



Secundum Artem

Current & Practical Compounding
Information for the Pharmacist.

COMPOUNDING WITH GLYCERIN AND PROPYLENE GLYCOL

GOALS AND OBJECTIVES

Goal: To provide information on the physical and chemical characteristics of glycerin and propylene glycol and their use in pharmaceutical compounding.

Objectives: After reading and studying the article, the reader will be able to:

1. Describe the physical and chemical characteristics of glycerin and propylene glycol.
2. Discuss the properties of glycerin and propylene glycol that contribute to their widespread use in pharmaceutical compounding.
3. List some of the therapeutic uses of glycerin and propylene glycol.
4. Describe some formulations using either glycerin or propylene glycol.

INTRODUCTION

Many pharmacists and pharmacy technicians have a tendency to pay more attention to active drug substances in formulations and to minimize the importance of the excipients. However, excipients can dramatically alter the physical and chemical stability as well as the therapeutic effectiveness of the final drug preparation. Excipients can affect bioavailability, rate of drug release for all dosage forms, duration of action for many dosage forms, extent of penetration for many topicals/transdermals, and one of the most important considerations, patient compliance.

Two commonly used excipients in various dosage forms include glycerin and propylene glycol. These two substances are chemically related as they both contain three carbons; the primary difference is that one contains two hydroxyl groups and the other contains three (See Figure 1). The series of substances that are official in the USP could be viewed as starting with isopropanol with one hydroxyl group on the middle carbon atom, progressing to propylene glycol, with two hydroxyl groups, and then to glycerin with three hydroxyl groups.¹ Glycerin and propylene glycol have been used in pharmacy for over one hundred years and are extensively used in pharmaceutical compounding today.²

GLYCERIN

Properties

Glycerin is the simplest trihydric alcohol. It was discovered by Scheele in 1779, who called it the "sweet principle of fats".³ Glycerin is the alcohol present in the esters (glycerides) of oils and fats from which it may be released by saponification. It was more fully investigated by Chevreul who named it "glycerine" and it came into use in medicine and pharmacy about 1846.² It was first obtained in the United States

on a commercial scale, from the washings of lead plaster, by Shoemaker of Philadelphia.²

Glycerin ($C_3H_8O_3$, 1,2,3-Propanetriol; glycerol; glycerine; 1,2,3 propanetriol; trihydroxypropane glycerol; MW 92.10) occurs as a clear, colorless, syrupy liquid with a sweet warm taste, approximately 0.6 times as sweet as sucrose. It has not more than a slight characteristic odor, which is neither harsh nor disagreeable. It is hygroscopic and its solutions are neutral to litmus. It is miscible with water and with alcohol but is insoluble in chloroform, ether and in fixed and volatile oils. It has a solubility at 20° C as follows: acetone (slightly soluble); benzene (practically insoluble); ethyl acetate (1 in 11); methanol (soluble). It boils at 290° C with decomposition and melts at 17.8° C. It has a specific gravity of not less than 1.249. A 2.6% v/v aqueous solution is iso-osmotic with serum.^{4,5,6} It should be preserved in tight containers. Glycerin USP contains not less than 99.0% and not more than 101.0% of $C_3H_8O_3$, calculated on the anhydrous basis. Official USP products include Glycerin Ophthalmic Solution USP, Glycerin Oral Solution USP and Glycerin Suppositories USP.⁴

Uses

Glycerin is categorized in the NF as a humectant, plasticizer, solvent and tonicity-adjusting agent.⁴ It is listed as being used as an antimicrobial preservative emollient, humectant, plasticizer, solvent, sweetening agent and tonicity-adjusting agent. Topically, it is used as a humectant and emollient. Parenterally, it is used primarily as a solvent. In oral preparations, it is used as a solvent, sweetening agent, antimicrobial preservative and viscosity-increasing agent. In film coatings and in the preparation of soft gelatin capsules and gelatin suppositories, it is used as a plasticizer. It is also used in a number of therapeutic applications.^{4,6}

Glycerin is also used in the manufacturing of dynamite, cosmetics, soaps, confectioneries, blacking, printing and copying inks, lubricants, elastic glues, lead oxide cements, antifreeze, gas meters, hydraulic jacks, shock absorber fluid, ice collars, ice bags and as a fermentation nutrient in the production of antibiotics.⁷

Glycerin is an excellent solvent, but its range is not as extensive as that of water or alcohol. It is a solvent for fixed alkalies, a large number of salts, vegetable acids, pepsin, tannin, some active principles of plants, gums, soluble carbohydrates and starch.

