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## 15

# Pharmaceutical Solvents and Solubilizing Agents

Melgardt de Villiers, PhD

## CHAPTER OUTLINE

### General Information

Water

Alcohols

Glycols

Ketones

Oils

Cyclodextrins

## I.

### GENERAL INFORMATION

- A. Water is the most commonly used and most desirable solvent-vehicle for liquid drug products and preparations for all uses.
- B. Other solvent-vehicles frequently used as ingredients in drug products and compounded preparations include alcohol, isopropyl alcohol, glycerin, propylene glycol, and polyethylene glycol 400.
- C. Some other solvents are used pharmaceutically in processing drug products, for assays and tests, or for making specialty products and preparations such as Flexible Collodion. Examples include acetone, ether, and chloroform.
- D. Oils used as pharmaceutical solvents-vehicles include a variety of vegetable oils and mineral oil. Examples include corn oil, cottonseed oil, and almond oil. Some special vegetable and essential oils are used primarily as flavors and scents. The *National Formulary* section of the *USP-NF* (1) has monographs for various oils of this type, such as anise oil, lemon oil, and rose oil. These are discussed in Chapter 21, Colors, Flavors, Sweeteners, and Scents.
- E. The *USP-NF* lists official articles classified as solvents and vehicles by categories in a table of excipients in the Front Matter of the *NF* section (2). These are given in Table 15.1. Notice that some articles are listed in both categories and some, such as Sterile Water for Inhalation and Dehydrated Alcohol, are not listed at all. The following chapter describes those articles most frequently encountered in pharmacy compounding and practice.
- F. In reading and interpreting the current chapter, note that this text employs the usual convention of using upper-case first letters for words designating official *USP-NF* articles (e.g., Alcohol,

Table 15.1

## USP AND NF EXCIPIENTS CATEGORIZED AS SOLVENTS AND VEHICLES

SOLVENT	VEHICLE
Acetone	FLAVORED AND/OR SWEETENED
Alcohol	Aromatic Elixir
Alcohol, Diluted	Benzaldehyde Elixir, Compound
Amylene Hydrate	Dextrose
Benzyl Benzoate	Peppermint Water
Butyl Alcohol	Sorbitol Solution
Canola Oil	Syrup
Caprylocaproyl Polyoxylglycerides	OLEAGINOUS
Corn Oil	Alkyl (C12-15) Benzoate
Cottonseed Oil	Almond Oil
Diethylene Glycol Monoethyl Ether	Canola Oil
Ethyl Acetate	Corn Oil
Glycerin	Cottonseed Oil
Hexylene Glycol	Ethyl Oleate
Isopropyl Alcohol	Isopropyl Myristate
Lauroyl Polyoxylglycerides	Isopropyl Palmitate
Linoleoyl Polyoxylglycerides	Mineral Oil
Methyl Alcohol	Mineral Oil, Light
Methylene Chloride	Octyldodecanol
Methyl Isobutyl Ketone	Olive Oil
Mineral Oil	Peanut Oil
Oleoyl Polyoxylglycerides	Safflower Oil
Peanut Oil	Sesame Oil
Polyethylene Glycol	Soybean Oil
Polyethylene Glycol Monomethyl Ether	Squalane
Propylene Glycol	STERILE
Sesame Oil	Sodium Chloride Injection, Bacteriostatic
Stearoyl Polyoxylglycerides	Water for Injection, Bacteriostatic
Water for Injection	SOLID CARRIER
Water for Injection, Sterile	Sugar Spheres
Water for Irrigation, Sterile	
Water, Purified	

From the United States Pharmacopeial Convention Inc. USP 30/ NF 25. 2006: Front Matter—NF: Excipients. Rockville, MD: Author, 2007, with permission.

Source: 2007 USP 30/ NF 25. Rockville, MD: The United States Pharmacopeial Convention Inc., 2006: Front Matter—NF: Excipients.

Purified Water) and lower-case first letters for words designating the chemical substances (e.g., ethanol, water).

G. Recently, the *USP* also started listing some cyclodextrins that are used as solubilizing agents.

## II. WATER

### A. General information

1. Water is such an important substance and component of pharmaceutical dosage forms that the *USP* describes and sets standards for various types of water in the General Notices official monograph, and Chapter {1231} Water for Pharmaceutical Purposes.
2. There are eight official types of water. These are USP Purified Water; USP Water for Injection; USP Water for Hemodialysis; USP Sterile Water for Injection; USP Sterile Water for Inhalation; USP Bacteriostatic Water for Injection; USP Sterile Water for Irrigation; and USP Sterile Purified Water. (3). The *USP* designation means that the water is the subject of an official monograph in the current *USP* with various specifications for each type. The latter four waters are “finished” products that are packaged and labeled as such. The USP Purified Water, USP Water for Injection, and USP Water for Hemodialysis conversely, are components or “ingredient materials” as they are termed by the *USP*, intended to be used in the production of drug products.

