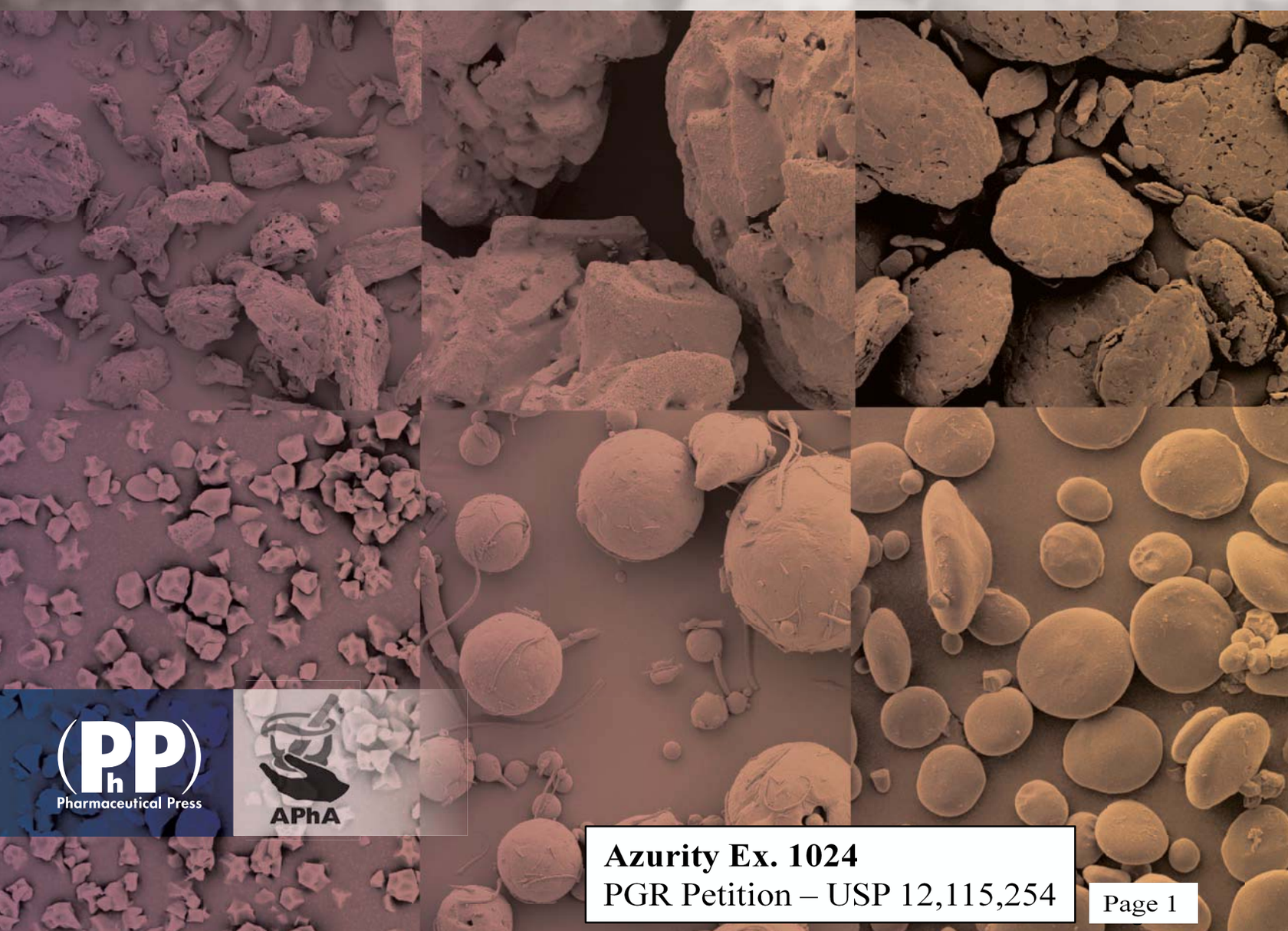
Handbook of Pharmaceutical Excipients

Sixth edition

Edited by
Raymond C Rowe, Paul J Sheskey and Marian E Quinn



Pharmaceutical Press
APhA

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Edited by

Raymond C Rowe BPharm, PhD, DSC, FRPharmS, FRSC, CPhys, MInstP

Chief Scientist

Intelligensys Ltd, Stokesley, North Yorkshire, UK

Paul J Sheskey BSc, RPh

Application Development Leader

The Dow Chemical Company, Midland, MI, USA

Marian E Quinn BSc, MSc

Development Editor

Royal Pharmaceutical Society of Great Britain, London, UK

London • Chicago

Pharmaceutical Press

18 Comments

A specification for glucose syrup is contained in the Food Chemicals Codex (FCC).[2] The PhEur 6.4 also includes a specification for glucose, liquid, spray-dried.

The EINECS number for glucose is 200-075-1.

19 Specific References

1 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 11th edn. New York: Wiley, 2004; 1860–1861.
2 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 403.

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21 Author

A Day.

22 Date of Revision

18 February 2009.

G

Glycerin

1 Nonproprietary Names

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

2 Synonyms

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

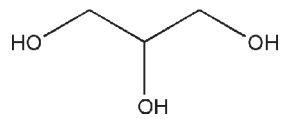
3 Chemical Name and CAS Registry Number

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; cosolvent; 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. Glycerin is used as a solvent or cosolvent in creams and emulsions.[1–3] Glycerin is additionally used in aqueous and nonaqueous gels and also as an additive in patch applications.[4–6] In parenteral formulations, glycerin is used mainly as a solvent and cosolvent.[7–10]

