# Remington: The Science and Practice of Pharmacy

Nineteenth Edition

Volume II

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# Remington: The Science and Practice of Pharmacy

## Volume II

19TH
EDITION

# Remington: Practice of

**ALFONSO R GENNARO**

*Chairman of the Editorial Board and Editor*

# The Science and Pharmacy

1995

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CHAPTER 80

# Pharmaceutical Necessities

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Significant changes are underway which could alter the rights of pharmacy practitioners. Extemporaneous compounding is being reviewed carefully by the FDA to ensure that manufacturing operations are not being conducted under the guise of pharmacy-practice rights. Additionally, some serious accidents have resulted from the improper compounding and handling of extemporaneously prepared prescriptions.

This chapter does not address the legalities of compounding by a practitioner, but rather is intended as a reference source which highlights substances of little or no therapeutic value which are useful in the compounding of pharmaceuticals. These substances, referred to as excipients, also are used for the bulk manufacture of pharmaceutical products, but usually for different purposes. The excipients described include antioxidants and preservatives; coloring and flavoring agents; diluents and binders; emulsifying and suspending agents, ointment bases, solvents and miscellaneous agents. A more detailed review of these excipients and their industrial applications can be found in the various chapters of **Part 8** of this text.

## Antioxidants and Preservatives

An antioxidant is a substance capable of inhibiting oxidation and that may be added for this purpose to pharmaceutical products subject to deterioration by oxidative processes as, for example, the development of rancidity in oils and fats or the inactivation of some medicinals in the environment of their dosage forms. A preservative is, in the common pharmaceutical sense, a substance that prevents or inhibits microbial growth and may be added to pharmaceutical preparations for this purpose to avoid consequent spoilage of the preparations by microorganisms. Both antioxidants and preservatives have many applications in making medicinal products.

**Alcohol**—page 1404.

**Ascorbyl Palmitate**—see RPS-18, page 1286.

**Anoxomer**—see RPS-18, page 1288.

**Benzoic Acid**—see RPS-18, page 1235.

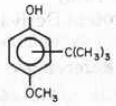
**Benzalkonium Chloride**—page 1264.

**Benzethonium Chloride**—page 1265.

**Benzyl Alcohol**—page 1151.

### Butylated Hydroxyanisole

Phenol, (1,1-dimethylethyl)-4-methoxy-, Tenox BHA (*Eastman*)




*tert*-Butyl-4-methoxyphenol [25013-16-5] $C_{11}H_{16}O_2$ (180.25).

**Preparation**—By an addition interaction of *p*-methoxyphenol and 2-methylpropene. US Pat 2,428,745.

**Description**—White or slightly yellow, waxy solid having a faint, characteristic odor.

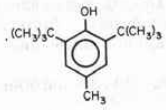
**Solubility**—Insoluble in water; 1 g in 4 mL alcohol, 2 mL chloroform or 1.2 mL ether.

**Uses**—An *antioxidant* in cosmetics and pharmaceuticals containing fats and oils.

**Butylparaben**—see RPS-18 page 1170.

### Butylated Hydroxytoluene

Phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl-, Butylated Hydroxytoluene Crystalline (*Diamond-Shamrock*); Tenox BHT (*Eastman*)




2,6-Di-*tert*-butyl-*p*-cresol [128-37-0] $C_{15}H_{24}O$ (220.35).

**Preparation**—By an addition interaction of *p*-cresol and 2-methylpropene. US Pat 2,428,745.

**Description**—White, tasteless crystals with a mild odor; stable in light or air; melts at 70°.

**Solubility**—Insoluble in water; 1 g in 4 mL alcohol, 1.1 mL chloroform or 1.1 mL ether.

**Uses**—An *antioxidant* employed to retard oxidative degradation of oils and fats in various cosmetics and pharmaceuticals.

**Cetylpyridinium Chloride**—see RPS-18, page 1171.

### Chlorobutanol

2-Propanol, 1,1,1-trichloro-2-methyl-, Chlorbutol; Chlorbutanol; Acetone chloroform; Chloretone (*Stauffer*)

$(CCl_3)C(CH_3)_2OH$

1,1,1-Trichloro-2-methyl-2-propanol [57-15-8] $C_4H_7Cl_3O$ (177.46); *hemihydrate* [6001-64-5] (186.46).

**Preparation**—Chloroform undergoes chemical addition to acetone under the catalytic influence of powdered potassium hydroxide.

**Description**—Colorless to white crystals, of a characteristic, somewhat camphoraceous odor and taste; anhydrous melts about 95°; hydrous melts about 76°; boils with some decomposition between 165 and 168°.

**Solubility**—1 g in 125 mL water, 1 mL alcohol or about 10 mL glycerin; freely soluble in chloroform, ether or volatile oils.

**Incompatibilities**—The anhydrous form must be used in order to prepare a clear solution in liquid petrolatum. It is decomposed by *alkalies; ephedrine* is sufficiently alkaline to cause its breakdown with the formation of ephedrine hydrochloride which will separate from a liquid petrolatum solution. It is only slightly soluble in water, hence alcohol must be used to dissolve the required amount in certain vehicles. A soft mass is produced by trituration with *antipyrine, menthol, phenol* and other substances.

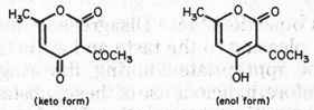
**Uses**—Topically, as a solution in clove oil as a *dental analgesic.* It has *local anesthetic* potency to a mild degree and has been employed as an anesthetic dusting powder (1 to 5%) or ointment (10%). It has antibacterial and germicidal properties. It is used chiefly as a *preservative* in solutions of epinephrine, posterior pituitary, etc. When administered orally, it has much the same therapeutic use as chloral hydrate. Hence, it has been employed as a sedative and hypnotic. It has been taken orally to allay vomiting due to gastritis.

**Dose**—*Topical,* as a **25%** solution in clove oil.

*Other Dose Information*—The oral dose is 300 mg to 1 g, given in tablets or capsules.

### Dehydroacetic Acid

Keto form: 2*H*-Pyran-2,4(3*H*)-dione, 3-acetyl-6-methyl-,




Enol form: 3-Acetyl-4-hydroxy-6-methyl-2H-pyran-2-one [520-45-6 (Keto)], [771-03-9 (enol)] $C_8H_8O_4$ (168.15).

**Preparation**—By fractional distillation of a mixture of ethyl acetoacetate and sodium bicarbonate, maintaining almost total reflux conditions, allowing only ethanol to be removed. The residue is distilled under vacuum. *Org Syn Coll III:* 231, 1955.

**Description**—White to creamy-white crystalline powder melting about 110° with sublimation.

**Solubility**—1 g dissolves in 25 g acetone, 18 g benzene, 5 g methanol or 3 g alcohol.

**Uses**—Preservative.

### Ethylenediamine

1,2-Ethanediamine

$H_2NCH_2CH_2NH_2$

Ethylenediamine [107-15-3] $C_2H_8N_2$ (60.10).

*Caution—Use care in handling because of its caustic nature and the irritating properties of its vapor.*

*Note—It is strongly alkaline and may readily absorb carbon dioxide from the air to form a nonvolatile carbonate. Protect it against undue exposure to the atmosphere.*

**Preparation**—By reacting ethylene dichloride with ammonia, then adding NaOH and distilling.

**Description**—Clear, colorless or only slightly yellow liquid, having an ammonia-like odor and strong alkaline reaction; miscible with water and alcohol; anhydrous boils 116 to 117° and solidifies at about 8°; volatile with steam; a strong base and readily combines with acids to form salts with the evolution of much heat.

**Uses**—A *pharmaceutical necessity* for *Aminophylline Injection.* It is irritating to skin and mucous membranes. It also may cause sensitization characterized by asthma and allergic dermatitis.

**Ethylparaben**—see RPS-18, page 1171.

**Ethyl Vanillin**—page 1386.

**Glycerin**—pages 1041 and 1405.

**Hypophosphorus Acid**—page 1410.

**Malic Acid BP**—see RPS-18, page 1288.

**Methylparaben**—see RPS-18, page 1171.

**Monothioglycerol**—see RPS-18, page 1287.

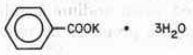
**Phenol**—page 1412.

**Phenylethyl Alcohol**—page 1389.

**Phenylmercuric Nitrate**—page 1270.

### Potassium Benzoate

Benzoic acid, potassium salt




[582-25-2] $C_7H_5KO_2$ (160.21) (anhydrous).

**Description**—Crystalline powder.

**Solubility**—Soluble in water or alcohol.

**Uses**—Preservative.

### Potassium Metabisulfite

Dipotassium pyrosulfite

[16731-55-8] $K_2S_2O_5$ (222.31).

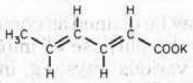
**Description**—White crystals or crystalline powder with an odor of $SO_2$. Oxidizes in air to the sulfate. May ignite on powdering in a mortar if too much heat develops.

**Solubility**—Freely soluble in water; insoluble in alcohol.

**Uses**—Antioxidant.

### Potassium Sorbate

2,4-Hexadienoic acid, (*E,E*)-, potassium salt; 2,4-Hexadienoic acid, potassium salt; Potassium 2,4-Hexadienoate




Potassium (*E,E*)-sorbate; potassium sorbate [590-00-1] [24634-61-5] $C_6H_7KO_2$ (150.22).

**Preparation**—Sorbic Acid is reacted with an equimolar portion of KOH. The resulting potassium sorbate may be crystallized from aqueous ethanol. US Pat 3,173,948.

**Description**—White crystals or powder with a characteristic odor; melts about 270° with decomposition.

**Solubility**—1 g in 4.5 mL water, 35 mL alcohol, > 1000 mL chloroform or > 1000 mL ether.

**Uses**—A water-soluble salt of sorbic acid used in pharmaceuticals to *inhibit the growth of molds and yeasts.* Its toxicity is low, but it may irritate the skin.

**Propyl Gallate BP**—see RPS-18, page 1288.

**Propylparaben**—see RPS-18, page 1171.

**Sassafras Oil**—page 1392.

**Sodium Benzoate**—page 1271.

### Sodium Bisulfite

Sulfurous acid, monosodium salt; Sodium Hydrogen Sulfite; Sodium Acid Sulfite; Leucogen

Monosodium sulfite [7631-90-5] $NaHSO_3$ and sodium metabisulfite ($Na_2S_2O_5$) in varying proportions; yields 58.5–67.4% of $SO_2$.

**Description**—White or yellowish white crystals or granular powder having the odor of sulfur dioxide; unstable in air.

**Solubility**—1 g in 4 mL water; slightly soluble in alcohol.

**Uses**—An *antioxidant* and *stabilizing agent.* Epinephrine hydrochloride solutions may be stabilized by the addition of small quantities of the salt. It also is used to help solubilize kidney stones. It is useful for removing permanganate stains and for solubilizing certain dyes and other chemicals (see *Menadione Sodium Bisulfite,* RPS-17, page 1011).

**Sodium Metabisulfite**

Disulfurous acid, disodium salt

Disodium pyrosulfite [7681-57-4] $Na_2S_2O_5$ (190.10).

**Preparation**—Formed when sodium bisulfite undergoes thermal dehydration. It also may be prepared by passing sulfur dioxide over sodium carbonate.

**Description**—White crystals or white to yellowish crystalline powder having an odor of sulfur dioxide; on exposure to air and moisture, it is slowly oxidized to sulfate.

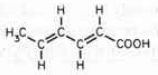
**Solubility**—1 g in 2 mL water; slightly soluble in alcohol; freely soluble in glycerin.

**Uses**—A *reducing agent.* It is used in easily oxidized pharmaceuticals, such as epinephrine hydrochloride and phenylephrine hydrochloride injections, to retard oxidation.

**Sodium Propionate**—see RPS-18, page 1236.

**Sorbic Acid**

2,4-Hexadienoic acid, (*E,E*)-, 2,4-Hexadienoic acid



(*E,E*)-Sorbic acid; Sorbic acid [22500-92-1] [110-44-1] $C_6H_8O_2$ (112.13).

**Preparation**—By various processes. Refer to US Pat 2,921,090.

**Description**—Free-flowing, white, crystalline powder, having a characteristic odor; melts about 133°.

**Solubility**—1 g in 1000 mL water, 10 mL alcohol, 15 mL chloroform, 30 mL ether or 19 mL propylene glycol.

**Uses**—A *mold and yeast inhibitor.* It also is used as a fungistatic agent for foods, especially cheeses.

**Sulfur Dioxide**—see RPS-18, page 1288.

**Thimerosal**—page 1271.

# Coloring, Flavoring and Diluting Agents

The use of properly colored and flavored medicinal substances, although offering no particular therapeutic advantage, is of considerable importance psychologically. A water-clear medicine is not particularly acceptable to most patients, and, in general, is thought to be inert. Many very active medicinal substances are quite unpalatable, and the patient may fail to take the medicine simply because the taste or appearance is objectionable. Disagreeable medication can be made both pleasing to the taste and attractive by careful selection of the appropriate coloring, flavoring and diluting agents. Therefore, judicious use of these substances is important in securing patient cooperation in taking or using the prescribed medication and continued compliance with the prescriber's intent.

## *Coloring Agents or Colorants*

Coloring agents may be defined as compounds employed in pharmacy solely for the purpose of imparting color. They may be classified in various ways, eg, inorganic or organic. For the purpose of this discussion two subdivisions are used: *Natural Coloring Principles* and *Synthetic Coloring Principles.* The members of these groups are used as colors for pharmaceutical preparations, cosmetics, foods and as bacteriological stains and diagnostic agents.

### Natural Coloring Principles

Natural coloring principles are obtained from mineral, plant and animal sources. They are used primarily for artistic purposes, as symbolic adornments of natives, as colors for foods, drugs and cosmetics and for other psychological effects.

Mineral colors frequently are termed *pigments* and are used to color lotions, cosmetics and other preparations, usually for external application. Examples are *Red Ferric Oxide* (page 1416) and *Yellow Ferric Oxide* (page 1416), titanium dioxide (page 884) and carbon black.

The term pigment also is applied generically to plant colors by phytochemists. Many plants contain coloring principles that may be extracted and used as colorants, eg, chlorophyll. Anattenes are obtained from annatto seeds and give yellow to orange water-soluble dyes. Natural beta-carotene is a yellow color extracted from carrots and used to color margarine. Alizarin is a reddish-yellow dye obtained from the madder plant. The indigo plant is the source of a blue pigment called indigo. Flavones, such as riboflavin, rutin, hesperidin and quercetin, are yellow pigments. Saffron is a glycoside that gives a yellow color to drugs and foods. Cudbear and red saunders are two other dyes obtained from plants. Most plant colors now have been characterized and synthesized, however, and those with the desirable qualities of stability, fastness and pleasing hue are available commercially as synthetic products.

Animals have been a source of coloring principles from the earliest periods of recorded history. For example, *Tyrian purple*, once a sign of royalty, was prepared by air oxidation of a colorless secretion obtained from the glands of a snail (*Murex brandaris*). This dye now is known to be 6,6′-dibromoindigo, and has been synthesized, but cheaper dyes of the same color are available. Cochineal from the insect *Coccus cacti* contains the bright-red coloring principle *carminic acid*, a derivative of anthraquinone. This dye is no longer used in foods and pharmaceuticals due to *Salmonella* contamination.

### Synthetic Coloring Principles

Synthetic coloring principles date from 1856 when WH Perkin accidentally discovered *mauveine*, also known as a *Perkin's purple*, while engaged in unsuccessful attempts to synthesize quinine. He obtained the dye by oxidizing aniline containing *o*- and *p*-toluidines as impurities. Other discoveries of this kind followed soon after, and a major industry grew up in the field of coal-tar chemistry.

The earliest colors were prepared from aniline and for many years all coal-tar dyes were called aniline colors, irrespective of their origin. The coal-tar dyes include more than a dozen well-defined groups among which are *nitroso-dyes, nitro-dyes, azo-dyes, oxazines, thiazines, pyrazolones, xanthenes, indigoids, anthraquinones, acridines, rosanilines, phthaleins, quinolines* and others. These in turn are classified, according to their method of use, as *acid dyes* and *basic dyes*, or *direct dyes* and *mordant dyes.*

Certain structural elements in organic molecules, called *chromophore* groups, give color to the molecules, eg, azo (—N=N—), nitroso (—N=O), nitro (—$NO_2$), azoxy (—N=N—O—), carbonyl (>C=O) and ethylene (>C=C<). Other such combinations augment the chromophore groups, eg, methoxy, hydroxy and amino groups and are known as *auxochromes.*

**Stability**—Most dyes are relatively unstable chemicals due to their unsaturated structures. They are subject to fading due to light, metals, heat, microorganisms, oxidizing and re-

ducing agents plus strong acids and bases. In tablets, fading may appear as spotting and specking.

**Uses**—Most synthetic coloring principles are used in coloring fabrics and for various artistic purposes. They also find application as indicators, bacteriological stains, diagnostic aids, reagents in microscopy, etc.

Many coal-tar dyes originally were used in foodstuffs and beverages without careful selection or discrimination between those that were harmless and those that were toxic and without any supervision as to purity or freedom from poisonous constituents derived from their manufacture.

After the passage of the Food and Drugs Act in 1906, the US Department of Agriculture established regulations by which a few colors came to be known as *permitted colors.* Certain of these colors may be used in foods, drugs and cosmetics, but only after certification by the FDA that they meet certain specifications. From this list of permitted colors may be produced, by skillful blending and mixing, other colors that may be used in foods, beverages and pharmaceutical preparations. Blends of certified dyes must be recertified.

The word "permitted" is used in a restricted sense. It does not carry with it the right to use colors for purposes of deception, even though they are "permitted" colors, for all food laws have clauses prohibiting the coloring of foods and beverages in a manner so as to conceal inferiority or to give a false appearance of value.

The certified colors are classified into three groups: FD&C dyes which legally may be used in foods, drugs and cosmetics, D&C dyes which legally may be used in drugs and cosmetics and External D&C dyes which legally may be used only in externally applied drugs and cosmetics. There are specific limits for the pure dye, sulfated ash, ether extractives, soluble and insoluble matter, uncombined intermediates, oxides, chlorides and sulfates. As the use status of these colors is subject to change, the latest regulations of the FDA should be consulted to determine how they may be used—especially since several FD&C dyes formerly widely used have been found to be carcinogenic even when "pure" and, therefore, have been banned from use.

The Coal-Tar Color Regulations specify that the term "externally applied drugs and cosmetics" means drugs and cosmetics which are applied only to external parts of the body and not to the lips or any body surface covered by mucous membrane. No certified dye, regardless of its category, legally may be used in any article which is to be applied to the area of the eye.

Lakes are calcium or aluminum salts of certified dyes extended on a substrate of alumina. They are insoluble in water and organic solvents, hence are used to color powders, pharmaceuticals, foods, hard candies and food packaging.

The application of dyes to pharmaceutical preparations is an art that can be acquired only after an understanding of the characteristics of dyes and knowledge of the composition of the products to be colored has been obtained. Specific rules for the choice or application of dyes to pharmaceutical preparations are difficult to formulate. Each preparation may present unique problems.

Preparations which may be colored include most liquid pharmaceuticals, powders, ointments and emulsions. Some general hints may be offered in connection with solutions and powders, but desired results usually can be obtained only by a series of trials. In general, an inexperienced operator tends to use a much higher concentration of the dye than is necessary, resulting in a dull color. The amount of dye present in any pharmaceutical preparation should be of a concentration high enough to give the desired color and low enough to prevent toxic reactions and permanent staining of fabrics and tissues.

**Liquids (Solutions)**—The dye concentration in liquid preparations and solutions usually should come within a range of 0.0005% (1 in 200,000) and 0.001% (1 in 100,000), depending upon the depth of color wanted and the thickness of column to be viewed in the container. With some dyes, concentrations as low as 0.0001% (1 in 1,000,000) may have a distinct tinting effect. Dyes are used most conveniently in the form of stock solutions.

**Powders**—White powders usually require the incorporation of 0.1% (1 in 1000) of a dye to impart a pastel color. The dyes may be incorporated into the powder by dry-blending in a ball mill or, on a small scale, with a mortar and pestle. The dye is incorporated by trituration and geometric dilution. Powders also may be colored evenly by adding a solution of the dye in alcohol or some other volatile solvent having only a slight solvent action on the powder being colored. When this procedure is employed, the solution is added in portions, with thorough mixing after each addition, after which the solvent is allowed to evaporate from the mixture.

Many of the syrups and elixirs used as flavoring and diluting agents are colored. When such agents are used no further coloring matter is necessary. The use of colored flavoring agents is discussed in a subsequent section. However, when it is desired to add color to an otherwise colorless mixture, one of the agents described in the first section may be used.

**Incompatibilities**—FD&C dyes are mainly anionic (sodium salts), hence are incompatible with cationic substances. Since the concentrations of these substances are generally very low, no precipitate is evident. Polyvalent ions such as calcium, magnesium and aluminum also may form insoluble compounds with dyes. A pH change may cause the color to change. Acids may release the insoluble acid form of the dye.