3. When water is used in making official *USP* preparations, it must meet the criteria specified in the *USP* for the type of preparation being made. For example, the water used for making parenteral products must meet the requirements for injections found in Chapter (1) Injections of the *USP* (4).
4. The basic starting ingredient for all *USP* water items is potable (drinking) water as defined in the General Notices of the *USP*: "Potable water meeting the requirements for drinking water as set forth in the regulations of the federal Environmental Protection Agency may be used in the preparation of official substances" (1). This means that drinking water may be used in the manufacturing and preparation of *USP* drug substances, including water articles. Drinking or tap water does not, however, meet the standards as an ingredient in dosage forms. Water for making dosage forms must be one of the official *USP* monograph water articles as described further.
5. In addition to Water for Injection and Purified Water *USP*, in Europe there is a third class of water called *highly purified water*, like a super grade of Purified Water *USP*. Unlike Water for Injection, which is traditionally produced with a still, highly purified water is not boiled. Instead, it goes through various pretreatment steps, one or two reverse osmosis passes, a deionization step, and sometimes ultraviolet radiation and a final filtration step. The end result is highly purified water that is equivalent to Water for Injection but produced at a lower cost.

#### B. *USP-NF* water articles

##### 1. Purified Water *USP* (3,5)

H<sub>2</sub>O MW = 18.02

- a. Preparation
    - (1) Made from water complying with the U.S. Environmental Protection Agency (EPA) National Primary Drinking Water Regulations or comparable regulations of the European Union or Japan
    - (2) Processed by distillation, ion-exchange treatment, reverse osmosis, or other suitable method
    - (3) No added substances (such as preservatives)
  - b. Description: clear, colorless, odorless liquid
  - c. Standards
    - (1) Meets *USP* requirements for Total Organic Carbon (643) and Water Conductivity (645)
    - (2) Bacterial endotoxins (pyrogens): no standard
    - (3) Bacteriologic purity: complies with EPA regulations for drinking water
  - d. Packaging and storage: When packaged, use tight containers.
  - e. Labeling: When packaged, label method of preparation.
  - f. Uses
    - (1) *USP* Chapter (795) states that for nonsterile compounding, pharmacists must use *USP*-grade purified water (6), which must meet criteria (e.g., for dissolved solids, pH) that ensure the stability of preparations.
    - (2) It is used as a solvent-vehicle for the preparation of pharmaceutical dosage forms for internal or external use.
    - (3) It is not for use when sterility is required unless it meets the requirements under *USP* Sterility Tests (71) or is first sterilized by filtration or autoclaving. It must then be protected from microbial contamination.
    - (4) It is not for use in making parenteral products unless it can be assured that it meets the requirements for sterility and bacterial endotoxins for parenteral administration.
- ##### 2. Sterile Purified Water *USP* (3,5)
- a. Preparation
    - (1) Made from Purified Water that has been sterilized and suitably packaged
    - (2) No added substances (such as preservatives)
  - b. Description: clear, colorless, odorless liquid
  - c. Standards
    - (1) Meets *USP* requirements for Total organic carbon (642) and Water conductivity (645). Total organic carbon (TOC) is an indirect measure of organic molecules present in pharmaceutical waters measured as carbon. Electrical conductivity in water is a measure of the ion-facilitated electron flow through it and Water conductivity is therefore a measure of the presence of extraneous ions
    - (2) Bacterial endotoxins (pyrogens): no standard

- (3) Bacteriologic purity: meets requirements in Chapter <71> for Sterility. Portions of this general chapter in the USP have been harmonized with the corresponding texts of the European Pharmacopeia and/or the Japanese Pharmacopeia
  - (4) pH: between 5.0 and 7.0
  - (5) Other standards as given in the *USP* for ammonia, calcium, chloride, sulfate, and oxidizable substances
  - d. Packaging and storage: suitable tight containers
  - e. Labeling: Label with method of preparation and that this is not for parenteral use.
  - f. Uses
    - (1) It is used as a solvent-vehicle for the preparation of pharmaceutical dosage forms for internal or external use.
    - (2) It is not for parenteral administration.
3. Water for Injection USP (3,5)
- a. Preparation
    - (1) Purified by distillation or reverse osmosis not by deionization because bacterial endotoxins can grow in a deionizing chamber to a level exceeding USP requirements
    - (2) No added substances (such as preservatives)
  - b. Description: clear, colorless, odorless liquid
  - c. Standards
    - (1) Bacterial endotoxins (pyrogens, *USP* Chapter <151> Pyrogen Test): not more than 0.25 USP Endotoxin Units per mL (*USP* Chapter <85> Bacterial Endotoxins Test)
    - (2) All requirements for Purified Water
  - d. Uses: Water for Injection is a starting material for making parenteral products. It must be processed further either before use or during product preparation. The *USP* monograph has the following note on its use:

