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Handbook of PHARMACEUTICAL EXCIPIENTS

Third Edition

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Glycerin

1 Nonproprietary Names

BP: Glycerol
JP: Concentrated glycerin
PhEur: Glycerolum
USP: Glycerin

2 Synonyms

Croderol; E422; glycerine; *Glycon G-100*; *Kemstrene*; *Optim*; *Pricerine*; 1,2,3-propanetriol; trihydroxypropane glycerol.

3 Chemical Name and CAS Registry Number

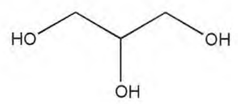
Propane-1,2,3-triol [56-81-5]

4 Empirical Formula and Molecular Weight

$C_3H_8O_3$

92.09

5 Structural Formula



6 Functional Category

Antimicrobial preservative; emollient; humectant; plasticizer; solvent; sweetening agent; tonicity agent.

7 Applications in Pharmaceutical Formulation or Technology

Glycerin is used in a wide variety of pharmaceutical formulations including oral, otic, ophthalmic, topical, and parenteral preparations; *see* Table I.

In topical pharmaceutical formulations and cosmetics, glycerin is used primarily for its humectant and emollient properties. In parenteral formulations, glycerin is used mainly as a solvent.[1]

In oral solutions, glycerin is used as a solvent, sweetening agent, antimicrobial preservative, and viscosity-increasing agent. It is also used as a plasticizer and in film coatings.[2,3] Glycerin is additionally used in topical formulations such as creams and emulsions.[4]

Glycerin is used as a plasticizer of gelatin in the production of soft-gelatin capsules and gelatin suppositories.

Glycerin is employed as a therapeutic agent in a variety of clinical applications,[5] and is also used as a food additive.

Table I: Uses of glycerin.

Use	Concentration (%)
Antimicrobial preservative	<20
Emollient	⩽30
Humectant	⩽30
Ophthalmic formulations	0.5–3.0
Plasticizer in tablet film coating	Variable
Solvent for parenteral formulations	⩽50
Sweetening agent in alcoholic elixirs	⩽20

8 Description

Glycerin is a clear, colorless, odorless, viscous, hygroscopic liquid; it has a sweet taste, approximately 0.6 times as sweet as sucrose.

9 Pharmacopeial Specifications

See Table II. *See also* Section 18.

Table II: Pharmacopeial specifications for glycerin.

Test	JP 2001	PhEur 2002	USP 25
Identification	+	+	+
Characters	+	+	—
Appearance of solution	+	+	+
Acidity or alkalinity	+	+	—
Refractive index	⩽1.470	1.470–1.475	—
Aldehydes	—	+	—
Related substances	—	+	—
Halogenated compounds	—	+	—
Limit of chlorinated compounds	—	—	+
Sugars	—	+	—
Chloride	⩽0.001%	⩽10 ppm	⩽0.001%
Heavy metals	⩽5 ppm	⩽5 ppm	⩽5 ppm
Water	—	⩽2.0%	⩽5.0%
Sulfated ash	⩽0.01%	⩽0.01%	⩽0.01%
Specific gravity	⩾1.258	—	⩾1.249
Sulfate	⩽0.002%	—	⩽0.002%
Ammonium	+	—	—
Calcium	+	—	—
Arsenic	⩽2 ppm	—	—
Acrolein, glucose or other reducing substances	+	—	—
Fatty acids and esters	+	+	+
Organic volatile impurities	—	—	+
Readily carbonizable substances	+	—	—
Assay	⩾98.0%	98.0–101.0%	99.0–101.0%

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10 Typical Properties

Boiling point: 290°C (with decomposition)
Density:
1.2656 g/cm^3 at 15°C
1.2636 g/cm^3 at 20°C
1.2620 g/cm^3 at 25°C
Flash point: 176°C (open cup)
Freezing point: *see* Table III.
Hygroscopicity: hygroscopic.
Melting point: 17.8°C
Osmolarity: a 2.6% v/v aqueous solution is isoosmotic with serum.
Refractive index:
n_D^{15} = 1.4758
n_D^{20} = 1.4746
n_D^{25} = 1.4730
Solubility: *see* Table IV.
Specific gravity: *see* Table V.
Surface tension: 63.4 mN/m (63.4 dynes/cm) at 20°C.
Vapor density (relative): 3.17 (air = 1)
Viscosity (dynamic): *see* Table VI.