**Caramel** —see RPS-18, page 1290.

## *Flavoring Agents*

### Flavor

The word flavor refers to a mixed sensation of taste, touch, smell, sight and sound, all of which combine to produce an infinite number of gradations in the perception of a substance. The four primary tastes—*sweet*, *bitter*, *sour* and *saline*—appear to be the result partly of physicochemical and partly of psychological action. Taste buds (Fig 1), located mainly on the tongue, contain very sensitive nerve endings that react, in the presence of moisture, with the flavors in the mouth and as a result of physicochemical activity electrical impulses are produced and transmitted via the seventh, ninth and tenth cranial nerves to the areas of the brain which are devoted to the perception of taste. Some of the taste buds are specialized in their function, giving rise to areas on the tongue which are sensitive to only one type of taste. The brain, however, usually perceives taste as a composite sensation, and accordingly the components of any flavor are not readily discernible. Children have more taste buds than adults, hence are more sensitive to tastes.

Taste partly depends on the ions which are produced in the mouth, but psychologists have demonstrated that sight (color) and sound also play a definite role when certain reflexes

**Fig 1.** Upper Surface of the tongue. a: Taste receptors for all tastes; b: sweet, salty and sour; c: salty and sour; d: sour only; e: no taste sensation; f: sweet and sour; g: bitter, sweet and sour (adapted from Crocker EC: *Flavor,* McGraw-Hill, New York, 22, 1945).

become conditioned through custom and association of sense perceptions. Thus, in the classic experiments of Pavlov demonstrating "conditioned reflexes," the ringing of a bell or the showing of a circle of light caused the gastric juices of a dog to flow although no food was placed before it, and much of the enjoyment derived from eating celery is due to its crunchy crispness as the fibrovascular bundles are crushed. The effect of color is just as pronounced; oleomargarine is unpalatable to most people when it is uncolored, but once the dye has been incorporated gourmets frequently cannot distinguish it from butter. Color and taste must coincide, eg, cherry flavor is associated with a red color.

A person suffering from a head cold finds his food much less palatable than usual because his sense of smell is impaired, and, if the nostrils are held closed, raw onions taste sweet and it is much easier to ingest castor oil and other nauseating medicines. The volatility of a substance is an important factor that is influenced by the warmth and moisture of the mouth since the more volatile a compound, the more pronounced its odor. The sense of smell detects very minute amounts of material and is usually much more sensitive in detecting the presence of volatile chemicals, but the tongue is able to detect infinitesimal amounts of some vapors if it is protruded from the mouth so that solution of the gases in the saliva may take place. In this manner traces of sulfur dioxide can be detected in the air since it dissolves in the saliva and creates a sour taste.

Flavors described as hot are those that exert a mild counterirritant effect on the mucosa of the mouth, those that are astringent and pucker the mouth contain tannins and acids that produce this effect by reacting with the lining of the mouth and wines possess a bouquet due to the odor of the volatile constituents. Indian turnip (Jack-in-the-pulpit) owes its flavor largely to the stinging sensation caused by the minute acicular crystals of calcium oxalate which penetrate the mucous membrane.

Other physiological and physical factors that also may affect taste are coarseness or grittiness due to small particles, eg, ion-exchange resins. Antidiarrheal preparations have a chalky taste. Menthol imparts a cool taste because it affects the coldness receptors. Mannitol gives a cool sensation when it dissolves because its negative of heat of solution will cause the temperature to drop. For this reason, mannitol often is used as the base for chewable tablets.

There is a definite threshold of taste for every substance, which varies somewhat with the individual and with the environment. The experienced chef tastes his delicacies at the temperature at which they will be served since heat and cold alter the flavor of many preparations. Thus, lemon loses its sour taste entirely at an elevated temperature and other flavors become almost nonvolatile, tasteless and odorless when cooled sufficiently. In addition to the influence of temperature, the sensitivity of each individual must be considered. For example, it has been determined by experiment that the amount of sugar that can just be detected by the average individual is about 7 mg. However, this amount cannot be tasted by some and it is definitely sweet to others.

People are more sensitive to odor than to taste. There are about 10,000 to 30,000 identifiable scents, of which the average person can identify about 4000. Women are more sensitive to odors than men. Additional insights can be obtained by reading Cagan RH, Kare MR: *Biochemistry of Taste and Olfaction*, Academic, NY 1981, and Beidler LM, ed: *Handbook of Sensory Physiology*, vol IV, pts 1 and 2, Springer-Verlag, Berlin 1971.

**Preservation of Flavors**—Most monographs of official products contain specific directions for storage. Proper methods of storage are essential to prevent deterioration which in many instances results in destruction of odor and taste. Under adverse conditions undesirable changes occur due to one or a combination of the following: enzymatic activity, oxidation, change in moisture content, absorption of odors, activity of microorganisms and effects of heat and light. In certain products some of the changes wrought by these factors are desirable, as when esters are formed due to the activity of enzymes and when blending and mellowing results from the interchange of the radicals of esters (*transesterification*).

One method for protecting readily oxidizable substances, such as lemon oil, from deteriorating, and thus preserving their original delicate flavor, is to microencapsulate them by spray-drying. The capsules containing the flavors then are enclosed in various packaged products (eg, powdered gelatins) or tablets which are flavored deliciously when the capsule is disintegrated by mixing and warming with water or saliva.

**Correlation of Chemical Structure with Flavor and Odor**—The compounds employed as flavors in vehicles vary considerably in their chemical structure, ranging from simple esters (methyl salicylate), alcohols (glycerin) and aldehydes (vanillin) to carbohydrates (honey) and the complex volatile oils (anise oil). Synthetic flavors of almost any desired type are now available. These frequently possess the delicate flavor and aroma of the natural products and also the desirable characteristics of stability, reproducibility and comparatively low cost. Synthetic products such as cinnamaldehyde and benzaldehyde, first officially recognized when several of the essential oils became scarce during World War II, have been used widely.

There is a close relationship between chemical structure and taste. Solubility, the degree of ionization and the type of ions produced in the saliva definitely influence the sensation interpreted by the brain.

Sour taste is caused by hydrogen ions and it is proportional to the hydrogen-ion concentration and the lipid solubility of the compound. It is characteristic of acids, tannins, alum, phenols and lactones. Saltiness is due to simultaneous presence of anions and cations, eg, KBr, $NH_4Cl$ and sodium salicylate. High-molecular-weight salts may have a bitter taste. Sweet taste is due to polyhydroxy compounds, polyhalogenated aliphatic compounds and α-amino acids. Amino and amide groups, especially if the positive effect is balanced by the proximity of a negative group, may produce a sweet taste. Sweetness increases with the number of hydroxy groups, possibly due to increase in solubility. Imides such as saccharin and sulfamates such as cyclamates are intensely sweet. Cyclamates have been removed from the market because they reportedly cause bladder tumors in rats. Free bases such as alkaloids and amides such as amphetamines give bitter tastes. Polyhydroxy compounds with a molecular weight greater than 300, halogenated substances and aliphatic thio compounds also may have bitter tastes. Unsaturation frequently bestows a sharp, biting odor and taste upon compounds.

No precise relationship between chemical structure and odor has been found. There are no primary odors, and odors blend into each other. Polymerization reduces or destroys odor; high valency gives odor and unsaturation enhances odor. A tertiary carbon atom often will give a camphoraceous odor, esters and lactones have a fruity odor and ketones have a pleasant odor. Strong odors often are accompanied by volatility and chemical reactivity.

## Selection of Flavors

The proper selection of flavors for disguising nauseating medicines aids in their ingestion. Occasionally, sensitive patients have become nauseated sufficiently to vomit at the thought of having to take disagreeable medication, and it is particularly difficult to persuade children to continue to use and retain distasteful preparations. There is a need to know the allergies and idiosyncrasies of the patient; thus, it is foolish to use a chocolate-flavored vehicle for the patient who dislikes the flavor or who is allergic to it, notwithstanding the fact that this flavor is generally acceptable.

## Flavoring Methodology

Each flavoring problem is unique and requires an individual solution. The problem of flavoring is further complicated because flavor and taste depend on individual preferences. In solving flavoring problems the following techniques have been used:

**Blending**—Fruit flavors blend with sour taste; bitter tastes can be blended with salty, sweet and sour tastes; salt reduces sourness and increases sweetness; chemicals such as vanillin, monosodium glutamate and benzaldehyde are used for blending.

**Overshadow**—Addition of a flavor whose intensity is longer and stronger than the obvious taste, eg, methyl salicylate, glycyrrhiza and oleoresins.

**Physical**—Formation of insoluble compounds of the offending drug, eg, sulfonamides; emulsification of oils; effervescence, eg, magnesium citrate solution; high viscosity of fluids to limit contact of drug with the tongue, and mechanical procedures such as coating tablets, are physical methods to reduce flavoring problems.

**Chemical**—Adsorption of the drug on a substrate, or formation of a complex of the drug with ion-exchange resins or complexing agents.

**Physiological**—The taste buds may be anesthetized by menthol or mint flavors.

Flavors, as used by the pharmacist in compounding prescriptions, may be divided into four main categories according to the type of taste which is to be masked, as follows:

**Salty Taste**—Cinnamon syrup has been found to be the best vehicle for ammonium chloride, and other salty drugs such as sodium salicylate and ferric ammonium citrate. In a study of the comparative efficiency of flavoring agents for disguising salty taste, the following additional vehicles were arranged in descending order of usefulness: orange syrup, citric acid syrup, cherry syrup, cocoa syrup, wild cherry syrup, raspberry syrup, glycyrrhiza elixir, aromatic elixir and glycyrrhiza syrup. The last-named is particularly useful as a vehicle for the salines by virtue of its colloidal properties and the sweetness of both glycyrrhizin and sucrose.

**Bitter Taste**—Cocoa syrup was found to be the best vehicle for disguising the bitter taste of quinine bisulfate, followed, in descending order of usefulness, by raspberry syrup, cocoa syrup, cherry syrup, cinnamon syrup, compound sarsaparilla syrup, citric acid syrup, licorice syrup, aromatic elixir, orange syrup and wild cherry syrup.

**Acrid or Sour Taste**—Raspberry syrup and other fruit syrups are especially efficient in masking the taste of sour substances such as hydrochloric acid. Acacia syrup and other mucilaginous vehicles are best for disguising the acrid taste of substances, such as capsicum, since they tend to form a colloidal protective coating over the taste buds of the tongue. Tragacanth, unlike acacia, may be used in an alcoholic vehicle.

**Oily Taste**—Castor oil may be made palatable by emulsifying with an equal volume of aromatic rhubarb syrup or with compound sarsaparilla syrup. Cod liver oil is disguised effectively by adding wintergreen oil or peppermint oil. Lemon, orange and anise or combinations of these are also useful. It is better to mix most of the flavor with the oil before emulsifying it, and then the small remaining quantity can be added after the primary emulsion is formed.

Those flavors that are most pleasing to the majority of people are associated with some stimulant of a physical or physiological nature. This may be a central nervous stimulant such as caffeine, which is the reason so many enjoy tea and coffee as a beverage, or it may be a counterirritant such as one of the spices that produce a "biting" sensation or an agent which "tickles" the throat such as soda water. Sherry owes its sharp flavor to its acetaldehyde content, and some of the volatile oils contain terpenes that are stimulating to the mucous surfaces.

## Selection of Vehicles

Too few pharmacists realize the unique opportunity they have in acquainting physicians with a knowledge of how to increase both the palatability and efficacy of their prescribed medicines through the judicious selection of vehicles. Because of the training a pharmacist receives, his knowledge of the characteristics of various pharmaceuticals and therapeutic agents and his technique and skill in preparing elegant preparations are well-developed, so that he is qualified admirably to advise concerning the proper use of vehicles.

A large selection of flavors is available as well as a choice of colors, so that one may prescribe a basic drug for a prolonged period, but by changing the vehicle from time to time, the taste and appearance are so altered that the patient does not tire of the prescription or show other psychological reactions to it.

The statement of the late Dr Bernard Fantus that "the best solvent is the best vehicle" helps to explain the proper use of a flavoring vehicle. For example, a substance that is soluble in alcohol, eg, phenobarbital, will not leave an alcoholic vehicle readily to dissolve in the aqueous saliva.

**Waters**—These are the simplest of the vehicles and are available with several flavors. They contain no sucrose, a fact to be considered at times, since sucrose under certain circumstances may be undesirable. They are likewise nonalcoholic, another fact which frequently influences vehicle selection.

**Elixirs**—These have added sweetness that waters lack, and they usually contain alcohol, which imparts an added sharpness to the flavor of certain preparations, making the latter more pleasing to the taste. Elixirs are suitable for alcohol-soluble drugs.

**Syrups**—These vehicles, like elixirs, offer a wide selection of flavors and colors from which to choose. Their specific value, however, lies particularly in the fact that they are intensely sweet and contain little or no alcohol, a combination which makes them of singular value as masking agents for water-soluble drugs.

Vehicles consisting of a solution of pleasantly flavored volatile oils in syrup or glycerin (1:500) have been employed successfully in producing uniform and stable preparations. These vehicles are prepared by adding 2 mL of the volatile oil, diluted with 6 mL of alcohol, to 500 mL of glycerin or syrup, which has been warmed gently. The solution is added a little at a time with continuous shaking, and then sufficient glycerin or syrup is added to make 1000 mL, and mixed well.

Alcohol solutions of volatile oils are sometimes used as "stock solutions" for flavoring pharmaceuticals.

A listing of substances, most of them official, used as flavors, flavored vehicles or as sweeteners, is given in Table 1. Additional information on flavoring ingredients may be obtained in Furia TE, Bellanca A: *Fenaroli's Handbook of Flavor Ingredients*, Chemical Rubber, Cleveland, 1971.

**Acacia Syrup**—page 1393.

**Anethole**—see RPS-18, page 1292.

### Anise Oil

Aniseed Oil; Star Anise Oil

The volatile oil distilled with steam from the dried, ripe fruit of *Pimpinella anisum* Linné (Fam *Umbelliferae*) or from the dried, ripe fruit of *Illicium verum* Hooker filius (Fam *Magnoliaceae*).

*Note—If solid material has separated, carefully warm the oil until it is completely liquefied, and mix it before using.*

**Constituents**—The official oil varies somewhat in composition, depending upon whether it was obtained from *Pimpinella anisum* or the star anise, *Illicium verum*. *Anethole* is the chief constituent of both oils, occurring to the extent of 80 to 90%. *Methyl chavicol*, an isomer of anethole, and *anisic ketone* [$C_{10}H_{12}O_2$] also are found in both oils, as are small amounts of many other constituents.

**Description**—Colorless or pale yellow, strongly refractive liquid, having the characteristic odor and taste of anise; specific gravity 0.978 to 0.988; congeals not below 15°.

**Solubility**—Soluble in 3 volumes of 90% alcohol.

**Uses**—Extensively as a *flavoring agent*, particularly for licorice candies. It has been given as a *carminative* in a dose of about 0.1 mL.

**Aromatic Elixir**—page 1394.

**Aromatic Elixir, Red**—see RPS-15, page 1240.

**Table 1—Flavoring Agents**

| | |
|---|---|
| Acacia syrup | Lavender oil |
| Anethole | Lemon oil |
| Anise oil | Lemon tincture |
| Aromatic elixir | Mannitol |
| Benzaldehyde | Methyl salicylate |
| Benzaldehyde elixir, compound | Nutmeg oil |
| Caraway | Orange, bitter, elixir |
| Caraway oil | Orange, bitter, oil |
| Cardamom oil | Orange flower oil |
| Cardamom seed | Orange flower water |
| Cardamom spirit, compound | Orange oil |
| Cardamom tincture, compound | Orange peel, bitter |
| Cherry juice | Orange peel, sweet, tincture |
| Cherry syrup | Orange spirit, compound |
| Cinnamon | Orange syrup |
| Cinnamon oil | Peppermint |
| Cinnamon water | Peppermint oil |
| Citric acid | Peppermint spirit |
| Citric acid syrup | Peppermint water |
| Clove oil | Phenylethyl alcohol |
| Cocoa | Raspberry juice |
| Cocoa syrup | Raspberry syrup |
| Coriander oil | Rosemary oil |
| Dextrose | Rose oil |
| Eriodictyon | Rose water |
| Eriodictyon fluidextract | Rose water, stronger |
| Eriodictyon syrup, aromatic | Saccharin |
| Ethyl acetate | Saccharin calcium |
| Ethyl vanillin | Saccharin sodium |
| Fennel oil | Sarsaparilla syrup, compound |
| Ginger | Sorbitol solution |
| Ginger fluidextract | Spearmint |
| Ginger oleoresin | Spearmint oil |
| Glucose | Sucrose |
| Glycerin | Syrup |
| Glycyrrhiza | Thyme oil |
| Glycyrrhiza elixir | Tolu balsam |
| Glycyrrhiza extract | Tolu balsam syrup |
| Glycyrrhiza extract, pure | Vanilla |
| Glycyrrhiza fluidextract | Vanilla tincture |
| Glycyrrhiza syrup | Vanillin |
| Honey | Wild cherry syrup |
| Iso-Alcoholic elixir | |

### Benzaldehyde

Artificial Essential Almond Oil

Benzaldehyde [100-52-7] $C_7H_6O$ (106.12).

**Preparation**—By the interaction of benzal chloride with lime in the resence of water. Benzal chloride is obtained by treating boiling toluene with chlorine.

**Description**—Colorless, strongly refractive liquid, having an odor resembling that of bitter almond oil, and a burning aromatic taste; affected by light; specific gravity 1.041 to 1.046; boils about 180°, solidifies about −56.5° and on exposure to air it gradually oxidizes to benzoic acid.

**Solubility**—Dissolves in about 350 volumes of water; miscible with alcohol, ether, chloroform or fixed and volatile oils.

**Uses**—In place of bitter almond oil for *flavoring* purposes; it is much safer than the latter because it contains no hydrocyanic acid. It also is used extensively in *perfumery* and in the manufacture of dyestuffs and many other organic compounds, such as aniline, acetanilid or mandelic acid.

**Compound Benzaldehyde Elixir**—*Preparation:* Dissolve benzaldehyde (0.5 mL) and vanillin (1 g) in alcohol (50 mL); add syrup (400 mL), orange flower water (150 mL) and sufficient purified water, in several portions, shaking the mixture thoroughly after each addition, to make the product measure 1000 mL; then filter, if necessary, until the product is clear. *Alcohol Content:* 3 to 5%. *Uses:* A useful vehicle for administering bromides and other salts, especially when a low alcoholic content is desired.

**Camphor Water**—see RPS-13, page 436.

**Caraway**—see RPS-18, page 1293.

**Caraway Oil**—see RPS-18, page 1293.

### Cardamom Seed

Cardamom Fruit; Cardamom; Ceylon or Malabar Cardamom

The dried ripe seed of *Elettaria cardamomum* (Linné) Maton (Fam. *Zingiberaceae*).

*It should be removed recently from the capsule.*

**Constituents**—A *volatile oil*, the yield of which is 1.3% from Malabar Ceylon Seeds and 2.6% from Mysore-Ceylon Seeds. *Fixed oil* is present to the extent of 10%, also starch, mucilage, etc.

**Uses**—A *flavor*. For many years it was employed empirically as a *carminative*.

**Cardamom Oil**—The volatile oil distilled from the seed of *Elettaria cardamomum* (Linné) Maton (Fam *Zingiberaceae*). Varieties of the oil contain *d-α-terpineol* [$C_{10}H_{17}OH$] both free and as the acetate, 5 to 10% *cineol* [$C_{10}H_{18}O$] and *limonene* [$C_{10}H_{16}$]. The Ceylon Oil, however, contains the alcohol *4-terpineol (4-carbomenthenol)* [$C_{10}H_{17}OH$], the terpenes *terpinene* and *sabinene*, and *acetic* and *formic acids*, probably combined as esters. *Description and Solubility:* Colorless or very pale yellow liquid possessing the aromatic, penetrating and somewhat camphoraceous odor of cardamom, and a persistently pungent, strongly aromatic taste; affected by light; specific gravity 0.917 to 0.947. Miscible with alcohol; dissolves in 5 volumes of 70% alcohol. *Uses:* A *flavor*.

**Cardamom Tincture, Compound**—see RPS-18, page 1302.

**Cherry Juice**—see RPS-18, page 1320.

**Cherry Syrup**—page 1393.

### Cinnamon

Saigon Cinnamon; True Cinnamon; Saigon Cassia

The dried bark of *Cinnamomum loureirii* Nees (Fam. *Lauraceae*).

It contains, in each 100 g, not less than 2.5 mL of volatile oil.

**Uses**—A *flavoring agent*. Formerly, it was used as a carminative.

**Cinnamon Oil** [Cassia Oil; Oil of Chinese Cinnamon]—The volatile oil distilled with steam from the leaves and twigs of *Cinnamomum cassia* (Nees) Nees ex Blume (Fam *Lauraceae)*, rectified by distillation; contains not less than 80%, by volume, of the total aldehydes of cinnamon oil. Cinnamaldehyde is the chief constituent. *Description and Solubility:* Yellowish or brownish liquid, becoming darker and thicker on aging or exposure to the air, and having the characteristic odor and taste of cassia cinnamon; specific gravity 1.045 to 1.063. Soluble in an equal volume of alcohol, 2 volumes of 70% alcohol or an equal volume of glacial acetic acid. *Uses:* A *flavor*. It formerly was used in a dose of 0.1 mL for flatulent colic.