NOTE—Water for Injection is intended for use as a solvent for the preparation of parenteral solutions. Where used for the preparation of parenteral solutions subject to final sterilization, use suitable means to minimize microbial growth, or first render the Water for Injection sterile and thereafter protect it from microbial contamination. For parenteral solutions that are prepared under aseptic conditions and are not sterilized by appropriate filtration or in the final container, first render the Water for Injection sterile and thereafter, protect it from microbial contamination (5).
4. Sterile Water for Injection USP (3,5)
- a. Preparation
    - (1) Made from Water for Injection that is sterilized and suitably packaged
    - (2) No added substances (such as preservatives)
  - b. Description: clear, colorless, odorless liquid
  - c. Standards
    - (1) All requirements given for Sterile Purified Water
    - (2) Particulate matter: Meets requirements in *USP* Chapter <788> Particulate Matter in Injections. In this context, particulate matter is defined as mobile, randomly sourced, extraneous substances, other than gas bubbles, that cannot be quantitated by chemical analysis because of the small amount of material present (7). Injectable solutions, including solutions constituted from sterile solids intended for parenteral use, must be free from particulate matter that can be observed on visual inspection (4,7).
    - (3) Bacterial endotoxins (pyrogens): not more than 0.25 USP Endotoxin Units per mL
    - (4) Bacteriologic purity: meets requirements given for Sterile Purified Water (Chapter <71> Sterility Tests)
  - d. Packaging and storage: single-dose glass or plastic containers not larger than 1 liter. Glass containers of Type I or Type II glass are preferred.
  - e. Labeling: Label to indicate that no preservative or other substance has been added. Also label that it is not suitable for intravascular injection unless it is first made approximately isotonic by the addition of a suitable solute.
  - f. Uses
    - (1) Base vehicle for large-volume parenteral fluids
    - (2) Solvent for drugs intended for parenteral use
5. Sterile Water for Inhalation USP (3,5)
- a. Preparation
    - (1) Made using Water for Injection that is sterilized and suitably packaged

- (2) No added substances, except that antimicrobial agents may be added when the water is to be used in humidifiers or other devices in which it may become contaminated
  - b. Description: clear, colorless solution
  - c. Standards
    - (1) All requirements given for Sterile Purified Water except pH
    - (2) Bacterial endotoxins (pyrogens): not more than 0.5 USP Endotoxin Units per mL
    - (3) Bacteriologic purity: meets USP sterility requirements
    - (4) pH: 4.5 to 7.5
  - d. Packaging and storage: Glass or plastic containers; Type I and II glass preferred for glass containers
  - e. Labeling: Label that it is for inhalation therapy only and not for parenteral use.
  - f. Uses
    - (1) In humidifiers to add moisture to the environment
    - (2) As a solvent for drugs to be administered by inhalation
    - (3) The following is a note on use in the *USP* monograph:  
NOTE—"Do not use Sterile Water for Inhalation for parenteral administration or for other sterile compendial dosage forms" (5).
6. Sterile Water for Irrigation USP (3,5)
- a. Preparation
    - (1) Made from Water for Injection that is sterilized and suitably packaged
    - (2) No added substances (such as preservatives)
  - b. Description: clear, colorless, odorless liquid
  - c. Standards
    - (1) All requirements given for Sterile Purified Water
    - (2) Bacterial endotoxins (pyrogens): meets the endotoxin test under Water for Injection
    - (3) Bacteriologic purity: meets requirements given for Sterile Purified Water
  - d. Packaging and storage: single-dose glass or plastic containers. Glass containers of Type I or Type II glass are preferred. Containers may have volumes in excess of 1 liter and may be designed with a closure to facilitate easy, rapid emptying.
  - e. Labeling: Label to indicate that no preservative or other substance has been added. Also, the labels "For irrigation only" and "Not for injection" must be conspicuous.
  - f. Uses
    - (1) Irrigation fluid
    - (2) Solvent for drugs to be administered by irrigation, usually for local effect
7. Bacteriostatic Water for Injection USP (3,5)
- a. Preparation
    - (1) Made from Sterile Water for Injection that has been sterilized and suitably packaged
    - (2) Added substances: one or more suitable antimicrobial agents are added
  - b. Description: clear, colorless liquid, odorless, or possibly having the odor of the added antimicrobial agent(s)
  - c. Standards
    - (1) Particulate matter: meets requirements for Sterile Water for Injection
    - (2) Bacterial endotoxins (pyrogens): not more than 0.5 USP Endotoxin Units per mL
    - (3) Bacteriologic purity: meets USP sterility requirements
    - (4) pH: 4.5 to 7.0
    - (5) Meets the effectiveness requirements of Chapter (51) Antimicrobial Effectiveness Testing and label claim for content of the antimicrobial agent(s) in Chapter (341) Antimicrobial Agents—Contain
    - (6) Meets all requirements for Sterile Purified Water except pH, ammonia, chloride, and oxidizable substances
  - d. Packaging and storage: single-dose or multiple-dose glass or plastic containers not larger than 30 mL. Glass containers of Type I or Type II glass are preferred.
  - e. Labeling: Label with name and quantity of preservative(s). Also label in boldface capital letters with contrasting color (preferably red): **NOT FOR USE IN NEWBORNS.**
  - f. Uses
    - (1) As a solvent for drugs to be given parenterally when a preserved solution is desired and when the antimicrobial agent(s) do not cause compatibility problems with the chosen drug or drugs
    - (2) Is not to be used when large volumes are needed for parenteral administration. If large volumes are needed (>30 mL), Sterile Water for Injection should be used. Even with moderate volumes (>5 mL), Sterile Water for Injection is preferred.