Table III: Freezing points of aqueous glycerin solutions.

Concentration of aqueous glycerin solution (% w/w)	Freezing point (°C)
10.0	–1.6
20.0	–4.8
30.0	–9.5
40.0	–15.4
50.0	–23
60.0	–34.7
66.7	–46.5
80.0	–20.3
90.0	–1.6

Table IV: Solubility of glycerin.

Solvent	Solubility at 20°C
Acetone	Slightly soluble
Benzene	Practically insoluble
Chloroform	Practically insoluble
Ethanol (95%)	Soluble
Ether	1 in 500
Ethyl acetate	1 in 11
Methanol	Soluble
Oils	Practically insoluble
Water	Soluble

Table V: Specific gravity of glycerin.

Concentration of aqueous glycerin solution (% w/w)	Specific gravity at 20°C
10	1.024
20	1.049
30	1.075
40	1.101
50	1.128
60	1.156

Table VI: Viscosity (dynamic) of aqueous glycerin solutions.

Concentration of aqueous glycerin solution (% w/w)	Viscosity at 20°C (mPa s)
5	1.143
10	1.311
25	2.095
50	6.05
60	10.96
70	22.94
83	111.0

11 Stability and Storage Conditions

Glycerin is hygroscopic. Pure glycerin is not prone to oxidation by the atmosphere under ordinary storage conditions but it decomposes on heating, with the evolution of toxic acrolein. Mixtures of glycerin with water, ethanol, and propylene glycol are chemically stable.

Glycerin may crystallize if stored at low temperatures; the crystals do not melt until warmed to 20°C.

Glycerin should be stored in an airtight container, in a cool, dry place.

12 Incompatibilities

Glycerin may explode if mixed with strong oxidizing agents such as chromium trioxide, potassium chlorate, or potassium permanganate. In dilute solution, the reaction proceeds at a slower rate with several oxidation products being formed. Black discoloration of glycerin occurs in the presence of light, or on contact with zinc oxide or basic bismuth nitrate.

An iron contaminant in glycerin is responsible for the darkening in color of mixtures containing phenols, salicylates, and tannin.

Glycerin forms a boric acid complex, glyceroboric acid, that is a stronger acid than boric acid.

13 Method of Manufacture

Glycerin is mainly obtained from oils and fats as a by-product in the manufacture of soaps and fatty acids. It may also be obtained from natural sources by fermentation of, for example, sugar beet molasses in the presence of large quantities of sodium sulfite. Synthetically, glycerin may be prepared by the chlorination and saponification of propylene.

14 Safety

Glycerin occurs naturally in animal and vegetable fats and oils that are consumed as part of a normal diet. Glycerin is readily absorbed from the intestine and is either metabolized to carbon dioxide and glycogen or used in the synthesis of body fats.

Glycerin is used in a wide variety of pharmaceutical formulations including oral, ophthalmic, parenteral, and topical preparations. Adverse effects are mainly due to the dehydrating properties of glycerin.[5]

Oral doses are demulcent and mildly laxative in action. Large doses may produce headache, thirst, nausea, and hyperglycemia. The therapeutic parenteral administration of very large glycerin doses, 70–80 g over 30–60 minutes in adults to reduce cranial pressure, may induce hemolysis, hemoglobinuria, and renal failure.[6] Slower administration has no deleterious effects.[7]

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Glycerin may also be used orally in doses of 1.0–1.5 g/kg body-weight to reduce intraocular pressure.