**Cocoa** —see RPS-18, page 1293.

**Cocoa Syrup**—page 1393.

**Coriander**—page 1391.

**Coriander Oil**—see RPS-18 page 1294.

**Denatonium Benzoate**—page 1409.

**Eriodictyon**—see RPS-18, page 1294.

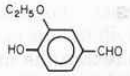
**Eriodictyon Fluidextract**—see RPS-18, page 1294.

**Eriodictyon Syrup, Aromatic**—see RPS-18, page 1301.

**Ethyl Acetate**—see RPS-18, page 1294.

### Ethyl Vanillin

Benzaldehyde, 3-ethoxy-4-hydroxy-, Bourbanal; Ethovan; Vanillal; Vanirome




3-Ethoxy-4-hydroxybenzaldehyde [121-32-4] $C_9H_{10}O_3$ (166.18).

**Preparation**—By reacting *o*-ethoxyphenol with formaldehyde and *p*- nitrosodimethylaniline in the presence of aluminum and water.

**Description**—Fine, white or slightly yellowish crystals; odor and taste

similar to vanillin; affected by light; solutions are acid to litmus; melts about 77°.

**Solubility**—1 g in about 100 mL water at 50°; freely soluble in alcohol, chloroform, ether or solutions of fixed alkali hydroxides.

**Uses**—A *flavor*, like vanillin, but stronger.

### Eucalyptus Oil

The volatile oil distilled with steam from the fresh leaf of *Eucalyptus globulus* Labillardière or of some other species of *Eucalyptus* L'Heritier (Fam *Myrtaceae*). It contains not less than 70% of $C_{10}H_{18}O$ (eucalyptol).

**Constituents**—The most important constituent is *eucalyptol (cineol)*. Other compounds include *d-a-pinene, globulol, pinocarveol, pinocarvone* and several aldehydes.

**Description**—Colorless or pale yellow liquid, having a characteristic, aromatic, somewhat camphoraceous odor, and a pungent, spicy, cooling taste; specific gravity 0.905 to 0.925 at 25°.

**Solubility**—Soluble in 5 volumes of 70% alcohol.

**Uses**—A *flavoring agent* and an *expectorant* in chronic bronchitis. It also has *bacteriostatic* properties. This oil may be toxic.

### Fennel Oil

The volatile oil distilled with steam from the dried ripe fruit of *Foeniculum vulgare* Miller (Fam *Umbelliferae*).

*Note—If solid material has separated, carefully warm the oil until it is completely liquefied, and mix it before using.*

**Constituents**—*Anethole* [$C_{10}H_{12}O$] is the chief constituent, occurring to the extent of 50 to 60%. Some of the other constituents are *d*-pinene, phellandrene, dipentene, fenchone, methylchavicol, anisaldehyde and anisic acid.

**Description**—Colorless or pale yellow liquid, having the characteristic odor and taste of fennel; specific gravity 0.953 to 0.973; congealing temperature is not below 3°.

**Solubility**—Soluble in 8 volumes of 80% alcohol or in 1 volume of 90% alcohol.

**Uses**—A flavoring agent. It formerly was employed in a dose of 0.1 mL as a *carminative*.

### Glycyrrhiza

Licorice Root; Liquorice Root; Sweetwood; Italian Juice Root; Spanish Juice Root

The dried rhizome and roots of *Glycyrrhiza glabra* Linné, known in commerce as Spanish Licorice, or of *Glycyrrhiza glabra* Linné var *glandulifera* Waldstein et Kitaibel, known in commerce as Russian Licorice, or of other varieties of *Glycyrrhiza glabra* Linné, yielding a yellow and sweet wood (Fam. *Leguminosae*).

**Constituents**—This well-known root contains 5 to 7% of the sweet principle *glycyrrhizin*, or *glycyrrhizic acid* which is 50 times as sweet as cane sugar. There also is present an oleoresinous substance to which its slight acridity is due. If alcohol or an alkali is used as a menstruum for the root and the preparation not treated to deprive it of acridity, it will have a disagreeable aftertaste. For this reason boiling water is used for its extraction in both the extract and the fluidextract.

**Description**—The USP/NF provides descriptions of *Unground Spanish and Russian Glycyrrhizas, Histology* and *Powdered Glycyrrhiza*.

**Uses**—Valuable in pharmacy chiefly for its *sweet flavor*. It is one of the most efficient substances known for masking the taste of bitter substances, like quinine. Acids precipitate the glycyrrhizin and should not be added to mixtures in which glycyrrhiza is intended to mask disagreeable taste. Most of the imported licorice is used by tobacco manufacturers to flavor tobacco. It also is used in making candy.

**Pure Glycyrrhiza Extract** [Pure Licorice Root Extract]—*Preparation:* Moisten 1000 g of glycyrrhiza, in granular powder, with boiling water, transfer it to a percolator, and percolate with boiling water until the glycyrrhiza is exhausted. Add enough diluted ammonia solution to the percolate to impart a distinctly ammoniacal odor, then boil the liquid under normal atmospheric pressure until it is reduced to a volume of about 1500 mL. Filter the liquid, and immediately evaporate the filtrate until the residue has a pilular consistency. Pure extract of glycyrrhiza differs from the commercial extract in that it is almost completely soluble in aqueous mixtures. The large amount of filler used in the commercial extract to give it firmness renders it unfit to use as a substitute for the pure extract. *Description:* Black, pilular mass having a characteristic, sweet taste. *Uses:* A *flavoring agent*. One of the ingredients in *Aromatic Cascara Sagrada Fluidextract*.

**Glycyrrhiza Fluidextract** [Licorice Root Fluidextract; Liquid Extract of Liquorice]—*Preparation:* To 1000 g of coarsely ground glycyrrhiza add about 3000 mL of boiling water, mix and allow to macerate in a suitable, covered percolator for 2 hr. Then allow the percolation to proceed at a rate of 1 to 3 mL/min, gradually adding boiling water until the glycyrrhiza is exhausted. Add enough diluted ammonia solution to the percolate to impart a distinctly ammoniacal odor, then boil the liquid actively under normal atmospheric pressure until it is reduced to a volume of about 1500 mL. Filter the liquid, evaporate the filtrate on a steam bath until the residue measures 750 mL, cool, gradually add 250 mL of alcohol and enough water to make the product measure 1000 mL and mix. *Alcohol Content:* 20 to 24%, by volume. *Uses:* A pleasant *flavor* for use in syrups and elixirs to be employed as vehicles and correctives.

**Glycyrrhiza Elixir**—page 1394.
**Glycyrrhiza Syrup**—page 1393.
**Honey**—page 1416.
**Hydriodic Acid Syrup**—page 1393.
**Iso-Alcoholic Elixir**—page 1416.

### Lavender Oil

Lavender Flowers Oil

The volatile oil distilled with steam from the fresh flowering tops of *Lavandula officinalis* Chaix ex Villars (*Lavandula vera* DeCandolle) (Fam *Labiatae*) or produced synthetically. It contains not less than 35% of esters calculated as $C_{12}H_{20}O_2$ (linalyl acetate).

**Constituents**—It is a product of considerable importance in perfumery. *Linalyl acetate* is the chief constituent. *Cineol* appears to be a normal constituent of English oils. Other constituents include *amyl alcohol, d-borneol* (small amount); *geraniol, lavandulol* ($C_{10}H_{18}O$); *linaloöl; nerol; acetic, butyric, valeric,* and *caproic acids* (as esters); traces of *d-pinene, limonene* (in English oils only) and the sesquiterpene *caryophyllene; ethyl n-amyl ketone;* an aldehyde (probably *valeric aldehyde*) and *coumarin*.

**Description**—Colorless or yellow liquid, having the characteristic odor and taste of lavender flowers; specific gravity 0.875 to 0.888.

**Solubility**—1 volume in 4 volumes of 70% alcohol.

**Uses**—Primarily as a *perfume*. It formerly was used in doses of 0.1 mL as a *carminative*.

### Lemon Oil

The volatile oil obtained by expression, without the aid of heat, from the fresh peel of the fruit of *Citrus limon* (Linné) Burmann filius (Fam *Rutaceae*), with or without the previous separation of the pulp and the peel. The total aldehyde content, calculated as citral ($C_{10}H_{16}O$), is 2.2–3.8% for California-type oil, and 3.0–5.5% for Italian-type oil.

*Note—Do not use oil that has a terebinthine odor.*

**Constituents**—From the standpoint of odor and flavor, the most noteworthy constituent is the aldehyde *citral*, which is present to the extent of about 4%. About 90% of *d-limonene* is present; small amounts of *l-α-pinene, β-pinene, camphene, β-phellandrene* and γ-terpinene also occur. About 2% of a solid, nonvolatile substance called *citroptene, limettin* or *lemon-camphor*, which is dissolved out of the peel, also is present. In addition, there are traces of several other compounds: *α-terpineol;* the *acetates of linaloöl* and *geraniol; citronellal, octyl* and *nonyl aldehydes;* the sesquiterpenes *bisabolene* and *cadinene* and the ketone *methylheptenone*.

When fresh, the oil has the fragrant odor of lemons. Because of the instability of the terpenes present, the oil readily undergoes deterioration by oxidation, acquiring a terebinthinate odor.

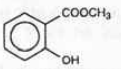
**Description**—Pale yellow to deep yellow or greenish yellow liquid, with the characteristic odor and taste of the outer part of fresh lemon peel; specific gravity 0.849 to 0.855.

**Solubility**—In 3 volumes of alcohol; miscible in all proportions with dehydrated alcohol, carbon disulfide or glacial acetic acid.

**Uses**—A *flavor* in pharmaceutical preparations and in certain candies and foods.

### Methyl Salicylate

Benzoic acid, 2-hydroxy-, methyl ester; Gaultheria Oil; Wintergreen Oil; Betula Oil; Sweet Birch Oil; Teaberry Oil; Artificial Wintergreen Oil; Synthetic Wintergreen Oil




Methyl salicylate [119-36-8] $C_6H_4(OH)COOCH_3$ (152.15); produced synthetically or obtained by maceration and subsequent distillation with

steam from the leaves of *Gaultheria procumbens* Linné (Fam *Ericaceae*) or from the bark of *Betula lenta* Linné (Fam *Betulaceae*).

*Note*—It must be labeled to indicate whether it was made synthetically or distilled from either of the plants mentioned above.

**Preparation**—Found naturally in gaultheria and betula oils and in many other plants but the commercial product is usually synthetic, made by esterifying salicylic acid with methyl alcohol in the presence of sulfuric acid and distilling.

**Description**—Colorless, yellowish or reddish liquid, having the characteristic odor and taste of wintergreen; specific gravity (synthetic), 1.180 to 1.185, (from gaultheria or betula), 1.176 to 1.182; boils between 219 and 224° with some decomposition.

**Solubility**—Slightly soluble in water; soluble in alcohol or glacial acetic acid.

**Uses**—A pharmaceutical necessity and *counterirritant* (local analgesic). As a pharmaceutical necessity, it is used to flavor the official *Aromatic Cascara Sagrada Fluidextract*, and it is equal in every respect to wintergreen oil or sweet birch oil. As a counterirritant, it is applied to the skin in the form of a liniment, ointment or cream; care should be exercised since salicylate is absorbed through the skin.

*Caution*—Because it smells like wintergreen candy, it is ingested frequently by children and has caused many fatalities. *Keep out of the reach of children.*

**Dose**—*Topical*, in lotions and solutions in **10** to **25%** concentration.

### Monosodium Glutamate

Glutamic acid, monosodium salt, monohydrate

[142-47-2] $C_5H_8NNaO_4 \cdot H_2O$ (187.13)

**Preparation**—From the fermentation of beet sugar or molasses or by hydrolysis of vegetable proteins.

**Description**—White, crystalline powder. The pentahydrate effloresces in air to form the monohydrate.

**Solubility**—Very soluble in water; sparingly soluble in alcohol.

**Uses**—Flavoring agent and perfume.

### Nutmeg Oil

Myristica Oil NF XIII; East Indian Nutmeg Oil;
West Indian Nutmeg Oil

The volatile oil distilled with steam from the dried kernels of the ripe seeds of *Myristica fragrans* Houttuyn (Fam *Myristicaceae*).

**Constituents**—It contains about 80% of *d-pinene* and *d-camphene*, 8% of *dipentene*, about 6% of the alcohols *d-borneol*, *geraniol*, *d-linaloöl* and *terpineol*, 4% of *myristicin*, 0.6% of *safrol*, 0.3% of *myristic acid* free and as esters, 0.2% of *eugenol* and *isoeugenol* and traces of the alcohol *terpineol-4*, a citral-like aldehyde and several acids, all present as esters.

**Description**—Colorless or pale yellow liquid having the characteristic odor and taste of nutmeg; specific gravity (East Indian Oil) 0.880 to 0.910, (West Indian Oil) 0.854 to 0.880.

**Solubility**—In an equal amount of alcohol; 1 volume of East Indian Oil in 3 volumes of 90% alcohol; 1 volume of West Indian Oil in 4 volumes of 90% alcohol.

**Uses**—Primarily as a *flavoring agent*. It is used for this purpose in *Aromatic Ammonia Spirit* (page 873). The oil also is employed as a *flavor* in foods, certain alcoholic beverages, dentifrices and tobacco; to some extent, it also is used in perfumery. It *formerly* was used as a *carminative* and *local stimulant* to the gastrointestinal tract in a dose of 0.03 mL. In overdoses, it acts as a narcotic poison. *This oil is very difficult to keep and even if slightly terebinthinate is unfit for flavoring purposes.*

### Orange Oil

Sweet Orange Oil

The volatile oil obtained by expression from the fresh peel of the ripe fruit of *Citrus sinensis* (Linné) Osbeck (Fam *Rutaceae*). The total aldehyde content, calculated as decanal ($C_{10}H_{20}O$), is 1.2 to 2.5%.

*Note—Do not use oil that has a terebinthine odor.*

**Constituents**—Consists of *d-limonene* to the extent of at least 90%; in the remaining 5 to 10% are the odorous constituents, among which, in samples of American origin, are *n-decylic aldehyde*, *citral*, *d-linaloöl*, *n-nonyl alcohol* and traces of *esters* of *formic*, *acetic*, *caprylic* and *capric* acids.

In addition to most of these compounds, Italian-produced oil contains *d-terpineol*, *terpinolene*, *α-terpinene* and *methyl anthranilate*.

Kept under the usual conditions it is very prone to decompose, and rapidly acquires a terebinthine odor.

**Description**—Intensely yellow orange or deep orange liquid, which possesses the characteristic odor and taste of the outer part of fresh sweet orange peel; specific gravity 0.842 to 0.846.

**Solubility**—Miscible with dehydrated alcohol or carbon disulfide; dissolves in an equal volume of glacial acetic acid.

**Uses**—A *flavoring agent* in elixirs and other preparations.

**Orange Flower Oil**—see RPS-18, page 1296.

**Orange Flower Water**—page 1392.

### Sweet Orange Peel Tincture

**Preparation**—From sweet orange peel, which is the outer rind of the nonartificially colored, fresh, ripe fruit of *Citrus sinensis* (Linné) Osbeck (Fam *Rutaceae*), by Process M (page 1522). Macerate 500 g of the sweet orange peel (*Note—Exclude the inner, white portion of the rind*) in 900 mL of alcohol, and complete the preparation with alcohol to make the product measure 1000 mL. Use talc as the filtering medium.

The white portion of the rind must not be used, as the proportion of oil, which is only in the yellow rind, is reduced, and the bitter principle *hesperidin* is introduced.

**Alcohol Content**—62 to 72%.

**Uses**—A *flavor*, used in syrups, elixirs and emulsions. This tincture was introduced to provide a delicate orange flavor direct from the fruit instead of depending upon orange oil which so frequently is terebinthinate and unfit for use. The tincture keeps well.

### Compound Orange Spirit

Contains, in each 100 mL, 25 to 30 mL of the mixed oils.

| | |
|---|---|
| **Orange Oil** | **200 mL** |
| **Lemon Oil** | **50 mL** |
| **Coriander Oil** | **20 mL** |
| **Anise Oil** | **5 mL** |
| **Alcohol,** a sufficient quantity, | |
| To make | **1000 mL** |

Mix the oils with sufficient alcohol to make the product measure 1000 mL.

**Alcohol Content**—65 to 75%.

**Uses**—A *flavor* for elixirs. An alcoholic solution of this kind permits the uniform introduction of small proportions of oils and also preserves orange and lemon oils from rapid oxidation. These two oils should be bought in small quantities by the pharmacist, since the spirit is made most satisfactorily from oils taken from bottles not previously opened. This will insure that delicacy of flavor which should always be characteristic of elixirs.

### Orange Syrup

Syrup of Orange Peel

Contains, in each 100 mL, 450 to 550 mg of citric acid ($C_6H_8O_7$).

| | |
|---|---|
| **Sweet Orange Peel Tincture** | **50 mL** |
| **Citric Acid** (anhydrous) | **5 g** |
| **Talc** | **15 g** |
| **Sucrose** | **820 g** |
| **Purified Water,** a sufficient quantity, | |
| To make | **1000 mL** |

Triturate the talc with the tincture and citric acid, and gradually add 400 mL of purified water. Then filter, returning the first portions of the filtrate until it becomes clear, and wash the mortar and filter with enough purified water to make the filtrate measure 450 mL. Dissolve the sucrose in this filtrate by agitation, without heating, and add enough purified water to make the product measure 1000 mL. Mix and strain.

Note—*Do not use syrup that has a terebinthine odor or taste or shows other indications of deterioration.*

**Alcohol Content**—2 to 5%.

**Uses**—A pleasant, acidic vehicle.

### Peppermint

American Mint; Lamb Mint; Brandy Mint

Consists of the dried leaf and flowering top of *Mentha piperita* Linné (Fam *Labiatae*).

**Uses**—The source of green color for *Peppermint Spirit* (page 902). The odor of fresh peppermint is due to the presence of about 2% of a volatile oil, much of which is lost on drying the leaves in air. It is

cultivated widely both in the US and France. It formerly was used as a carminative.

**Peppermint Oil**—The volatile oil distilled with steam from the fresh overground parts of the flowering plant of *Mentha piperita* Linné (Fam *Labiatae*), rectified by distillation and neither partially nor wholly dementholized. It yields not less than 5% of esters, calculated as menthyl acetate [$C_{12}H_{22}O_2$], and not less than 50% of total menthol [$C_{10}H_{20}O$], free and as esters. *Constituents:* This is one of the most important of the group of volatile oils. The chief constituent is *Menthol* (page 875) which occurs in the levorotatory form; its ester, *menthyl acetate*, is present in a much smaller amount. Other compounds which are present include the ketone *menthone, piperitone, α-pinene, l-limonene, phellandrene, cadinene, menthyl isovalerate, isovaleric aldehyde, acetaldehyde, menthofuran, cineol*, an unidentified *lactone* [$C_{10}H_{16}O_2$] and probably *amyl acetate*.

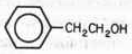
*Description and Solubility*—Colorless or pale yellow liquid, having a strong, penetrating odor of peppermint and a pungent taste, followed by a sensation of cold when air is drawn into the mouth; specific gravity 0.896 to 0.908. 1 volume dissolves in 3 volumes of 70% alcohol. *Uses:* A *flavoring agent, carminative, antiseptic* and *local anesthetic*. It also is used extensively as a *flavor* in candy, chewing gum, etc.

**Peppermint Spirit**—page 902.

**Peppermint Water**—page 1392.

### Phenylethyl Alcohol

Benzeneethanol; 2-Phenylethanol




Phenethyl alcohol [60-12-8] $C_8H_{10}O$ (122.17); occurs in a number of essential oils such as those of rose, neroli, hyacinth, carnation and others.

**Description**—Colorless liquid with a rose-like odor and a sharp, burning taste; solidifies at −27°; specific gravity 1.017 to 1.020.

**Solubility**—1 g in 60 mL water or < 1 mL alcohol, chloroform or ether; very soluble in fixed oils, glycerin or propylene glycol; slightly soluble in mineral oil.

**Uses**—Introduced for use as an antibacterial agent in ophthalmic solutions, but it is of limited effectiveness.

It is used in *flavors*, as a *soap perfume* and in the preparation of synthetic oils of rose and similar flower oils. It is also a valuable perfume fixative.

**Pine Needle Oil**—see RPS-18, page 1297.

**Raspberry Syrup**—see RPS-18, page 1302.

### Rose Oil

Otto of Rose; Attar of Rose

The volatile oil distilled with steam from the fresh flowers of *Rosa gallica* Linné, *Rosa damascena* Miller, *Rosa alba* Linné, *Rosa centifolia* Linné and varieties of these species (Fam *Rosaceae*).

