ (mouse, SC): 8.29 g/kg

LD₅₀ (rabbit, IP): 0.96 g/kg

LD₅₀ (rabbit, IV): 2.37 g/kg

LD₅₀ (rabbit, oral): 6.3 g/kg

LD₅₀ (rat, IP): 3.75 g/kg

LD₅₀ (rat, IV): 1.44 g/kg

LD₅₀ (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 1900 mg/m³ (1000 ppm).⁽⁶⁾ Ethanol may be irritant to the eyes and mucous membranes and eye protection and gloves are therefore 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 prepara-

tions). Included in nonparenteral and parenteral medicines licensed in the UK.

17. Pharmacopeias

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

18. Related Substances

Dehydrated alcohol; denatured alcohol; dilute alcohol; Isopropyl Alcohol.

Dehydrated alcohol

Synonyms: absolute alcohol; 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)

Hygroscopicity: absorbs water rapidly from the air.

Melting point: -112°C

Refractive index: n_D²⁰ = 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, for external use only, that 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:

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 1993 lists eight strengths of dilute alcohol (dilute ethanol) containing 90, 80, 70, 60, 50, 45, 25 and 20% v/v respectively of ethanol.

19. Comments

Possession and use of non-denatured alcohols are usually subject to close control by excise authorities.

20. Specific References

- Chiori CO, Ghobashy AA. A potentiating effect of EDTA on the bactericidal activity of lower concentrations of ethanol. *Int J Pharmaceutics* 1983; 17: 121-128.

2. Karabit MS, Juneskans OT, Lundgren P. The determination of antimicrobial characteristics of some pharmaceutical compounds in aqueous solutions. *Int J Pharmaceutics* 1989; 54: 51-56.
3. Liu P, Higuchi WI, Song W, Kurihara-Bergstrom T, Good WR. Quantitative evaluation of ethanol effects on diffusion and metabolism of β -estradiol in hairless mouse skin. *Pharm Res* 1991; 8: 865-872.
4. Lloyd JW. Use of anaesthesia: the anaesthetist and the pain clinic. *Br Med J* 1980; 281: 432-434.
5. Sweet DV, editor. Registry of toxic effects of chemical substances. Cincinnati: US Department of Health, 1987.
6. Health and Safety Executive. Occupational exposure limits 1993: EH40/93. London: HMSO, 1993.

21. General References

- Lund W, editor. *The Pharmaceutical Codex: principles and practice of pharmaceutics*, 12th edition. London: The Pharmaceutical Press, 1994: 694-695.
- Spiegel AJ, Noseworthy MN. Use of nonaqueous solvents in parenteral products. *J Pharm Sci* 1963; 52: 917-927.
- Wade A, editor. *Pharmaceutical handbook*, 19th edition. London: The Pharmaceutical Press, 1980: 227-230.

22. Authors

UK: SJ Lewis.

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.