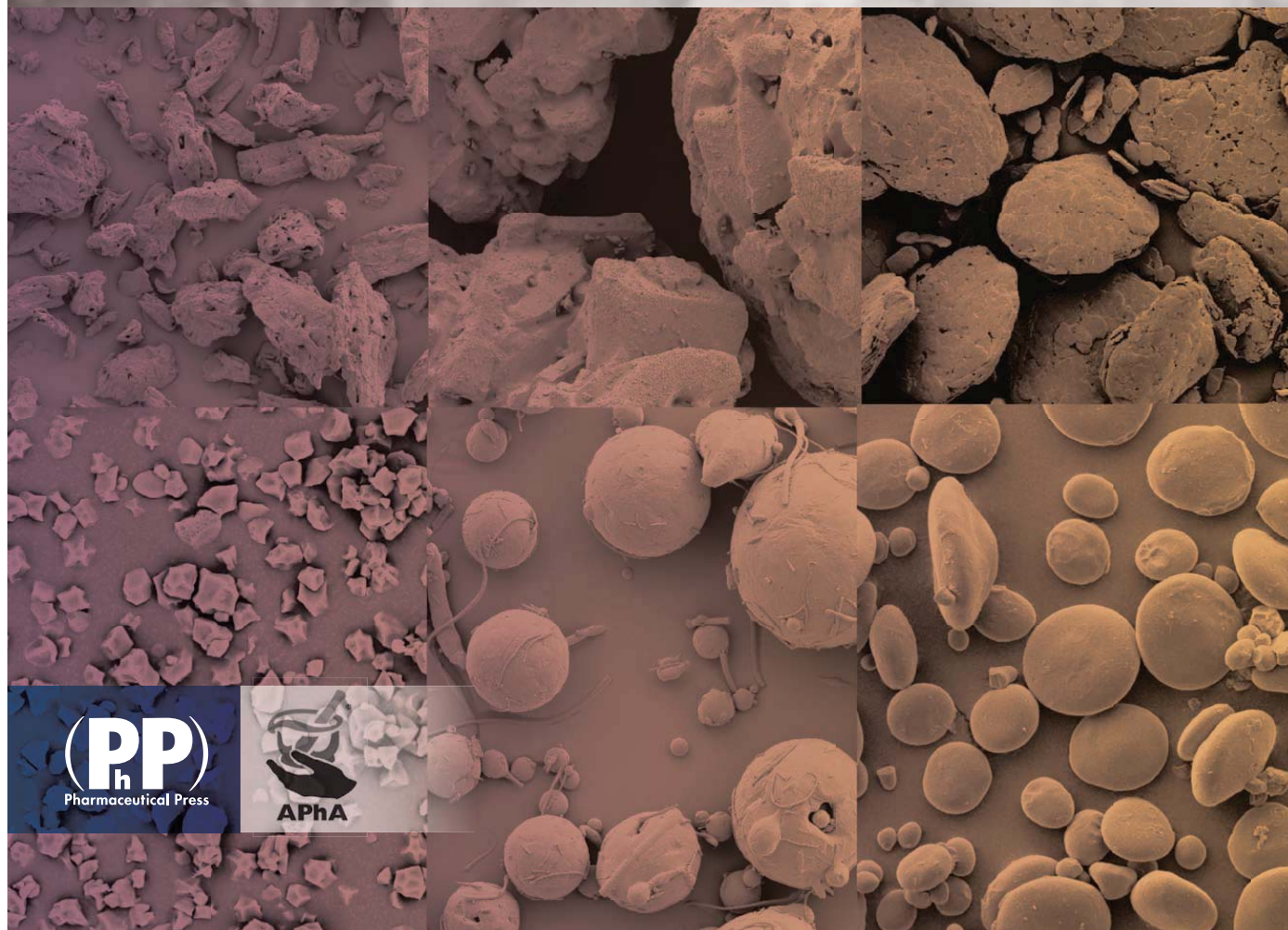


Handbook of Pharmaceutical Excipients

Sixth edition

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



(PP)
Pharmaceutical Press



KINDERFARMS Ex. 1029
KINDERFARMS LLC. v. GENEXA INC.
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SIXTH EDITION

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1 Nonproprietary Names

JP: Agar
PhEur: Agar
USP-NF: Agar

2 Synonyms

Agar-agar; agar-agar flake; agar-agar gum; Bengal gelatin; Bengal gum; Bengal isinglass; Ceylon isinglass; Chinese isinglass; E406; gelosa; gelose; Japan agar; Japan isinglass; layor carang.

3 Chemical Name and CAS Registry Number

Agar [9002-18-0]

4 Empirical Formula and Molecular Weight

See Section 5.

5 Structural Formula

Agar is a dried, hydrophilic, colloidal polysaccharide complex extracted from the agarocytes of algae of the Rhodophyceae. The structure is believed to be a complex range of polysaccharide chains having alternating α -(1 $\rightarrow$ 3) and β -(1 $\rightarrow$ 4) linkages. There are three extremes of structure noted: namely neutral agarose; pyruvated agarose having little sulfation; and a sulfated galactan. Agar can be separated into a natural gelling fraction, agarose, and a sulfated nongelling fraction, agaropectin.

6 Functional Category

Emulsifying agent; stabilizing agent; suppository base; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Agar is widely used in food applications as a stabilizing agent. In pharmaceutical applications, agar is used in a handful of oral tablet and topical formulations. It has also been investigated in a number of experimental pharmaceutical applications including as a sustained-release agent in gels, beads, microspheres, and tablets.⁽¹⁻⁴⁾ It has also been reported to work as a disintegrant in tablets.⁽⁵⁾ Agar has been used in a floating controlled-release tablet; the buoyancy in part being attributed to air entrapped in the agar gel network.⁽⁶⁾ It can be used as a viscosity-increasing agent in aqueous systems. Agar can also be used as a base for nonmelting, and nondisintegrating suppositories.⁽⁷⁾ Agar has an application as a suspending agent in pharmaceutical suspensions.⁽⁸⁾

8 Description

Agar occurs as transparent, odorless, tasteless strips or as a coarse or fine powder. It may be weak yellowish-orange, yellowish-gray to pale-yellow colored, or colorless. Agar is tough when damp, brittle when dry.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for agar.

Test	JP XV	PhEur 6.3	USP32-NF27
Identification	+	+	+
Characters	+	+	—
Swelling index	—	+	—
Arsenic	—	—	≤ 3 ppm
Lead	—	—	$\leq 0.001\%$
Sulfuric acid	+	—	—
Sulfurous acid and starch	+	—	—
Gelatin	—	+	+
Heavy metals	—	—	$\leq 0.004\%$
Insoluble matter	≤ 15.0 mg	$\leq 1.0\%$	≤ 15.0 mg
Water absorption	≤ 75 mL	—	≤ 75 mL
Loss on drying	$\leq 22.0\%$	$\leq 20.0\%$	$\leq 20.0\%$
Microbial contamination	—	$\leq 10^3$ cfu/g ^(a)	+
Total ash	$\leq 4.5\%$	$\leq 5.0\%$	$\leq 6.5\%$
Acid-insoluble ash	$\leq 0.5\%$	—	$\leq 0.5\%$
Foreign organic matter	—	—	$\leq 1.0\%$
Limit of foreign starch	—	—	+

(a) Total viable aerobic count, determined by plate-count.

10 Typical Properties

NIR spectra see Figure 1.

Solubility Soluble in boiling water to form a viscous solution; practically insoluble in ethanol (95%), and cold water. A 1% w/v aqueous solution forms a stiff jelly on cooling.

11 Stability and Storage Conditions

Agar solutions are most stable at pH 4–10.

Agar should be stored in a cool, dry, place. Containers of this material may be hazardous when empty since they retain product residues (dust, solids).

12 Incompatibilities

Agar is incompatible with strong oxidizing agents. Agar is dehydrated and precipitated from solution by ethanol (95%). Tannic acid causes precipitation; electrolytes cause partial dehydration and decrease in viscosity of sols.⁽⁹⁾

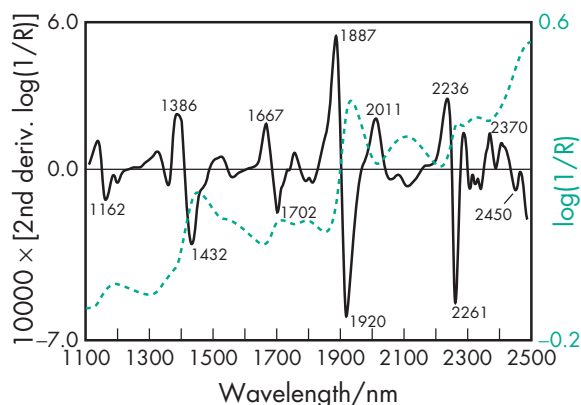


Figure 1: Near-infrared spectrum of agar measured by reflectance.

A

13 Method of Manufacture

Agar is obtained by freeze-drying a mucilage derived from *Gelidium amansii* Lamouroux, other species of the same family (Gelidiaceae), or other red algae (Rhodophyta).

14 Safety

Agar is widely used in food applications and has been used in oral and topical pharmaceutical applications. It is generally regarded as relatively nontoxic and nonirritant when used as an excipient.

LD₅₀ (hamster, oral): 6.1 g/kg⁽¹⁰⁾

LD₅₀ (mouse, oral): 16.0 g/kg

LD₅₀ (rabbit, oral): 5.8 g/kg

LD₅₀ (rat, oral): 11.0 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of the material handled. When heated to decomposition, agar emits acrid smoke and fumes.

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (oral tablets). Included in the Canadian List of Acceptable Non-medicinal Ingredients. Included in nonparenteral medicines licensed in the UK.

17 Related Substances

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18 Comments

The drug release mechanism of agar spherules of felodipine has been studied and found to follow Higuchi kinetics.⁽¹¹⁾ Agar has also been used to test the bioadhesion potential of various polymers.⁽¹²⁾

The EINECS number for agar is 232-658-1.

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20 General References

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21 Author

VK Gupta.

22 Date of Revision

10 February 2009.



Albumin

1 Nonproprietary Names

BP: Albumin Solution

PhEur: Human Albumin Solution

USP: Albumin Human

2 Synonyms

Alba; *Albuconn*; *Albuminar*; albumin human solution; albumini humani solutio; *Albumisol*; *Albuspan*; *Albutein*; *Buminate*; human serum albumin; normal human serum albumin; *Octalbin*; *Plasbumin*; plasma albumin; *Pro-Bumin*; *Proserum*; *Zenalb*.

3 Chemical Name and CAS Registry Number

Serum albumin [9048-49-1]

4 Empirical Formula and Molecular Weight

Human serum albumin has a molecular weight of about 66 500 and is a single polypeptide chain consisting of 585 amino acids.

Characteristic features are a single tryptophan residue, a relatively low content of methionine (6 residues), and a large number of cysteine (17) and of charged amino acid residues of aspartic acid (36), glutamic acid (61), lysine (59), and arginine (23).

5 Structural Formula

Primary structure Human albumin is a single polypeptide chain of 585 amino acids and contains seven disulfide bridges.