**Constituents**—From the quantitative standpoint the chief components are the alcohols *geraniol* [$C_{10}H_{18}O$] and *l-citronellol* [$C_{10}H_{20}O$]. The sesquiterpene alcohols *farnesol* and *nerol* occur to the extent of 1% and 5 to 10%, respectively. Together, the four alcohols constitute 70 to 75% of the oil. *Phenylethyl alcohol*, which comprises 1% of the oil, is an important odoriferous constituent. Other compounds present are *linaloöl, eugenol, nonyl aldehyde*, traces of *citral* and two solid hydrocarbons of the paraffin series.

**Description and Solubility**—A colorless or yellow liquid, which has the characteristic odor and taste of rose; at 25°, a viscous liquid; on gradual cooling it changes to a translucent, crystalline mass, which may be liquefied easily by warming; specific gravity 0.848 to 0.863 at 30° compared with water at 15°; 1 mL mixes with 1 mL of chloroform without turbidity; on the addition of 20 mL of 90% alcohol to this solution, the resulting liquid is neutral or acid to moistened litmus paper and deposits a crystalline residue within 5 min on standing at 20°.

**Uses**—Principally as a *perfume*. It is recognized officially for its use as an ingredient in *Rose Water Ointment* and cosmetics.

### Stronger Rose Water

Triple Rose Water

A saturated solution of the odoriferous principles of the flowers of *Rosa centifolia* Linné (Fam *Rosaceae*), prepared by distilling the fresh flowers with water and separating the excess volatile oil from the clear, water portion of the distillate.

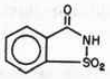
*Note*—When diluted with an equal volume of purified water, it may be supplied when *Rose Water* is required.

**Description**—Nearly colorless and clear liquid which possesses the pleasant odor and taste of fresh rose blossoms; must be free from empyreuma, mustiness and fungal growths.

**Uses**—An ingredient in *Rose Water Ointment*. It sometimes is prepared extemporaneously from concentrates or from rose oil, but such water is not official and rarely compares favorably with the fresh distillate from rose petals.

### Saccharin

1,2-Benzisothiazol-3(2*H*)-one, 1,1-dioxide; Gluside; *o*-Benzosulfimide (*Boots; Reisman*) (*Various Mfrs*)




1,2-Benzisothiazolin-3-one 1,1-dioxide [81-07-2] $C_7H_5NO_3S$ (183.18).

**Preparation**—Toluene is reacted with chlorosulfonic acid to form *o*-toluenesulfonyl chloride, which is converted to the sulfonamide with ammonia. The methyl group then is oxidized with dichromate yielding *o*-sulfamoylbenzoic acid which, when heated, forms the cyclic imide.

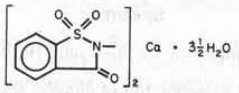
**Description**—White crystals or a white crystalline powder; odorless or has a faint aromatic odor; in dilute solution it is intensely sweet; solutions are acid to litmus; melts between 226 and 230°.

**Solubility**—1 g in 290 mL water, 31 mL alcohol or 25 mL boiling water; slightly soluble in chloroform or ether; readily dissolved by dilute solution of ammonia, solutions of alkali hydroxides or solutions of alkali carbonates with the evolution of $CO_2$.

**Uses**—A sweetening agent in *Aromatic Cascara Sagrada Fluidextract* and highly alcoholic preparations. It is an intensely sweet substance. A 60-mg portion is equivalent in sweetening power to approximately 30 g of sucrose. It is used as a *sweetening agent* in vehicles, canned foods, beverages and in diets for diabetics to replace the sucrose. The relative sweetening power of saccharin is increased by dilution.

### Saccharin Calcium

1,2-Benzisothiazol-3(2*H*)-one, 1,1-dioxide, calcium salt, hydrate (2:7) Calcium *o*-Benzosulfimide




1,2-Benzisothiazolin-3-one 1,1-dioxide calcium salt hydrate (2:7) [6381-91-5] $C_{14}H_8CaN_2O_6S_2.3\frac{1}{2}H_2O$ (467.48); *anhydrous* [6485-34-3] (404.43).

**Preparation**—Saccharin is reacted with a semimolar quantity of calcium hydroxide in aqueous medium and the resulting solution is concentrated to crystallization.

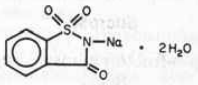
**Description**—White crystals or a white, crystalline powder; odorless or has a faint aromatic odor; and an intensely sweet taste even in dilute solutions; in dilute solution it is about 300 times as sweet as sucrose.

**Solubility**—1 g in 2.6 mL water or 4.7 mL alcohol.

**Uses and Dose**—See *Saccharin*.

### Saccharin Sodium

1,2-Benzisothiazol-3(2*H*)-one, 1,1-dioxide, sodium salt, dihydrate; Soluble Saccharin; Soluble Gluside; Sodium o-Benzosulfimide




1,2-Benzisothiazolin-3-one 1,1-dioxide sodium salt dihydrate [6155-57-3] $C_7H_4NNaO_3S.2H_2O$ (241.19); *anhydrous* [128-44-9] (205.16).

**Preparation**—Saccharin is dissolved in an equimolar quantity of aqueous sodium hydroxide and the solution is concentrated to crystallization.

**Description**—White crystals or a white crystalline powder; odorless or has a faint aromatic odor and an intensely sweet taste even in dilute solutions; in dilute solution it is about 300 times as sweet as sucrose; when in powdered form it usually contains about ⅓ the theoretical amount of water of hydration due to efflorescence.

**Solubility**—1 g in 1.5 mL water or 50 mL alcohol.

**Uses**—Same as *Saccharin* but has the advantage of being more soluble in neutral aqueous solutions.

**Application**—**15** to **60 mg** as necessary.

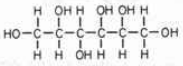
**Dosage Form**—Tablets: 15, 30 and 60 mg.

**Sarsaparilla Syrup, Compound**—see RPS-13, page 445.

**Sherry Wine**—see page RPS-15, page 1240.

### Sorbitol

Sionin; Sorbit; D-Sorbitol; D-Glucitol Sorbo (*EM Labs*)



D-Glucitol [50-70-4] $C_6H_{14}O_6$ (182.17); it may contain small amounts of other polyhydric alcohols.

**Preparation**—Commercially by reduction (hydrogenation) of certain sugars, such as glucose.

**Description**—White, hygroscopic powder, granules or flakes, having a sweet taste; the usual form melts about 96°.

**Solubility**—1 g in about 0.45 mL of water; slightly soluble in alcohol, methanol or acetic acid.

**Uses**—An *osmotic diuretic* given intravenously in 50% (*w/v*) solution to diminish edema, lower cerebrospinal pressure or reduce intraocular pressure in glaucoma. It also is used as a laxative, sweetener, humectant, plasticizer and, in 70% (*w/w*) solution, as a vehicle.

**Dose**—**50** to **100 mL** of a **50%** solution; *laxative, oral*, **30** to **50 g.**

**Sorbitol Solution** is a water solution containing, in each 100 g, 69–71 g of total solids consisting essentially of D-sorbitol and a small amount of mannitol and other isomeric polyhydric alcohols. The content of D-sorbitol [$C_6H_8(OH)_6$] in each 100 g is not less than 64 g. *Description:* Clear, colorless, syrupy liquid, having a sweet taste and no characteristic odor; neutral to litmus; specific gravity not less than 1.285; refractive index at 20° 1.455 to 1.465. *Uses:* It is not to be injected. It has been used as a replacement for propylene glycol and glycerin.

### Spearmint

Spearmint Leaves; Spearmint Herb; Mint

The dried leaf and flowering top of *Mentha spicata* Linné (*Mentha viridis* Linné) (Common Spearmint) or of *Mentha cardiaca* Gerard ex Baker (Scotch Spearmint) (Fam *Labiatae*).

Fresh spearmint is used in preparing mint sauce and also the well-known mint julep. The volatile oil is the only constituent of importance in this plant; the yield is from ½ to 1%.

**Uses**—A flavoring agent.

**Spearmint Oil** is the volatile oil distilled with steam from the fresh over-ground parts of the flowering plant of *Mentha spicata* or of *Mentha cardiaca;* contains not less than 55%, by volume, of $C_{10}H_{14}O$ (carvone = 150.22). The chief odoriferous constituent is the ketone *l-carvone.* American oil also contains *dihydrocarveol acetate* [$CH_3COOC_{10}H_{17}$], *l-limonene* [$C_{10}H_{16}$], a small amount of *phellandrene* [$C_{10}H_{16}$] and traces of *esters of valeric* and *caproic acids.*

**Description and Solubility:** Colorless, yellow or greenish yellow liquid, having the characteristic odor and taste of spearmint; specific gravity 0.917 to 0.934. Soluble in 1 volume of 80% alcohol, but upon further dilution may become turbid. *Uses:* Primarily as a flavoring agent. It also has been used as a *carminative* in doses of 0.1 mL.

### Sucrose

α-D-Glucopyranoside, β-D-fructofuranosyl-, Sugar; Cane Sugar; Beet Sugar

Sucrose [57-50-1] $C_{12}H_{22}O_{11}$ (342.30); a sugar obtained from *Saccharum officinarum* Linné (Fam *Gramineae*), *Beta vulgaris* Linné (Fam *Chenopodiaceae*), and other sources. It contains no added substances. For the structural formula, see page 384.

**Preparation**—Commercially from the sugar cane, beet root and sorghum. Originally, sugar cane was the only source, but at present the root of *Beta vulgaris* is used largely in Europe, and to an increasing degree in this country, for making sucrose.

The sugar cane is crushed and the juice amounting to about 80% is expressed with roller mills. The juice after "defecation" with lime and removal of excess of lime by carbonic acid gas, is run into vacuum pans for concentration and the saccharine juice is evaporated in this until it begins to crystallize. After the crystallization is complete, the warm mixture of crystals and syrup is run into centrifuges, in which the crystals of raw sugar are drained and dried. The syrup resulting as a by-product from raw sugar is known as *molasses.* Raw beet sugar is made by a similar process, but is more troublesome to purify than that made from sugar cane.

The refined sugar from either raw cane or beet sugar is prepared by dissolving the raw sugar in water, clarifying, filtering and, finally, decolorizing the solution by passing it through bone-black filters. The water-white solution finally is evaporated under reduced pressure to the crystallizing point and then forced to crystallize in small granules which are collected and drained in a centrifuge.

**Description**—Colorless or white crystals, crystalline masses or blocks, or a white, crystalline powder; odorless; sweet taste; stable in air; solutions neutral to litmus; melts with decomposition from 160 to 185°; specific gravity of about 1.57; specific rotation at 20° not less than +65.9°; unlike the other official sugars (dextrose, fructose and lactose), it does not reduce Fehling's solution even in hot solutions; also differs from these sugars in that it is darkened and charred by sulfuric acid in the cold; fermentable and, in dilute aqueous solutions, it ferments into alcohol and eventually acetic acid.

Sucrose is hydrolyzed by dilute mineral acids, slowly in the cold, and rapidly on heating into one molecule each of dextrose or levulose. This process is known technically as "inversion" and the product is referred to as "invert sugar"; the term inversion being derived from the change, through the hydrolysis, in the optical rotation from dextro of the sucrose to levo of the hydrolyzed product. The enzyme *invertase* also hydrolyzes sucrose.

**Solubility**—1 g in 0.5 mL water, 170 mL alcohol or in slightly more than 0.2 mL boiling water; insoluble in chloroform or ether.

**Uses**—Principally as a pharmaceutical necessity for making syrups and lozenges. It gives viscosity and consistency to fluids.

Intravenous administration of hypertonic solutions has been employed chiefly to initiate *osmotic diuresis.* Such a procedure is not completely safe and renal tubular damage may result, particularly in patients with existing renal pathology. Safer and more effective diuretics are available.

**Sugar, Compressible**—see RPS-18, page 1298.

### Confectioner's Sugar

Sucrose ground together with corn starch to a fine powder; contains 95.0 to 97.0% of sucrose.

**Description**—Fine, white, odorless powder; sweet taste; stable in air; specific rotation not less than +62.6°.

**Solubility**—The sucrose portion is soluble in cold water; this is entirely soluble in boiling water.

**Uses**—A *pharmaceutic aid* as a *tableting excipient* and *sweetening agent.* See also *Sucrose.*

**Syrup**—page 1393.

### Tolu Balsam

Tolu

A balsam obtained from *Myroxylon balsamum* (Linné) Harms (Fam *Leguminosae*).

**Constituents**—Up to 80% *resin*, about 7% *volatile oil*, 12 to 15% free *cinnamic acid*, 2 to 8% benzoic acid and 0.05% *vanillin.* The volatile oil is composed chiefly of *benzyl benzoate* and *benzyl cinnamate, ethyl benzoate, ethyl cinnamate*, a terpene called *tolene* (possibly identical with *phellandrene*) and the sesquiterpene alcohol *farnesol* also have been reported to be present.

**Description**—Brown or yellowish brown, plastic solid; transparent in thin layers and brittle when old, dried or exposed to cold temperatures; pleasant, aromatic odor resembling that of vanilla and a mild, aromatic taste.

**Solubility**—Nearly insoluble in water or solvent hexane; soluble in alcohol, chloroform or ether, sometimes with slight residue or turbidity.

**Uses**—A *vehicle, flavoring agent* and stimulating *expectorant* as a syrup. It is also an ingredient of *Compound Benzoin Tincture* (page 869).

**Tolu Balsam Syrup** [Syrup of Tolu; Tolu Syrup]—*Preparation:* Add tolu balsam tincture (50 mL, all at once) to magnesium carbonate (10 g) and sucrose (60 g) in a mortar, and mix intimately. Gradually add purified water (430 mL) with trituration, and filter. Dissolve the remainder of sucrose (760 g) in the clear filtrate with gentle heating, strain the syrup while warm and add purified water (qs) through the strainer to make the product measure 1000 mL. Mix thoroughly. *Note:* May be made also in the following manner: Place the remaining sucrose (760 g) in a suitable percolator, the neck of which nearly is filled with loosely packed cotton, moistened after packing with a few drops of water. Pour the filtrate, obtained as directed in the formula above, upon the sucrose, and regulate the outflow to a steady drip of percolate. When all of the liquid has run through, return portions of the percolate, if necessary, to dissolve all of the sucrose. Then pass enough purified water through the cotton to make the product measure 1000 mL. Mix thoroughly. *Alcohol Content:* 3 to 5%. *Uses:* Chiefly for its agreeable *flavor* in cough syrups. *Dose:* 10 mL.

**Tolu Balsam Tincture** [Tolu Tincture]—*Preparation:* With tolu balsam (200 g), prepare a tincture by Process M (page 1522), using alcohol as the menstruum. *Alcohol Content:* 77 to 83%. *Uses:* A balsamic preparation employed as an addition to expectorant mixtures; also used in the preparation of *Tolu Balsam Syrup*. *Dose:* 2 mL.

## Vanilla

Vanilla Bean

The cured, full-grown, unripe fruit of *Vanilla planifolia* Andrews, often known in commerce as Mexican or Bourbon Vanilla, or of *Vanilla tahitensis* J W Moore, known in commerce as Tahiti Vanilla (Fam *Orchidaceae*); yields not less than 12% of anhydrous extractive soluble in diluted alcohol.

**Constituents**—Contains a trace of a volatile oil, fixed oil, 4% resin, sugar, *vanillic acid* and about 2.5% *vanillin* (see below). This highest grade of vanilla comes from Madagascar; considerable quantities of the drug also are produced in Mexico.

**Uses**—A flavor.

*Note—Do not use if it has become brittle.*

**Vanilla Tincture** [Extract of Vanilla]—*Preparation:* Add water (200 mL) to comminuted vanilla (cut into small pieces, 100 g) in a suitable covered container, and macerate during 12 hr, preferably in a warm place. Add alcohol (200 mL) to the mixture of vanilla and water, mix well and macerate about 3 days. Transfer the mixture to a percolator containing sucrose (in coarse granules, 200 g), and drain; then pack the drug firmly, and percolate slowly, using diluted alcohol (qs) as the menstruum. If the percolator is packed with an evenly distributed mixture of the comminuted vanilla, sucrose and clean, dry sand, the increased surface area permits more efficient percolation. This tincture is unusual in that it is the only official one in which sucrose is specified as an ingredient. *Alcohol Content:* 38 to 42%. *Uses:* A *flavoring agent*. *See Flavors*, page 1384.

## Vanillin

Benzaldehyde, 4-hydroxy-3-methoxy-

4-Hydroxy-3-methoxybenzaldehyde [121-33-5] $C_8H_8O_3$ (152.15).

**Preparation**—From vanilla, which contains 2 to 3%. It also is found in many other substances, including tissues of certain plants, crude beet sugar, asparagus and even asafetida. Commercially, it is made synthetically. While chemically identical with the product obtained from the "vanilla bean," "flavoring preparations" made from it never equal in flavor the preparation in which vanilla alone is used because vanilla contains other odorous products. It is synthesized by oxidation processes from either coniferin or eugenol, by treating guaiacol with chloroform in the presence of an alkali, and by other methods.

**Description**—Fine, white to slightly yellow crystals, usually needle-like having an odor and taste suggestive of vanilla; affected by light; solutions are acid to litmus; melts 81 to 83°.

**Solubility**—1 g in about 100 mL water, about 20 mL glycerin or 20 mL water at 80°; freely soluble in alcohol, chloroform, ether or solutions of the fixed alkali hydroxides.

**Incompatibilities**—Combines with *glycerin*, forming a compound which is almost insoluble in alcohol. It is decomposed by *alkalies* and is oxidized slowly by the *air*.

**Uses**—Only as a *flavor*. Solutions of it sometimes are sold as a synthetic substitute for vanilla for flavoring foods but it is inferior in flavor to the real vanilla extract.

**Water**—page 1392.

**Water Purified**—page 1392.

**Wild Cherry Syrup**—page 1393.

### Other Flavoring Agents

**Anise NF IX** [Anise Seed; European Aniseed; Sweet Cumin]—The dried ripe fruit of *Pimpinella anisum* Linné. It contains about 1.75% of volatile oil. *Uses:* A flavor and carminative.

**Ceylon Cinnamon**—The dried inner bark of the shoots of coppiced trees of *Cinnamomum zeylanicum* Nees (Fam *Lauraceae*); contains, in each 100 g, not less than 0.5 mL volatile oil. *Uses:* A *carminative* and *flavor*.

**Clove**—The dried flower-bud of *Eugenia caryophyllus* (Sprengel) Bullock et Harrison (Fam *Myrtaceae*). It contains, in each 100 g, not less than 16 mL of clove oil. *Uses:* An *aromatic* in doses of 0.25 g and as a condiment in foods.

**Coriander**—The dried ripe fruit of *Coriandrum sativum* Linné (Fam *Umbelliferae*); yields not less than 0.25 mL volatile coriander oil/100 g. *Uses:* Seldom used alone, but sometimes is combined with other agents, chiefly as a *flavor*. It also is used as a condiment and flavor in cooking.

**Eucalyptol** [Cineol; Cajeputol; $C_{10}H_{18}O$ (154.25)]— Obtained from eucalyptus oil and from other sources. Colorless liquid, having a characteristic, aromatic, distinctly camphoraceous odor and a pungent, cooling, spicy taste. 1 volume is soluble in 5 volumes of 60% alcohol; miscible with alcohol, chloroform, ether, glacial acetic acid or fixed or volatile oils; insoluble in water. *Uses:* Primarily as a *flavoring agent*. Locally it is employed for its *antiseptic* effect in inflammations of the nose and throat and in certain skin diseases. It sometimes is used by inhalation in bronchitis.

**Fennel** [Fennel Seed]—The dried ripe fruit of cultivated varieties of *Foeniculum vulgare* Miller (Fam *Umbelliferae*); contains 4 to 6% of an oxygenated volatile oil and 10% of a fixed oil. *Uses:* A *flavor* and *carminative*.

**Ginger NF** [Zingiber]—The dried rhizome of *Zingiber officinale* Roscoe (Fam *Zingiberaceae*), known in commerce as Jamaica Ginger, African Ginger and Cochin Ginger. The outer cortical layers often are removed either partially or completely. *Constituents:* A pungent substance, *gingerol;* volatile oil (Jamaica Ginger, about 1%; African Ginger, 2 to 3%), containing the terpenes *d-camphene* and β-*phellandrene* and the sesquiterpene *zingiberene; citral cineol* and *borneol*. *Uses:* A *flavoring agent*. It formerly was employed in a dose of 600 mg as an intestinal stimulant and carminative in colic and in diarrhea.

**Ginger Oleoresin**—Yields 18 to 35 mL of volatile ginger oil/100 g of oleoresin. *Preparation:* Extract the oleoresin from ginger, in moderately coarse powder, by percolation, using either acetone, alcohol or ether as the menstruum.