Orally, glycerin is readily absorbed from the intestine and is metabolized to carbon dioxide and glycogen or is used in the synthesis of body fats.⁵ Therapeutically, glycerin is used in large doses (70-80 g over 30-60 minutes) to reduce cranial pressure.⁵ Slow administration has no deleterious effects, but rapid administration can cause hemolysis, hemoglobinuria and renal failure. Glycerin is used orally in doses of 1.0 to 1.5 g/kg body weight to reduce intraocular pressure and vitreous volume before and after ophthalmic surgery, and as an adjunct in the management of acute glaucoma. Glycerin is also applied topically to reduce corneal edema but this effect is only transient, primarily for facilitating ocular examination and diagnosis.⁵ Oral doses are demulcent and can be mildly laxative, promoting fecal evacuation in the management of constipation; usually acting within 15 to 30 minutes. It is classified as an osmotic laxative but may also act through local irritant effects. Glycerin has lubricating and fecal softening effects as well. Glycerin is used in ear drops for the removal of ear wax for its lubricating and softening action.

Adverse Effects

Often the adverse effects of glycerin are due to its dehydrating properties.⁶ In contact with mucous membranes, glycerin absorbs moisture and causes temporary irritation; this is the action primarily responsible for the effectiveness of glycerin when applied rectally in suppository form to produce fecal discharge in habitual constipation. Glycerin suppositories contain 91% glycerin and 9% sodium stearate. Headache, thirst, nausea, vomiting and hyperglycemia can be caused by oral administration of large doses.⁶

Safety

Glycerin is Generally Recognized as Safe (GRAS) and is listed in the FDA Inactive Ingredients Guide for use in inhalations; injections; nasal and ophthalmic preparations; oral capsules, solutions, suspensions and tablets; otic, rectal, topical, transdermal, and vaginal preparations.⁵

Dosage Forms

Glycerin is used in almost every dosage form available today. From a plasticizer in film coatings of tablets, to a solvent, preservative and sweetener in oral liquid dosage forms and in injections. An older dosage form, the glycerogelatin, were actually the forerunner of some contemporary dosage forms containing glycerin.

Glycerogelatin are plastic masses, composed of gelatin, glycerin and water, and a medicament suitable for application to the skin. For application, they are softened using heat and then painted on the surface with a brush. The combination of glycerin, gelatin and water has been further refined and the combination is now used as the basis of glycerin suppositories and soft, chewable gummy bears or chewable troches. Glycerinated gelatin suppositories have been used as vaginal suppositories for the local application of antibacterial agents.²

Stability

Pure glycerin, under ordinary storage conditions, is not prone to oxidation by the atmosphere. However, it does decompose on heating evolving toxic acrolein. Mixtures of glycerin with water, ethanol and/or propylene glycol are chemically stable. It should be stored in an airtight container in a cool, dry place. If stored at low temperatures, it may crystallize; but it will become a solution when warmed to 20° C. When mixed with strong oxidizing agents, glycerin may explode. Examples of strong oxidizing agents include chromium trioxide, potassium chlorate and potassium permanganate. In contact with zinc oxide or basic bismuth nitrate, black discoloration of glycerin occurs. Sometimes glycerin may contain an iron contaminant that can cause a darkening in color of mixtures containing phenols, salicylates and tannin. With boric acid, glycerin forms a boric acid complex called

glyceroboric acid that is a stronger acid than boric acid.^{2,5}

PROPYLENE GLYCOL

Properties

Propylene glycol came into use as a suggested replacement for glycerin when glycerin was in short supply during World War II.³ Its solvent and preservative properties at least in some instances combine the advantages of both glycerin and ethyl alcohol. It is often a better solvent than glycerin and also has greater power to inhibit mold growth and fermentation, being equal to ethyl alcohol for the latter purposes. An example of where propylene glycol has replaced glycerin is shown in a prior formulation for Hydrophilic Ointment, USP. Glycerin imparted a "softening" effect to the ointment when it was triturated; the use of propylene glycol corrected this problem.^{4,6,8}

