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Handbook of PHARMACEUTICAL EXCIPIENTS

Third Edition

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Contents

<i>Committees</i>	vii	Cholesterol	138
<i>Contributors</i>	ix	Citric Acid Monohydrate	140
<i>Additions to the Third Edition</i>	xii	Colloidal Silicon Dioxide	143
<i>Related Substances</i>	xiii	Coloring Agents	146
<i>Preface</i>	xv	✓Corn Oil	154
<i>Acknowledgments</i>	xvii	Cottonseed Oil	156
<i>Notice to Readers</i>	xviii	Cresol	158
<i>Selected Bibliography</i>	xviii	Croscarmellose Sodium	160
<i>Abbreviations</i>	xix	Crospovidone	163
<i>Units of Measurement</i>	xx	Cyclodextrins	165
		Dextrates	169
		Dextrin	172
Monographs		✓Dextrose	175
Acacia	1	Dibutyl Sebacate	178
Acesulfame Potassium	3	Diethanolamine	180
Albumin	5	Diethyl Phthalate	182
✓Alcohol	7	Difluoroethane (HFC)	184
Alginic Acid	10	Dimethyl Ether	186
Aliphatic Polyesters	13	Docusate Sodium	188
Alpha Tocopherol	18	Edetic Acid	191
Ascorbic Acid	21	Ethylcellulose	195
Ascorbyl Palmitate	25	Ethyl Maltol	201
Aspartame	27	Ethyl Oleate	203
Bentonite	30	Ethylparaben	205
Benzalkonium Chloride	33	Ethyl Vanillin	208
Benzethonium Chloride	36	✓Fructose	210
Benzoic Acid	38	Fumaric Acid	213
Benzyl Alcohol	41	✓Gelatin	215
Benzyl Benzoate	44	✓Glucose, Liquid	218
Bronopol	46	✓Glycerin	220
Butylated Hydroxyanisole	49	Glyceryl Monooleate	223
Butylated Hydroxytoluene	51	Glyceryl Monostearate	225
Butylparaben	53	Glyceryl Palmitostearate	228
✓Calcium Carbonate	56	Glycofurool	230
Calcium Phosphate, Dibasic Anhydrous	60	Guar Gum	232
Calcium Phosphate, Dibasic Dihydrate	63	Heptafluoropropane (HFC)	234
Calcium Phosphate, Tribasic	68	Hydrocarbons (HC)	236
Calcium Stearate	70	Hydrochloric Acid	238
Calcium Sulfate	73	Hydroxyethyl Cellulose	240
✓Canola Oil	77	Hydroxypropyl Cellulose	244
Carbomer	79	Hydroxypropyl Cellulose, Low-substituted	249
Carbon Dioxide	83	✓Hydroxypropyl Methylcellulose	252
Carboxymethylcellulose Calcium	85	Hydroxypropyl Methylcellulose Phthalate	256
Carboxymethylcellulose Sodium	87	Imidurea	261
✓Carrageenan	91	Isopropyl Alcohol	263
Castor Oil, Hydrogenated	94	Isopropyl Myristate	265
Cellulose Acetate	96	Isopropyl Palmitate	267
Cellulose Acetate Phthalate	99	Kaolin	269
Cellulose, Microcrystalline	102	✓Lactic Acid	272
Cellulose, Powdered	107	Lactitol	274
Cellulose, Silicified Microcrystalline	110	✓Lactose	276
Cetostearyl Alcohol	112	Lanolin	286
Cetrimide	114	Lanolin Alcohols	288
Cetyl Alcohol	117	Lanolin, Hydrous	290
Chlorhexidine	121	Lecithin	292
Chlorobutanol	126	Magnesium Aluminum Silicate	295
Chlorocresol	129	Magnesium Carbonate	299
Chlorodifluoroethane (HCFC)	132	Magnesium Oxide	303
Chlorofluorocarbons (CFC)	134	Magnesium Stearate	305
		Magnesium Trisilicate	309