In oral solutions, glycerin is used as a solvent,[10] sweetening agent, antimicrobial preservative, and viscosity-increasing agent. It is also used as a plasticizer and in film coatings.[11–14]

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,[15] and is also used as a food additive.

Table I: Uses of glycerin.

Use	Concentration (%)
Antimicrobial preservative	<20
Emollient	⩽30
Gel vehicle, aqueous	5.0–15.0
Gel vehicle, nonaqueous	50.0–80.0
Humectant	⩽30
Ophthalmic formulations	0.5–3.0
Patch additive	Variable
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.

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

Table II: Pharmacopeial specifications for glycerin.

Test	JP XV	PhEur 6.0	USP 32
Identification	+	+	+
Characters	—	+	—
Appearance of solution	+	+	+
Acidity or alkalinity	+	+	—
Refractive index	⩽1.470	1.470–1.475	—
Aldehydes	—	⩽10 ppm	—
Related substances	—	+	—
Halogenated compounds	—	⩽35 ppm	—
Limit of chlorinated compounds	—	—	+
Sugars	—	+	—
Chloride	⩽0.001%	⩽10 ppm	⩽0.001%
Heavy metals	⩽5 ppm	⩽5 ppm	⩽5 µg/g
Water	—	⩽2.0%	⩽5.0%
Sulfated ash	⩽0.01%	⩽0.01%	⩽0.01%
Specific gravity	⩾1.258	—	⩾1.249
Sulfate	⩽0.002%	—	⩽0.002%
Esters	—	+	—
Ammonium	+	—	—
Calcium	+	—	—
Arsenic	⩽2 ppm	—	—
Acrolein, glucose or other reducing substances	+	—	—
Fatty acids and esters	+	—	+
Diethylene glycol and ethylene glycol impurities	—	—	+
Readily carbonizable substances	+	—	—
Assay	98.0–101.0%	98.0–101.0%	99.0–101.0%

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

NIR spectra *see* Figure 1.
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.

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 (95%), and propylene glycol are chemically stable.

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 15°C	Specific gravity at 20°C
5	1.01	—
10	—	1.024
20	1.049	1.049
30	—	1.075
40	—	1.101
50	1.129	1.128
60	1.157	1.156
70	1.185	—
80	1.213	—
90	1.240	1.238
95	1.253	1.251