Secondary structure Human albumin is known to have a secondary structure that is about 55% α -helix. The remaining 45% is believed to be divided among turns, disordered, and β structures.⁽¹⁾

Albumin is the only major plasma protein that does not contain carbohydrate constituents. Assays of crystalline albumin show less than one sugar residue per molecule.

6 Functional Category

Stabilizing agent; therapeutic agent.

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1 Nonproprietary Names

BP: Gelatin

JP: Gelatin

PhEur: Gelatin

USP-NF: Gelatin

2 Synonyms

Byco; Cryogel; E441; gelatina; gelatine; Instagel; Kolatin; Solugel; Vitagel.

3 Chemical Name and CAS Registry Number

Gelatin [9000-70-8]

4 Empirical Formula and Molecular Weight

Gelatin is a generic term for a mixture of purified protein fractions obtained either by partial acid hydrolysis (type A gelatin) or by partial alkaline hydrolysis (type B gelatin) of animal collagen obtained from cattle and pig bone, cattle skin (hide), pigskin, and fish skin. Gelatin may also be a mixture of both types.

The protein fractions consist almost entirely of amino acids joined together by amide linkages to form linear polymers, varying in molecular weight from 20 000–200 000.

The JP XV also includes a monograph for purified gelatin.

5 Structural Formula

See Section 4.

6 Functional Category

Coating agent; film-forming agent; gelling agent; suspending agent; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Gelatin is widely used in a variety of pharmaceutical formulations, including its use as a biodegradable matrix material in an implantable delivery system,⁽¹⁾ although it is most frequently used to form either hard or soft gelatin capsules.^(2–4)

Gelatin capsules are unit-dosage forms designed mainly for oral administration. Soft capsules on the market also include those for rectal and vaginal administration. Hard capsules can be filled with solid (powders, granules, pellets, tablets, and mixtures thereof), semisolid and liquid fillings, whereas soft capsules are mainly filled with semisolid or liquid fillings. In hard capsules, the active drug is always incorporated into the filling, while in soft capsules the drug substance can also be incorporated into the thick soft capsule shell. Gelatin is soluble in warm water (>30°C), and a gelatin capsule will initially swell and finally dissolve in gastric fluid to release its contents rapidly.⁽⁵⁾

Hard capsules are manufactured in two pieces by dipping lubricated stainless steel mold pins into a 45–55°C gelatin solution of defined viscosity, which depends on the size of the capsules and whether cap or body are to be formed. The gelatin is taken up by the pins as a result of gelation, and the resulting film thickness is governed by the viscosity of the solution. The capsule shells are passed through a stream of cool air to aid setting of the gelatin, and afterwards they are slowly dried with large volumes of humidity controlled air heated to a few degrees above ambient temperature and blown directly over the pins. The capsule halves are removed from their pins, trimmed and fitted together. Gelatin that is used to

produce hard capsules may contain various coloring agents and antimicrobial preservatives. Surfactants may be present in small quantities in the shells being a residue of the pin lubricant. However, the use of preservatives is no longer encouraged in line with current GMP principles. Capsule shells may be treated with formaldehyde to make them insoluble in gastric fluid. Standard capsules vary in volume from 0.13 to 1.37 mL. For veterinary use, capsules with a volume between 3 and 28 mL are available, and capsules with a capacity of 0.025 mL are available for toxicity studies in rats.

In contrast to two-piece hard capsules, soft gelatin capsules are manufactured, filled and sealed in one process. The gelatin used to form the soft shells has a lower gel strength than that used for hard capsules, and the viscosity of the solutions is also lower, which results in more flexible shells. Additives to soft shell formulations are plasticizers such as polyalcohols (glycerin, propylene glycol, polyethylene glycol). Sorbitol can be added as moisturizing agent, whereby the larger amount of water will act as plasticizer. Coloring and opacifying agents are also added. The filling can interact with the gelatin and the plasticizer chemically. There may be migration of filling components into the shell and plasticizer from the shell into the filler. These interactions have to be taken into account during the formulation of the gelatin shell and the filling. The main method to produce soft gelatin capsules is the rotary die method (RP Scherer), and an alternative method for small volumes of round capsules is the Globex system (Industrial Techno-logic Solutions Ltd).⁽⁴⁾ *Softlet Gelcaps* (Banner Pharmacaps) are tablets that have been coated with a gelatin film.

Gelatin is also used for the microencapsulation of drugs, where the active drug is sealed inside a micro-sized capsule or beadlet, which may then be handled as a powder. The first microencapsulated drugs (beadlets) were fish oils and oily vitamins in gelatin beadlets prepared by coacervation.

Low-molecular-weight gelatin has been investigated for its ability to enhance the dissolution of orally ingested drugs.⁽⁶⁾ Ibuprofen-gelatin micropellets have been prepared for the controlled release of the drug.⁽⁷⁾ Other uses of gelatin include the preparation of pastes, pastilles, pessaries, and suppositories. In addition, it is used as a tablet binder and coating agent, and as a viscosity-increasing agent for solutions and semisolids.

Therapeutically, gelatin has been used in the preparation of wound dressings⁽⁸⁾ and has been used as a plasma substitute, although anaphylactoid reactions have been reported in the latter application.⁽⁹⁾ Absorbable gelatin is available as sterile film, ophthalmic film, sterile sponge, sterile compressed sponge, and sterile powder from sponge. Gelatin sponge has hemostatic properties.

Gelatin is also widely used in food products and photographic emulsions.

8 Description

Gelatin occurs as a light-amber to faintly yellow-colored, vitreous, brittle solid. It is practically odorless and tasteless, and is available as translucent sheets, flakes, and granules, or as a coarse powder.

9 Pharmacopeial Specifications

See Table I. See also Section 18.

Table I: Pharmacopeial specifications for gelatin.

Test	JP XV	PhEur 6.3	USP32-NF27
Identification	+	+	+
Characters	—	+	—
Microbial	—	+	+
contamination			
Aerobic bacteria	—	$\leq 10^3$ cfu/g	$\leq 10^3$ cfu/g
Fungi	+	$\leq 10^2$ cfu/g	—
Residue on ignition	$\leq 2.0\%$	—	$\leq 2.0\%$
Loss on drying	$\leq 15.0\%$	$\leq 15.0\%$	—
Odor and water-insoluble substances	+	—	+
Isoelectric point	+	+	+
Type A	7.0–9.0	6.0–9.5	—
Type B	4.5–5.0	4.7–5.6	—
Conductivity	—	≤ 1 mS/cm	—
Sulfur dioxide	—	≤ 50 ppm	$\leq 0.15\%$
Sulfite	+	—	—
Arsenic	≤ 1 ppm	—	≤ 0.8 ppm
Iron	—	≤ 30 ppm	—
Chromium	—	≤ 10 ppm	—
Zinc	—	≤ 30 ppm	—
Heavy metals	≤ 50 ppm	—	$\leq 0.005\%$
pH	—	3.8–7.6	—
Mercury	≤ 0.1 ppm	—	—
Peroxides	—	≤ 10 ppm	—
Gel strength	—	+	—

10 Typical Properties

Acidity/alkalinity

For a 1% w/v aqueous solution at 25°C (depending on source and grade):

pH = 3.8–5.5 (type A);

pH = 5.0–7.5 (type B).

Density

1.32 g/cm³ for type A;

1.28 g/cm³ for type B.

Isoelectric point

7.0–9.0 for type A;

4.7–5.4 for type B.

Moisture content 9–11%.⁽¹⁰⁾ See also Figures 1 and 2.

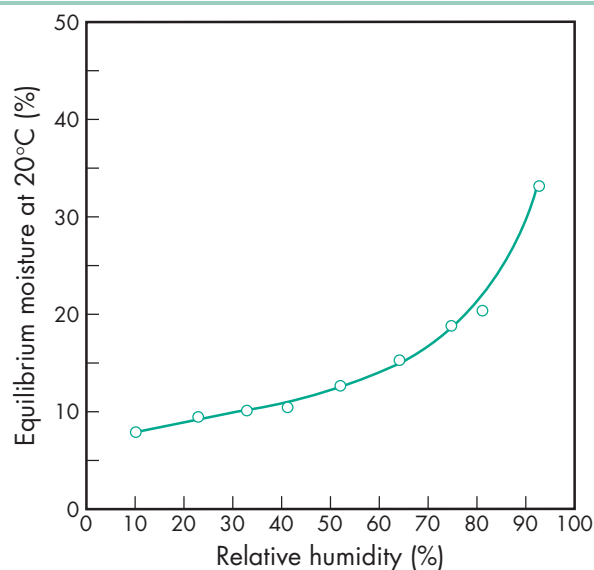
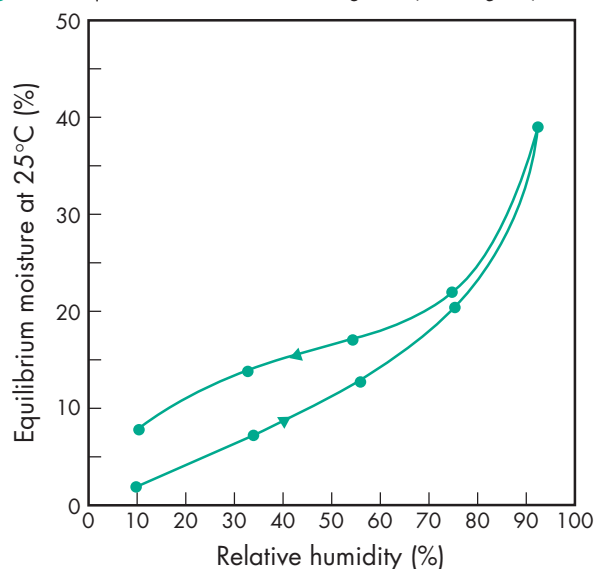
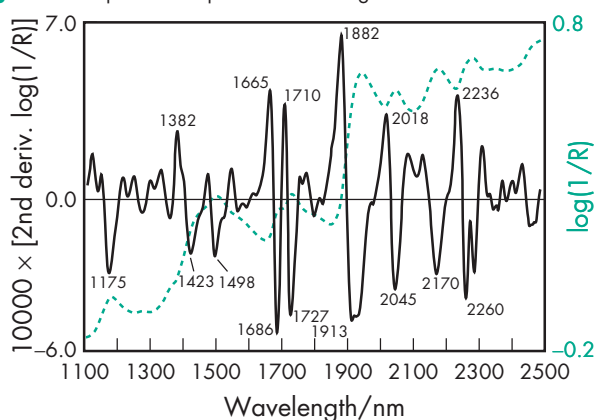
NIR spectra see Figure 3.

Solubility Practically insoluble in acetone, chloroform, ethanol (95%), ether, and methanol. Soluble in glycerin, acids, and alkalis, although strong acids or alkalis cause precipitation. In water, gelatin swells and softens, gradually absorbing between five and 10 times its own weight of water. Gelatin is soluble in water above 40°C, forming a colloidal solution, which gels on cooling to 35–40°C. This gel-sol system is thixotropic and heat-reversible, the melting temperature being slightly higher than the setting point; the melting point can be varied by the addition of glycerin.

Viscosity (dynamic) see Table II.⁽⁴⁾

Table II: Dynamic viscosity of gelatin solutions at 60°C.