Malic Acid	311	Sodium Ascorbate	468
Maltitol	313	Sodium Benzoate	471
Maltitol Solution	315	Sodium Bicarbonate	474
✓ Maltodextrin	317	Sodium Chloride	478
✓ Maltol	320	Sodium Citrate Dihydrate	482
✓ Maltose	322	Sodium Cyclamate	485
Mannitol	324	✓ Sodium Lauryl Sulfate	487
Medium Chain Triglycerides	329	Sodium Metabisulfite	490
Meglumine	332	Sodium Phosphate, Dibasic	493
Menthol	334	Sodium Phosphate, Monobasic	496
Methylcellulose	336	Sodium Propionate	498
Methylparaben	340	Sodium Starch Glycolate	501
✓ Mineral Oil	345	Sodium Stearyl Fumarate	505
Mineral Oil, Light	347	✓ Sorbic Acid	508
Mineral Oil and Lanolin Alcohols	349	Sorbitan Esters (Sorbitan Fatty Acid Esters)	511
Monoethanolamine	350	Sorbitol	515
✓ Nitrogen	352	✓ Soybean Oil	519
Nitrous Oxide	354	✓ Starch	522
Oleic Acid	356	✓ Starch, Pregelatinized	528
Paraffin	358	✓ Starch, Sterilizable Maize	531
✓ Peanut Oil	360	Stearic Acid	534
Petrolatum	362	Stearyl Alcohol	537
Petrolatum and Lanolin Alcohols	365	Sucrose	539
Phenol	367	Sugar, Compressible	544
Phenoxyethanol	370	Sugar, Confectioner's	546
Phenylethyl Alcohol	372	✓ Sugar Spheres	548
Phenylmercuric Acetate	374	✓ Suppository Bases, Hard Fat	550
Phenylmercuric Borate	377	✓ Talc	555
Phenylmercuric Nitrate	379	Tartaric Acid	558
Polacrilin Potassium	383	Tetrafluoroethane (HFC)	560
Poloxamer	386	Thimerosal	562
Polydextrose	389	Titanium Dioxide	565
Polyethylene Glycol	392	Tragacanth	568
Polyethylene Oxide	399	Triacetin	570
Polymethacrylates	401	Triethanolamine	572
Polyoxyethylene Alkyl Ethers	407	Triethyl Citrate	574
Polyoxyethylene Castor Oil Derivatives	412	Vanillin	576
Polyoxyethylene Sorbitan Fatty Acid Esters	416	Vegetable Oil, Hydrogenated, Type I	578
Polyoxyethylene Stearates	420	Water	580
Polyvinyl Alcohol	424	Wax, Anionic Emulsifying	585
Potassium Chloride	426	Wax, Carnauba	587
Potassium Citrate	429	Wax, Cetyl Esters	589
Potassium Sorbate	431	Wax, Microcrystalline	591
Povidone	433	Wax, Nonionic Emulsifying	593
Propylene Carbonate	440	Wax, White	595
Propylene Glycol	442	Wax, Yellow	597
Propylene Glycol Alginate	445	Xanthan Gum	599
Propyl Gallate	447	Xylitol	602
Propylparaben	450	Zein	606
Saccharin	454	Zinc Stearate	608
Saccharin Sodium	457		
✓ Sesame Oil	460	<i>Appendix I: Suppliers' Directory</i>	611
Shellac	462	<i>Appendix II: HPE Laboratory Methods</i>	641
✓ Sodium Alginate	465	<i>Index</i>	645

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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.

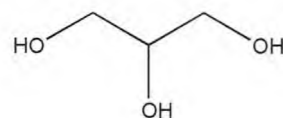
3 Chemical Name and CAS Registry Number

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

4 Empirical Formula Molecular Weight

C₃H₈O₃ 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%

10 Typical Properties

Boiling point: 290°C (with decomposition)

Density:

1.2656 g/cm³ at 15°C1.2636 g/cm³ at 20°C1.2620 g/cm³ 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⁾

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.

LD₅₀ (guinea pig, oral): 7.75 g/kg⁽⁸⁾
 LD₅₀ (mouse, IP): 8.98 g/kg
 LD₅₀ (mouse, IV): 4.25 g/kg
 LD₅₀ (mouse, oral): 4.1 g/kg
 LD₅₀ (mouse, SC): 0.09 g/kg
 LD₅₀ (rabbit, IV): 0.05 g/kg
 LD₅₀ (rat, IP): 4.42 g/kg
 LD₅₀ (rat, oral): 12.6 g/kg
 LD₅₀ (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/m³.⁽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

—

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 (C₃H₈O₃). The PhEur 2002 contains a monograph for 'glycerol 85 per cent' that contains 83.5–88.5% of propane-1,2,3-triol (C₃H₈O₃).

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 Hågnevik 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, 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 viscosogens to stabilize vitamin B₁₂ 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.

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