### III. ALCOHOLS

#### A. General information

- In organic chemistry, alcohols have the general formula R-OH, where R represents a general hydrocarbon group. In pharmacy, when the term *alcohol* is used, it has a more restricted meaning. The General Notices section of the *USP* states (1):

**Alcohol**—All statements of percentages of alcohol, such as under the heading *Alcohol content*, refer to percentage, by volume of C<sub>2</sub>H<sub>5</sub>OH at 15.56°. Where reference is made to C<sub>2</sub>H<sub>5</sub>OH, the chemical entity possessing absolute (100%) strength is intended.

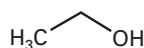
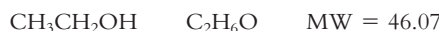
*Alcohol*—Where “alcohol” is called for in formulas, tests, and assays, the monograph article *Alcohol* is to be used (1).

Therefore, when a prescription order or pharmaceutical formula calls for alcohol, the monograph product Alcohol USP is to be used. Another alcohol, such as isopropyl alcohol, should not be used when the term *alcohol*, without modifier, is written.

- If a prescription order calls for a specific alcohol, such as isopropyl alcohol, that specified alcohol must be used. Different alcohols may not be substituted in prescription or medications orders without the consent of the prescriber, any more than, for example, aspirin may be substituted for acetaminophen. Alcohols vary greatly in their relative toxicities; a single carbon atom separates the pharmaceutically useful ethanol from the toxic methanol. Be sure to use only alcohols that are approved for the intended purpose, either external or internal use, or as a solvent for processing. Methanol is very toxic and is never used in the preparation of dosage forms.
- Calculations involving content and labeling of alcohol have been the subject of some confusion. Explanations and multiple examples can be found in Chapter 8, Quantity and Concentration Expressions and Calculations.

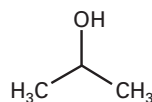
#### B. USP-NF Alcohol (R-OH) articles

- Alcohol (Ethanol, Ethyl Alcohol) (5)



- Alcohol USP (1,5,8)
  - Content: not less than 92.3% and not more than 93.8%, by weight (w/w), corresponding to not less than 94.9% and not more than 96.0%, by volume (v/v), of C<sub>2</sub>H<sub>5</sub>OH
  - Description: clear, colorless, mobile, volatile liquid; flammable; boils at 78°; has a characteristic odor
  - Specific gravity: between 0.812 and 0.816
  - Labeling: “The content of alcohol in a liquid preparation shall be stated on the label as a percentage (v/v) of C<sub>2</sub>H<sub>5</sub>OH” (1).
  - Solubility: miscible with water, isopropyl alcohol, glycerin, acetone, propylene glycol, polyethylene glycol 400, ether, and chloroform; will mix with castor oil, but not other fixed oils and not with mineral oil
  - It is used as a solvent-vehicle for the preparation of pharmaceutical dosage forms for internal or external use. It is an effective antiseptic-disinfectant, being germicidal in concentrations above 60%. Its usual concentration as an antiseptic-disinfectant is 70%.
  - Packaging and storage: tight containers, remote from fire
- Dehydrated Alcohol USP (5,8)
  - Content: not less than 99.2%, by weight (w/w), corresponding to not less than 99.5%, by volume (v/v), of C<sub>2</sub>H<sub>5</sub>OH
  - Description: clear, colorless, mobile, volatile liquid; flammable; boils at 78°; has a characteristic odor
  - Specific gravity: not more than 0.7964
  - Use this preparation when “dehydrated” or “absolute” alcohol is written in a formula (1).
  - Packaging and storage: tight containers, remote from fire
- Dehydrated Alcohol for Injection USP (5,8)
  - The injection is dehydrated alcohol that is suitable for parenteral use.
  - Description: clear, colorless, mobile, volatile liquid; flammable; boils at 78°; has a characteristic odor
  - Specific gravity: not more than 0.8035

- (4) It meets the requirements for Dehydrated Alcohol plus the requirements for parenteral products found in *USP* Chapter <1> Injections. These include specifications for sterility, pyrogenicity, particulate matter, and other contaminants.
- (5) Packaging and storage: single-dose containers with Type I glass preferred. Container headspace may have inert gas.
- d. Diluted Alcohol NF (8,9)
- (1) Content: a mixture of Alcohol and water with not less than 41.0% and not more than 42.0%, by weight (w/w), corresponding to not less than 48.4% and not more than 49.5%, by volume (v/v), of C<sub>2</sub>H<sub>5</sub>OH  
Diluted Alcohol may be prepared as follows:  
Alcohol 500 mL  
Purified Water 500 mL  
Measure the Alcohol and the Purified Water separately at the same temperature, and mix. If the water and the Alcohol and the resulting mixture are measured at 25°C, the volume of the mixture will be about 970 mL.
- (2) Description: clear, colorless, mobile liquid with a characteristic odor
- (3) Specific gravity: between 0.935 and 0.937
- (4) Packaging and storage: tight containers, remote from fire
- e. Rubbing Alcohol USP (5,8)
- RUBBING ALCOHOL SHOULD NEVER BE CONFUSED WITH ISOPROPYL RUBBING ALCOHOL, WHICH IS DISCUSSED LATER.**
- (1) Alcohol content: 68.5% to 71.5% by volume of dehydrated alcohol
- (2) Other content: It is made in accordance with the specifications of Formula 23-H (U.S. Treasury Department, Bureau of Alcohol, Tobacco, and Firearms): 8 parts by volume of acetone, 1.5 parts by volume of methyl isobutyl ketone, and 100 parts by volume of ethanol. In addition to containing water, ethanol, and denaturants, Rubbing Alcohol may also contain stabilizers, perfumes, or dyes that are FDA-approved for use in drugs. In each 100 mL, it has not less than 355 mg sucrose octaacetate or not less than 1.4 mg of denatonium benzoate.
- (3) Description: like Alcohol, except it may be colored because of addition of dye; odor depends on presence of other additives such as perfumes.
- (4) Specific gravity: between 0.869 and 0.877
- (5) Rubbing Alcohol is for external use only. It may be used as a solvent-vehicle for drugs that are being formulated into topical products. It is an effective antiseptic-disinfectant.
- (6) Labeling: Label that it is flammable.
- (7) Packaging and storage: tight containers, remote from fire
2. Isopropyl alcohol (2-Propanol) (5)