Grade	Viscosity (dynamic)/mPa s	
	6.67% w/v aqueous solution	12.5% w/c aqueous solution
Acid ossein	2.7–3.7	12.5–14.5
Acid pigskin	4.2–4.8	19.0–20.5
Fish skin	3.0–4.5	13.0–20.0
Limed ossein/hide	3.6–4.8	19.0–20.5

**Figure 1:** Equilibrium moisture content of gelatin (Pharmagel A).**Figure 2:** Sorption-desorption isotherm of gelatin.**Figure 3:** Near-infrared spectrum of gelatin measured by reflectance.

11 Stability and Storage Conditions

Dry gelatin is stable in air. Aqueous gelatin solutions are also stable for long periods if stored under cool conditions but they are subject to bacterial degradation.⁽⁴⁾ At temperatures above about 50°C, aqueous gelatin solutions may undergo slow depolymerization and a reduction in gel strength may occur on resetting. Depolymerization becomes more rapid at temperatures above 65°C, and gel strength may be reduced by half when a solution is heated at 80°C for 1 hour. The rate and extent of depolymerization depends on the molecular weight of the gelatin, with a lower-molecular-weight material decomposing more rapidly.⁽¹¹⁾

Gelatin may be sterilized by dry heat.

The bulk material should be stored in an airtight container in a cool, well-ventilated and dry place.

G

12 Incompatibilities

Gelatin is an amphoteric material and will react with both acids and bases. It is also a protein and thus exhibits chemical properties characteristic of such materials; for example, gelatin may be hydrolyzed by most proteolytic systems to yield its amino acid components.

Gelatin will also react with aldehydes and aldehydic sugars, anionic and cationic polymers, electrolytes, metal ions, plasticizers, preservatives, strong oxidizers, and surfactants. It is precipitated by alcohols, chloroform, ether, mercury salts, and tannic acid. Gels can be liquefied by bacteria unless preserved.

Some of these interactions are exploited to favorably alter the physical properties of gelatin: for example, gelatin is mixed with a plasticizer, such as glycerin, to produce soft gelatin capsules and suppositories; gelatin is treated with formaldehyde to produce gastroresistance; *see* Section 7.

13 Method of Manufacture

Gelatin is extracted from animal tissues rich in collagen such as skin, sinews, and bone. Although it is possible to extract gelatin from these materials using boiling water, it is more practical to first pretreat the animal tissues with either acid or alkali. Gelatin obtained from the acid process is called type A, whereas gelatin obtained from the alkali process is called type B.

The acid-conditioning process (manufacture of type A gelatin) is restricted to soft bone ossein (demineralized bones), sinew, pigskin, calfskin and fish skins for reasons of gaining sufficient yield. The material is cut in pieces and washed in cold water for a few hours to remove superficial fat. It is then treated with mineral acid solutions, mainly HCl or H₂SO₄, at pH 1–3 and 15–20°C until maximum swelling has occurred. This process takes approximately 24 hours. The swollen stock is then washed with water to remove excess acid, and the pH is adjusted to pH 3.5–4.0 (pigskin, fish skin) or 2.0–3.5 (all other tissues) for the conversion to gelatin by hot-water extraction.

The hydrolytic extraction is carried out in a batch-type operation using successive portions of hot water at progressively higher temperatures (50–75°C) until the maximum yield of gelatin is obtained. The gelatin solution is then filtered through previously sterilized cellulose pads, deionized, concentrated to about 20–25% w/v and sterilized by flashing it to 138°C for 4 seconds. The dry gelatin is then formed by chilling the solution to form a gel, which is air-dried in temperature-controlled ovens. The dried gelatin is ground to the desired particle size.

In the alkali process (liming), demineralized bones (ossein) or cattle skins are usually used. The animal tissue is held in a calcium hydroxide (2–5% lime) slurry for a period of 2–4 months at 14–18°C. At the end of the liming, the stock is washed with cold water for about 24 hours to remove as much of the lime as possible. The stock solution is then neutralized with acid (HCl, H₂SO₄, H₃PO₄) and the gelatin is extracted with water in an identical

manner to that in the acid process, except that the pH is kept at values between 5.0–6.5 (neutral extraction).

During the preparation of the bovine bones used in the production of gelatin, specified risk materials that could contain transmissible spongiform encephalopathies (TSEs) vectors are removed. TSE infectivity is not present in pharmaceutical grade gelatin.

14 Safety

Gelatin is widely used in a variety of pharmaceutical formulations, including oral and parenteral products.

In general, when used in oral formulations gelatin may be regarded as a nontoxic and nonirritant material. However, there have been rare reports of gelatin capsules adhering to the esophageal lining, which may cause local irritation.⁽¹²⁾ Hypersensitivity reactions, including serious anaphylactoid reactions, have been reported following the use of gelatin in parenteral products.^(9,13)

There have been concerns over the potential spread of BSE/TSE infections through bovine derived products. However, the risk of such contamination of medicines is extremely low.

LD₅₀ (rat, oral): 5 g/kg⁽¹⁴⁾

TD_{Lo} (mouse, IP): 700 mg/kg⁽¹⁵⁾

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Gelatin should be handled in a well-ventilated environment and kept away from sources of ignition and heat. Empty containers pose a fire risk, and the gelatin residues should be evaporated under a fume hood.

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Database (dental preparations; inhalations; injections; oral capsules, pastilles, solutions, syrups and tablets; topical and vaginal preparations). Included in medicines licensed in the UK, Europe, and Japan. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

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18 Comments

Gelatin 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.

In the past there has been a significant amount of regulatory activity and legislation due to the attention given to bovine sourced gelatin manufacturing processes and the potential transmission of TSE vectors from raw bovine materials into gelatin.⁽⁴⁾ In Europe, the criteria by which the safety is assured involves controlling the geographical sourcing of animals used; the nature of the tissue used (based on scientific data showing where animal BSE infectivity is located); and the method of production.

Gelatin produced with hides as the starting material is considered much safer than using bones, although it is recommended that measures are undertaken to prevent cross-contamination with potentially contaminated materials. When gelatin is produced from bones, the bones should ideally not be sourced from countries classified as Geographical BSE Risk (GBR) I and II,

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although bones from GBR III countries can be used if the removal of vertebrae from the raw materials is assured (see Table III).⁽¹⁶⁾

Various grades of gelatin are commercially available that differ in particle size, molecular weight, and other properties. Grading is usually by gel strength, expressed as 'Bloom strength', which is the weight in grams that, when applied under controlled conditions to a plunger 12.7 mm in diameter, will produce a depression exactly 4 mm deep in a matured gel containing 6.66% w/w of gelatin in water.

Gelatin-acacia complex coacervation has been used in the preparation of microcapsules of vitamin A.⁽¹⁷⁾ Pindolol-loaded alginate-gelatin beads have been developed for the sustained release of pindolol.⁽¹⁸⁾

A specification for gelatin is contained in the Food Chemicals Codex (FCC).⁽¹⁹⁾

The EINECS number for gelatin is 232-554-6.

Table III: The European Scientific Steering Committee classification of geographical BSE risk (GBR).

GBR level	Presence of one or more cattle clinically or pre-clinically infected with BSE in a geographical region/country
I	Highly unlikely
II	Unlikely but not excluded
III	Likely but not confirmed or confirmed at a lower level
IV	Confirmed at a higher level

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21 Author

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22 Date of Revision

23 February 2009.

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

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21 Author

A Day.

22 Date of Revision

18 February 2009.

 Glycerin
1 Nonproprietary Names

BP: Glycerol

JP: Concentrated Glycerin

PhEur: Glycerol

USP: Glycerin

2 Synonyms

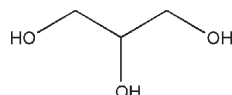
Croderol; E422; glicerol; glycerine; glycerolum; *Glycon G-100*; *Kemstrene*; *Optim*; *Pricerine*; 1,2,3-propanetriol; trihydroxypropane glycerol.

3 Chemical Name and CAS Registry Number

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

4 Empirical Formula and Molecular Weight

C₃H₈O₃ 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 co-solvent.^(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/cm³ at 15°C;

1.2636 g/cm³ at 20°C;

1.2620 g/cm³ 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

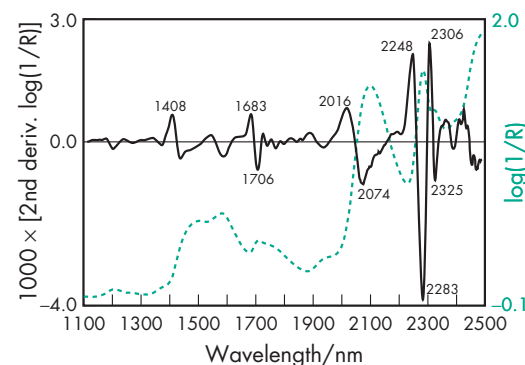


Figure 1: Near-infrared spectrum of glycerin measured by transmittance (1 mm path-length). The small peak at approx. 1950 nm is due to a trace of water (<0.5% m/m).

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 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⁽¹⁸⁾

LD₅₀ (mouse, IP): 8.70 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 (rabbit, oral): 27 g/kg⁽¹⁹⁾

LD₅₀ (rat, IP): 4.42 g/kg

LD₅₀ (rat, oral): 5.57 g/kg⁽¹⁹⁾

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) workplace exposure limit for glycerin mist is 10 mg/m³.⁽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 (C₃H₈O₃). The PhEur 6.0 contains a monograph for ‘glycerol 85 per cent’ that contains 83.5–88.5% of propane-1,2,3-triol (C₃H₈O₃).

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

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

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- 19 CDC National Institute for Occupational Safety and Health. *Registry of toxic effects of chemical substances (RTECS)*, 1993–2008.
- 20 Health and Safety Executive. *EH40/2005: Workplace Exposure Limits*. Sudbury: HSE Books, 2005 (updated 2007). <http://www.hse.gov.uk/coshh/table1.pdf> (accessed 5 February 2009).
- 21 *Food Chemicals Codex*, 6th edn. Bethesda, MD: United States Pharmacopeia, 2008; 407.

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21 Authors

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22 Date of Revision

5 February 2009.

G

Glyceryl Behenate

1 Nonproprietary Names

BP: Glycerol Dibehenate
PhEur: Glycerol Dibehenate
USP-NF: Glyceryl Behenate

2 Synonyms

Compritol 888 ATO; 2,3-dihydroxypropyl docosanoate; docosanoic acid, 2,3-dihydroxypropyl ester; E471; glycerol behenate; glyceroli dibehenas; glyceryl monobehenate.

Note that tribehenin is used as a synonym for glyceryl tribehenate.

3 Chemical Name and CAS Registry Number

Docosanoic acid, monoester with glycerin [30233-64-8] (glyceryl behenate)
Docosanoic acid, diester with glycerin [94201-62-4] (glyceryl dibehenate)
Docosanoic acid, triester with glycerin [18641-57-1] (glyceryl tribehenate)

4 Empirical Formula and Molecular Weight

Glyceryl dibehenate is a mixture of glycerol esters. The PhEur 6.0 describes glyceryl dibehenate as a mixture of diacylglycerols, mainly dibehenoylglycerol, together with variable quantities of mono- and triacylglycerols (*see* Section 9). The USP32–NF27 describes glyceryl behenate as a mixture of glycerides of fatty acids, mainly behenic acid. It specifies that the content of 1-monoglycerides should be 12.0–18.0%.