**Glycyrrhiza Extract** [Licorice Root Extract; Licorice]—An extract prepared from the rhizome and roots of species of *Glycyrrhiza* Tournefort ex Linné (Fam *Leguminosae*). *Description:* Brown powder or in flattened, cylindrical rolls or in masses; the rolls or masses have a glossy black color externally, and a brittle, sharp, smooth, conchoidal fracture; the extract has a characteristic and sweet taste which is not more than very slightly acrid. *Uses:* A *flavoring agent*.

**Lavender** [Lavendula]—The flowers of *Lavandula spica* (*Lavandula officinalis* or *Lavandula vera*); contains a volatile oil with the principal constituent *l*-linalyl acetate. *Uses:* A *perfume*.

**Lemon Peel USP XV, BP** [Fresh Lemon Peel]—The outer yellow rind of the fresh ripe fruit of *Citrus limon* (Linné) Burmann filius (Fam *Rutaceae*); contains a volatile oil and hesperidin. *Uses:* A *flavor*.

**Lemon Tincture USP XVIII** [Lemon Peel Tincture]—*Preparation:* From lemon peel, which is the outer yellow rind of the fresh, ripe fruit of *Citrus limon* (Linné) Burmann filius (Fam *Rutaceae*), by *Process M* (page 1522), 500 g of the peel being macerated in 900 mL alcohol and the preparation being completed with alcohol to make the product measure 1000 mL. Use talc as the filtering medium. The white portion of the rind must not be used, as the proportion of oil, which is found only in the yellow rind, is reduced and the bitter principle, hesperidin, introduced. *Alcohol Content:* 62 to 72%. *Uses:* A flavor, its fineness of flavor being assured as it comes from the fresh fruit, and being an alcoholic solution it is more stable than the oil.

**Myrcia Oil** [Bay Oil; Oil of Bay]—The volatile oil distilled from leaves of *Pimenta racemosa* (Miller) J W Moore (Fam *Myrtaceae*); contains the phenolic compounds eugenol and chavicol. *Uses:* In the preparation of bay rum as a *perfume*.

**Orange Oil, Bitter**—The volatile oil obtained by expression from the fresh peel of the fruit of *Citrus aurantium* Linné (Fam *Rutaceae*); contains primarily *d*-limonene. Pale yellow liquid with a characteristic; aro-

matic odor of the Seville orange; if it has a terebinthinate odor, it should not be dispensed; refractive index 1.4725 to 1.4755 at 20°. It differs little from *Orange Oil* (page 1388) except for the botanical source. Miscible with anhydrous alcohol and with about 4 volumes alcohol. *Uses:* A *flavor*.

**Orange Peel, Bitter** [Bitter Orange; Curacao Orange Peel; Bigarade Orange]—The dried rind of the unripe but fully grown fruit of *Citrus aurantium* Linné (Fam *Rutaceae*). *Constituents:* The inner part of the peel from the bitter orange contains a volatile oil and the glycoside *hesperidin* ($C_{28}H_{34}O_{15}$). This, upon hydrolysis in the presence of $H_2SO_4$, yields *hesperetin* ($C_{16}H_{14}O_6$), *rhamnose* ($C_6H_{12}O_5$), and D-glucose ($C_6H_{12}O_6$). *Uses:* A *flavoring agent*. It has been used as a bitter.

**Orange Peel, Sweet USP XV**—The fresh, outer rind of the non-artificially colored, ripe fruit of *Citrus sinensis* (Linné) Osbeck (Fam *Rutaceae*); the white, inner portion of the rind is to be excluded. Contains a volatile oil but no hesperidin, since the glycoside occurs in the white portion of the rind. *Uses:* A *flavor*.

**Orris** [Orris Root; Iris; Florentine Orris]—The peeled and dried rhizome of *Iris germanica* Linné, including its variety *florentina* Dykes (*Iris florentina* Linné), or of *Iris pallida* Lamarck (Fam *Iridaceae*); contains about 0.1 to 0.2% of a volatile oil (orris butter), myristic acid and the ketone irone; irone provides the fragrant odor of orris. *Uses:* A *perfume*.

**Pimenta Oil** [Pimento Oil; Allspice Oil]—The volatile oil distilled from the fruit of *Pimenta officinalis* Lindley (Fam *Myrtaceae*). *Uses:* A *carminative* and *stimulant* and also as a *condiment* in foods.

**Rosemary Oil**—The volatile oil distilled with steam from the fresh flowering tops of *Rosmarinus officinalis* Linné (Fam *Labiatae*); yields not less than 1.5% of esters calculated as bornyl acetate ($C_{12}H_{20}O_2$), and not less than 8% of total borneol ($C_{10}H_{18}O$), free and as esters. *Constituents:* The amount of esters, calculated as bornyl acetate, and of total borneol, respectively, varies somewhat with its geographic source. Cineol is present to the extent of about 19–25%, depending on the source. The terpenes *d-* and *l-α-pinene*, *dipentene* and *camphene*, and the ketone *camphor* also occur in this oil. *Description and Solubility:* Colorless or pale yellow liquid, having the characteristic odor of rosemary, and a warm, camphoraceous taste; specific gravity 0.894 to 0.912. Soluble in 1 volume of 90% alcohol, by volume, but upon further dilution may become turbid. *Uses:* A *flavor* and *perfume*, chiefly, in rubefacient liniments such as *Camphor and Soap Liniment*.

**Sassafras**—The dried bark of the root of *Sassafras albidum* (Nuttall) Nees (Fam *Lauraceae*). *Uses:* Principally because of its high content of volatile oil which serves to disguise the taste of disagreeable substances. An infusion (*sassafras tea*) formerly was used extensively as a home remedy, particularly in the southern states.

**Sassafras Oil**—The volatile oil distilled with steam from *Sassafras*. *Uses:* A *flavor* by confectioners, particularly in hard candies. Either the oil or safrol is used as a *preservative* in mucilage and library paste, being far superior to methyl salicylate for this purpose. Since the oil is *antiseptic*, it sometimes is employed in conjunction with other agents for local application in diseases of the nose and throat; safrol also is used in this way.

**Wild Cherry** [Wild Black Cherry Bark]—The carefully dried stem bark of *Prunus serotina* Ehrhart (Fam *Rosaceae*), free of borke and preferably having been collected in autumn. *Constituents:* A glucoside of *d-mandelonitrile* ($C_6H_5$.CHOH.CN) known as *prunasin* (page 387), the enzyme *emulsin*, tannin, a bitter principle, starch, resin, etc. In the BP and the English literature this drug has been termed "Virginian Prune"—a literal but incorrect translation of the older botanical name, *Prunus virginiana*. *Uses:* A *flavoring agent*, especially in cough preparations. It is an ingredient in *Wild Cherry Syrup*. As with bitter almond, contact with water, in the presence of emulsin, results in the production of benzaldehyde and HCN. All preparations of wild cherry should be made without heat in order to avoid destruction of the enzyme which is responsible for the production of the free active principles.

# Diluting Agents

Diluting agents (vehicles or carriers) are indifferent substances which are used as solvents for active medicinals. They are of primary importance for diluting and flavoring drugs which are intended for oral administration, but a few such agents are designed specifically for diluting parenteral injections. The latter group is considered separately.

The expert selection of diluting agents has been an important factor in popularizing the "specialties" of manufacturing pharmacists. Since a large selection of diluting agents is available in a choice of colors and flavors, the prescriber has an opportunity to make his own prescriptions more acceptable to the patient. The best diluting agent is usually the best solvent for the drug. Water-soluble substances, for example, should be flavored and diluted with an aqueous agent and alcohol-soluble drugs with an alcoholic vehicle. Thus, the diluting agents presented herein are divided into three groups on the basis of their physical properties: aqueous, hydroalcoholic and alcoholic.

## Aqueous Diluting Agents

Aqueous diluting agents include aromatic waters, syrups and mucilages. Aromatic waters are used as diluting agents for water-soluble substances and salts, but cannot mask the taste of very disagreeable drugs. Some of the more common flavored aqueous agents and the official forms of water are listed below.

### Orange Flower Water

Stronger Orange Flower Water; Triple Orange Flower Water

A saturated solution of the odoriferous principles of the flowers of *Citrus aurantium* Linné (Fam. *Rutaceae*), prepared by distilling the fresh flowers with water and separating the excess volatile oil from the clear, water portion of the distillate.

**Description**—Should be nearly colorless, clear or only faintly opalescent; the odor should be that of the orange blossoms; it must be free from empyreuma, mustiness and fungoid growths.

**Uses**—A *vehicle flavor* and *perfume* in syrups, elixirs and solutions.

### Peppermint Water

A clear, saturated solution of peppermint oil in purified water, prepared by one of the processes described under *Aromatic Waters* (page 1498).

**Uses**—A *carminative* and *flavored vehicle*.

**Dose**—15 mL.

**Tolu Balsam Syrup**—page 1391.

### Water

Water [7732-18-5] $H_2O$ (18.02).

Drinking water, which is subject to EPA regulations with respect to drinking water, and which is delivered by the municipal or other local public system or drawn from a private well or reservoir, is the starting material for all forms of water covered by Pharmacopeial monographs.

Drinking water may be used in the preparation of USP drug substances (eg, in the extraction of certain vegetable drugs and in the manufacture of a few preparations used externally) but not in the preparation of dosage forms, or in the preparation of reagents or test solutions. It is no longer the subject of a separate monograph (in the USP), inasmuch as the cited standards vary from one community to another and generally are beyond the control of private parties or corporations.

### Purified Water

Water obtained by distillation, ion-exchange treatment, reverse osmosis or any other suitable process; contains no added substance.

*Caution—Do not use this in preparations intended for parenteral administration. For such purposes, use Water for Injection, Bacteriostatic Water for Injection*, or *Sterile Water for Injection*, page 1395.

**Preparation**—From water complying with EPA regulations with respect to drinking water. A former official process for water, when prepared by distillation, is given below. The pharmacist who is preparing sterile solutions, and must have freshly distilled water of exceptionally high grade, not only free from all bacterial or other microscopic growths but also free from the products of metabolic processes resulting from the growth of such organisms in the water, advantageously may follow this plan. The metabolic products commonly are spoken of as pyrogens and usually consist of complex organic compounds which cause febrile reactions if present in the solvent for parenteral medicinal substances.

#### Distillation Process

| | |
|---|---|
| **Water** | **1000 Vol** |
| To make | **750 Vol** |

Distil the water from a suitable apparatus provided with a block-tin or glass condenser. Collect the first 100 volumes and reject this portion. Then collect 750 volumes and keep the distilled water in glass-stoppered bottles, which have been rinsed with steam or very hot distilled water immediately before being filled. The first 100 volumes are discarded to eliminate foreign volatile substances found in ordinary water and only 750 volumes are collected, since the residue in the still contains concentrated dissolved solids.

**Description**—Colorless, clear liquid, without odor or taste.

**Uses**—A *pharmaceutic aid* (vehicle and solvent). It must be used in compounding dosage forms for internal (oral) administration as well as sterile pharmaceuticals applied externally, such as collyria and dermatological preparations, but these must be sterilized before use.

Whenever water is called for in official tests and assays, this must be used.

## Syrups Used as Diluting Agents

Syrups are useful as diluting agents for water-soluble drugs and act both as solvents and flavoring agents. The flavored syrups usually consist of simple syrup (85% sucrose in water) containing appropriate flavoring substances. *Glycyrrhiza Syrup* is an excellent vehicle for saline substances because of its colloidal properties, sweet flavor and lingering taste of licorice. *Acacia Syrup* is valuable in disguising the taste of urea. Fruit syrups are especially effective for masking sour tastes. *Aromatic Eriodictyon Syrup* is the diluting agent of choice for masking the bitter taste of alkaloids. *Cocoa Syrup* and *Cherry Syrup* are good general flavoring agents.

### Acacia Syrup

| | |
|---|---|
| **Acacia, granular or powdered** | **100 g** |
| **Sodium Benzoate** | **1 g** |
| **Vanilla Tincture** | **5 mL** |
| **Sucrose** | **800 g** |
| **Purified Water,** a sufficient quantity, To make | **1000 mL** |

Mix the acacia, sodium benzoate and sucrose; then add 425 mL of purified water, and mix well. Heat the mixture on a steam bath until solution is completed. When cool, remove the scum, add the vanilla tincture and sufficient purified water to make the product measure 1000 mL and strain, if necessary.

**Uses**—A *flavored vehicle* and *demulcent.*

### Cherry Syrup

Syrupus Cerasi

| | |
|---|---|
| **Cherry Juice** | **475 mL** |
| **Sucrose** | **800 g** |
| **Alcohol** | **20 mL** |
| **Purified Water,** a sufficient quantity, To make | **1000 mL** |

Dissolve the sucrose in cherry juice by heating on a steam bath, cool and remove the foam and floating solids. Add the alcohol and sufficient purified water to make 1000 mL, and mix.

**Alcohol Content**—1 to 2%.

**Uses**—A pleasantly *flavored vehicle* which is particularly useful in masking the taste of saline and sour drugs.

**Citric Acid Syrup USP XVIII**—see RPS-18, page 1302.

### Cocoa Syrup

Cacao Syrup; Chocolate-flavored Syrup; Chocolate Syrup

| | |
|---|---|
| **Cocoa** | **180 g** |
| **Sucrose** | **600 g** |
| **Liquid Glucose** | **180 g** |
| **Glycerin** | **50 mL** |
| **Sodium Chloride** | **2 g** |
| **Vanillin** | **0.2 g** |
| **Sodium Benzoate** | **1 g** |
| **Purified Water,** a sufficient quantity, To make | **1000 mL** |

Mix the sucrose and the cocoa, and to this mixture gradually add a solution of the liquid glucose, glycerin, sodium chloride, vanillin and sodium benzoate in 325 mL of hot purified water. Bring the entire mixture to a boil, and maintain at boiling temperature for 3 min. Allow to cool to room temperature and add sufficient purified water to make the product measure 1000 mL.

*Note*—Cocoa containing not more than 12% nonvolatile, ether-soluble extractive ("fat") yields a syrup having a minimum tendency to separate. "Breakfast cocoa" contains over 22% "fat."

**Uses**—A pleasantly *flavored vehicle.*

**Aromatic Eriodictyon Syrup**—see RPS-18, page 1301.

**Raspberry Syrup USP XVIII**—see RPS-18, page 1302.

### Syrup

Simple Syrup

| | |
|---|---|
| **Sucrose** | **850 g** |
| **Purified Water,** a sufficient quantity, To make | **1000 mL** |

May be prepared by using boiling water or, preferably, without heat, by the following process:

Place the sucrose in a suitable percolator the neck of which is nearly filled with loosely packed cotton moistened, after packing, with a few drops of water. Pour carefully about 450 mL of purified water upon the sucrose, and regulate the outflow to a steady drip of percolate. Return the percolate, if necessary, until all of the sucrose has dissolved. Then wash the inside of the percolator and the cotton with sufficient purified water to bring the volume of the percolate to 1000 mL, and mix.

**Specific Gravity**—Not less than 1.30.

**Uses**—A *sweet vehicle,* sweetening agent and as the basis for many flavored and medicated syrups.

### Other Syrups Used As Diluting Agents

**Glycyrrhiza Syrup USP XVIII** [Licorice Syrup]—*Preparation:* Add fennel oil (0.05 mL) and anise oil (0.5 mL) to glycyrrhiza fluidextract (250 mL) and agitate until mixed. Then add syrup (qs) to make the product measure 1000 mL, and mix. *Alcohol Content:* 5 to 6%. *Incompatibilities:* The characteristic flavor is destroyed by acids due to a precipitation of the glycyrrhizin. *Uses:* A *flavored vehicle,* especially adapted to the administration of bitter or nauseous substances.

**Hydriodic Acid Syrup**—Contains, in each 100 mL 1.3 to 1.5 g HI (127.91). *Preparation:* Mix diluted hydriodic acid (140 mL) with purified water (550 mL), and dissolve dextrose (450 g) in this mixture by agitation. Add purified water (qs) to make the product measure 1000 mL, and filter. *Caution: It must not be dispensed if it contains free iodine, as evidenced by a red coloration. Description:* Transparent, colorless, or not more than pale straw-colored, syrupy liquid; odorless and has a sweet, acidulous taste; specific gravity about 1.18; hydriodic acid is decomposed easily in simple aqueous solution (unless protected by hypophosphorous acid) free iodine being liberated, and if taken internally, when in this condition, it is irritating to the alimentary tract. The dextrose used in this syrup should be of the highest grade obtainable. *Incompatibilities:* The reactions of the *acids* (page 1499) as well as those of the water-soluble iodide salts. Oxidizing agents liberate iodine; alkaloids may be precipitated. *Uses:* Traditionally as a *vehicle for expectorant* drugs. Its therapeutic properties are those of the iodides. *Dose: Usual,* 5 mL.

**Wild Cherry Syrup USP XVIII**—*Preparation:* Pack wild cherry (in coarse powder, 150 g), previously moistened with water (100 mL), in a cylindrical percolator, and add water (qs) to leave a layer of it above the powder. Macerate for 1 hr, then proceed with rapid percolation, using added water, until 400 mL of percolate is collected. Filter the percolate, if necessary, add sucrose (675 g) and dissolve it by agitation, then add glycerin (150 mL), alcohol (20 mL) and water (qs) to make the product measure 1000 mL. Strain if necessary. *It may be made also in the following manner:* The sucrose may be dissolved by placing it in a second percolator as directed for preparing *Syrup,* and allowing the percolate from the wild cherry to flow through it and into a graduated vessel containing the glycerin and alcohol until the total volume measures 1000 mL. *Note:* Heat is avoided, lest the enzyme emulsin be inactivated. If this should happen, the preparation would contain no free HCN, upon which its action as a sedative for coughs mainly depends. For a discus-

sion of the chemistry involved, see *Wild Cherry* (page 1392). *Alcohol Content:* 1 to 2%. *Uses:* Chiefly as a *flavored vehicle* for cough syrups.

## Mucilages Used as Diluting Agents

Mucilages are also suitable as diluting agents for water-soluble substances, and are especially useful in stabilizing suspensions and emulsions.

The following mucilage used for this purpose is described under *Emulsifying and Suspending Agents*, page 1395.

**Acacia Mucilage**—page 1395.

## Hydroalcoholic Diluting Agents

Hydroalcoholic diluting agents are suitable for drugs soluble in either water or diluted alcohol. The most important agents in this group are the elixirs. These solutions contain approximately 25% alcohol. *Medicated* elixirs which have therapeutic activity in their own right are not included in this section. Listed below are the common, nonmedicated elixirs which are used purely as diluting agents or solvents for drugs.

### Aromatic Elixir

Simple Elixir

| | |
|---|---|
| **Orange Oil** | **2.4 mL** |
| **Lemon Oil** | **0.6 mL** |
| **Coriander Oil** | **0.24 mL** |
| **Anise Oil** | **0.06 mL** |
| **Syrup** | **375 mL** |
| **Talc** | **30 g** |
| **Alcohol,** | |
| **Purified Water,** each, a sufficient quantity, | |
| To make | **1000 mL** |

Dissolve the oils in alcohol to make 250 mL. To this solution add the syrup in several portions, agitating vigorously after each addition, and afterwards add, in the same manner, the required quantity of purified water. Mix the talc with the liquid, and filter through a filter wetted with diluted alcohol, returning the filtrate until a clear liquid is obtained.

**Alcohol Content**—21 to 23%.

**Uses**—A pleasantly *flavored vehicle*, employed in the preparation of many other elixirs. The chief objection to its extensive use is the high alcohol content (about 22%) which at times may counteract the effect of other medicines.

**Cardamom Spirit, Compound**—see RPS-15, page 1236.

### Other Hydroalcoholic Diluting Agents

**Glycyrrhiza Elixir** [Elixir Adjuvans; Licorice Elixir]—*Preparation:* Mix glycyrrhiza fluidextract (125 mL) and aromatic elixir (875 mL) and filter. *Alcohol Content:* 21 to 23%. *Uses:* A *flavored vehicle.*

## Flavored Alcoholic Solutions

Flavored alcoholic solutions, of high alcoholic concentration, are useful as flavors to be added in small quantities to syrups or elixirs. The alcohol content of these solutions is approximately 50%. There are two types of flavored alcoholic solutions: tinctures and spirits. Only nonmedicated tinctures and spirits are used as flavoring agents.

**Compound Cardamom Tincture**—see RPS-18, page 1302.

**Lemon Tincture**—page 1391.

**Myrcia Spirit, Compound**—see RPS-13, page 452.

**Orange Spirit, Compound**—page 1388.

**Orange Peel, Sweet, Tincture**—page 1388.

**Peppermint Spirit**—see RPS-18, page 798.

## Diluting Agents for Injections

Injections are liquid preparations, usually solutions or suspensions of drugs, intended to be injected through the skin into the body. Diluting agents used for these preparations may be aqueous or nonaqueous and must meet the requirements for sterility and also of the pyrogen test. Aqueous diluting agents include such preparations as *Sterile Water for Injection* and various sterile, aqueous solutions of electrolytes and/or dextrose. Nonaqueous diluting agents are generally fatty oils of vegetable origin, fatty esters and polyols such as propylene glycol and polyethylene glycol. These agents are used to dissolve or dilute oil-soluble substances and to suspend water-soluble substances when it is desired to decrease the rate of absorption and, hence, prolong the duration of action of the drug substances. Preparations of this type are given intramuscularly. See *Parenteral Preparations*, page 1524.