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

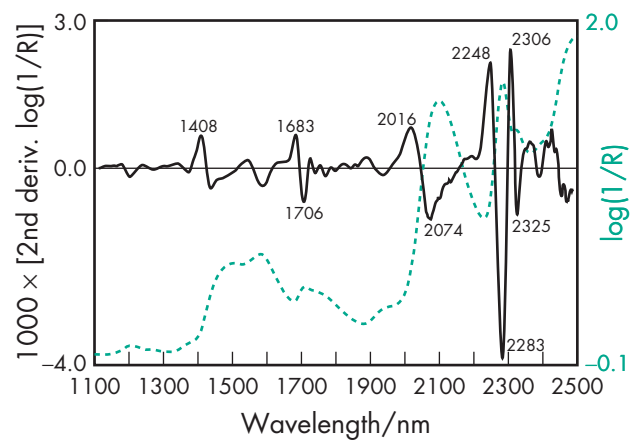


Figure 1: Near-infrared spectrum of glycerin measured by transflectance (1 mm path-length). The small peak at approx. 1950 nm is due to a trace of water (<0.5% m/m).

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.[15]

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.[16] Slower administration has no deleterious effects.[17]

Glycerin may also be used orally in doses of 1.0–1.5 g/kg bodyweight 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[18]
LD_{50} (mouse, IP): 8.70 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} (rabbit, oral): 27 g/kg[19]
LD_{50} (rat, IP): 4.42 g/kg
LD_{50} (rat, oral): 5.57 g/kg[19]
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) workplace exposure limit for glycerin mist is 10 mg/m^3.[20] Glycerin is combustible and may react explosively with strong oxidizing agents; *see* Section 12.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (dental pastes; buccal preparations; 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. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

Glycerin is one of the materials that have been selected for harmonization by the Pharmacopeial Discussion Group. For further information see the General Information Chapter <1196> in the USP32–NF27, the General Chapter 5.8 in PhEur 6.0, along with the 'State of Work' document on the PhEur EDQM website, and also the General Information Chapter 8 in the JP XV.

Some pharmacopeias also contain specifications for diluted glycerin solutions. The JP XV contains a monograph for 'glycerin' that contains 84–87% of propane-1,2,3-triol ($C_3H_8O_3$). The PhEur 6.0 contains a monograph for 'glycerol 85 per cent' that contains 83.5–88.5% of propane-1,2,3-triol ($C_3H_8O_3$).

A specification for glycerin is contained in the Food Chemicals Codex (FCC).[21]

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

19 Specific References

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25 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 247.
26 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 529.

20 General References

Babu R.J *et al*. Fatty alcohols and fatty acids. Smith EW, Maibach HI, eds. *Percutaneous Penetration Enhancers*. Boca Raton, FL: CRC Press, 2006; 137–158.

21 Author

PE Luner.

22 Date of Revision

27 February 2009.

Lecithin

1 Nonproprietary Names

USP-NF: Lecithin

See also Section 4.

2 Synonyms

E322; egg lecithin; *LSC 5050*; *LSC 6040*; mixed soybean phosphatides; ovolecithin; *Phosal 53 MCT*; *Phospholipon 100 H*; *ProKote LSC*; soybean lecithin; soybean phospholipids; *Sternpur*; vegetable lecithin.

3 Chemical Name and CAS Registry Number

Lecithin [8002-43-5]

The chemical nomenclature and CAS Registry numbering of lecithin is complex. The commercially available lecithin, used in cosmetics, pharmaceuticals, and food products, is a complex mixture of phospholipids and other materials. However, it may be referred to in some literature sources as 1,2-diacyl-*sn*-glycero-3-phosphocholine (trivial chemical name, phosphatidylcholine). This material is the principal constituent of egg lecithin and has the same CAS Registry Number. The name lecithin and the CAS Registry Number above are thus used to refer to both lecithin and phosphatidylcholine in some literature sources.

Another principal source of lecithin is from an extract of soybeans (CAS [8030-76-0]). Egg yolk lecithin (CAS [93685-90-6]) is also listed in *Chemical Abstracts*.

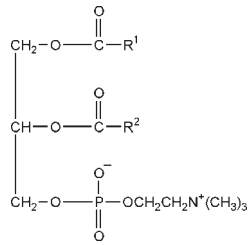
See also Section 4.

4 Empirical Formula and Molecular Weight

The USP32–NF27 describes lecithin as a complex mixture of acetone-insoluble phosphatides that consists chiefly of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol, combined with various amounts of other substances such as triglycerides, fatty acids, and carbohydrates as separated from a crude vegetable oil source.