5 Structural Formula

See Section 4.

6 Functional Category

Coating agent; tablet binder; tablet and capsule lubricant; thickening agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Glyceryl behenate is used in cosmetics, foods, and oral pharmaceutical formulations; *see* Table I.

In pharmaceutical formulations, glyceryl behenate is mainly used as a lubricant in the preparation of oral tablets and capsules.^(1–3) It has good binding properties, it does not affect tablet hardness and is unaffected by mixing or production parameters. Glyceryl behenate has been investigated for the encapsulation of various drugs such as retinoids.⁽⁴⁾ It has also been investigated for use in the preparation of sustained-release tablets;^(5–10) as a matrix-forming agent for the controlled release of water-soluble drugs;⁽¹⁰⁾ and it can also be used as a hot-melt coating agent sprayed onto a powder or drug-loaded sugar beads and granules.^(11,12) It may also be incorporated via extrusion/spheronization into pellets, which can be further compressed into tablets.

Glyceryl behenate is used in oral enteric-coated pellets, powders and suspensions. It is also used in controlled, extended-release and orally disintegrating tablets. For oral preparations, glyceryl behenate forms a lipidic matrix for sustained-release formulations. It has been used along with acid-soluble or swellable polymers to mask the bitter or unpleasant taste of the medicament with improved palatability.⁽¹³⁾

Glyceryl behenate has been used for the preparation of ophthalmic inserts.^(14,15)

In cosmetics, glyceryl behenate is used as a skin conditioning agent, emollient and viscosity-increasing agent in emulsions. It also improves the heat stability of emulsions and is a gelifying agent for various oils. For topical formulations, it is used as a thickening agent for oily phases. It is also used as a surfactant or emulsifying agent.

See also Section 18.

Table I: Uses of glyceryl behenate.

Use	Concentration (%)
Lipophilic matrix or coating for sustained-released tablets and capsules	>10.0
Tablet and capsule lubricant	1.0–3.0
Viscosity-increasing agent in silicon gels (cosmetics)	1.0–15.0
Viscosity-increasing agent in w/o or o/w emulsions (cosmetics)	1.0–5.0

Propylene Glycol

1 Nonproprietary Names

BP: Propylene Glycol
JP: Propylene Glycol
PhEur: Propylene Glycol
USP: Propylene Glycol

2 Synonyms

1,2-Dihydroxypropane; E1520; 2-hydroxypropanol; methyl ethylene glycol; methyl glycol; propane-1,2-diol; propylenglycolum.

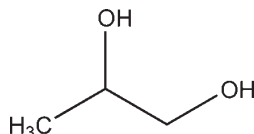
3 Chemical Name and CAS Registry Number

1,2-Propanediol [57-55-6]
(-)-1,2-Propanediol [4254-14-2]
(+)-1,2-Propanediol [4254-15-3]

4 Empirical Formula and Molecular Weight

C₃H₈O₂ 76.09

5 Structural Formula



P

6 Functional Category

Antimicrobial preservative; disinfectant; humectant; plasticizer; solvent; stabilizing agent; water-miscible cosolvent.

7 Applications in Pharmaceutical Formulation or Technology

Propylene glycol has become widely used as a solvent, extractant, and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations. It is a better general solvent than glycerin and dissolves a wide variety of materials, such as corticosteroids, phenols, sulfa drugs, barbiturates, vitamins (A and D), most alkaloids, and many local anesthetics.

As an antiseptic it is similar to ethanol, and against molds it is similar to glycerin and only slightly less effective than ethanol.

Propylene glycol is commonly used as a plasticizer in aqueous film-coating formulations.

Propylene glycol is also used in cosmetics and in the food industry as a carrier for emulsifiers and as a vehicle for flavors in preference to ethanol, since its lack of volatility provides a more uniform flavor. See Table I.

Table I: Uses of propylene glycol.

Use	Dosage form	Concentration (%)
Humectant	Topicals	≈15
Preservative	Solutions, semisolids	15–30
Solvent or cosolvent	Aerosol solutions	10–30
	Oral solutions	10–25
	Parenterals	10–60
	Topicals	5–80

8 Description

Propylene glycol is a clear, colorless, viscous, practically odorless liquid, with a sweet, slightly acid taste resembling that of glycerin.

9 Pharmacopeial Specifications

See Table II. See also Section 18.

Table II: Pharmacopeial specifications for propylene glycol.

Test	JP XV	PhEur 6.0	USP 32
Identification	+	+	+
Appearance	—	+	—
Specific gravity	1.035–1.040	1.035–1.040	1.035–1.037
Acidity	+	+	+
Water	≤0.5%	≤0.2%	≤0.2%
Residue on ignition	≤0.005%	—	≤3.5 mg/50 g
Sulfated ash	—	≤0.01%	—
Chloride	≤0.007%	—	≤0.007%
Sulfate	≤0.002%	—	≤0.006%
Heavy metals	≤5 ppm	≤5 ppm	≤5 ppm
Refractive index	—	1.431–1.433	—
Oxidizing substances	—	+	—
Reducing substances	—	+	—
Arsenic	≤2 ppm	—	—
Glycerin	+	—	—
Boiling point	184–189°C	184–189°C	—
Assay	—	—	≥99.5%

10 Typical Properties

Autoignition temperature 371°C

Boiling point 188°C

Density 1.038 g/cm³ at 20°C

Flammability Upper limit, 12.6% v/v in air; lower limit, 2.6% v/v in air.

Flash point 99°C (open cup)

Heat of combustion 1803.3 kJ/mol (431.0 kcal/mol)

Heat of vaporization 705.4 J/g (168.6 cal/g) at b.p.

Melting point –59°C

Osmolarity A 2.0% v/v aqueous solution is iso-osmotic with serum.

Refractive index n_D^{20} = 1.4324

Specific rotation

$[\alpha]_D^{20}$ = –15.0° (neat) for (R)-form;

$[\alpha]_D^{20}$ = +15.8° (neat) for (S)-form.

Solubility Miscible with acetone, chloroform, ethanol (95%), glycerin, and water; soluble at 1 in 6 parts of ether; not miscible with light mineral oil or fixed oils, but will dissolve some essential oils.

Specific heat 2.47 J/g (0.590 cal/g) at 20°C.

Surface tension 40.1 mN/m (40.1 dynes/cm) at 25°C.

Vapor density (relative) 2.62 (air = 1)

Vapor pressure 9.33 Pa (0.07 mmHg) at 20°C.

Viscosity (dynamic) 58.1 mPa s (58.1 cP) at 20°C.

11 Stability and Storage Conditions

At cool temperatures, propylene glycol is stable in a well-closed container, but at high temperatures, in the open, it tends to oxidize, giving rise to products such as propionaldehyde, lactic acid, pyruvic acid, and acetic acid. Propylene glycol is chemically stable when mixed with ethanol (95%), glycerin, or water; aqueous solutions may be sterilized by autoclaving.

Propylene glycol is hygroscopic and should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Propylene glycol is incompatible with oxidizing reagents such as potassium permanganate.

13 Method of Manufacture

Propylene is converted to chlorohydrin by chlorine water and hydrolyzed to 1,2-propylene oxide. With further hydrolysis, 1,2-propylene oxide is converted to propylene glycol.

14 Safety

Propylene glycol is used in a wide variety of pharmaceutical formulations and is generally regarded as a relatively nontoxic material. It is also used extensively in foods and cosmetics. Probably as a consequence of its metabolism and excretion, propylene glycol is less toxic than other glycols. Propylene glycol is rapidly absorbed from the gastrointestinal tract; there is also evidence that it is absorbed topically when applied to damaged skin. It is extensively metabolized in the liver, mainly to lactic and pyruvic acids, and is also excreted unchanged in the urine.^(1,2)

In topical preparations, propylene glycol is regarded as minimally irritant,⁽³⁾ although it is more irritant than glycerin. There have been some reports of contact dermatitis associated with propylene glycol.^(4,5) Some local irritation is produced upon application to mucous membranes or when it is used under occlusive conditions.⁽⁶⁾ Parenteral administration may cause pain or irritation when propylene glycol is used in high concentration.

Propylene glycol is estimated to be one-third as intoxicating as ethanol, with administration of large volumes being associated with adverse effects most commonly on the central nervous system, especially in neonates and children.⁽⁷⁻⁹⁾ Other adverse reactions reported, though generally isolated, include: ototoxicity;⁽¹⁰⁾ cardiovascular effects; seizures; and hyperosmolality⁽¹¹⁾ and lactic acidosis, both of which occur most frequently in patients with renal impairment. Adverse effects are more likely to occur following consumption of large quantities of propylene glycol or on administration to neonates, children under 4 years of age, pregnant women, and patients with hepatic or renal failure. Adverse events may also occur in patients treated with disulfiram or metronidazole.⁽¹²⁾

On the basis of metabolic and toxicological data, the WHO has set an acceptable daily intake of propylene glycol at up to 25 mg/kg body-weight.⁽¹³⁾ Formulations containing 35% propylene glycol can cause hemolysis in humans.

In animal studies, there has been no evidence that propylene glycol is teratogenic or mutagenic. Rats can tolerate a repeated oral daily dose of up to 30 mL/kg body-weight in the diet over 6 months, while the dog is unaffected by a repeated oral daily dose of 2 g/kg in the diet for 2 years.⁽¹⁴⁾

LD₅₀ (mouse, IP): 9.72 g/kg⁽¹⁵⁾

LD₅₀ (mouse, IV): 6.63 g/kg

LD₅₀ (mouse, oral): 22.0 g/kg

LD₅₀ (mouse, SC): 17.34 g/kg

LD₅₀ (rat, IM): 0.01 g/kg

LD₅₀ (rat, IP): 6.66 g/kg

LD₅₀ (rat, IV): 6.42 g/kg

LD₅₀ (rat, oral): 0.02 g/kg

LD₅₀ (rat, SC): 22.5 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Propylene glycol should be handled in

a well-ventilated environment; eye protection is recommended. In the UK, the long-term (8-hour TWA) workplace exposure limit for propylene glycol vapor and particulates is 474 mg/m³ (150 ppm) and 10 mg/m³ for particulates.⁽¹⁶⁾

16 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (dental preparations; IM and IV injections; inhalations; ophthalmic, oral, otic, percutaneous, 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

Propylene glycol alginate.

18 Comments

Propylene glycol 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.

In addition to its uses as an excipient, propylene glycol is used in veterinary medicine as an oral glucogenic in ruminants.⁽¹⁷⁾

A specification for potassium glycol is contained in the Food Chemicals Codex (FCC).⁽¹⁸⁾

The EINECS number for propylene glycol is 200-338-0. The PubChem Compound ID (CID) for propylene glycol is 1030.

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21 Author

PJ Weller.

22 Date of Revision

3 February 2009.

Propylene Glycol Alginate

1 Nonproprietary Names

USP-NF: Propylene Glycol Alginate

2 Synonyms

Alginic acid, propylene glycol ester; E405; hydroxypropyl alginate; *Kelcoloid*; *Kimiloid*; *Manucol Ester*; *Profoam*; *Pronova*; propane-1,2-diol alginate; *Protanal*; *TIC Pretested*.