### Corn Oil

Maize Oil

The refined fixed oil obtained from the embryo of *Zea mays* Linné (Fam *Gramineae*).

**Preparation**—Expressed from the Indian corn embryos or germs separated from the grain in starch manufacture.

**Description**—Clear, light yellow, oily liquid with a faint characteristic odor and taste; specific gravity 0.914 to 0.921.

**Solubility**—Slightly soluble in alcohol; miscible with ether, chloroform, benzene or solvent hexane.

**Uses**—Main official use is as a *solvent* and *vehicle for injections.* It is used as an edible oil substitute for solid fats in the management of hypercholesterolemia. Other uses include making soaps and for burning. It is a semidrying oil and therefore unsuitable for lubricating or mixing paint.

### Cottonseed Oil

Cotton Seed Oil; Cotton Oil

The refined fixed oil obtained from the seed of cultivated plants of various varieties of *Gossypium hirsutum* Linné or of other species of *Gossypium* (Fam *Malvaceae*).

**Preparation**—Cotton seeds contain about 15% oil. The testae of the seeds are first separated, and the kernels are subjected to high pressure in hydraulic presses. The crude oil thus has a bright red to blackish red color. It requires purification before it is suitable for medicinal or food purposes.

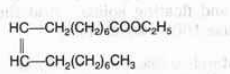
**Description**—Pale yellow, oily liquid with a bland taste; odorless or nearly so; particles of solid fat may separate below 10°; solidifies at about 0° to −5°; specific gravity 0.915 to 0.921.

**Solubility**—Slightly soluble in alcohol; miscible with ether, chloroform, solvent hexane or carbon disulfide.

**Uses**—Official as a *solvent* and *vehicle for injections.* It is sometimes taken orally as a mild cathartic in the dose of 30 mL or more. Taken internally, digestible oils retard gastric secretion and motility and increase the caloric intake. It also is used in the manufacture of soaps, oleomargarine, lard substitutes, glycerin, lubricants and cosmetics.

### Ethyl Oleate

(*Z*)-9-Octadecenoic acid, ethyl ester



Ethyl oleate [111-62-6] $C_{20}H_{38}O_2$ (310.52).

**Preparation**—Among other ways, by reacting ethanol with oleoyl chloride in the presence of a suitable dehydrochlorinating agent.

**Description**—Mobile, practically colorless liquid, having an agreeable taste; specific gravity 0.866 to 0.874; acid value not greater than 0.5; iodine value 75 to 85; sterilized by heating at 150° for 1 hr; properties similar to those of almond and arachis oils, but is less viscous and more rapidly absorbed by the tissues; boils about 207°.

**Solubility**—Does not dissolve in water; miscible with vegetable oils, mineral oil, alcohol or most organic solvents.

**Uses**—A *vehicle* for certain intramuscular injectable preparations.

### Peanut Oil

Arachis Oil; Groundnut Oil; Nut Oil; Earth-Nut Oil

The refined fixed oil obtained from the seed kernels of one or more of the cultivated varieties of *Arachis hypogaea* Linné (Fam *Leguminosae*).

**Description**—Colorless or pale yellow, oily liquid, with a characteristic nutty odor and a bland taste; specific gravity 0.912 to 0.920.

**Solubility**—Very slightly soluble in alcohol; miscible with ether, chloroform or carbon disulfide.

**Uses**—A *solvent* in preparing oil solutions for injection (page 1549). It also is used for making liniments, ointments, plasters and soaps, as a substitute for olive oil.

### Sesame Oil

Teel Oil; Benne Oil; Gingili Oil

The refined fixed oil obtained from the seed of one or more cultivated varieties of *Sesamum indicum* Linné (Fam *Pedaliaceae*).

**Description**—Pale yellow, almost odorless, oily liquid with a bland taste; specific gravity 0.916 to 0.921.

**Solubility**—Slightly soluble in alcohol; miscible with ether, chloroform, solvent hexane or carbon disulfide.

**Uses**—A *solvent* and *vehicle* in official injections. It is used much like olive oil both medicinally and for food. It does not readily turn rancid. It also is used in the manufacture of cosmetics, iodized oil, liniments, ointments and oleomargarine.

### Water for Injection

Water purified by distillation or by reverse osmosis. It contains no added substance.

*Caution—It is intended for use as a solvent for the preparation of parenteral solutions. For parenteral solutions that are prepared under aseptic conditions and are not sterilized by appropriate filtration or in the final container, first render it sterile and thereafter protect it from microbial contamination.*

**Description**—Clear, colorless, odorless liquid.

**Uses**—*Pharmaceutic aid* (vehicle and solvent).

### Bacteriostatic Water for Injection

Sterile water for injection containing one or more suitable antimicrobial agents.

*Note—Use it with due regard for the compatibility of the antimicrobial agent or agents it contains with the particular medicinal substance that is to be dissolved or diluted.*

**Uses**—*Sterile vehicle* for parenteral preparations.

### Sterile Water for Injection

Water for Parenterals

Water for injection sterilized and suitably packaged. It contains no antimicrobial agent or other added substance.

**Description**—Clear, colorless, odorless, liquid.

**Uses**—For the preparation of *all aqueous parenteral solutions*, including those used in *animal assays*. See page 1526 for a detailed discussion.

### Sterile Water for Irrigation

Water for injection that has been sterilized and suitably packaged. It contains no antimicrobial agent or other added substance.

**Description**—Clear, colorless, odorless liquid.

**Uses**—An *irrigating solution*.

# Emulsifying and Suspending Agents

An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid that is immiscible with the first liquid. Emulsions are formed and stabilized with the help of emulsifying agents, which are surfactants and/or viscosity-producing agents. A suspension is defined as a preparation containing finely divided insoluble material suspended in a liquid medium. The presence of a suspending agent is required to overcome agglomeration of the dispersed particles and to increase the viscosity of the medium so that the particles settle more slowly. Emulsifying and suspending agents are used extensively in the formulation of elegant pharmaceutical preparations for oral, parenteral and external use. For the theoretical and practical aspects of emulsions the interested reader is referred to pages 283 and 1395. More detailed information on the use of suspending agents is given on page 1395.

### Acacia

Gum Arabic

The dried gummy exudate from the stems and branches of *Acacia senegal* (Linné) Willdenow or of other related African species of *Acacia* (Fam *Leguminosae*).

**Constituents**—Principally calcium, magnesium and potassium salts of the polysaccharide *arabic acid*, which on acid hydrolysis yields L-arabinose, L-rhamnose, D-galactose and an aldobionic acid containing D-glucuronic acid and D-galactose.

**Description**—*Acacia:* Spheroidal tears up to 32 mm in diameter or angular fragments of white to yellowish white color; translucent or somewhat opaque; very brittle; almost odorless; produces a mucilaginous sensation on the tongue. *Flake Acacia:* White to yellowish white, thin flakes. *Powdered Acacia:* White to yellowish white, angular microscopic fragments. *Granular Acacia:* White to pale yellowish white, fine granules. *Spray-dried Acacia:* White to off-white compacted microscopic fragments or whole spheres.

**Solubility**—Insoluble in alcohol, but almost completely soluble in twice its weight of water at room temperature; the resulting solution flows readily and is acid to litmus.

**Incompatibilities**—*Alcohol or alcoholic solutions* precipitate acacia as a stringy mass when the alcohol amounts to more than about 35% of the total volume. Solution is effected by dilution with water. The mucilage is destroyed through precipitation of the acacia by *heavy metals*. *Borax* also causes a precipitation which is prevented by glycerin. It contains calcium and, therefore, possesses the incompatibilities of this ion.

It contains a *peroxidase* which acts as an oxidizing agent and produces colored derivatives of *aminopyrine, antipyrine, cresol, guaiacol, phenol, tannin, thymol, vanillin* and other substances. Among the alkaloids affected are *atropine, apomorphine, cocaine, homatropine, hyoscyamine, morphine, physostigmine* and *scopolamine*. A partial destruction of the alkaloid occurs in the reaction. Heating the solution of acacia for a few minutes at 100° destroys the peroxidase and the color reactions are avoided.

**Uses**—Extensively as a *suspending agent* for insoluble substances in water (page 1515), in the preparation of emulsions (pages 282 and 1509) and for making pills and troches (page 1648).

It is used for its *demulcent* action in inflammations of the throat or stomach.

Its solutions should not be used as a substitute for serum protein in the treatment of *shock* and as a *diuretic* in hypoproteinemic edema, since it produces serious syndromes that may result in death.

**Acacia Mucilage** [Mucilage of Gum Arabic]—*Preparation:* Place acacia (in small fragments, 350 g) in a graduated bottle having a wide mouth and a capacity not greatly exceeding 1000 mL, wash the drug with cold purified water, allow it to drain and add enough warm purified water, in which benzoic acid (2 g) has been dissolved, to make the product measure 1000 mL. After stoppering, lay the bottle on its side, rotate it occasionally, and when the acacia has dissolved strain the mucilage. *It also may be prepared as follows:* dissolve benzoic acid (2 g) in purified water (400 mL) with the aid of heat, and add the solution to powdered or granular acacia (350 g), in a mortar, triturating until the acacia is dissolved. Then add sufficient purified water to make the product measure 1000 mL, and strain if necessary. This second method is primarily for extemporaneous preparation. *Uses:* A *demulcent* and a *suspending agent*. It also has been employed as an *excipient* in making pills and troches, and as an *emulsifying agent* for cod liver oil and other substances. *Caution—It must be free from mold or any other indication of decomposition.*

### Agar

Agar-Agar; Vegetable Gelatin; Gelosa; Chinese or Japanese Gelatin

The dried, hydrophilic, colloidal substance extracted from *Gelidium cartilagineum* (Linné) Gaillon (Fam *Gelidiaceae*), *Gracilaria confervoides* (Linné) Greville (Fam *Sphaerococcaceae*) and related red algae (Class *Rhodophyceae*).

**Constituents**—Chiefly of the calcium salt of a galactan mono- (acid sulfate).

**Description**—Usually in bundles of thin, membranous, agglutinated strips or in cut, flaked, or granulated forms; may be weak yellowish orange, yellowish gray to pale yellow or colorless; tough when damp, brittle when dry; odorless or with a slight odor; produces a mucilaginous sensation on the tongue. Also supplied as a white to yellowish white or pale-yellow powder.

**Solubility**—Insoluble in cold water; soluble in boiling water.

**Incompatibilities**—Like other gums, it is dehydrated and precipitated from solution by *alcohol*. *Tannic acid* causes precipitation; *electrolytes* cause partial dehydration and decrease in viscosity of sols.

**Uses**—A relatively ineffective bulk-producing laxative used in a variety of proprietary cathartics. In mineral oil emulsions it acts as a stabilizer.

**Dose**—**4** to **16 g** once or twice a day.

It also is used in culture media for bacteriological work and in the manufacture of ice cream, confectionaries, etc.

## Alginic Acid

Alginic acid [9005-32-7] (average equivalent weight 200); a hydrophilic colloidal carbohydrate extracted with dilute alkali from various species of brown seaweeds (*Phaeophyceae*).

**Preparation**—Precipitates when an aqueous solution of *Sodium Alginate* is treated with mineral acid.

**Description**—White to yellowish white, fibrous powder; odorless or practically odorless, and tasteless; pH (3 in 100 dispersion in water) 1.5 to 3.5; $pK_a$ (0.1*N* NaCl, 20°) 3.42.

**Solubility**—Insoluble in water or organic solvents; soluble in alkaline solutions.

**Uses**—A *pharmaceutic aid* (tablet binder and emulsifying agent). It is used as a sizing agent in the paper and textile industries.

## Sodium Alginate

Alginic acid, sodium salt; Algin; Manucol; Norgine; Kelgin (*Kelco*)

Sodium alginate [9005-38-3] (average equivalent weight 220); the purified carbohydrate product extracted from brown seaweeds by the use of dilute alkali. It consists chiefly of the sodium salt of alginic acid, a polyuronic acid composed of beta-D-mannuronic acid residues linked so that the carboxyl group of each unit is free while the aldehyde group is shielded by a glycosidic linkage.

**Description**—Nearly odorless and tasteless, coarse or fine powder, yellowish white in color.

**Solubility**—Dissolves in water, forming a viscous, colloidal solution; insoluble in alcohol or in hydroalcoholic solutions in which the alcohol content is greater than about 30% by weight; insoluble in chloroform, ether or acids, when the pH of the solution becomes lower than about 3.

**Uses**—A *thickening* and *emulsifying agent*. This property makes it useful in a variety of areas. For example, it is used to impart smoothness and body to ice cream and to prevent formation of ice particles.

## Bentonite

Wilhinite; Soap Clay; Mineral Soap

Bentonite [1302-78-9]; a native, colloidal, hydrated aluminum silicate.

**Occurrence**—Bentonite is found in the Midwest of the US and Canada. Originally called *Taylorite* after its discoverer in Wyoming, its name was changed to bentonite after its discovery in the Fort Benton formation of the Upper Cretaceous of Wyoming.

**Description**—Very fine, odorless powder with a slightly earthy taste, free from grit; the powder is nearly white, but may be a pale buff or cream-colored.

The US Geological Survey has defined bentonite as "a transported stratified clay formed by the alteration of volcanic ash shortly after deposition." Chemically, it is $Al_2O_3.4SiO_2.H_2O$ plus other minerals as impurities. It consists of colloidal crystalline plates, of less than microscopic dimensions in thickness, and of colloidal dimensions in breadth. This fact accounts for the extreme swelling that occurs when it is placed in water, since the water penetrates between an infinite number of plates. A good specimen swells 12 to 14 times its volume.

**Solubility**—Insoluble in water or acids, but it has the property of adsorbing large quantities of water, swelling to approximately 12 times its original volume, and forming highly viscous thixotropic suspensions or *gels*. This property makes it highly useful in pharmacy. Its gel-forming property is augmented by the addition of small amounts of alkaline substances, such as magnesium oxide. It does not swell in organic solvents.

**Incompatibilities**—*Acids* and *acid salts* decrease its water-absorbing power and thus cause a breakdown of the magma. Suspensions are most stable at a pH above 7.

**Uses**—A *protective colloid* for the *stabilization of suspensions*. It also has been used as an emulsifier for oil and as a base for plasters, ointments and similar preparations.

**Bentonite Magma**—*Preparation:* Sprinkle bentonite (50 g), in portions, on hot purified water (800 g), allowing each portion to become thoroughly wetted without stirring. Allow it to stand with occasional stirring for 24 hr. Stir until a uniform magma is obtained, add purified water to make 1000 g, and mix. The magma may be prepared also by mechanical means such as by use of a blender, as follows: Place purified water (about 500 g) in the blender, and while the machine is running, add bentonite (50 g). Add purified water to make up to about 1000 g or up to the operating capacity of the blender. Blend the mixture for 5 to 10 min, add purified water to make 1000 g, and mix. *Uses:* A *suspending agent* for insoluble medicaments.

## Carbomer

Carboxypolymethylene (*Goodrich*)

A synthetic high-molecular-weight cross-linked polymer of acrylic acid; contains 56 to 68% of carboxylic acid (—COOH) groups. The viscosity of a neutralized preparation (2.5 g/500 mL water) is 30,000 to 40,000 centipoises.

**Description**—White, fluffy powder with a slight characteristic odor; hygroscopic; pH (1 in 100 dispersion) about 3; specific gravity about 1.41.

**Solubility** (neutralized with alkali hydroxides or amines)—Dissolves in water, alcohol or glycerin.

**Uses**—A *thickening, suspending, dispersing* and *emulsifying agent* for pharmaceuticals, cosmetics, waxes, paints and other industrial products.

## Carrageenan

(*FMC*)

Carrageenan [9000-07-1].

**Preparation**—The hydrocolloid extracted with water or aqueous alkali from certain red seaweeds of the class *Rhodophyceae*, and separated from the solution by precipitation with alcohol (methanol, ethanol or isopropanol) or by drum-roll drying or freezing.

**Constituents**—It is a variable mixture of potassium, sodium, calcium, magnesium and ammonium sulfate esters of galactose and 3,6-anhydrogalactose copolymers, the hexoses being alternately linked α-1,3 and β-1,4 in the polymer. The three main types of copolymers present are *kappa*-carrageenan, *iota*-carrageenan and *lambda*-carrageenan, which differ in the composition and manner of linkage of monomeric units and the degree of sulfation (the ester sulfate content for carrageenans varies from 18 to 40%). *Kappa*-carrageenan and *iota*-carrageenan are the gelling fractions; *lambda*-carrageenan is the nongelling fraction. The gelling fractions may be separated from the nongelling fraction by addition of potassium chloride to an aqueous solution of carrageenan. Carrageenan separated by drum-roll drying may contain mono- and di-glycerides or up to 5% of polysorbate 80 used as roll-stripping agents.

**Description**—Yellow-brown to white, coarse to fine powder; odorless; tasteless, producing a mucilaginous sensation on the tongue.

**Solubility**—All carrageenans hydrate rapidly in cold water, but only *lambda*-carrageenan and sodium carrageenans dissolve completely. Gelling carrageenans require heating to about 80° for complete solution where potassium and calcium ions are present.

**Uses**—In the pharmaceutical and food industries as an emulsifying, suspending and gelling agent.

## Carboxymethylcellulose Sodium

Carbose D; Carboxymethocel S; CMC; Cellulose Gum (*Aqualon*)

Cellulose, carboxymethyl ether, sodium salt [9004-32-4]; contains 6.5–9.5% of sodium (Na), calculated on the dried basis. It is available in several viscosity types: low, medium, high and extra high.

**Description**—White to cream-colored powder or granules; the powder is hygroscopic; pH (1 in 100 aqueous solution) about 7.5.

**Solubility**—Easily dispersed in water to form colloidal solutions; insoluble in alcohol, ether or most other organic solvents.

**Uses**—*Pharmaceutic aid* (suspending agent, tablet excipient or viscosity-increasing agent). In tablet form it is used as a hydrophilic colloid laxative.

**Dose**—*Usual, adult, laxative,* **1.5 g** 3 or 4 times a day.

**Dosage Form:** Tablets: 500 mg.

### Powdered Cellulose

(*Degussa*)

Cellulose [9004-34-6] $(C_6H_{10}O_5)_n$; purified, mechanically disintegrated cellulose prepared by processing alpha cellulose obtained as a pulp from fibrous plant materials.

**Description**—White, odorless substance, consisting of fibrous particles, which may be compressed into self-binding tablets which disintegrate rapidly in water; exists in various grades, exhibiting degrees of fineness ranging from a free-flowing dense powder to a coarse, fluffy, nonflowing material; pH (supernatant liquid of a 10 g/90 mL aqueous suspension after 1 hr) 5 to 7.5.

**Solubility**—Insoluble in water, dilute acids or nearly all organic solvents; slightly soluble in NaOH solution (1 in 20).

**Uses**—*Pharmaceutic aid* (tablet diluent, adsorbent or suspending agent).

**Cetyl Alcohol**—page 1401.

### Cholesterol

Cholest-5-en-3-ol, (3β)-, Cholesterin; (*Croda*)

Cholest-5-en-3β-ol [57-88-5] $C_{27}H_{46}O$ (386.66).

For the structural formula, see page 391.

A steroid alcohol widely distributed in the animal organism. In addition to cholesterol and its esters, several closely related steroid alcohols occur in the yolk of eggs, the brain, milk, fish oils, wool fat (10 to 20%), etc. These closely resemble it in properties. One of the methods of commercial production involves extraction of it from the unsaponifiable matter in the spinal cord of cattle, using petroleum benzin. Wool fat also is used as a source.

**Description**—White or faintly yellow, almost odorless pearly leaflets or granules; usually acquires a yellow to pale tan color on prolonged exposure to light or to elevated temperatures; melts 147 to 150°.

**Solubility**—Insoluble in water; 1 g slowly dissolves in 100 mL alcohol or about 50 mL dehydrated alcohol; soluble in acetone, hot alcohol, chloroform, dioxane, ether, ethyl acetate, solvent hexane or vegetable oils.

**Uses**—To enhance incorporation and emulsification of medicinal products in oils or fats. It is a *pharmaceutical necessity* for *Hydrophilic Petrolatum*, in which it enhances water-absorbing capacity. See Chapter 20.

**Docusate Sodium**—page 900.

### Gelatin

White Gelatin; (*Fallek*)

A product obtained by the partial hydrolysis of collagen derived from the skin, white connective tissues and bones of animals. Gelatin derived from an acid-treated precursor is known as Type A and exhibits an isoelectric point between pH 7 and 9, while gelatin derived from an alkali-treated precursor is known as Type B and exhibits an isoelectric point between pH 4.7 and 5.2.

Gelatin for use in the manufacture of capsules in which to dispense medicines, or for the coating of tablets, may be colored with a certified color, may contain not more than 0.15% of sulfur dioxide, may contain a suitable concentration of sodium lauryl sulfate and suitable antimicrobial agents, and may have any suitable gel strength that is designated by Bloom Gelometer number.