When used as an excipient or food additive, glycerin is not usually associated with any adverse effects and is generally regarded as a nontoxic and nonirritant material.

LD_{50} (guinea pig, oral): 7.75 g/kg[8]
LD_{50} (mouse, IP): 8.98 g/kg
LD_{50} (mouse, IV): 4.25 g/kg
LD_{50} (mouse, oral): 4.1 g/kg
LD_{50} (mouse, SC): 0.09 g/kg
LD_{50} (rabbit, IV): 0.05 g/kg
LD_{50} (rat, IP): 4.42 g/kg
LD_{50} (rat, oral): 12.6 g/kg
LD_{50} (rat, SC): 0.1 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 recommended long-term (8-hour TWA) exposure limit for glycerin mist is 10 mg/m^3.[9] Glycerin is combustible and may react explosively with strong oxidizing agents; *see* Section 12.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (inhalations; injections; nasal and ophthalmic preparations; oral capsules, solutions, suspensions and tablets; otic, rectal, topical, transdermal, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK.

17 Related Substances

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18 Comments

The EINECS number for glycerin is 200-289-5.

Some pharmacopeias also contain specifications for diluted glycerin solutions. The JP 2001 contains a monograph for 'glycerin' that contains 84–87% of propane-1,2,3-triol ($C_3H_8O_3$). The PhEur 2002 contains a monograph for 'glycerol 85 per cent' that contains 83.5–88.5% of propane-1,2,3-triol ($C_3H_8O_3$).

19 Specific References

1 Spiegel AJ, Noseworthy MM. Use of nonaqueous solvents in parenteral products. *J Pharm Sci* 1963; **52**: 917–927.
2 Kumar V, Kang J, Yang T. Preparation and characterization of spray-dried oxidized cellulose particles. *Pharm Dev Technol* 2001; **6**(3): 449–458.
3 Palviainen P, Heinamaki J, Myllarinen P, *et al.* Corn starches as film formers in aqueous-based film coating. *Pharm Dev Technol* 2001; **6**(3): 353–361.
4 Viegas TX, Van-Winkle LL, Lehman PA, *et al.* Evaluation of creams and ointments as suitable formulations for peldesine. *Int J Pharm* 2001; **219**(1–2): 73–80.
5 Sweetman SC, ed. *Martindale: The Complete Drug Reference*, 33rd edn. London: Pharmaceutical Press, 2002: 1616–1617.
6 Hägnevik K, Gordon E, Lins LE, *et al.* Glycerol-induced haemolysis with haemoglobinuria and acute renal failure. *Lancet* 1974; i: 75–77.
7 Welch KMA, Meyer JS, Okamoto S, *et al.* Glycerol-induced haemolysis. Report of three cases. [letter]. *Lancet* 1974; **1**(7847): 416–417.
8 8, Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 10th edn. New York: Wiley, 2000: 1874–1875.
9 Health and Safety Executive. EH40/2002: *Occupational Exposure Limits 2002*. Sudbury: Health and Safety Executive, 2002.

20 General References

Grissom CB, Chagovetz AM, Wang Z. Use of viscosigens to stabilize vitamin B_{12} solutions against photolysis. *J Pharm Sci* 1993; **82**(6): 641–643.
Jungermann E, Sonntag NOV, eds. *Glycerine: A Key Cosmetic Ingredient*. New York: Marcel Dekker, 1991.
Smolinske SC. *Handbook of Food, Drug, and Cosmetic Excipients*. Boca Raton, FL: CRC Press, 1992: 199–204.
Staples R, Misher A, Wardell J. Gastrointestinal irritant effect of glycerin as compared with sorbitol and propylene glycol in rats and dogs. *J Pharm Sci* 1967; 56: 398–400.

21 Author

JC Price.

22 Date of Revision

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