3 Chemical Name and CAS Registry Number

Propylene glycol alginate [9005-37-2]

4 Empirical Formula and Molecular Weight

Propylene glycol alginate is a propylene glycol ester of alginic acid, a linear glycuronan polymer consisting of a mixture of β -(1 $\rightarrow$ 4)-D-mannosyluronic acid and α -(1 $\rightarrow$ 4)-L-gulosyluronic acid residues.

5 Structural Formula

See Section 4.

6 Functional Category

Emulsifying agent; foam stabilizer; stabilizing agent; suspending agent; viscosity increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Propylene glycol alginate is used as a stabilizing, suspending, gelling, and emulsifying agent in oral and topical pharmaceutical formulations. Typically, a concentration of 0.3–5% w/v is used, although this may vary depending upon the specific application and the grade of propylene glycol alginate used.

Propylene glycol alginate is also used in cosmetics and food products.

8 Description

Propylene glycol alginate occurs as a white to yellowish colored, practically odorless and tasteless, fibrous or granular powder.

9 Pharmacopeial Specifications

See Table I. See also Section 18.

Table I: Pharmacopeial specifications for propylene glycol alginate.

Test	USP32-NF27
Identification	+
Microbial limits	≤ 200 cfu/g
Loss on drying	$\leq 20.0\%$
Ash	$\leq 10.0\%$
Arsenic	≤ 3 ppm
Lead	$\leq 0.001\%$
Heavy metals	$\leq 0.004\%$
Free carboxyl groups	+
Esterified carboxyl groups	+
Assay (of alginates)	+

10 Typical Properties

NIR spectra see Figure 1.

Solubility Soluble in dilute organic acids and water, forming stable, viscous, colloidal solutions at pH 3. Depending upon the degree of esterification, propylene glycol alginate is also soluble in aqueous ethanol/water mixtures containing up to 60% w/w of ethanol (95%).

Viscosity (dynamic) The viscosity of aqueous solutions depends upon the grade of material used. Typically, a 1% w/v aqueous solution has a viscosity of 20–400 mPa s (20–400 cP). Viscosity may vary depending upon concentration, pH, temperature, or the presence of metal ions. See also Sodium Alginate.

11 Stability and Storage Conditions

Propylene glycol alginate is a stable material, although it will gradually become less soluble if stored at elevated temperatures for extended periods.

Propylene glycol alginate solutions are most stable at pH 3–6. In alkaline solutions, propylene glycol alginate is rapidly saponified. Alginate solutions are susceptible to microbial spoilage and should be sterilized or preserved with an antimicrobial preservative. However, sterilization processes may adversely affect the viscosity of propylene glycol alginate solutions; see Sodium Alginate.

19 Specific References

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21 Authors

BA Langdon, MP Mullarney.

22 Date of Revision

19 February 2009.

Sucrose

1 Nonproprietary Names

BP: Sucrose
JP: Sucrose
PhEur: Sucrose
USP-NF: Sucrose

2 Synonyms

Beet sugar; cane sugar; α -D-glucopyranosyl- β -D-fructofuranoside; refined sugar; saccharose; saccharum; sugar.

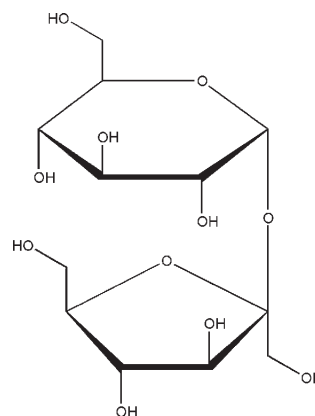
3 Chemical Name and CAS Registry Number

β -D-fructofuranosyl- α -D-glucopyranoside [57-50-1]

4 Empirical Formula and Molecular Weight

$C_{12}H_{22}O_{11}$ 342.30

5 Structural Formula



6 Functional Category

Confectionery base; coating agent; granulation aid; suspending agent; sweetening agent; tablet binder; tablet and capsule diluent; tablet filler; therapeutic agent; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Sucrose is widely used in oral pharmaceutical formulations.

Sucrose syrup, containing 50–67% w/w sucrose, is used in tableting as a binding agent for wet granulation. In the powdered form, sucrose serves as a dry binder (2–20% w/w) or as a bulking agent and sweetener in chewable tablets and lozenges.^(1–3) Tablets that contain large amounts of sucrose may harden to give poor disintegration.

Sucrose syrups are used as tablet-coating agents at concentrations between 50% and 67% w/w. With higher concentrations, partial inversion of sucrose occurs, which makes sugar coating difficult.

Sucrose syrups are also widely used as vehicles in oral liquid-dosage forms to enhance palatability or to increase viscosity.^(4,5)

Sucrose has been used as a diluent in freeze-dried protein products.^(6,7)

Sucrose is also widely used in foods and confectionery, and therapeutically in sugar pastes that are used to promote wound healing.^(8,9) See Table I.

Table I: Uses of sucrose.

Use	Concentration (% w/w)
Syrup for oral liquid formulations	67
Sweetening agent	67
Tablet binder (dry granulation)	2–20
Tablet binder (wet granulation)	50–67
Tablet coating (syrup)	50–67

8 Description

Sucrose is a sugar obtained from sugar cane (*Saccharum officinarum* Linné (Fam. Gramineae)), sugar beet (*Beta vulgaris* Linné (Fam. Chenopodiaceae)), and other sources. It contains no added substances. Sucrose occurs as colorless crystals, as crystalline masses or blocks, or as a white crystalline powder; it is odorless and has a sweet taste.

9 Pharmacopeial Specifications

See Table II. See also Section 18.

10 Typical Properties

Density (bulk)

0.93 g/cm³ (crystalline sucrose);

0.60 g/cm³ (powdered sucrose).

Density (tapped)

1.03 g/cm³ (crystalline sucrose);

0.82 g/cm³ (powdered sucrose).

Density (true)

1.6 g/cm³

Dissociation constant

pK_a = 12.62

Flowability

Crystalline sucrose is free flowing, whereas powdered sucrose is a cohesive solid.

Melting point

160–186°C (with decomposition)

Moisture content

Finely divided sucrose is hygroscopic and absorbs up to 1% water.⁽¹⁰⁾ See Figure 1.

NIR spectra

see Figure 2.

Osmolarity

A 9.25% w/v aqueous solution is isoosmotic with serum.

Particle size distribution

Powdered sucrose is a white, irregular-sized granular powder. The crystalline material consists of colorless crystalline, roughly cubic granules. See Figures 3 and 4.

Refractive index

$n_D^{25} = 1.34783$ (10% w/v aqueous solution)

Solubility

see Table III.

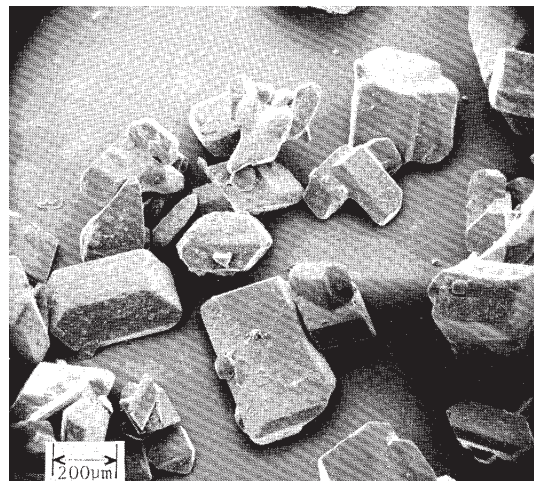
Specific gravity

see Table IV.

11 Stability and Storage Conditions

Sucrose has good stability at room temperature and at moderate relative humidity. It absorbs up to 1% moisture, which is released upon heating at 90°C. Sucrose caramelizes when heated to temperatures above 160°C. Dilute sucrose solutions are liable to fermentation by microorganisms but resist decomposition at higher concentrations, e.g. above 60% w/w concentration. Aqueous solutions may be sterilized by autoclaving or filtration.

SEM 1: Excipient: sucrose; manufacturer: Great Western Sugar Co.; lot no.: 1-2-80; magnification: 60×; voltage: 10 kV.



SEM 2: Excipient: sucrose; manufacturer: Great Western Sugar Co.; lot no.: 1-2-80; magnification: 600×; voltage: 10 kV.

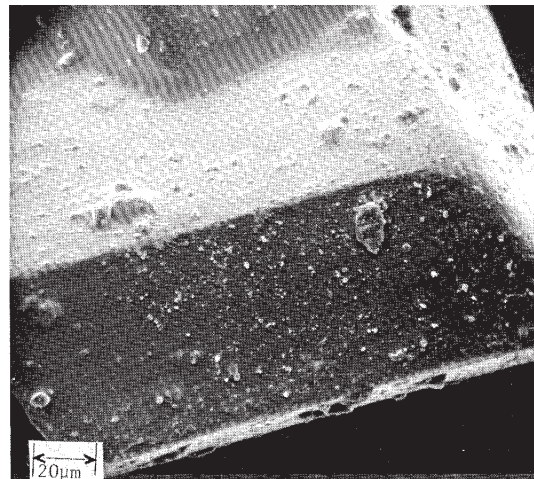


Table III: Solubility of sucrose.

Solvent	Solubility at 20°C unless otherwise stated
Chloroform	Practically insoluble
Ethanol	1 in 400
Ethanol (95%)	1 in 170
Propan-2-ol	1 in 400
Water	1 in 0.5
	1 in 0.2 at 100°C

When sucrose is used as a base for medicated confectionery, the cooking process, at temperatures rising from 110 to 145°C, causes some inversion to form dextrose and fructose (invert sugar). The fructose imparts stickiness to confectionery but prevents cloudiness due to graining. Inversion is accelerated particularly at temperatures above 130°C and by the presence of acids.

Table II: Pharmacopeial specifications for sucrose.

Test	JP XV	PhEur 6.3	USP32-NF27
Identification	+	+	—
Characters	—	+	—
Appearance of solution	+	+	—
Acidity or alkalinity	+	+	—
Specific optical rotation	+66.3° to +67.0°	+66.3° to +67.0°	≥ +65.9°
Color value	—	≤ 45	—
Conductivity	+	35 μS cm ⁻¹	—
Loss on drying	≤ 0.1%	≤ 0.1%	—
Bacterial endotoxins ^(a)	—	—	—
≤ 0.25 IU/mg	—	—	—
≤ 0.25 IU/mg	—	—	—
Dextrins ^(a)	+	+	—
Reducing sugars	—	+	—
Invert sugar	+	—	+
Chloride	—	—	≤ 0.0035%
Sulfate	—	—	≤ 0.006%
Sulfites	≤ 15 ppm	≤ 10 ppm	—
Calcium	—	—	+
Heavy metals	—	—	≤ 5 ppm
Lead	≤ 0.5 ppm	≤ 0.5 ppm	—
Residue on ignition	—	—	≤ 0.05%

(a) If sucrose is to be used in large volume infusions.

Table IV: Specific gravity of aqueous sucrose solutions.