- a. Isopropyl Alcohol USP (5,8)
- (1) Content: not less than 99.0% of C<sub>3</sub>H<sub>8</sub>O
- (2) Description: transparent, colorless, mobile, volatile, flammable liquid with a characteristic odor
- (3) Specific gravity: between 0.783 and 0.787
- (4) Solubility: miscible with water, alcohol, glycerin, propylene glycol, polyethylene glycol 400, acetone, ether, and chloroform. It is immiscible with fixed oils and mineral oil.
- (5) Isopropyl Alcohol is for external use only. It may be used as a solvent-vehicle for drugs that are being formulated into topical products. In concentrations  $\geq 70\%$ , it is an effective disinfectant. It is somewhat superior to ethanol as an antiseptic.
- (6) Packaging and storage: tight containers, remote from heat
- b. Isopropyl Rubbing Alcohol USP (5,8)
- (1) Content: not less than 68.0% and not more than 72.0% by volume (v/v) of isopropyl alcohol, the remainder consisting of water, with or without stabilizers, perfume oils, and color additives that are certified by the FDA for use in drugs

- (2) Description: like Isopropyl Alcohol, except it may be colored because of addition of dye. Odor depends on the presence of other additives, such as perfumes.
  - (3) Specific gravity: between 0.872 and 0.883
  - (4) Isopropyl Rubbing Alcohol is for external use only. It may be used as a solvent-vehicle for drugs that are being formulated into topical products. It is an effective antiseptic-disinfectant.
  - (5) Packaging and storage: tight containers, remote from heat
  - c. Azeotropic Isopropyl Alcohol USP (5,8)
    - (1) Content: not less than 91.0% and not more than 93.0% of isopropyl alcohol, by volume (v/v), the remainder consisting of water
    - (2) Description: like Isopropyl Alcohol
    - (3) Specific gravity: between 0.815 and 0.810
    - (4) Packaging and storage: tight containers, remote from heat
- C. The use of alcohol in drug products for children**
1. For a long time the American Academy of Pediatrics has warned about the use of alcohol in oral medications for children (10). This eventually led the FDA to set the following maximum limits on alcohol concentration in over-the-counter (OTC) drug products intended for oral ingestion (11).
    - a. For products labeled for use by adults and children 12 years of age and over, the amount of alcohol in the product shall not exceed 10%.
    - b. For products labeled for use by children 6 to younger than 12 years of age, the amount of alcohol in the product shall not exceed 5%.
    - c. For products labeled for use by children younger than 6 years of age, the amount of alcohol in the product shall not exceed 0.5%.
  2. In addition the amount of alcohol present in a product shall be stated in terms of v/v% of absolute alcohol at 60°F (15.56°C) and a statement expressing the percentage of alcohol present in a product shall appear prominently and conspicuously on the “principal display panel.” In addition, for any OTC drug product intended for oral ingestion containing >0.5% alcohol and labeled for use by children ages 6 to younger than 12 years of age, the labeling shall contain the following statement in the directions section: “Consult a physician for use in children under 6 years of age.”
  3. The following drug products are temporarily exempt from these provisions: (i) Aromatic Cascara Fluidextract, (ii) Cascara Sagrada Fluidextract, and (iii) orally ingested homeopathic drug products. Ipecac syrup is exempt from the provisions for children younger than 6 years of age because ipecac syrup is an important OTC product that is used to cause vomiting when poisoning occurs. Alcohol is used in the preparation of the syrup to ensure complete extraction of the alkaloids from the ipecac powder. As a result, ipecac syrups contain between 1.0 and 2.5% alcohol. To comply with this exception ipecac product labels must contain a statement conspicuously boxed and in red letters that states: “For emergency use to cause vomiting in poisoning. Before using, call physician, the poison Control Center, or hospital emergency room immediately for advice.” The labeling must also state: “Usual dosage: 1 tablespoon (15 milliliters) in person over 1 year of age.”
  4. These FDA regulations only affect orally ingested OTC medications; thus, products such as mouthwashes, which contain a high alcohol content, remain exempt. Furthermore, greater flexibility is allowed for prescription products and preparations. See Sample Prescription 31.2 in Chapter 31 for considerations and sample calculations involving alcohol in a prescribed pediatric compounded preparation.