Propylene Glycol USP (C₃H₈O₃, 1,2-Propanediol; 1,2-Dihydroxypropane, 2-hydroxypropanol; methyl ethylene glycol; methyl glycol; propane-1,2-diol, MW 76.09) contains not less than 99.5% of C₃H₈O₃. It should be preserved in tight, light-resistant containers in a cool, dry place. It has a specific gravity between 1.035 and 1.037. It has a boiling point of 188° C and a melting point of -59° C. It occurs as a clear, colorless, viscous, practically odorless liquid with a slight, characteristic taste resembling that of glycerin. It absorbs moisture when exposed to moist air. It is miscible with water, acetone and with chloroform. It is soluble in ether (1 in 6 parts) and will dissolve many essential oils but is immiscible with fixed oils and light mineral oil. It is miscible with acetone, chloroform, ethanol (95%), glycerin and water. A 2.0% v/v aqueous solution is iso-osmotic with serum.^{4,6,8}

Uses

Propylene glycol is classified in the NF as a humectant, plasticizer and solvent. Its functional category is as an antimicrobial preservative, disinfectant, humectant, plasticizer, solvent, stabilizer for vitamins and as a water-miscible cosolvent.⁴

Propylene glycol has been used as an aerosol antiseptic; when dispersed in air in concentrations as low as 1 part in 2,000,000 propylene glycol kills air-borne staphylococci.³

In film-coating formulations, propylene glycol is used as a plasticizer. As a carrier, it is used with emulsifiers and as a vehicle for flavors, rather than using ethanol, since it is nonvolatile. Propylene glycol is also used in veterinary medicine as an oral glucogenic in ruminants.⁸ Other uses include as a nontoxic antifreeze in dairy establishments, substitute for ethylene glycol and glycerin, in the manufacture of synthetic resins and de-icing solutions, emulsifier in foods, solvent for food colors and flavors, humectant, solvent, as a mist to disinfect air and to create artificial smoke and mist for theatrical use.⁷

Overall, propylene glycol is a better solvent than glycerin and will dissolve a variety of drugs, including corticosteroids, phenols, sulfonamides, barbiturates, vitamins (A and D), most alkaloids and many local anesthetics. It is similar to ethanol as an antiseptic and is similar to glycerin in its activity against molds. It is only slightly less effective than ethanol.

Adverse Effects

Propylene glycol is generally regarded as a relatively nontoxic material and is extensively used in foods, drugs and cosmetics. Orally ingested propylene glycol is rapidly absorbed and is metabolized in the liver, primarily to lactic and pyruvic acids, and is also excreted unchanged in the urine.^{8,9}

Topically, propylene glycol is more irritant than glycerin, but is regarded as minimally irritant. When applied to mucous membranes, it may produce some local irritation as well as when it is used under occlusive conditions. Otic preparations using propylene glycol have been reported to cause some local sensitivity.⁶ Injections containing high concentrations of propylene glycol may produce pain or irritation.

Propylene glycol is approximately one-third as intoxicating as ethanol; administration of large volumes has been associated with adverse effects on the central nervous system as well as ototoxicity, cardiovascular effects, seizures, hyperosmolarity and lactic acidosis. The World Health Organization has set an acceptable daily intake at up to 25 mg/kg of body weight. For intravenous administration, formulations containing 35% propylene glycol can cause hemolysis in humans.⁸

Safety

Propylene glycol has not been demonstrated to be teratogenic or mutagenic in humans. It is GRAS listed and is included in the FDA Inactive Ingredients Guide (dental preparations, IM and IV injections, inhalations; ophthalmic; oral, otic, percutaneous, rectal, topical and vaginal preparations).⁸

Stability

Propylene glycol is stable when stored in a well-closed container but at high temperatures and exposed to air, it will oxidize yielding products such as propionaldehyde, lactic acid, pyruvic acid and acetic acid.⁷

It should be stored in a well-closed container, protected from light, in a cool, dry place. Propylene glycol is chemically stable with ethanol (95%), glycerin and water. Its aqueous solutions may be autoclaved. Propylene glycol is incompatible with oxidizing reagents such as potassium permanganate.⁸

COMPOUNDED FORMULAS USING GLYCERIN

Vehicle-Plasticizer

Rx Chewable Lozenges/Troches/Gummy Bears

Gelatin Base (100 g)		
Glycerin		75 g
Gelatin		17 g
Methylparaben		440 mg
Purified water	qs	100 g
Product (100 g)		
Gelatin base		92.5 g
Bentonite		1.7 g
Aspartame		1.95 g
Acacia powder		1.55 g
Citric acid monohydrate		2.3 g
Flavor		qs
Active ingredient		qs

Gelatin Base:

Using a water bath heated to boiling, insert a beaker or other suitable container and add the water, glycerin and methylparaben. Stir and heat for 5 minutes. Very slowly, over about 3 minutes, add the gelatin with stirring until it is thoroughly dispersed and free of lumps. Continue to heat for 45 minutes; remove from the heat, cool and refrigerate until used.