The composition of lecithin (and hence also its physical properties) varies enormously depending upon the source of the lecithin and the degree of purification. Egg lecithin, for example, contains 69% phosphatidylcholine and 24% phosphatidylethanolamine, while soybean lecithin contains 21% phosphatidylcholine, 22% phosphatidylethanolamine, and 19% phosphatidylinositol, along with other components.[1]

5 Structural Formula



α-Phosphatidylcholine

R^1 and R^2 are fatty acids, which may be different or identical.

Lecithin is a complex mixture of materials; *see* Section 4. The structure above shows phosphatidylcholine, the principal component of egg lecithin, in its α-form. In the β-form, the phosphorus-containing group and the R^2 group exchange positions.

6 Functional Category

Emollient; emulsifying agent; solubilizing agent.

7 Applications in Pharmaceutical Formulation or Technology

Lecithins are used in a wide variety of pharmaceutical applications; *see* Table I. They are also used in cosmetics[2] and food products.

Lecithins are mainly used in pharmaceutical products as dispersing, emulsifying, and stabilizing agents, and are included in intramuscular and intravenous injections, parenteral nutrition formulations, and topical products such as creams and ointments.

Lecithins are also used in suppository bases,[3] to reduce the brittleness of suppositories, and have been investigated for their absorption-enhancing properties in an intranasal insulin formulation.[4] Lecithins are also commonly used as a component of enteral and parenteral nutrition formulations.

There is evidence that phosphatidylcholine (a major component of lecithin) is important as a nutritional supplement to fetal and

infant development. Furthermore, choline is a required component of FDA-approved infant formulas.[5] Other studies have indicated that lecithin can protect against alcohol cirrhosis of the liver, lower serum cholesterol levels, and improve mental and physical performance.[6]

Liposomes in which lecithin is included as a component of the bilayer have been used to encapsulate drug substances; their potential as novel delivery systems has been investigated.[7] This application generally requires purified lecithins combined in specific proportions.

Therapeutically, lecithin and derivatives have been used as a pulmonary surfactant in the treatment of neonatal respiratory distress syndrome.

Table I: Uses of lecithin.

Use	Concentration (%)
Aerosol inhalation	0.1
Biorelevant dissolution media	0.059–0.295
IM injection	0.3–2.3
Oral suspensions	0.25–10.0

8 Description

Lecithins vary greatly in their physical form, from viscous semiliquids to powders, depending upon the free fatty acid content. They may also vary in color from brown to light yellow, depending upon whether they are bleached or unbleached or on the degree of purity. When they are exposed to air, rapid oxidation occurs, also resulting in a dark yellow or brown color.

Lecithins have practically no odor. Those derived from vegetable sources have a bland or nutlike taste, similar to that of soybean oil.

9 Pharmacopeial Specifications

See Table II. *See also* Section 18.

Table II: Pharmacopeial specifications for lecithin.

Test	USP32–NF27
Identification	+
Water	≤1.5%
Lead	≤0.001%
Heavy metals	≤20 µg/g
Acid value	+
Peroxide value	≤10
Hexane-insoluble matter	≤0.3%
Acetone-insoluble matter	+

10 Typical Properties

Density

0.97 g/cm^3 for liquid lecithin;

0.5 g/cm^3 for powdered lecithin.

Iodine number

95–100 for liquid lecithin;

82–88 for powdered lecithin.

Isoelectric point ≈3.5

NIR spectra *see* Figure 1.

Saponification value 196

Solubility Lecithins are soluble in aliphatic and aromatic hydrocarbons, halogenated hydrocarbons, mineral oil, and fatty acids. They are practically insoluble in cold vegetable and animal oils, polar solvents, and water. When mixed with water, however, lecithins hydrate to form emulsions.