Concentration of aqueous sucrose solution (% w/w)	Specific gravity at 20°C
2	1.0060
6	1.0219
10	1.0381
20	1.0810
30	1.1270
40	1.1764
50	1.2296
60	1.2865
70	1.3471
76	1.3854

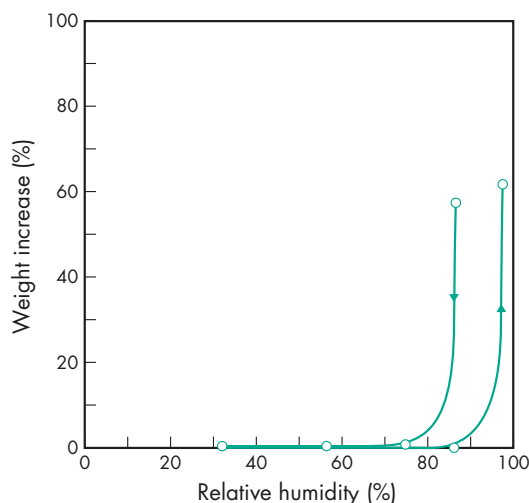


Figure 1: Moisture sorption-desorption isotherm of powdered sucrose. Samples dried initially at 60°C over silica gel for 24 hours. Note: at 90% relative humidity, sufficient water was absorbed to cause dissolution of the solid.

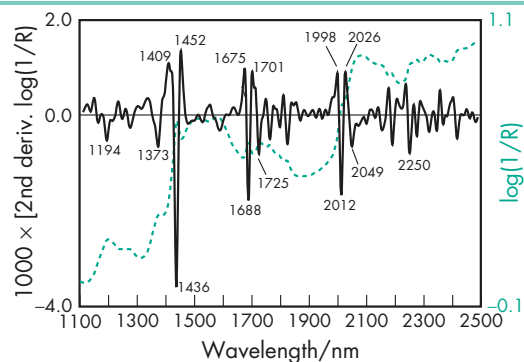


Figure 2: Near-infrared spectrum of sucrose measured by reflectance.

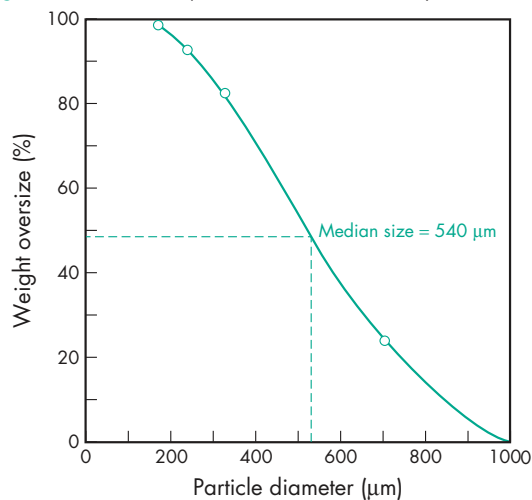


Figure 3: Particle size distribution of crystalline sucrose.

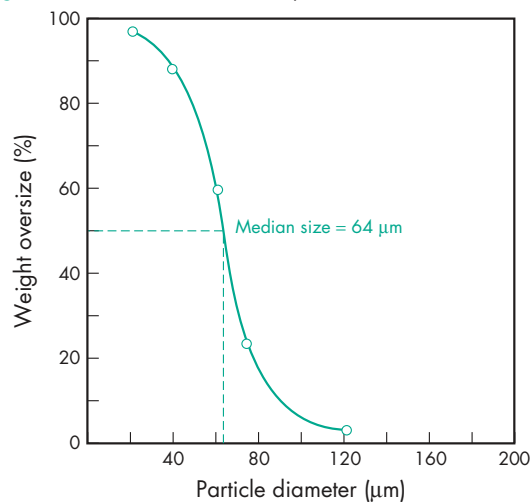


Figure 4: Particle size distribution of powdered sucrose.

S

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Powdered sucrose may be contaminated with traces of heavy metals, which can lead to incompatibility with active ingredients, e.g. ascorbic acid. Sucrose may also be contaminated with sulfite from the refining process. With high sulfite content, color changes can occur in sugar-coated tablets; for certain colors used in sugar-coating the maximum limit for sulfite content, calculated as sulfur, is 1 ppm. In the presence of dilute or concentrated acids, sucrose is hydrolyzed or inverted to dextrose and fructose (invert sugar). Sucrose may attack aluminum closures.⁽¹¹⁾

13 Method of Manufacture

Sucrose is obtained from the sugar cane plant, which contains 15–20% sucrose, and sugar beet, which contains 10–17% sucrose. Juice from these sources is heated to coagulate water-soluble proteins, which are removed by skimming. The resultant solution is then decolorized with an ion-exchange resin or charcoal and concentrated. Upon cooling, sucrose crystallizes out. The remaining solution is concentrated again and yields more sucrose, brown sugar, and molasses.

14 Safety

Sucrose is hydrolyzed in the small intestine by the enzyme sucrase to yield dextrose and fructose, which are then absorbed. When administered intravenously, sucrose is excreted unchanged in the urine.

Although sucrose is very widely used in foods and pharmaceutical formulations, sucrose consumption is a cause of concern and should be monitored in patients with diabetes mellitus or other metabolic sugar intolerance.⁽¹²⁾

Sucrose is also considered to be more cariogenic than other carbohydrates since it is more easily converted to dental plaque. For this reason, its use in oral pharmaceutical formulations is declining.

Although sucrose has been associated with obesity, renal damage, and a number of other diseases, conclusive evidence linking sucrose intake with some diseases could not be established.^(13,14) It was, however, recommended that sucrose intake in the diet should be reduced.⁽¹⁴⁾

LD₅₀ (mouse, IP): 14 g/kg⁽¹⁵⁾

LD₅₀ (rat, oral): 29.7 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 workplace exposure limit for sucrose is 10 mg/m³ long-term (8-hour TWA) and 20 mg/m³ short-term.⁽¹⁶⁾

16 Regulatory Status

GRAS listed. Included in the FDA Inactive Ingredients Database (injections; oral capsules, solutions, syrups, and tablets; topical preparations). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Compressible sugar; confectioner's sugar; invert sugar; sugar spheres.

Invert sugar

Empirical formula C₆H₁₂O₆

Molecular weight 180.16

CAS number [8013-17-0]

Comments An equimolecular mixture of dextrose and fructose prepared by the hydrolysis of sucrose with a suitable mineral acid such as hydrochloric acid. Invert sugar may be used as a stabilizing agent to help prevent crystallization of sucrose syrups and graining in confectionery. A 10% aqueous solution is also used in parenteral nutrition.

18 Comments

Sucrose 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.

For typical boiling points of sucrose syrups, without inversion of the sugar, see Table V.

A specification for sucrose is contained in the Food Chemicals Codex (FCC).⁽¹⁷⁾

The EINECS number for sucrose is 200-334-9. The PubChem Compound ID (CID) for sucrose includes 5988 and 1115.

Table V: Boiling points of sucrose syrups.

Sucrose concentration (% w/v)	Boiling point (°C)
50	101.5
60	103
64	104
72	105.5
75	107
77.5	108.5
80	110.5

19 Specific References

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system consisting of xanthan gum, carboxy methylcellulose and a polyvinyl pyrrolidone backbone polymer has been used for relieving the symptoms of xerostomia.⁽³⁷⁾ Xanthan gum can also be used as an excipient for spray-drying and freeze-drying processes for better results.^(38,39) It has been successfully used alone or in combination with agar for microbial culture media.⁽⁴⁰⁾

Xanthan gum is also used as a hydrocolloid in the food industry, and in cosmetics it has been used as a thickening agent in shampoo.⁽⁴¹⁾ Polyphosphate with xanthum gum in soft drinks is suggested to be effective at reducing erosion of enamel.^(42,43)

8 Description

Xanthan gum occurs as a cream- or white-colored, odorless, free-flowing, fine powder.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for xanthan gum.

Test	PhEur 6.4	USP32-NF27
Identification	+	+
Characters	+	—
pH	6.0–8.0	—
Viscosity	≥ 600 mPa s	≥ 600 mPa s
Propan-2-ol	≤ 750 ppm	≤ 0.075%
Other polysaccharides	+	—
Loss on drying	≤ 15.0%	≤ 15.0%
Total ash	6.5–16.0%	6.5–16.0%
Microbial contamination	+	+
Bacteria	≤ 10 ³ cfu/g	—
Fungi	≤ 10 ² cfu/g	—
Pyruvic acid	—	≤ 1.5%
Arsenic	—	≤ 3 µg/g
Lead	—	≤ 5 µg/g
Heavy metals	—	≤ 0.003%
Assay	—	91.0–108.0%

10 Typical Properties

Acidity/alkalinity pH = 6.0–8.0 for a 1% w/v aqueous solution.

Freezing point 0°C for a 1% w/v aqueous solution.

Heat of combustion 14.6 J/g (3.5 cal/g)

Melting point Chars at 270°C.

NIR spectra see Figure 1.

Particle size distribution Various grades with different particle sizes are available; see Table II.

Refractive index n_D^{20} = 1.333 (1% w/v aqueous solution).

Solubility Practically insoluble in ethanol and ether; soluble in cold or warm water.

Specific gravity 1.600 at 25°C

Viscosity (dynamic) 1200–1600 mPa s (1200–1600 cP) for a 1% w/v aqueous solution at 25°C.

11 Stability and Storage Conditions

Xanthan gum is a stable material. Aqueous solutions are stable over a wide pH range (pH 3–12), although they demonstrate maximum stability at pH 4–10 and temperatures of 10–60°C. Xanthan gum solutions of less than 1% w/v concentration may be adversely affected by higher than ambient temperatures: for example, viscosity is reduced. Xanthan gum provides the same thickening, stabilizing, and suspending properties during long-term storage at elevated temperatures as it does at ambient conditions. In addition, it ensures excellent freeze–thaw stability. Solutions are also stable in the presence of enzymes, salts, acids, and bases. *Vanzan NF-ST* is especially designed for use in systems containing high salt concentrations as it dissolves directly in salt solutions, and its

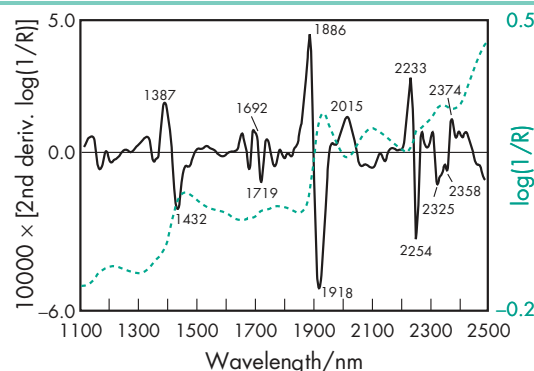


Figure 1: Near-infrared spectrum of xanthan gum measured by reflectance.

Table II: Particle size distribution of selected commercially available grades of xanthan gum.

Grade	Particle size (µm)
Keltrol CG	100% < 180
Grindsted Xanthan 80	180
Grindsted Xanthan 200	75
Grindsted Xanthan Easy	850
Grindsted Xanthan Supra	1180
Grindsted Xanthan Ultra	180
Grindsted Xanthan TSC	250
Grindsted Xanthan Clear 80	180
Grindsted Xanthan Clear 200	75
Grindsted Xanthan Clear Easy	850
Grindsted Xanthan Clear Supra	1180
Vanzan NF	180
Vanzan NF-F	75
Vanzan NF-C	180
Vanzan NF-ED	1180
Vanzan NF-ST	75

viscosity is relatively unaffected by high salt levels as compared with general purpose grades.