Product:

Calibrate the mold to be used for the prescription. Using a water bath, melt the gelatin base. Triturate all the powders together and add to the melted base and mix until evenly dispersed. Add the desired flavor, mix and pour into appropriate molds and allow to cool. Package and label.

Dispersing/Wetting/Levigating Agent

Rx Rifabutin 20 mg/mL Oral Liquid (100 mL)

Rifabutin		2.1 g
Glycerin		10 mL
Ora Plus		45 mL
Ora Sweet	qs	105 mL

Empty 14 Mycobutin 150 mg capsules into a glass mortar. Pulverize the powder until uniform. Add the glycerin and mix until uniform. Add the Ora Plus in small portions and mix well. Add sufficient Ora Sweet to volume and mix well. Package and label.

Rx Midazolam 2 mg/mL Oral Solution (100 mL)

Midazolam		200 mg
Stevia		300 mg
Sorbitol 70% solution		10 mL
Glycerin		10 mL
Flavor		qs
Sodium benzoate		200 mg
Purified water	qs	100 mL

Disperse the midazolam powder in about 70 mL of purified water. If

necessary, add hydrochloric acid 2 N solution drop by drop to achieve a pH of 3.0, which is necessary to convert the midazolam to midazolam hydrochloride and continue to mix for 15 to 20 minutes. Add the stevia powder and sodium benzoate and mix well. Add the flavor to the glycerin and then to the mixture. Add the sorbitol and sufficient purified water to volume and mix well. Package and label.

Dispersing/Wetting/Levigating/Sweetening

Rx Radiation Burn Mouth Rinse (100 mL)

Misoprostol		2.4 mg
Glycerin		10 mL
Diphenhydramine hydrochloride		
oral liquid		40 mL
Lidocaine hydrochloride		1 g
Methylcellulose		1 g
Flavor		qs
Preserved water	qs	100 mL

Pulverize the misoprostol tablets to a fine powder. Incorporate the lidocaine hydrochloride and methylcellulose powders together and add the glycerin to form a smooth paste. Add about 45 mL of preserved water and mix well. Add the diphenhydramine hydrochloride oral liquid, flavors and sufficient preserved water to volume and mix well. Package and label.

Vehicle-Topical

Rx Glycerogelatin/Glycerinated Gelatin (100 g)

Gelatin		50 g
Glycerin		50 g
Purified water	qs	100 g

Pour upon the gelatin sufficient distilled water to cover it, allow it to stand for one hour, pour off the water and allow the gelatin to drain for a few minutes. Transfer to a dish, add the glycerin and heat on a water bath until the gelatin is dissolved. Strain the solution while hot, transfer to a tared dish and heat on a water bath until the product weighs 100 g. When cooled, cut into pieces.

Rx Glycerogelatin with Active Ingredient (100 g)

Glycerinated gelatin		34 g
Glycerin		27 g
Distilled water		39 mL
Active ingredient		qs

Mix the active ingredient with the glycerin, add the water and incorporate this mixture with the glycerinated gelatin, which has been previously melted on a water bath. Continue to heat and stir until a homogeneous mixture is obtained. Pour into chilled molds and allow to congeal. Package and label.

Vehicle-Rectal

Rx Glycerinated Gelatin Suppositories (100 g; number depends upon the mold used)

Active drug		qs
Purified water		10 mL
Gelatin		20 g
Glycerin		70 g

Mix the active drug with the water; add the glycerin and mix well. Add the gelatin and heat on a water bath and mix well without incorporating air into the mixture. When the gelatin has dissolved, pour the melted mixture into chilled molds and allow to solidify. Package and label.