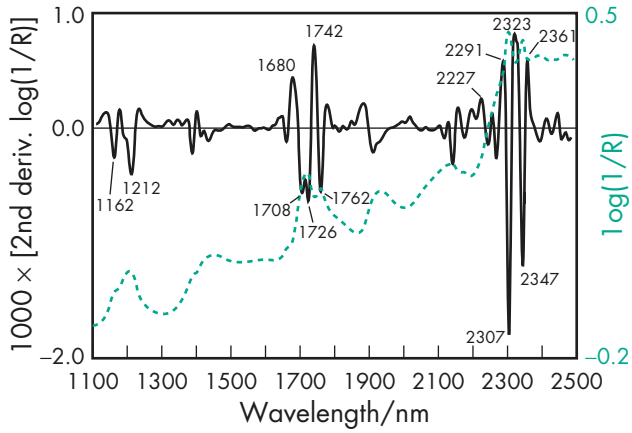


Figure 1: Near-infrared spectrum of lecithin measured by reflectance.

11 Stability and Storage Conditions

Lecithins decompose at extreme pH. They are also hygroscopic and subject to microbial degradation. When heated, lecithins oxidize, darken, and decompose. Temperatures of 160–180°C will cause degradation within 24 hours.

Fluid or waxy lecithin grades should be stored at room temperature or above; temperatures below 10°C may cause separation.

All lecithin grades should be stored in well-closed containers protected from light and oxidation. Purified solid lecithins should be stored in tightly closed containers at subfreezing temperatures.

12 Incompatibilities

Incompatible with esterases owing to hydrolysis.

13 Method of Manufacture

Lecithins are essential components of cell membranes and, in principle, may be obtained from a wide variety of living matter. In practice, however, lecithins are usually obtained from vegetable products such as soybean, peanut, cottonseed, sunflower, rapeseed, corn, or groundnut oils. Soybean lecithin is the most commercially important vegetable lecithin. Lecithin obtained from eggs is also commercially important and was the first lecithin to be discovered.

Vegetable lecithins are obtained as a by-product in the vegetable oil refining process. Polar lipids are extracted with hexane and, after removal of the solvent, a crude vegetable oil is obtained. Lecithin is then removed from the crude oil by water extraction. Following drying, the lecithin may be further purified.[1]

With egg lecithin, a different manufacturing process must be used since the lecithin in egg yolks is more tightly bound to proteins than in vegetable sources. Egg lecithin is thus obtained by solvent extraction from liquid egg yolks using acetone or from freeze-dried egg yolks using ethanol (95%).[1]

Synthetic lecithins may also be produced.

14 Safety

Lecithin is a component of cell membranes and is therefore consumed as a normal part of the diet. Although excessive consumption may be harmful, it is highly biocompatible and oral doses of up to 80 g daily have been used therapeutically in the treatment of tardive dyskinesia.[8] When used in topical formulations, lecithin is generally regarded as a nonirritant and nonsensitizing material.[2] The Cosmetic Ingredients Review Expert Panel (CIR) has reviewed lecithin and issued a tentative report revising the safe concentration of the material from 1.95% to 15.0% in rinse-off and leave-in products. They note, however, that there are insufficient data to rule on products that are likely to be inhaled.[9]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Lecithins may be irritant to the eyes; eye protection and gloves are recommended.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (inhalations; IM and IV injections; otic preparations; oral capsules, suspensions and tablets; rectal, topical, and vaginal preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

Poloxamer lecithin organogels have been used in topical formulations for the delivery of non-steroidal anti-inflammatory drugs.[10]

Lecithins contain a variety of unspecified materials; care should therefore be exercised in the use of unpurified lecithin in injectable or topical dosage forms, as interactions with the active substance or other excipients may occur. Unpurified lecithins may also have a greater potential for irritancy in formulations.

A specification for soybean lecithin is contained in the *Japanese Pharmaceutical Excipients* (JPE).[11] Suppliers' literature should be consulted for information on the different grades of lecithin available and their applications in formulations.

A specification for lecithin is contained in the Food Chemicals Codex (FCC).[12]

The EINECS number for lecithin is 232-307-2. The PubChem Compound ID (CID) for lecithin is 24798685.

19 Specific References

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21 Author

JJ Sheng.