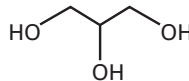
## IV. GLYCOLS

### A. General information

1. Glycols are simply dihydroxy alcohols. Because of their chemical structure, they have more than one site for hydrogen bonding and therefore, relative to their molecular weights, they have higher water solubility and higher boiling points (are less volatile) than a comparable single hydroxy alcohol. For example, ethanol boils at 78°C, whereas the structurally comparable dihydroxy ethylene glycol has a boiling point of 197°C. Ethylene glycol owes its usefulness as an antifreeze to its unique glycol properties of low freezing point, high boiling point, and high water solubility. Similarly, polyethylene glycols have high water solubility even though they are high-molecular-weight organic compounds.
2. As with alcohols, glycols vary greatly in their relative toxicities, and a single carbon atom separates the pharmaceutically useful and nontoxic propylene glycol from the very toxic ethylene glycol. Be sure to use only glycols approved for the intended purpose, either external or internal use.

## B. USP–NF glycol articles

## 1. Glycerin USP (glycerol) (5,8)



- a. Content: not less than 99.0% and not more than 101.0% of  $\text{C}_3\text{H}_8\text{O}_3$
- b. Description: clear, colorless, viscous liquid; practically odorless, hygroscopic, neutral pH
- c. Specific gravity: not less than 1.249
- d. Solubility: miscible with water, ethanol, isopropyl alcohol, propylene glycol, and polyethylene glycol 400; is soluble to the degree of 1 g/15 mL in acetone; insoluble in chloroform, ether, fixed oils, mineral oil, and volatile oils
- e. It is used as a solvent-vehicle for the preparation of pharmaceutical dosage forms for internal or external use. It has humectant and preservative properties.
- f. Packaging and storage: tight container

**Note:** In May 2007, the FDA issued a warning to pharmaceutical manufacturers, suppliers, drug repackers, and health professionals who compound medications to be especially vigilant in ensuring that glycerin, a sweetener commonly used worldwide in liquid OTC and prescription drug products, is not contaminated with diethylene glycol (DEG). DEG is a known poison used in antifreeze and as a solvent. The most recent poisoning incident occurred in Panama in September 2006 and involved DEG-contaminated glycerin used in cough syrup, which resulted in dozens of hospitalizations for serious injury and more than 40 deaths. In late 1995 and early 1996, at least 80 children died in Haiti owing to DEG-contaminated glycerin in acetaminophen syrup. Between 1990 and 1998, similar incidents of DEG poisoning reportedly occurred in Argentina, Bangladesh, India, and Nigeria and resulted in hundreds of deaths. In 1937, more than 100 people died in the United States after ingesting DEG-contaminated Elixir Sulfanilamide, a drug used to treat infections. This incident led to the enactment of the Federal Food, Drug, and Cosmetic Act, which is the nation's primary statute on the regulation of drugs (12).

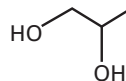
## 2. Glycerin Oral Solution USP (5,8)

- a. Content: not less than 95.0% and not more than 105.0% of  $\text{C}_3\text{H}_8\text{O}_3$
- b. Description: like Glycerin USP except pH between 5.5 and 7.5
- c. Solubility: like Glycerin USP
- d. It is used as a solvent-vehicle for the preparation of pharmaceutical oral dosage forms.
- e. Packaging and storage: tight containers

## 3. Glycerin Ophthalmic Solution USP (5,8)

- a. Content: not less than 98.5% of  $\text{C}_3\text{H}_8\text{O}_3$ ; may contain one or more suitable antimicrobial preservatives
- b. Description: like Glycerin Oral Solution USP except it is sterile
- c. Solubility: like Glycerin USP
- d. For ophthalmic use
- e. Packaging and storage: Tight containers of glass or plastic with volume not greater than 15 mL and protected from light. The container or carton is sealed and tamper-proof so that sterility is ensured at opening.

## 4. Propylene Glycol USP (5,8,13)



- a. Content: not less than 99.5% of  $\text{C}_3\text{H}_8\text{O}_2$
- b. Description: clear, colorless, viscous liquid; practically odorless, hygroscopic
- c. Specific gravity: between 1.035 and 1.037
- d. Solubility: miscible with water, ethyl and isopropyl alcohol, acetone, glycerin, polyethylene glycol 400, chloroform, and ether; dissolves many volatile oils, but is immiscible with fixed oils and mineral oil

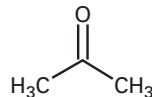
- e. It is used as a solvent-vehicle for the preparation of pharmaceutical dosage forms for internal or external use. It is also useful as a humectant and preservative.
5. Polyethylene Glycol NF (8,9,13)
  - a. Polyethylene Glycol, also known as PEG, is an addition polymer of ethylene oxide and water. It has the formula  $H(OCH_2CH_2)_nOH$ , where  $n$  represents the number of oxyethylene groups.
  - b. PEG is labeled with a number indicating the average nominal molecular weight of the polyethylene glycol. The numbers range from 200 to 8,000; polyethylene glycols 200, 300, 400, and 600 are liquids at room temperature, and the higher molecular polymers are waxy solids. (See Chapter 24, Table 24.1.)
  - c. Polyethylene glycol 400 is the most common liquid PEG used as a solvent-vehicle in making pharmaceutical dosage forms for both internal and external use. It is a clear, colorless, slightly hygroscopic, viscous liquid with a slight odor. It congeals at  $6^\circ\text{C}$  and has a specific gravity at  $25^\circ$  of 1.12.
  - d. Solubility: All PEGs are soluble in water, and many are organic solvents. PEG 400 is miscible with water, ethyl and isopropyl alcohol, acetone, glycerin, and propylene glycol. It is immiscible with fixed oils and mineral oil.
  - e. Recommended packaging: tight containers