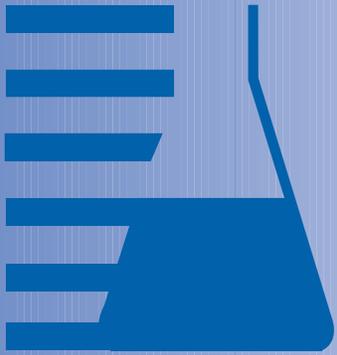
Active Ingredient, Vehicle-Rectal

Rx Glycerin Suppositories (105 g; number depends upon the mold used)

Glycerin		91 g
Sodium stearate		9 g
Purified water		5 g

Heat the glycerin in a suitable container to about 120° C. Dissolve the sodium stearate in the heated glycerin. Add the purified water, mix and immediately pour into suitable molds. Cool until solidified and remove, if appropriate. Package and label.

Continued.....



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Solvent-Emollient

Rx Nasal Decongestant Gel (100 mL)

Phenylephrine hydrochloride	500 mg
Methylcellulose	2 g
Methyl salicylate	0.01 mL
Eucalyptol	0.1 mL
Pine needle oil	0.01 mL
Glycerin	15 g
Purified water	qs 100 mL

Dissolve the phenylephrine hydrochloride in about 40 mL of the purified water. Mix the methylcellulose with about 10 g of glycerin. Add the phenylephrine hydrochloride solution to the methylcellulose mixture with stirring. Dissolve the oils in 5 g of the glycerin and slowly incorporate into the methylcellulose dispersion. Add sufficient purified water to volume and mix well. Package and label.

Active Drug

Rx Glycerin 50% Injection (100 mL)

Glycerin	50 g
Sterile water for injection	qs 100 mL

Using aseptic technique, place the glycerin in a suitable, clean, depyrogenated graduated cylinder. Add sufficient sterile water for injection to volume and mix well. Filter through an appropriate sterile 0.2 µm filter into single-dose, sterile USP Type I glass vials. Package and label; test appropriately.

COMPOUNDED FORMULAS USING PROPYLENE GLYCOL

Dispersing/Wetting/Solubilizing Agent

Rx Acyclovir and Chlorhexidine Cold Sore Gel (10 g)

Acyclovir	1 g
Chlorhexidine digluconate	200 mg
Hydroxypropyl methylcellulose	300 mg
Propylene glycol	1 mL
Preserved water	8 mL

Accurately weight or measure each of the ingredients. Mix the acyclovir and hydroxypropyl methylcellulose with the propylene glycol. Slowly incorporate the preserved water and the chlorhexidine digluconate solution (1 mL of a 20% solution) and mix well. Package and label. Note: In this formula, the propylene glycol is used as an aid in incorporating the acyclovir and hydroxypropyl methylcellulose into the aqueous system.

Vehicle/Solubilizer/Viscosity Enhancer

Rx 5-Aminosalicylic Acid Enema (100 mL)

5-Aminosalicylic acid	4 g
Sodium phosphate dibasic, anhydrous	400 mg
Sodium phosphate monobasic anhydrous	4.5 g
Sodium chloride	9 g
Sodium ascorbate	500 mg
Tragacanth	4 g
Methylparaben	2 g
Propylparaben	500 mg
Propylene glycol	25 mL
Distilled water	qs 100 mL

Dissolve the parabens in the propylene glycol with stirring. Add the tragacanth to this solution and thoroughly disperse. Add approximately 75 mL of distilled water to this mixture, followed by the remaining ingredients, with continued stirring. Add sufficient distilled water to volume and mix well. Package and label. Note: The propylene glycol is used to increase the viscosity of the product and as an aid in dissolving the parabens and dispersing the tragacanth.

Solubilizer-Vehicle

Rx Diazepam 5 mg/mL Injection (100 mL)

Diazepam	500 mg
Propylene glycol	40 mL
Ethyl alcohol	10 mL
Sodium benzoate and Benzoic acid	5 g

Benzyl alcohol	1.5 g
Sterile water for injection	qs 100 mL

Dissolve the diazepam in a mixture of the propylene glycol and ethyl alcohol. Add the sodium benzoate, benzoic acid and benzyl alcohol to about 30 mL of sterile water for injection. Combine the two liquids. Adjust the pH if necessary to the range of 6.2 to 6.9. Add sufficient sterile water for injection to volume and mix well. Filter through a sterile 0.2 µm filter into sterile vials. Package and label; test appropriately.