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Xanthan gum is an anionic material and is not usually compatible with cationic surfactants, polymers, or preservatives, as precipitation occurs. Anionic and amphoteric surfactants at concentrations above 15% w/v cause precipitation of xanthan gum from a solution.

Under highly alkaline conditions, polyvalent metal ions such as calcium cause gelation or precipitation; this may be inhibited by the addition of a glucoheptonate sequestrant. The presence of low levels of borates (<300 ppm) can also cause gelation. This may be avoided by increasing the boron ion concentration or by lowering the pH of a formulation to less than pH 5. The addition of ethylene glycol, sorbitol, or mannitol may also prevent this gelation.

Xanthan gum is compatible with most synthetic and natural viscosity-increasing agents, many strong mineral acids, and up to 30% inorganic salts. If it is to be combined with cellulose derivatives, then xanthan gum free of cellulase should be used to prevent depolymerization of the cellulose derivative. Xanthan gum solutions are stable in the presence of up to 60% water-miscible organic solvents such as acetone, methanol, ethanol, or propan-2-ol. However, above this concentration precipitation or gelation occurs.

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The viscosity of xanthan gum solutions is considerably increased, or gelation occurs, in the presence of some materials such as ceratonia, guar gum, and magnesium aluminum silicate.⁽⁹⁾ This effect is most pronounced in deionized water and is reduced by the presence of salt. This interaction may be desirable in some instances and can be exploited to reduce the amount of xanthan gum used in a formulation; see Section 7.

Xanthan gum is incompatible with oxidizing agents, some tablet film-coatings,⁽⁴⁾ carboxymethylcellulose sodium,⁽⁴⁴⁾ dried aluminum hydroxide gel,⁽⁴⁵⁾ and some active ingredients such as amitriptyline, tamoxifen, and verapamil.⁽³⁾

13 Method of Manufacture

Xanthan gum is a polysaccharide produced by a pure-culture aerobic fermentation of a carbohydrate with *Xanthomonas campestris*. The polysaccharide is then purified by recovery with propan-2-ol, dried, and milled.^(46,47)

14 Safety

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and food products, and is generally regarded as nontoxic and nonirritant at the levels employed as a pharmaceutical excipient.

The estimated acceptable daily intake for xanthan gum has been set by the WHO at up to 10 mg/kg body-weight.⁽⁴⁸⁾

No eye or skin irritation has been observed in rabbits and no skin allergy has been observed in guinea pigs following skin exposure. No adverse effects were observed in long term feeding studies with rats (up to 1000 mg/kg/day) and dogs (up to 1000 mg/kg/day). No adverse effects were observed in a three-generation reproduction study with rats (up to 500 mg/kg/day).⁽⁴⁹⁾

LD₅₀ (dog, oral): >20 g/kg⁽⁴⁸⁾

LD₅₀ (rat, oral): >45 g/kg

LD₅₀ (mouse, oral): >1 g/kg⁽⁵⁰⁾

LD₅₀ (mouse, IP): >50 mg/kg⁽⁵⁰⁾

LD₅₀ (mouse, IV): 100–250 mg/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. 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 (oral solutions, suspensions, and tablets; rectal and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Ceratonia; guar gum.

18 Comments

Xanthan gum is available in several different grades that have varying particle sizes. Fine-mesh grades of xanthan gum are used in applications where high solubility is desirable since they dissolve rapidly in water. However, fine-mesh grades disperse more slowly than coarse grades and are best used dry blended with the other ingredients of a formulation. In general, it is preferable to dissolve xanthan gum in water first and then add the other ingredients of a formulation.

Novel pH-sensitive hydrogel beads have been prepared using a copolymer of poly(acrylamide-g-xanthan) for targeting ketoprofen to the intestine.⁽⁵¹⁾ These beads were able to retard drug release in

the stomach, thus diminishing gastric side effects such as ulceration, hemorrhage and erosion of gastric mucosa.⁽⁵¹⁾ Bioadhesive nasal inserts prepared from xanthan gum have a high potential as a new nasal dosage form for extended drug delivery.⁽⁵²⁾ Xanthan gum wafers have potential as drug delivery systems for suppurating wounds.^(53,54)

The USP32–NF27 also includes a monograph for xanthan gum solution. A specification for xanthan gum is contained in the Food Chemicals Codex (FCC).⁽⁵⁵⁾

The EINECS number for xanthan gum is 234-394-2. The PubChem Compound ID (CID) for xanthan gum is 7107.

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21 Authors

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22 Date of Revision

10 March 2009.

1 Nonproprietary Names

BP: Xylitol
JP: Xylitol
PhEur: Xylitol
USP-NF: Xylitol

2 Synonyms

E967; *Klinit*; *meso*-xylitol; xilitol; *Xylifin*; *Xylisorb*; xylit; *Xylitab*; xylite; *Xylitolo*; xylitolium.

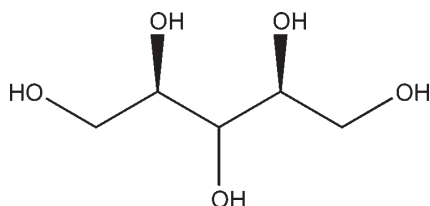
3 Chemical Name and CAS Registry Number

xylo-Pentane-1,2,3,4,5-pentol [87-99-0]

4 Empirical Formula and Molecular Weight

C₅H₁₂O₅ 152.15

5 Structural Formula



6 Functional Category

Coating agent; diluent; emollient; humectant; sweetening agent; tablet and capsule diluent; tablet filler.

7 Applications in Pharmaceutical Formulation or Technology

Xylitol is used as a noncariogenic sweetening agent in a variety of pharmaceutical dosage forms, including tablets, syrups, and coatings. It is also widely used as an alternative to sucrose in foods and as a base for medicated confectionery. Xylitol is finding increasing application in chewing gum,^(1,2) mouthrinses,⁽³⁾ and toothpastes⁽⁴⁾ as an agent that decreases dental plaque and tooth decay (dental caries). Unlike sucrose, xylitol is not fermented into cariogenic acid end products⁽⁵⁾ and it has been shown to reduce dental caries by inhibiting the growth of cariogenic *Streptococcus mutans* bacteria.^(6,7) As xylitol has an equal sweetness intensity to sucrose, combined with a distinct cooling effect upon dissolution of the crystal, it is highly effective in enhancing the flavor of tablets and syrups and masking the unpleasant or bitter flavors associated with some pharmaceutical actives and excipients.

In topical cosmetic and toiletry applications, xylitol is used primarily for its humectant and emollient properties, although it has also been reported to enhance product stability through a combination of potentiation of preservatives and its own bacteriostatic and bactericidal properties.

Granulates of xylitol are used as diluents in tablet formulations, where they can provide chewable tablets with a desirable sweet taste and cooling sensation, without the 'chalky' texture experienced with some other tablet diluents. Xylitol solutions are employed in tablet-coating applications at concentrations in excess of 65% w/w.

Xylitol coatings are stable and provide a sweet-tasting and durable hard coating.

In liquid preparations, xylitol is used as a sweetening agent and vehicle for sugar-free formulations. In syrups, it has a reduced tendency to 'cap-lock' by effectively preventing crystallization around the closures of bottles. Xylitol also has a lower water activity and a higher osmotic pressure than sucrose, therefore enhancing product stability and freshness. In addition, xylitol has also been demonstrated to exert certain specific bacteriostatic and bactericidal effects, particularly against common spoilage organisms.^(8,9)

Therapeutically, xylitol is additionally utilized as an energy source for intravenous infusion therapy following trauma.⁽¹⁰⁾

8 Description

Xylitol occurs as a white, granular solid comprising crystalline, equidimensional particles having a mean diameter of about 0.4–0.6 mm. It is odorless, with a sweet taste that imparts a cooling sensation. Xylitol is also commercially available in powdered form, and several granular, directly compressible forms.⁽¹¹⁾ See also Section 17.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity pH = 5.0–7.0 (10% w/v aqueous solution).

Boiling point 215–217°C

Compressibility see Figure 1. Crystalline xylitol, under the same test conditions as illustrated in Figure 1, produces 12.5 mm tablets of 40 N hardness at 20 kN compression force.

Density (true) 1.52 g/cm³

Density (bulk)

0.8–0.85 g/cm³ for crystalline xylitol;

0.5–0.7 g/cm³ for directly compressible granulated grades.

SEM 1: Excipient: xylitol (unsieved); magnification: 60×.

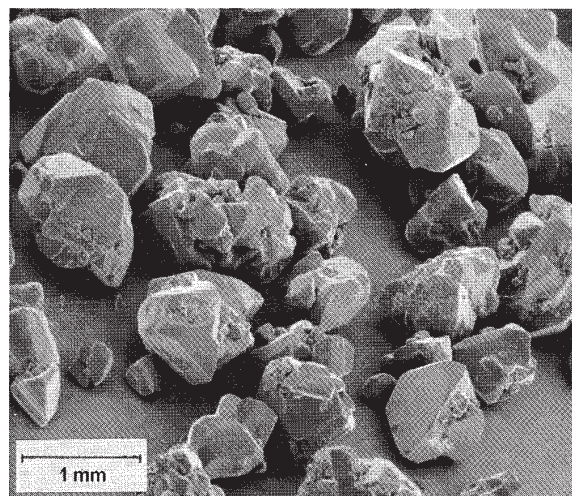
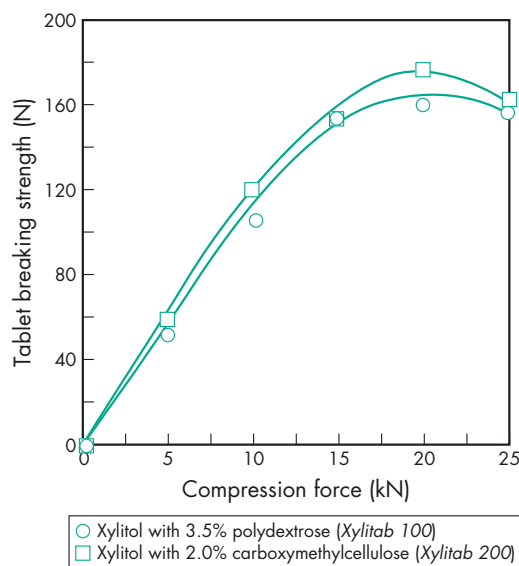


Table I: Pharmacopeial specifications for xylitol.