## V. KETONES

### A. General information

1. There are only two official solvent-vehicles in the ketone group, Acetone and Methyl Isobutyl Ketone. Methyl ethyl ketone is not an official substance, but it is described in the reagent section of the *USP* because it is used as a solvent for assays, tests, and processing.
2. Official ketones have limited usefulness because of their volatility, flammability, and toxicity. They do have some unique solvent properties that make them useful.

### B. Acetone NF (9,13)



1. Description: transparent, colorless, mobile, volatile liquid that boils at  $56.5^\circ\text{C}$ . Has a distinctive odor. A 1 in 2 solution with water has neutral pH.  
*CAUTION: Acetone is very flammable. Do not use where it may be ignited.*
2. Specific gravity: 0.788 (not  $>0.789$ )
3. Solubility: miscible with water, alcohol, ether, chloroform, and most oils
4. Packaging and storage: tight containers and stored remote from fire

## VI. OILS

### A. General information

1. The solvent-vehicle oils official in the *USP-NF* are listed in Table 15.1.
2. As stated in the introduction to this chapter, some special vegetable and essential oils are used primarily as flavors and scents. The *National Formulary* section of the *USP-NF* has monographs for various oils of this type such as Anise Oil, Lemon Oil, and Rose Oil. These are discussed in Chapter 21, Colors, Flavors, Sweeteners, and Scents.

### B. USP-NF oils

1. Almond Oil NF (8,9)
  - a. Description: clear, pale, straw-colored or colorless, oily liquid; clear at  $-10^\circ\text{C}$ , congeals at  $-20^\circ\text{C}$
  - b. Specific gravity: 0.910 to 0.915
  - c. Solubility: insoluble in water, slightly soluble in alcohol, miscible with mineral oil, other fixed oils, ether, chloroform, and solvent hexane
2. Castor Oil USP (5,8)
  - a. Description: pale, yellowish or nearly colorless, transparent, viscid liquid; has a faint, mild odor
  - b. Specific gravity: 0.957 to 0.961

- c. Solubility: insoluble in water and mineral oil, soluble in alcohol, miscible with dehydrated alcohol, other fixed oils, glacial acetic acid, chloroform, and ether
- 3. Corn Oil NF (8,9)
  - a. Description: clear, light yellow, oily liquid with a faint characteristic odor
  - b. Specific gravity: 0.914 to 0.921
  - c. Solubility: insoluble in water, slightly soluble in alcohol, miscible with mineral oil, other fixed oils, ether, chloroform, and solvent hexane
- 4. Cottonseed Oil NF (8,9)
  - a. Description: pale yellow, oily liquid. Odorless or nearly so. Particles of fat may separate beginning at 10°C, solidifies at 0° to -5°C.
  - b. Specific gravity: 0.915 to 0.921
  - c. Solubility: insoluble in water, slightly soluble in alcohol, miscible with mineral oil, other fixed oils, ether, chloroform, and solvent hexane
- 5. Mineral Oil USP (5,8)
  - a. Description: colorless, transparent, oily liquid; odorless at room temperature
  - b. Specific gravity: 0.845 to 0.905
  - c. Solubility: insoluble in water and in alcohol, soluble in volatile oils; miscible with most fixed oils but not with castor oil
- 6. Light Mineral Oil NF (8,9)
  - a. Description: colorless, transparent, oily liquid, odorless at room temperature
  - b. Specific gravity: 0.818 to 0.880
  - c. Solubility: insoluble in water and in alcohol, soluble in volatile oils; miscible with most fixed oils but not with castor oil
- 7. Olive Oil NF (8,9)
  - a. Description: pale yellow or light greenish-yellow oily liquid; has a characteristic odor
  - b. Specific gravity: 0.910 to 0.915
  - c. Solubility: insoluble in water, slightly soluble in alcohol, miscible with mineral oil, other fixed oils, ether, and chloroform
- 8. Peanut Oil NF (8,9)
  - a. Description: colorless or pale yellow oily liquid; may have a nutty odor
  - b. Specific gravity: 0.912 to 0.920
  - c. Solubility: insoluble in water, very slightly soluble in alcohol, miscible with mineral oil, other fixed oils, ether, and chloroform
- 9. Safflower Oil USP (5,8)
  - a. Description: light yellow oil; becomes thick and rancid on prolonged exposure to air
  - b. Specific gravity: 0.921
  - c. Solubility: insoluble in water, slightly soluble in alcohol, miscible with other fixed oils, ether, and chloroform
- 10. Sesame Oil NF (8,9)
  - a. Description: pale yellow, oily liquid; practically odorless
  - b. Specific gravity: 0.916 to 0.921
  - c. Solubility: insoluble in water, slightly soluble in alcohol, miscible with mineral oil, other fixed oils, ether, chloroform, and solvent hexane
- 11. Soybean Oil USP (5,8,14)
  - a. Description: clear, pale yellow oily liquid with a characteristic odor
  - b. Specific gravity: 0.916 to 0.922
  - c. Solubility: insoluble in water, slightly soluble in alcohol, miscible with mineral oil, other fixed oils, ether, and chloroform