Vehicle-Solubilizer-Penetration Enhancer

Rx Hydrocortisone Gel

Hydrocortisone	1 g
Carbomer 934	1.5 g
Trolamine	250 mg to 350 mg
Propylene glycol	qs 100 g

Accurately weigh the hydrocortisone and carbomer 934. Mix the hydrocortisone with about 95 g of propylene glycol. Add the carbomer 934 and mix well. Slowly add the trolamine until the desired viscosity is obtained. Add additional propylene glycol to make 100 g and mix well. Package and label.

Vehicle-Solubilizer-Penetration Enhancer

Rx Antipruritic Clear Lotion (100 mL)

Liquified phenol	0.4 mL
Tannic acid	8.4 g
Benzocaine	2.2 g
Ethanol	65 mL
Propylene glycol	20 mL
Purified water	qs 100 mL

Add the liquefied phenol to a clean mortar. Add the ethanol and mix well. Add the tannic acid and mix until finely dispersed. Add the benzocaine and propylene glycol. Add sufficient purified water to volume and thoroughly mix. Package and label.

Vehicle-Penetration Enhancer-Viscosity Enhancer

Rx Psoriasis Lotion (100 mL)

Coal tar solution	5 mL
Salicylic acid	5 g
Urea	10 g
Triamcinolone acetonide	160 mg
Propylene glycol	qs 100 mL

Dissolve the urea and salicylic acid in about 75 mL of propylene glycol; this may take 30 to 45 minutes. Add the triamcinolone acetonide and mix well. Incorporate the coal tar solution and mix well. Add sufficient propylene glycol to make 100 mL and thoroughly mix. Package and label.

Vehicle-Solubilizer-Penetration Enhancer

Rx Progesterone 50 mg/mL Topical Solution (100 mL)

Progesterone	5 g
Benzyl alcohol	20 mL
Dimethylsulfoxide	20 mL
Absolute alcohol	20 mL
Propylene glycol	qs 100 mL

Combine the benzyl alcohol, dimethylsulfoxide and absolute alcohol and mix well. Add the progesterone and sufficient propylene glycol to volume and mix well. Package and label.

Wetting-Dispersing Agent/Solubilizer/Penetration Enhancer

Rx Testosterone 2% Cream (100 g)

Testosterone	2 g
Propylene glycol	2 mL
Dermabase	qs 100 g

Mix the testosterone with the propylene glycol. Incorporate this mixture into the Dermabase and mix well. Package and label.

Vehicle-Penetration Enhancer

Rx Analgesic Stick (100 g)

Methyl salicylate	35 g
Menthol	15 g
Sodium stearate	13 g

Water 12 g
 Propylene glycol 25 g

Gently heat and melt the sodium stearate. Mix the water with the propylene glycol and add to the melted sodium stearate. Mix thoroughly, remove from heat, and allow this base to cool slightly. Dissolve the menthol in the methyl salicylate and add to the base slowly, with thorough mixing. As the product begins to thicken, continue mixing and pour into stick-type containers.

Wetting/Dispersing/Levigating Agent

Rx Clonidine, Gabapentin, Ketamine and Lidocaine PLO (100 mL)

Clonidine hydrochloride	200 mg
Gabapentin	6 g
Ketamine hydrochloride	10 g
Lidocaine hydrochloride	2 g
Propylene glycol	10 mL
Lecithin-Isopropyl palmitate 1:1	22 mL
Poloxamer 407, 20% gel qs	100 mL

Mix the four powders together and add the propylene glycol, mixing to form a smooth paste. Add the lecithin-isopropyl palmitate solution and mix well. Add the poloxamer 407, 20% gel to volume and mix thoroughly using a mechanical shearing force method. Package and label.

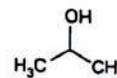
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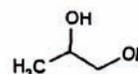
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Figure 1:
 Chemical structures of isopropanol,
 propylene glycol and glycerin.

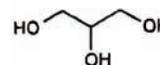
Isopropanol



Propylene Glycol



Glycerin



Use	Dosage Form	Concentration (%)	Propylene Glycerin
Emollient	Topicals	≤ 30	~15
	Humectant	≤ 30	
Preservative	Solutions, Semisolids	≤ 20	15-30
	Solvent/Cosolvent	Aerosol solutions	--
Oral solutions		--	10-25
Parenterals		≤ 50	10-60
Topicals		--	5-80
Ophthalmic Formulations		0.5-3.0	--
Plasticizer	Tablets	Variable	--
	Sweetener	Elixirs	≤ 20

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