22 Date of Revision

18 February 2009.

Leucine

1 Nonproprietary Names

BP: Leucine
JP: L-Leucine
PhEur: Leucine
USP: Leucine

2 Synonyms

α-Aminoisocaproic acid; L-α-aminoisocaproic acid; 2-amino-4-methylpentanoic acid; 2-amino-4-methylvaleric acid; α-amino-γ-methylvaleric acid; 1,2-amino-4-methylvaleric acid; D L-leucine; L-leucine; leu; leucinum; 4-methylnorvaline.

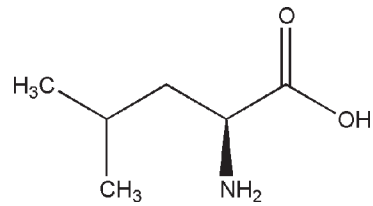
3 Chemical Name and CAS Registry Number

L-Leucine [61-90-5]

4 Empirical Formula and Molecular Weight

$C_6H_{13}NO_2$ 131.17

5 Structural Formula



6 Functional Category

Antiadherent; flavoring agent; lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Leucine is used in pharmaceutical formulations as a flavoring agent.[1] It has been used experimentally as an antiadherent to improve the deagglomeration of disodium cromoglycate micro-

Egg yolk lecithin, 385
Eglumine, 432
Elaic acid, 466
Elaol, 225
Elcema, 136
Elfan 240, 651
Elvanol, 564
Embanox BHT, 75
Embanox tocopherol, 33
Emcocel, 129
Emcompress, 96, 98
Emcompress Anhydrous, 94, 96
EmCon CO, 126
Emdex, 218
Emeressence 1160, 488
Emerest 2316, 350
Emersol, 466, 697
Emersol 140, 473
Emersol 143, 473
Emersol 310, 389
Emersol 315, 389
Emollients
  almond oil, 30
  aluminum stearate, 35
  canola oil, 108
  castor oil, 126
  ceratonia extract, 147
  cetostearyl alcohol, 150
  cetyl alcohol, 155
  cetyl esters wax, 774
  cholesterol, 178
  coconut oil, 184
  cottonseed oil, 202
  cyclomethicone, 215
  dibutyl sebacate, 228
  dimethicone, 233
  ethylene glycol palmitostearate, 267
  glycerin, 283
  glycerin monostearate, 290
  glyceryl monooleate, 289
  glyceryl monostearate, 292
  isopropyl myristate, 348
  isopropyl palmitate, 350
  lanolin, 379
  lecithin, 385
  light mineral oil, 447
  medium-chain triglycerides, 429
  mineral oil, 445
  mineral oil and lanolin alcohols, 449
  myristyl alcohol, 456
  octyldodecanol, 465
  oleyl alcohol, 468
  petrolatum, 482
  petrolatum and lanolin alcohols, 484
  safflower glycerides, 611
  safflower oil, 610
  soybean oil, 683
  stearyl alcohol, 700
  sunflower oil, 721–722
  tricaprylin, 751
  triolein, 757
  xylitol, 786
  zinc acetate, 791
Empilan KB, 536
Empilan KM, 536
Emprove, 424
Emulgade 1000NI, 777
Emulgen, 536
Emulsifing agents, ammonium alginate, 41
Emulsifying agent, capric acid, 384
Emulsifying agents
  acacia, 1
  agar, 13
  anionic emulsifying wax, 771
  calcium alginate, 83
  calcium stearate, 103
  carbomers, 110
  carboxymethylcellulose calcium, 117
  carrageenan, 122
  cetostearyl alcohol, 150
  cetyl alcohol, 155
  cholesterol, 178
  diethanolamine, 228
  ethylene glycol palmitostearate, 267
  glycerin monostearate, 290
  glyceryl monooleate, 289
  hectorite, 301
  hydroxypropyl cellulose, 318
  hydroxypropyl starch, 325
  hypromellose, 326
  lanolin, 378
    hydrous, 380
  lanolin alcohols, 382
  lauric acid, 383
  lecithin, 385
  linoleic acid, 389
  medium-chain triglycerides, 429
  methylcellulose, 438
  mineral oil and lanolin alcohols, 449
  monobasic sodium phosphate, 659
  monoethanolamine, 450
  myristic acid, 455
  nonionic emulsifying wax, 777
  octyldodecanol, 465