Regarding the special gelatin for use in the preparation of emulsions, see *Emulsions* (page 1509).

**Description**—Sheets, flakes or shreds, or a coarse to fine powder; faintly yellow or amber in color, the color varying in depth according to the particle size; slight, characteristic bouillon-like odor; stable in air when dry, but is subject to microbial decomposition when moist or in solution.

**Solubility**—Insoluble in cold water, but swells and softens when immersed in it, gradually absorbing from 5 to 10 times its own weight of water; soluble in hot water, acetic acid or hot mixtures of glycerin or water; insoluble in alcohol, chloroform, ether or fixed and volatile oils.

**Uses**—In pharmacy, to coat pills and form capsules, and as a vehicle for suppositories. It also is recommended as an emulsifying agent. See under *Emulsions* in Chapters 19 and 86, also *Suppositories* (page 1591), and *Absorbable Gelatin Sponge* (page 927). It also has been used as an adjuvant protein food in malnutrition.

**Glyceryl Monostearate**—page 1402.

### Hydroxyethyl Cellulose

Cellulose, 2-hydroxyethyl ether; Cellosize (*Union Carbide*); Natrosol (*Aqualon*)

Cellulose hydroxyethyl ether [9004-62-0].

**Preparation**—Cellulose is treated with NaOH and then reacted with ethylene oxide.

**Description**—White, odorless, tasteless, free-flowing powder; softens at about 137°; refractive index (2% solution) about 1.336; pH about 7; solutions are nonionic.

**Solubility**—Dissolves readily in cold or hot water to give clear, smooth, viscous solutions; partially soluble in acetic acid; insoluble in most organic solvents.

**Uses**—Resembles carboxymethylcellulose sodium in that it is a cellulose ether, but differs in being nonionic and, hence, its solutions are unaffected by cations. It is used pharmaceutically as a thickener, protective colloid, binder, stabilizer and suspending agent in emulsions, jellies and ointments, lotions, ophthalmic solutions, suppositories and tablets.

### Hydroxypropyl Cellulose

Cellulose, 2-hydroxypropyl ether; Klucel (*Aqualon*)

Cellulose hydroxypropyl ether [9004-64-2].

**Preparation**—After treating with NaOH, cellulose is reacted with propylene oxide at elevated temperature and pressure.

**Description**—Off-white, odorless, tasteless powder; softens at 130°; burns out completely about 475° in $N_2$ or $O_2$; refractive index (2% solution) about 1.337; pH (aqueous solution) 5 to 8.5; solutions are nonionic.

**Solubility**—Soluble in water below 40° (insoluble above 45°); soluble in many polar organic solvents.

**Uses**—A broad combination of properties useful in a variety of industries. It is used pharmaceutically as a binder, granulation agent and film-coater in the manufacture of tablets; an alcohol-soluble thickener and suspending agent for elixirs and lotions and a stabilizer for emulsions.

### Hydroxypropyl Methylcellulose

Cellulose, 2-hydroxypropyl methyl ether; (*Dow*)

Cellulose hydroxypropyl methyl ether [9004-65-3], available in grades containing 16.5 to 30.0% of methoxy and 4.0 to 32.0% of hydroxypropoxy groups, and thus in viscosity and thermal gelation temperatures of solutions of specified concentration.

**Preparation**—The appropriate grade of methylcellulose (see below) is treated with NaOH and reacted with propylene oxide at elevated temperature and pressure and for a reaction time sufficient to produce the desired degree of attachment of methyl and hydroxypropyl groups by ether linkages to the anhydroglucose rings of cellulose.

**Description**—White to slightly off-white, fibrous or granular, free-flowing powder.

**Solubility**—Swells in water and produces a clear to opalescent, viscous colloidal mixture; undergoes reversible transformation from sol to gel on heating and cooling, respectively. Insoluble in anhydrous alcohol, ether or chloroform.

**Uses**—A protective colloid that is useful as a dispersing and thickening agent, and in ophthalmic solutions to provide the demulcent action and viscous properties essential for contact-lens use and in "artificial-tear" formulations. See *Hydroxypropyl Methylcellulose Ophthalmic Solution* (page 869).

**Lanolin, Anhydrous**—page 1401.

### Methylcellulose

Cellulose, methyl ether; Methocel (*Dow*)

Cellulose methyl ether [9004-67-5]; a methyl ether of cellulose containing 27.5 to 31.5% of methoxy groups.

**Preparation**—By the reaction of methyl chloride or of dimethyl sulfate on cellulose dissolved in sodium hydroxide. The cellulose methyl ether so formed is coagulated by adding methanol or other suitable agent and centrifuged. Since cellulose has 3 hydroxyl groups/glucose residue, several methylcelluloses can be made varying, among other properties, in solubility and viscosity. Types useful for pharmaceutical application contain from 1 to 2 methoxy radicals/glucose residue.

**Description**—White, fibrous powder or granules; aqueous suspensions neutral to litmus; stable to alkalies and dilute acids.

**Solubility**—Insoluble in ether, alcohol or chloroform; soluble in glacial acetic acid or in a mixture of equal parts of alcohol and chloroform; swells in water, producing a clear to opalescent, viscous colloidal solution; insoluble in hot water and saturated salt solutions; salts of minerals acids and particularly of polybasic acids, phenols and tannins coagulate its

solutions, but this can be prevented by the addition of alcohol or of glycol diacetate.

**Uses**—A synthetic substitute for natural gums that has both pharmaceutic and therapeutic applications. Pharmaceutically, it is used as a *dispersing, thickening, emulsifying, sizing* and *coating agent*. It is an ingredient of many nose drops, eye preparations, burn medications, cosmetics, tooth pastes, liquid dentifrices, hair fixatives, creams and lotions. It functions as a protective colloid for many types of dispersed substances and is an effective stabilizer for oil-in-water emulsions.

Therapeutically, it is used as a *bulk laxative* in the treatment of *chronic constipation*. Taken with 1 or 2 glassesful of water, it forms a colloidal solution in the upper alimentary tract; this solution loses water in the colon, forming a gel that increases the bulk and softness of the stool. The gel is bland, demulcent and nonirritating to the gastrointestinal tract. Once a normal stool develops, the dose should be reduced to a level adequate for maintenance of good function. Although it takes up water from the gastrointestinal tract quite readily, methylcellulose tablets have caused fecal impaction and intestinal obstruction when taken with a limited amount of water. It also is used as a topical ophthalmic protectant, in the form of 0.5 to 1% solution serving as artificial tears or a contact-lens solution applied to the conjunctiva, 0.05 to 0.1 mL at a time, 3 or 4 times a day as needed.

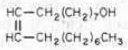
**Dose**—*Usual*, as laxative, **1** to **1.5 g**, with water, 2 to 4 times a day.

**Dosage Forms**—Tablets: 500 mg; Ophthalmic Solution: 0.5 and 1%; Syrup: 5.91 g/30 mL.

## Octoxynol 9—see RPS-18, page 1307.

### Oleyl Alcohol

9-Octadecen-1-ol, (*Z*)-, Aldol 85 (*Sherex*)



(*Z*)-9-Octadecen-1-ol [143-28-2] $C_{18}H_{36}O$ (268.48); a mixture of unsaturated and saturated high-molecular-weight fatty alcohols consisting chiefly of oleyl alcohol.

**Preparation**—One method reacts ethyl oleate with absolute ethanol and metallic sodium (*Org Syn Coll III:* 673, 1955).

**Description**—Clear, colorless to light yellow, oily liquid; faint characteristic odor and bland taste; iodine value between 85 and 90; hydroxyl value between 205 and 215.

**Solubility**—Soluble in alcohol, ether, isopropyl alcohol or light mineral oil; insoluble in water.

**Uses**—*A pharmaceutic aid* (emulsifying agent or emollient).

### Polyvinyl Alcohol

Ethenol, homopolymer; (*Du Pont*)

Vinyl alcohol polymer [9002-89-5] $(C_2H_4O)_n$.

**Preparation**—Polyvinyl acetate is approximately 88% hydrolyzed in a methanol-methyl acetate solution using either mineral acid or alkali as a catalyst.

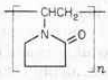
**Description**—White to cream-colored powder or granules; odorless.

**Solubility**—Freely soluble in water; solution effected more rapidly at somewhat elevated temperatures.

**Uses**—A *suspending agent* and *emulsifier*, either with or without the aid of a surfactant. It commonly is employed as a lubricant and protectant in various ophthaimic preparations, such as decongestants, artificial tears and contact-lens products (see page 1574).

### Povidone

2-Pyrrolidinone, 1-ethenyl-, homopolymer; Polyvinylpyrrolidone; PVP (*ISP*; *BASF*)



1-Vinyl-2-pyrrolidinone polymer [9003-39-8] $(C_6H_9NO)_n$; a synthetic polymer consisting of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights. It is produced commercially as a series of products having mean molecular weights ranging from about 10,000 to about 700,000. The viscosity of solutions containing 10% or less is essentially the same as that of water; solutions more concentrated than 10% become more viscous, depending upon the concentration and the molecular weight of the polymer used. It contains 12 to 13% of nitrogen.

**Preparation**—1,4-Butanediol is dehydrogenated thermally with the aid of copper to γ-butyrolactone, which is then reacted with ammonia to form 2-pyrrolidinone. Addition of the latter to acetylene yields vinylpyrrolidinone (monomer) which is polymerized thermally in the presence of hydrogen peroxide and ammonia.

**Description**—White to creamy white, odorless powder, hygroscopic; pH (1 in 20 solution) 3 to 7.

**Solubility**—Soluble in water, alcohol or chloroform; insoluble in ether.

**Uses**—A *dispersing* and *suspending* agent in pharmaceutical preparations.

### Propylene Glycol Monostearate

Octadecanoic acid, monoester with 1,2-propanediol

1,2-Propanediol monostearate [1323-39-3]; a mixture of the propylene glycol mono- and diesters of stearic and palmitic acids. It contains not less than 90% of monoesters of saturated fatty acids, chiefly propylene glycol monostearate ($C_{21}H_{42}O_3$) and propylene glycol monopalmitate ($C_{19}H_{38}O_3$).

**Preparation**—By reacting propylene glycol with stearoyl chloride in a suitable dehydrochlorinating environment.

**Description**—White, wax-like solid or white, wax-like beads or flakes; slight, agreeable, fatty odor and taste; congeals not lower than 45°; acid value not more than 2; saponification value 155 to 165; hydroxyl value 150 to 170; iodine value not more than 3.

**Solubility**—Dissolves in organic solvents such as alcohol, mineral or fixed oils, benzene, ether or acetone; insoluble in water but may be dispersed in hot water with the aid of a small amount of soap or other suitable surface-active agent.

**Uses**—A *surfactant*. It is particularly useful as a dispersing agent for perfume oils or oil-soluble vitamins in water, and in cosmetic preparations.

## Silicon Dioxide, Colloidal—page 1413.

### Sodium Lauryl Sulfate

Sulfuric acid monododecyl ester sodium salt; Irium; Duponol C (*Du Pont*); Gardinol WA (*Procter & Gamble*)

Sodium monododecyl sulfate [151-21-3]; a mixture of sodium alkyl sulfates consisting chiefly of sodium lauryl sulfate. The combined content of sodium chloride and sodium sulfate is not more than 8%.

**Preparation**—The fatty acids of coconut oil, consisting chiefly of lauric acid, are catalytically hydrogenated to form the corresponding alcohols. The latter are then esterified with sulfuric acid (sulfated) and the resulting mixture of alkyl bisulfates (alkylsulfuric acids) is converted into a mixture of sodium salts by reacting with alkali under controlled conditions of pH.

**Description**—Small, white or light yellow crystals having a slight, characteristic odor.

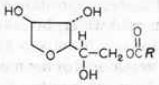
**Solubility**—1 g in 10 mL water, forming an opalescent solution.

**Incompatibilities**—Reacts with *cationic surface-active agents* with loss of activity, even in concentrations too low to cause precipitation. Unlike soaps, it is compatible with dilute acids, and calcium and magnesium ions.

**Uses**—An emulsifying, detergent and wetting agent in ointments, tooth powders and other pharmaceutical preparations, and in the metal, paper and pigment industries.

### Sorbitan Esters

Spans (*Atlas*)



Sorbitan esters (*monolaurate* [1338-39-2]; *monooleate* [1338-43-8]; *monopalmitate* [26266-57-9]; *monostearate* [1338-41-6]; *trioleate* [26266-58-0]; *tristearate* [26658-19-5]).

**Preparation**—Sorbitol is dehydrated to form a *hexitan* which is then esterified with the desired fatty acid. See *Polysorbates*, page 1403, which are polyethylene glycol ethers of sorbitan fatty acid esters.

**Description**—*Monolaurate:* Amber, oily liquid; may become hazy or form a precipitate; viscosity about 4250 cps; HLB no 8.6; acid no 7.0 max; saponification no 158 to 170; hydroxyl no 330 to 358. *Monooleate:* Amber liquid; viscosity about 1000 cps; HLB no 4.3; acid no 8.0 max; saponification no 145 to 160; hydroxyl no 193 to 210. *Monopalmitate:* Tan, granular waxy solid; HLB no 6.7; acid no 4 to 7.5; saponification no 140 to 150; hydroxyl no 275 to 305. *Monostearate:* Cream to tan beads; HLB no 4.7; acid no 5 to 10; saponification no 147 to 157; hydroxyl no 235 to 260. *Trioleate:* Amber, oily liquid; viscosity about 200 cps; HLB no 1.8; acid no 15 max; saponification no 170 to 190; hydroxyl no 55 to 70. *Tristearate:* Tan, waxy beads; HLB no 2.1; acid no 12 to 15; saponification no 176 to 188; hydroxyl no 66 to 80.

**Solubility**—*Monolaurate:* Soluble in methanol or alcohol; dispersible in distilled water and hard water (200 ppm); insoluble in hard water (20,000 ppm). *Monooleate:* Soluble in most mineral or vegetable oils; slightly soluble in ether; dispersible in water; insoluble in acetone. *Monopalmitate:* Dispersible (50°) in distilled water or hard water (200 ppm); soluble in ethyl acetate; insoluble in cold distilled water or hard water (20,000 ppm). *Monostearate:* Soluble (above melting point) in vegetable oils or mineral oil; insoluble in water, alcohol or propylene glycol. *Trioleate:* Soluble in mineral oil, vegetable oils, alcohol or methanol; insoluble in water. *Tristearate:* Soluble in isopropyl alcohol; insoluble in water.

**Uses**—Nonionic *surfactants* used as *emulsifying agents* in the preparation of water-in-oil emulsions.

**Stearic Acid**—page 1402.

### Stearyl Alcohol

1-Octadecanol [112-92-5] $C_{18}H_{38}O$ (270.50); contains not less than 90% of stearyl alcohol, the remainder consisting chiefly of cetyl alcohol [$C_{16}H_{34}O$ = 242.44].

**Preparation**—Through the reducing action of lithium aluminum hydride on ethyl stearate.

**Description**—White, unctuous flakes or granules having a faint, characteristic odor and a bland taste; melts 55 to 60°.

**Solubility**—Insoluble in water; soluble in alcohol, chloroform, ether or vegetable oils.

**Uses**—A surface-active agent used to *stabilize emulsions* and increase their ability to retain large quantities of water. See *Hydrophilic Ointment* (page 1402). *Hydrophilic Petrolatum* (page 1401).

**Sterculia Gum**—see RPS-18, page 788.

### Tragacanth

Gum Tragacanth; Hog Gum; Goat's Thorn

The dried gummy exudation from *Astragalus gummifer* Labillardière, or other Asiatic species of *Astragalus* (Fam. *Leguminosae*).

**Constituents**—60 to 70% bassorin and 30 to 40% soluble gum (*tragacanthin*). The bassorin swells in the presence of water to form a gel and tragacanthin forms a colloidal solution. Bassorin, consisting of complex methoxylated acids, resembles pectin. Tragacanthin yields glucuronic acid and arabinose when hydrolyzed.

**Description**—Flattened, lamellated, frequently curved fragments or straight or spirally twisted linear pieces 0.5 to 2.5 mm in thickness; white to weak-yellow in color; translucent; horny in texture; odorless; insipid, mucilaginous taste. When powdered, it is white to yellowish white.

Introduced into water, tragacanth absorbs a certain proportion of that liquid, swells very much, and forms a soft adhesive paste, but does not dissolve. If agitated with an excess of water, this paste forms a uniform mixture; but in the course of 1 or 2 days the greater part separates, and is deposited, leaving a portion dissolved in the supernatant fluid. The finest mucilage is obtained from the whole gum or *flake* form. Several days should be allowed for obtaining a uniform mucilage of the maximum gel strength. A common adulterant is *Karaya Gum*, and the USP/NF has introduced tests to detect its presence.

**Solubility**—Insoluble in alcohol.

**Uses**—A *suspending agent* in lotions, mixtures and extemporaneous preparations and prescriptions. It is used with emulsifying agents largely to increase consistency and retard creaming. It is sometimes used as a *demulcent* in sore throat, and the jelly-like product formed when the gum is allowed to swell in water serves as a basis for pharmaceutical jellies, eg, *Ephedrine Sulfate Jelly*. It also is used in various confectionery products. In the form of a glycerite, it has been used as a pill excipient.

**Tragacanth Mucilage**—*Preparation:* Mix glycerin (18 g) with purified water (75 mL) in a tared vessel, heat the mixture to boiling, discontinue the application of heat, add tragacanth (6 g) and benzoic acid (0.2 g) and macerate the mixture during 24 hr, stirring occasionally. Then add enough purified water to make the mixture weigh 100 g, stir actively until of uniform consistency, and strain forcibly through muslin. *Uses:* A suspending agent for insoluble substances in internal mixtures. It is also a *protective* agent.

### Xanthan Gum

Keltrol (*Kelco*)

A high-molecular-weight polysaccharide gum produced by a pure-culture fermentation of a carbohydrate with *Xanthomonas campestris*, then purified by recovery with isopropyl alcohol, dried and milled; contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid, and is prepared as sodium, potassium or calcium salt; yields 4.2 to 5% of carbon dioxide.

**Preparation**—See above and US Pats 3,433,708 and 3,557,016.

**Description**—White or cream-colored, tasteless powder with a slight organic odor; powder and solutions stable at 25° or less; does not exhibit polymorphism; aqueous solutions are neutral to litmus.

**Solubility**—1 g in about 3 mL alcohol; soluble in hot or cold water.

**Uses**—A hydrophilic colloid to thicken, suspend, emulsify and stabilize water-based systems.

### Other Emulsifying and Suspending Agents

**Chondrus** [Irish Moss; Carrageenan]—The dried sun-bleached plant of *Chondrus crispus* (Linné) Stackhouse (Fam *Gigartinaceae*). *Uses:* Principally, as an emulsifying agent for liquid petrolatum and for cod liver oil. It is also a protective. See also page 1396.

**Malt**—The partially germinated grain of one or more varieties of *Hordeum vulgare* Linné (Fam *Gramineae*) and contains amylolytic enzymes. Yellowish or amber-colored grains, having a characteristic odor and a sweet taste. The evaporated aqueous extract constitutes malt extract.

**Malt Extract**—The product obtained by extracting malt, the partially and artificially germinated grain of one or more varieties of *Hordeum vulgare* Linné (Fam *Gramineae*). *Uses:* An infrequently used emulsifying agent.

# Ointment Bases

Ointments are semisolid preparations for external application to the body. They should be of such composition that they soften, but not necessarily melt, when applied to the skin. Therapeutically, ointments function as protectives and emollients for the skin, but are used primarily as vehicles or bases for the topical application of medicinal substances. Ointments also may be applied to the eye or eyelids.

Ideally, an ointment base should be compatible with the skin, stable, permanent, smooth and pliable, nonirritating, nonsensitizing, inert and readily able to release its incorporated medication. Since there is no single ointment base which possesses all these characteristics, continued research in this field has resulted in the development of numerous new bases. Indeed, ointment bases have become so numerous as to require classification. Although ointment bases may be grouped in several ways, it is generally agreed that they can be classified best according to composition. Hence, the following four classes are recognized herein: oleaginous, emulsifiable, emulsion bases and water-soluble.

For completeness, substances are included that, although not used alone as ointment bases, contribute some pharmaceutical property to one or more of the various bases.

## Oleaginous Ointment Bases and Components

The oleaginous ointment bases include fixed oils of vegetable origin, fats obtained from animals and semisolid hydrocarbons obtained from petroleum. The vegetable oils are used chiefly in ointments to lower the melting point or to soften bases. These oils can be used as a base in themselves when a high percentage of powder is incorporated.

The vegetable oils and the animal fats have two marked disadvantages as ointment bases: their water-absorbing capacity is low and they have a tendency to become rancid. Insofar as vegetable oils are concerned, the second disadvantage can be overcome by hydrogenation, a process which converts many fixed oils into white, semisolid fats or into hard, almost brittle, waxes.