## VII. CYCLODEXTRINS

### A. General information

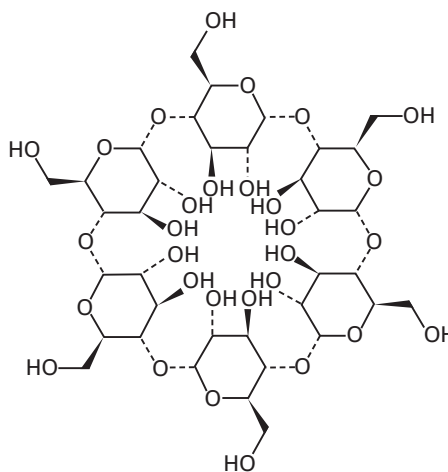
1. Cyclodextrins, cyclic oligosaccharides, were discovered more than 100 years ago (15). Cyclodextrins are chemically and physically stable molecules formed by the enzymatic modification of starch. Typical cyclodextrins contain a number of glucose monomers ranging from six to eight units in a ring, creating a cone shape. The most common cyclodextrins are  $\alpha$ -cyclodextrin: six-sugar-ring molecule;  $\beta$ -cyclodextrin: seven sugar-ring-molecule; and  $\gamma$ -cyclodextrin: eight-sugar-ring molecule.
2. Being starch derivatives, cyclodextrins are generally regarded as essentially nontoxic materials. Worldwide  $\alpha$ ,  $\beta$  and  $\gamma$ -cyclodextrin are fully registered in all major chemical inventories (16).

In the United States, both  $\beta$  and  $\gamma$ -cyclodextrin have Generally Regarded As Safe (GRAS) status. However,  $\beta$ -cyclodextrin can form insoluble complexes with cholesterol that disrupt the function of the kidneys, so it should not be used in parenteral applications, and its oral use should be limited to a daily maximum dose of 5 mg/kg.

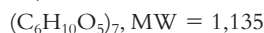
3. In the presence of water, hydrophobic molecules or functional groups of molecules can be included in the cyclodextrin cavity if their molecular dimensions correspond to those of the cyclodextrin cavity. The formed inclusion complexes are relatively stable. One, two, or three cyclodextrin molecules contain one or more entrapped "guest" molecules; this is the essence of "molecular encapsulation."
4. In pharmaceutical dosage forms, cyclodextrins have mainly been used as complexing agents to increase the aqueous solubility of poorly water-soluble drugs and to increase their bioavailability and stability. See example 27.2 in Chapter 27 solutions for a compounded formulation that uses a cyclodextrin to solubilize a drug.

#### B. USP-NF cyclodextrins

1.  $\alpha$ -Cyclodextrin: Alfadex NF (9,16)



- a. Alfadex is composed of six alpha-(1-4) linked D-glucopyranosyl units. It contains not less than 98.0% and not more than 101.0% of  $(C_6H_{10}O_5)_6$ , calculated on the anhydrous basis.
  - b. Appearance: white crystalline powder
  - c. Water content: not more than 11.0%
  - d. Solubility: soluble in water, slightly soluble in alcohol (17)
2.  $\beta$ -Cyclodextrin: Betadex NF (9,16)



- a. Betadex is a nonreducing cyclic compound composed of seven alpha-(1-4) linked D-glucopyranosyl units. It contains not less than 98.0% and not more than 102.0% of  $(C_6H_{10}O_5)_7$ , calculated on the anhydrous basis.
  - b. Appearance: white crystalline powder
  - c. Water content: not more than 14.0%
  - d. Solubility: soluble in water, slightly soluble in alcohol (17)
3.  $\beta$ -Cyclodextrin derivatives (13,16)
    - a. 2-Hydroxypropyl-beta-cyclodextrin (HP- $\beta$ -CD) is an alternative to alpha-, beta- and gamma-cyclodextrin; it has improved water solubility and may be more toxicologically benign. It is well tolerated in humans, with the main adverse event being diarrhea, and there has been no adverse event on kidney function documented to date (18). Owing to its unique properties, it is frequently used to solubilize poorly soluble drugs. For example, Sporanox (itraconazole) injection is a sterile, pyrogen-free, clear, colorless-to-slightly-yellow solution for intravenous infusion. Each milliliter contains 10 mg of itraconazole, solubilized by hydroxypropyl- $\beta$ -cyclodextrin (400 mg) as a molecular inclusion complex.
    - b. Sulfobutylether- $\beta$ -cyclodextrin (Captisol) is another chemically modified cyclodextrin rationally designed to increase drug solubility yet, unlike natural cyclodextrins, it is toxicologically

acceptable in injectable formulations. Abilify (aripiprazole) Injection is a (7.5 mg/mL) clear, colorless, sterile, aqueous solution for intramuscular use that contains 150 mg/mL of sulfobutylether  $\beta$ -cyclodextrin as a solubilizer.

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