Test	JP XV	PhEur 6.3	USP32-NF27
Identification	+	+	+
Characters	+	+	—
Clarity and color of solution	+	+	—
Water	≤ 1.0%	≤ 1.0%	≤ 0.5%
pH (50% w/w solution)	5.0–7.0	—	—
Melting point	93.0–95.0°C	92–96°C	—
Residue on ignition	≤ 0.1%	—	≤ 0.5%
Chloride	≤ 0.005%	—	—
Sulfate	≤ 0.006%	—	—
Nickel	+	≤ 1 ppm	—
Arsenic	≤ 1.3 ppm	—	—
Heavy metals	≤ 5 ppm	—	≤ 0.001%
Reducing sugars (as dextrose)	+	≤ 0.2%	≤ 0.2%
Other polyols	—	—	≤ 2.0%
Related substances	—	≤ 2.0%	—
Lead	—	≤ 0.5 ppm	—
Bacterial endotoxins ^(a)	≤ 0.50 EU/mL	≤ 2.5 IU/g	—
Conductivity	—	≤ 20 μS cm ⁻¹	—
Assay (anhydrous basis)	≥ 98.0%	98.0–102.0%	98.5–101.0%

(a) If intended for use in parenteral products.

**Figure 1:** Compression characteristics of Xylitab 100 and Xylitab 200 (Danisco Sweeteners Ltd).

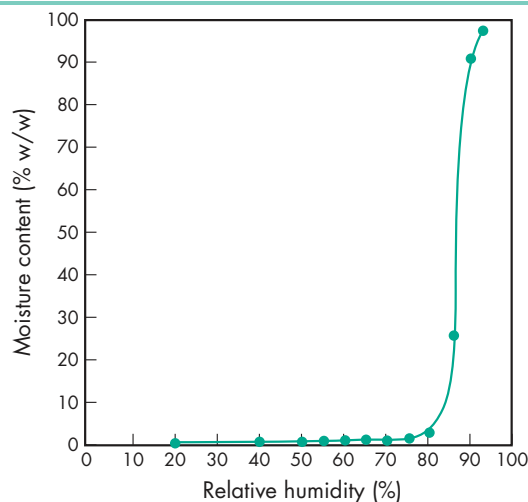
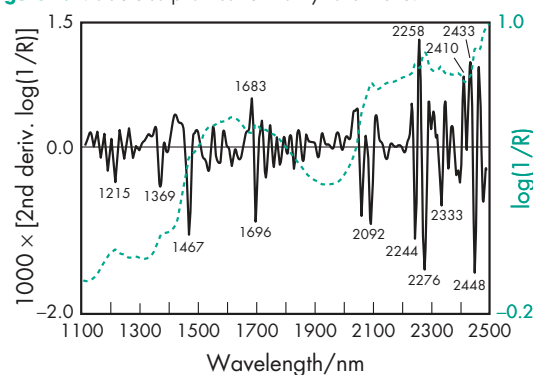
Flowability Flow characteristics vary depending upon the particle size of xylitol used. Fine-milled grades tend to be relatively poorly flowing, while granulated grades have good flow properties.

Heat of solution –157.1 kJ/kg (–36.7 cal/g)

Melting point 92.0–96.0°C

Moisture content Xylitol is a moderately hygroscopic powder under normal conditions; see also Figure 2. At 20°C and 52% relative humidity, the equilibrium moisture content of xylitol is 0.1% w/w. After drying in a vacuum, over P₂O₅ at 80°C for 4 hours, xylitol loses less than 0.5% w/w water.

NIR spectra see Figure 3.

**Figure 2:** Moisture sorption isotherm of xylitol at 20°C.**Figure 3:** Near-infrared spectrum of xylitol measured by reflectance.

Osmolarity A 4.56% w/v aqueous solution is iso-osmotic with serum.

Particle size distribution The particle size distribution of xylitol depends upon the grade selected. Normal crystalline material typically has a mean particle size of 0.4–0.6 mm. Milled grades are commercially available that offer mean particle sizes as low as 50 μm. Individual suppliers' literature should be consulted for further information. For particle size distributions of granulated xylitol, see Figure 4.

Solubility see Table II.

Table II: Solubility of xylitol.

Solvent	Solubility at 20°C
Ethanol	1 in 80
Glycerin	Very slightly soluble
Methanol	1 in 16.7
Peanut oil	Very slightly soluble
Propan-2-ol	1 in 500
Propylene glycol	1 in 15
Pyridine	Soluble
Water	1 in 1.6

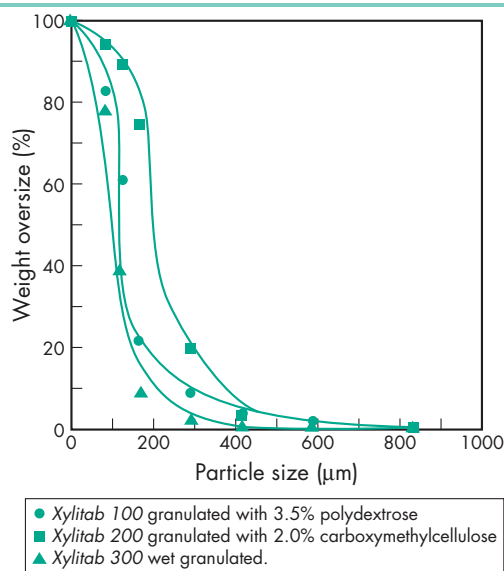


Figure 4: Particle size distribution of granulated xylitol (Xylitab, Danisco Sweeteners Ltd).

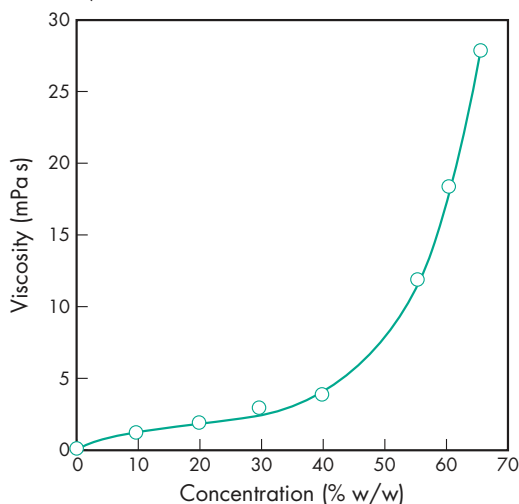


Figure 5: Viscosity of aqueous xylitol solutions at 20°C.

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Specific rotation Not optically active.
Viscosity (dynamic) see Figure 5.

11 Stability and Storage Conditions

Xylitol is stable to heat but is marginally hygroscopic. Caramelization can occur only if it is heated for several minutes near its boiling point. Crystalline material is stable for at least 3 years if stored at less than 65% relative humidity and 25°C. Milled and specialized granulated grades of xylitol have a tendency to cake and should therefore be used within 9 to 12 months. Aqueous xylitol solutions have been reported to be stable, even on prolonged heating and storage. Since xylitol is not utilized by most microorganisms,

products made with xylitol are usually safe from fermentation and microbial spoilage.^(8,9)

Xylitol should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Xylitol is incompatible with oxidizing agents.

13 Method of Manufacture

Xylitol occurs naturally in many fruits and berries, although extraction from such sources is not considered to be commercially viable. Industrially, xylitol is most commonly derived from various types of hemicellulose obtained from such sources as wood, corn cobs, cane pulp, seed hulls, and shells. These materials typically contain 20–35% xylan, which is readily converted to xylose (wood sugar) by hydrolysis. This xylose is subsequently converted to xylitol via hydrogenation (reduction). Following the hydrogenation step, there are a number of separation and purification steps that ultimately yield high-purity xylitol crystals. The nature of this process, and the stringent purification procedures employed, result in a finished product with a very low impurity content. Potential impurities that may appear in small quantities are mannitol, sorbitol, galactitol, or arabitol.

Less commonly employed methods of xylitol manufacture include the conversion of glucose (dextrose) to xylose followed by hydrogenation to xylitol, and the microbiological conversion of xylose to xylitol.

14 Safety

Xylitol is used in oral pharmaceutical formulations, confectionery, and food products, and is generally regarded as an essentially nontoxic, nonallergenic, and nonirritant material.

Xylitol has an extremely low relative glycemic response and is metabolized independently of insulin. Following ingestion of xylitol, the blood glucose and serum insulin responses are significantly lower than following ingestion of glucose or sucrose. These factors make xylitol a suitable sweetener for use in diabetic or carbohydrate-controlled diets.⁽¹²⁾

Up to 100 g of xylitol in divided oral doses may be tolerated daily, although, as with other polyols, large doses may have a laxative effect. The laxative threshold depends on a number of factors, including individual sensitivity, mode of ingestion, daily diet, and previous adaptation to xylitol. Single doses of 20–30 g and daily doses of 0.5–1.0 g/kg body-weight are usually well tolerated by most individuals. Approximately 25–50% of the ingested xylitol is absorbed, with the remaining 50–75% passing to the lower gut, where it undergoes indirect metabolism via fermentative degradation by the intestinal flora.

An acceptable daily intake for xylitol of 'not specified' has been set by the WHO since the levels used in foods do not represent a hazard to health.⁽¹³⁾

LD₅₀ (mouse, IP): 22.1 g/kg^(14,15)

LD₅₀ (mouse, IV): 12 g/kg

LD₅₀ (mouse, oral): 12.5 g/kg

LD₅₀ (rat, oral): 17.3 g/kg

LD₅₀ (rat, IV): 10.8 g/kg

LD₅₀ (rabbit, oral): 16.5 g/kg

LD₅₀ (rabbit, IV): 4 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Xylitol may cause transient gastrointestinal discomfort if ingested in large quantities; and may also be irritant to the eyes. Eye protection and gloves are recommended.

Conventional dust-control practices should be employed. Xylitol is flammable, but does not ignite readily.

16 Regulatory Status

GRAS listed. Approved for use as a food additive in over 70 countries worldwide, including Europe, the USA and Japan. Included in the FDA Inactive Ingredients Database (oral solution, chewing gum). Included in nonparenteral medicines licensed in the UK and USA. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

Various directly compressible forms of xylitol that contain other excipients are commercially available, e.g. *Xylitab 100*, which contains 3.5% polydextrose, and *Xylitab 200*, which contains 2.0% carboxymethylcellulose (both Danisco Sweeteners Ltd). A directly compressible form of pure xylitol is also available, *Xylitab 300* (Danisco Sweeteners Ltd), which is produced via wet granulation.

Pyrogen-free grades of xylitol suitable for parenteral use are also commercially available.

18 Comments

The sweetening power of xylitol is approximately equal to that of sucrose, although it has been shown to be pH-, concentration-, and temperature-dependent; xylitol is approximately 2.5 times as sweet as mannitol.

Xylitol is highly chemically stable, meaning that it will not interact with pharmaceutical actives or excipients, and can be utilized over a wide pH range (pH 1–11).

Xylitol has a negative heat of solution that is far larger than that of other alternative sweetening agents; see Table III. Because of this, xylitol produces an intense cooling effect as the crystalline material dissolves. Xylitol's combination of sweetness and cooling can create product appeal while helping to mask the undesirable taste of many pharmaceutical actives or excipients.

A specification for xylitol is contained in the Food Chemicals Codex (FCC).⁽¹⁶⁾

The EINECS number for xylitol is 201-788-0. The PubChem Compound ID (CID) for xylitol is 6912.

Table III: Comparison of the heat of solution of selected sweetening agents.

Sweetening agent	Heat of solution (kJ/kg)
Lactitol (anhydrous)	–35.0
Maltitol	–69.2
Mannitol	–120.9
Sorbitol	–106.3
Sucrose	–23.0
Xylitol	–157.1

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