  oleic acid, 466
  oleyl alcohol, 468
  palmitic acid, 473
  pectin, 478
  phospholipids, 499
  poloxamer, 507
  poloxamers, 508
  polycarbophil, 509
  polyoxyethylene alkyl ethers, 536
  polyoxyethylene castor oil derivatives, 542
  polyoxyethylene sorbitan fatty acid esters, 550
  polyoxyethylene stearates, 555
  polyoxylglycerides, 558
  potassium alginate, 566
  propylene glycol alginate, 594
  safflower glycerides, 611
  saponite, 612
  self-emulsifying glyceryl monostearate, 292
  sodium borate, 633
  sodium citrate dihydrate, 640
  sodium lactate, 650
  sodium lauryl sulfate, 651
  sorbitan esters, 675
  stearic acid, 697
  sunflower oil, 721
  tragacanth, 744
  triethanolamine, 754
  vitamin E polyethylene glycol succinate, 764
  xanthan gum, 782
Emulsifying ointment BP, 771
Emulsifying Wax, 770, 777
  anionic, 770–771, 778
    incompatibilities, quaternary ammonium compounds, 771
    with white soft paraffin, 771
  cationic, 778
    cetrimide emulsifying wax, 778
    incompatibilities, anionic surfactants/drugs, 778
  nomenclature, 772, 778
  nonionic, 541, 771, 777
    cetomacrogol emulsifying wax, 777
    phenol, 777
    quaternary ammonium compounds, 777
  surfactants, 772, 778
Emulsifying wax BP, 772, 778
Emulsifying wax USP, 772, 778
Emulsion stabilizers
  cellulose, microcrystalline and carboxymethylcellulose sodium, 134
  colloidal silicon dioxide, 185
  hydrophobic colloidal silica, 309
  hypromellose, 326
  myristyl alcohol, 456
  phospholipids, 499
  polyethylene glycol, 518
  poly(methylvinyl ether/maleic anhydride), 534
  zinc acetate, 791
Encapsin, 210
Encapsulating agents, shellac, 616
Enstatite, 403
Enteric formulations/coating agents
  acetyltributyl citrate, 8
  carbomers, 110
  cellulose acetate phthalate, 144
  colonic drug delivery, 298
  guar gum, 298
  hypromellose acetate succinate, 330
  hypromellose phthalate, 333
  polymethacrylates, 526
  polyvinyl acetate phthalate, 562
  potassium chloride, model drug, 572
  shellac, 616
  Sureteric, 562
  tributyl citrate, 749
  triethyl citrate, 756
  triolein, 757
  white wax, 779
  zein, 790
  see also Controlled-release agents
Entonox, 464
Equal, 48
Ergoplast FDB, 225
Erucic acid
  canola oil, 108
  colza oil, 108
  rapeseed oil, 108–109
Erycorbin, 250
Erythorbic acid, 45, 250
Erythorbic acid sodium salt, 251
Erythrite, 251
Erythritol, **251**
Erythritolum, 251
Erythroglucin, 251
D-*erythro*-hex-2-enoic acid, 250
D-*erythro*-hex-2-enoic acid sodium salt, 251
D-*erythro*-3-ketohexonic acid lactone, 250
Erythromycin stearate, 403, 408
Essential oils, 247, 443
  solubilizing agents
    polyethylene alkyl ethers, 537
    polyoxyethylene castor oil derivatives, 543
    polyoxyethylene sorbitan fatty acid esters, 550
Esterifying agents, propionic acid, 586
Esterwax NF, 777
Estol IPM, 348
Ethal, 155
Ethanecarboxylic acid, 586
N,*N*-1,2-Ethanediylbis[*N*-(carboxymethyl)glycine], 247
N,*N*′-1,2-ethanediylbis[*N*-(carboxymethyl)glycine] dipotassium salt, 248
N,*N*′-1,2-ethanediylbis[*N*-(carboxymethyl)glycine] tetrasodium salt, 249
N,*N*′-1,2-ethanediylbis[*N*-(carboxymethyl)glycine] trisodium salt, 249
Ethanoic acid, 5