The hydrocarbon bases comprise a group of substances with a wide range of melting points so that any desired consistency and melting point may be prepared with representatives of this group. They are stable, bland, chemically inert and will mix with virtually any chemical substance. Oleaginous bases are excellent emollients.

### White Ointment

Ointment USP XI; Simple Ointment

| | |
|---|---|
| **White Wax** | **50 g** |
| **White Petrolatum** | **950 g** |
| To make | **1000 g** |

Melt the white wax in a suitable dish on a water bath, add the white petrolatum, warm until liquefied, then discontinue the heating, and stir the mixture until it begins to congeal. It is permissible to vary the proportion of wax to obtain a suitable consistency of the ointment under different climatic conditions.

**Uses**—An emollient and vehicle for other ointments.

### Yellow Ointment

| | |
|---|---|
| **Yellow Wax** | **50 g** |
| **Petrolatum** | **950 g** |
| To make | **1000 g** |

Melt the yellow wax in a suitable dish on a steam bath, add the petrolatum, warm until liquefied, then discontinue the heating, and stir the mixture until it begins to congeal. It is permissible to vary the proportion of wax to obtain a suitable consistency of the ointment under different climatic conditions.

**Uses**—An emollient and vehicle for other ointments. Both white and yellow ointment are known as "simple ointment." White ointment should be used to prepare white ointments and yellow ointments should be used to prepare colored ointments when simple ointment is prescribed.

### Cetyl Esters Wax

"Synthetic Spermaceti"

A mixture consisting primarily of esters of saturated fatty alcohols ($C_{14}$ to $C_{18}$) and saturated fatty acids ($C_{14}$ to $C_{18}$). It has a saponification value of 109 to 120 and an acid value of not more than 5.

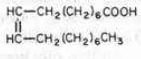
**Description**—White to off-white, somewhat translucent flakes; crystalline structure and pearly luster when caked; faint odor and a bland, mild taste; free from rancidity; specific gravity 0.820 to 0.840 at 50°; iodine value not more than 1; melts 43 to 47°.

**Solubility**—Insoluble in water; practically insoluble in cold alcohol; soluble in boiling alcohol, ether, chloroform or fixed and volatile oils; slightly soluble in cold solvent hexane.

**Uses**—A replacement for spermaceti used to give consistency and texture to ointments, eg, *Cold Cream* and *Rose Water Ointment.*

### Oleic Acid

(*Z*)-9-Octadecenoic acid; Oleinic Acid; Elaic Acid



Oleic acid [112-80-1] obtained from tallow and other fats, and consists chiefly of (*Z*)-9-octadecenoic acid (282.47). Oleic acid used in preparations for internal administration is derived from edible sources.

It usually contains variable amounts of the other fatty acids present in tallow such as linolenic and stearic acids.

**Preparation**—Obtained as a by-product in the manufacture of the solid stearic and palmitic acids used in the manufacture of candles, stearates and other products. The crude oleic acid is known as "red oil," the stearic and palmitic acids being separated by cooling.

**Description**—Colorless to pale yellow, oily liquid; lard-like odor and taste; specific gravity 0.889 to 0.895; congeals at a temperature not above 10°; pure acid solidifies at 4°; at atmospheric pressure it decomposes when heated at 80 to 100°; on exposure to air it gradually absorbs oxygen, darkens and develops a rancid odor.

**Solubility**—Practically insoluble in water; miscible with alcohol, chloroform, ether, benzene or fixed and volatile oils.

**Incompatibilities**—Reacts with *alkalies* to form soaps. *Heavy metals* and *calcium salts* form insoluble oleates. *Iodine solutions* are decolorized by formation of the iodine addition compound of the acid. It is oxidized to various derivatives by *nitric acid, potassium permanganate* and other agents.

**Uses**—Classified as an emulsion adjunct, which reacts with alkalis to form soaps that function as emulsifying agents; it is used for this purpose in such preparations as *Benzyl Benzoate Lotion* and *Green Soap.* It also is used to prepare oleate salts of bases.

**Olive Oil**—see RPS-18, page 1309.

### Paraffin

Paraffin Wax, Hard Paraffin

A purified mixture of solid hydrocarbons obtained from petroleum.

**Description**—Colorless or white, more or less translucent mass with a crystalline structure; slightly greasy to the touch; odorless and tasteless; congeals 47 to 65°.

**Solubility**—Freely soluble in chloroform, ether, volatile oils or most warm fixed oils; slightly soluble in dehydrated alcohol; insoluble in water or alcohol.

**Uses**—Mainly, to increase the consistency of some ointments.

### Petrolatum

Yellow Soft Paraffin; Amber Petrolatum; Yellow Petrolatum; Petroleum Jelly; Paraffin Jelly

A purified mixture of semisolid hydrocarbons obtained from petroleum. It may contain a suitable stabilizer.

**Preparation**—The "residuums," as they are termed technically, which are obtained by the distillation of petroleum, are purified by melting, usually treating with sulfuric acid and then percolating through recently burned bone black or adsorptive clays; this removes the odor and modifies the color. Selective solvents are also sometimes employed to extract impurities.

It has been found that the extent of purification required to produce *Petrolatum* and *Light Mineral Oil* of official quality removes antioxidants that are naturally present, and the purified product subsequently has a tendency to oxidize and develop an offensive odor. This is prevented by the addition of a minute quantity of α-tocopherol, or other suitable antioxidant, as is now permissible.

**Description**—Unctuous mass of yellowish to light amber color; not more than a slight fluorescence after being melted; transparent in thin layers; free or nearly free from odor and taste; specific gravity 0.815 to 0.880 at 60°; melts between 38 and 60°.

**Solubility**—Insoluble in water; almost insoluble in cold or hot alcohol or in cold dehydrated alcohol; freely soluble in benzene, carbon disulfide, chloroform or turpentine oil; soluble in ether, solvent hexane or in most

fixed and volatile oils, the degree of solubility in these solvents varying with the composition of the petrolatum.

**Uses**—A base for ointments. It is highly occlusive and therefore a good emollient but it may not release some drugs readily.

### White Petrolatum

White Petroleum Jelly; White Soft Paraffin

A purified mixture of semisolid hydrocarbons obtained from petroleum, and wholly or nearly decolorized. It may contain a suitable stabilizer.

**Preparation**—In the same manner as petrolatum, the purification treatment being continued until the product is practically free from yellow color.

**Description**—White or faintly yellowish, unctuous mass; transparent in thin layers, even after cooling to 0°; specific gravity 0.815 to 0.880 at 60°; melts 38 to 60°.

**Solubility**—Similar to that described under *Petrolatum*.

**Uses**—Similar to yellow petrolatum but often is preferred because of its freedom from color. It is employed as a protective, a base for ointments and cerates and to form the basis for burn dressings. See *Petrolatum Gauze* (page 867).

**Spermaceti**—see RPS-18, page 1310.

**Starch Glycerite**—see RPS-18, page 1310.

**White Wax**—see RPS-18, page 1310.

**Yellow Wax**—see RPS-18, page 1311.

## Absorbent Ointment Bases

The term absorbent is used here to denote the water-absorbing or emulsifying properties of these bases and not to describe their action on the skin. These bases, sometimes called *emulsifiable ointment bases*, are generally anhydrous substances which have the property of absorbing (emulsifying) considerable quantities of water and still retaining their ointment-like consistency. Preparations of this type do not contain water as a component of their basic formula, but if water is incorporated, when and as desired, a W/O emulsion results. The following official products fall into this category.

**Hydroxystearin Sulfate**—see RPS-18, page 1311.

### Anhydrous Lanolin

Wool Fat USP XVI; Refined Wool Fat

Lanolin that contains not more than 0.25% of water.

**Constituents**—Contains the sterols *cholesterol* [$C_{27}H_{45}OH$] and *oxycholesterol*, as well as triterpene and aliphatic alcohols. About 7% of the alcohols are found in the free state, the remainder occurring as esters of the following fatty acids: *carnaubic, cerotic, lanoceric, lanopalmitic, myristic* and *palmitic*. Some of these are found free. The emulsifying and emollient actions of lanolin are due to the alcohols that are found in the unsaponifiable fraction when lanolin is treated with alkali. Constituting approximately one-half of this fraction and known as *lanolin alcohols*, the latter is comprised of *cholesterol* (30%), *lanosterol* (25%), *cholestanol* (*dihydrocholesterol*) (3%), *agnosterol* (2%) and various other alcohols (40%).

**Preparation**—By purifying the fatty matter (*suint*) obtained from the wool of the sheep. This natural wool fat contains about 30% of free fatty acids and fatty acid esters of *cholesterol* and other higher alcohols. The cholesterol compounds are the important constituents and, to secure these in a purified form, many processes have been devised. In one of these the crude wool fat is treated with weak alkali, the saponified fats and emulsions centrifuged to secure the aqueous soap solution, from which, on standing, a layer of partially purified wool fat separates. This product is further purified by treating it with calcium chloride and then dehydrated by fusion with unslaked lime. It is finally extracted with acetone and the solvent subsequently separated by distillation. This differs from lanolin in that the former contains practically no water.

**Description**—Yellow, tenacious, unctuous mass; slight, characteristic odor; melts between 36 and 42°.

**Solubility**—Insoluble in water, but mixes without separation with about twice its weight of water; sparingly soluble in cold alcohol; more soluble in hot alcohol; freely soluble in ether or chloroform.

**Uses**—An ingredient of ointments, especially when an aqueous liquid is to be incorporated. It gives a distinctive quality to the ointment, increasing absorption of active ingredients and maintaining a uniform consistency for the ointment under most climatic conditions. However, it has been omitted from many ointments on the recommendation of dermatologists who have found that many patients are allergic to this animal wax.

### Hydrophilic Petrolatum

| | |
|---|---|
| **Cholesterol** | **30 g** |
| **Stearyl Alcohol** | **30 g** |
| **White Wax** | **80 g** |
| **White Petrolatum** | **860 g** |
| To make | **1000 g** |

Melt the stearyl alcohol, white wax, and white petrolatum together on a steam bath, then add the cholesterol, and stir until it completely dissolves. Remove from the bath, and stir until the mixture congeals.

**Uses**—A *protective* and *water-absorbable ointment base*. It will absorb a large amount of water from aqueous solutions of medicating substances, forming a W/O type of emulsion. See *Ointments* (page 1585).

## Emulsion Ointment Bases and Components

Emulsion ointment bases are actually semisolid emulsions. These preparations can be divided into two groups on the basis of emulsion type: emulsion ointment base water- in-oil (W/O) type and emulsion ointment base oil-in-water (O/W) type. Bases of both types will permit the incorporation of some additional amounts of water without reducing the consistency of the base below that of a soft cream. However, only O/W emulsion ointment bases can be removed readily from the skin and clothing with water. W/O emulsions are better emollients and protectants than are O/W emulsions. W/O emulsions can be diluted with oils.

### Cetyl Alcohol

Cetostearyl Alcohol; "Palmityl" Alcohol; Aldol 52 (*Sherex*)

$CH_3(CH_2)_{14}CH_2OH$

1-Hexadecanol [124-29-8] $C_{16}H_{34}O$ (242.44); a mixture of not less than 90% of cetyl alcohol, the remainder chiefly stearyl alcohol.

**Preparation**—By catalytic hydrogenation of palmitic acid, or saponification of spermaceti, which contains cetyl palmitate.

**Description**—Unctuous, white flakes, granules, cubes or castings; faint characteristic odor and a bland, mild taste; melts 45 to 50°; not less than 90% distils between 316 and 336°.

**Solubility**—Insoluble in water; soluble in alcohol, chloroform, ether or vegetable oils.

**Uses**—Similar to *Stearyl Alcohol* (page 1399). It also imparts a smooth texture to the skin and is used widely in cosmetic creams and lotions.

### Cold Cream

Petrolatum Rose Water Ointment USP XVI

| | |
|---|---|
| **Cetyl Esters Wax** | **125 g** |
| **White Wax** | **120 g** |
| **Mineral Oil** | **560 g** |
| **Sodium Borate** | **5 g** |
| **Purified Water** | **190 mL** |
| To make about | **1000 g** |

Reduce the cetyl esters wax and the white wax to small pieces, melt them on a steam bath with the mineral oil and continue heating until the temperature of the mixture reaches 70°. Dissolve the sodium borate in the

purified water, warmed to 70° and gradually add the warm solution to the melted mixture, stirring rapidly and continuously until it has congealed.

If the ointment has been chilled, warm it slightly before attempting to incorporate other ingredients (see USP for allowable variations).

**Uses**—Useful as an emollient, cleansing cream and ointment base. It resembles *Rose Water Ointment*, differing only in that mineral oil is used in place of almond oil and omitting the fragrance. This change produces an ointment base which is not subject to rancidity like one containing a vegetable oil. This is a W/O emulsion.

### Glyceryl Monostearate

Octadecanoic acid, monoester with 1,2,3-propanetriol

Monostearin [31566-31-1]; a mixture chiefly of variable proportions of glyceryl monostearate [$C_3H_5(OH)_2C_{18}H_{35}O_2$ = 358.56] and glyceryl monopalmitate [$C_3H_5(OH)_2C_{16}H_{31}O_2$ = 330.51].

**Preparation**—Among other ways, by reacting glycerin with commercial stearoyl chloride.

**Description**—White, wax-like solid or occurs in the form of white, wax-like beads, or flakes; slight, agreeable, fatty odor and taste; does not melt below 55°; affected by light.

**Solubility**—Insoluble in water, but may be dispersed in hot water with the aid of a small amount of soap or other suitable surface-active agent; dissolves in hot organic solvents such as alcohol, mineral or fixed oils, benzene, ether or acetone.

**Uses**—A thickening and emulsifying agent for ointments. See *Ointments* (page 1585).

### Hydrophilic Ointment

| | |
|---|---|
| **Methylparaben** | **0.25 g** |
| **Propylparaben** | **0.15 g** |
| **Sodium Lauryl Sulfate** | **10 g** |
| **Propylene Glycol** | **120 g** |
| **Stearyl Alcohol** | **250 g** |
| **White Petrolatum** | **250 g** |
| **Purified Water** | **370 g** |
| To make about | **1000 g** |

Melt the stearyl alcohol and the white petrolatum on a steam bath, and warm to about 75°. Add the other ingredients, previously dissolved in the water and warmed to 75°, and stir the mixture until it congeals.

**Uses**—A *water-removable ointment base* for the so-called "washable" ointments. This is an O/W emulsion.

### Lanolin

Hydrous Wool Fat

The purified, fat-like substance from the wool of sheep, *Ovis aries* Linné (Fam *Bovidae)*; contains 25 to 30% water.

**Description**—Yellowish white, ointment-like mass, having a slight, characteristic odor; when heated on a steam bath it separates into an upper oily and a lower water layer; when the water is evaporated a residue of *Lanolin* remains which is transparent when melted.

**Solubility**—Insoluble in water; soluble in chloroform or ether with separation of its water of hydration.

**Uses**—Largely as a vehicle for ointments, for which it is admirably adapted, on account of its compatibility with skin lipids. It emulsifies aqueous liquids. Lanolin is a W/O emulsion.

### Rose Water Ointment

Cold Cream; Galen's Cerate

| | |
|---|---|
| **Cetyl Esters Wax** | **125 g** |
| **White Wax** | **120 g** |
| **Almond Oil** | **560 g** |
| **Sodium Borate** | **5 g** |
| **Stronger Rose Water** | **25 mL** |
| **Purified Water** | **165 mL** |
| **Rose Oil** | **0.2 mL** |
| To make about | **1000 g** |

Reduce the cetyl esters wax and the white wax to small pieces, melt them on a steam bath, add the almond oil and continue heating until the temperature of the mixture reaches 70°. Dissolve the sodium borate in the purifed water and stronger rose water, warmed to 70°, and gradually add the warm solution to the melted mixture, stirring rapidly and continuously until it has cooled to about 45°. Incorporate the rose oil.

It must be free from rancidity. If the ointment has been chilled, warm it slightly before attempting to incorporate other ingredients (see USP for allowable variations).

**History**—Originated by Galen, the famous Roman physician-pharmacist of the 1st century AD, was known for many centuries by the name of *Unguentum* or *Ceratum Refrigerans*. It has changed but little in proportions or method of preparation throughout many centuries.

**Uses**—An *emollient* and *ointment base*. It is a W/O emulsion.

### Stearic Acid

Octadecanoic acid; Cetylacetic Acid; Stearophanic Acid

Stearic acid [57-11-4]; a mixture of stearic acid [$C_{18}H_{36}O_2$ = 284.48] and palmitic acid [$C_{16}H_{32}O_2$ = 256.43], which together constitute not less than 90.0% of the total content. The content of each is not less than 40.0% of the total.

*Purified Stearic Acid USP* is a mixture of the same acids which together constitute not less than 96.0% of the total content, and the content of $C_{18}H_{36}O_2$ is not less than 90.0% of the total.

**Preparation**—From edible fats and oils (see exception below) by boiling them with soda lye, separating the glycerin and decomposing the resulting soap with sulfuric or hydrochloric acid. The stearic acid subsequently is separated from any oleic acid by cold expression. It also is prepared by the hydrogenation and subsequent saponification of *olein*. It may be purified by recrystallization from alcohol.

**Description**—Hard, white or faintly yellowish somewhat glossy and crystalline solid, or a white or yellowish white powder; an odor and taste suggestive of tallow; melts about 55.5° and should not congeal at a temperature below 54°; the purified acid melts at 69 to 70° and congeals between 66 and 69°; slowly volatilizes between 90 and 100°.

**Solubility**—Practically insoluble in water; 1 g in about 20 mL alcohol, 2 mL chloroform, 3 mL ether, 25 mL acetone or 6 mL carbon tetrachloride; freely soluble in carbon disulfide; also soluble in amyl acetate, benzene or toluene.

**Incompatibilities**—Insoluble stearates are formed with many *metals*. Ointment bases made with stearic acid may show evidence of drying out or lumpiness due to such a reaction when *zinc* or *calcium* salts are compounded therein.

**Uses**—In the preparation of sodium stearate which is the solidifying agent for the official glycerin suppositories, in enteric tablet coating, ointments and for many other commercial products, such as toilet creams, vanishing creams, solidified alcohol, etc. (When labeled solely for external use, it is exempt from the requirement that it be prepared from edible fats and oils.)

**Wool Alcohols BP**—see RPS-18, page 1312.

## *Water-Soluble Ointment Bases and Components*

Included in this section are bases prepared from the higher ethylene glycol polymers (PEG). These polymers are marketed under the trademark of Carbowax. The polymers have a wide range in molecular weight. Those with molecular weights ranging from 200 to 700 are liquids; those above 1000 are wax-like solids. The polymers are water-soluble, nonvolatile and unctuous agents. They do not hydrolyze or deteriorate and will not support mold growth. These properties account for their wide use in washable ointments. Mixtures of PEG are used to give bases of various consistency, such as very soft to hard bases for suppositories.

### Glycol Ethers and Derivatives

This special class of ethers is of considerable importance in pharmaceutical technology. Both mono- and polyfunctional compounds are represented in the group. The simplest member is ethylene oxide [$\overline{CH_2CH_2O}$], the internal or cyclic ether of the simplest glycol, ethylene glycol [$HOCH_2CH_2OH$]. External mono- and diethers of ethylene glycol [$ROCH_2CH_2OH$ and $ROCH_2CH_2OR'$] are well-known due largely to research done by Union Carbide.

**Preparation**—In the presence of NaOH at temperatures of the order of 120° to 135° and under a total pressure of about 4 atmospheres, ethylene oxide reacts with ethylene glycol to form compounds having the general formula $HOCH_2(CH_2OCH_2)_nCH_2OH$, commonly referred to as condensation polymers and termed polyethylene (or polyoxyethylene) glycols. Other glycols besides ethylene glycol function in similar capacity, and the commercial generic term adopted for the entire group is polyalkylene (or polyoxyalkylene) glycols.

**Nomenclature**—It is to be noted that these condensation polymers are bifunctional; ie, they contain both ether and alcohol linkages. The compound wherein $n = 1$ is the commercially important diethylene glycol [$HOCH_2CH_2OCH_2CH_2OH$], and its internal ether is the familiar dioxane [$\overline{CH_2CH_2OCH_2CH_2O}$]. The mono- and diethers derived from diethylene glycol have the formulas $ROCH_2CH_2OCH_2CH_2OH$ and $ROCH_2CH_2OCH_2CH_2OR'$. The former commonly are termed "*Carbitols*" and the latter "*Cellosolves*," registered trademarks belonging to Union Carbide.

Polyethylene glycols are differentiated in commercial nomenclature by adding a number to the name which represents the average molecular weight. Thus, polyethylene glycol 400 has an average molecular weight of about 400 (measured values for commercial samples range between 380 and 420) corresponding to a value of $n$ for this particular polymer of approximately 8. Polymers have been produced in which the value of $n$ runs into the hundreds. Up to $n$ = approximately 15, the compounds are liquids at room temperature, viscosity and boiling point increasing with increasing molecular weight. Higher polymers are waxy solids and are termed commercially *Carbowaxes* (another Union Carbide trademark).

It should be observed that the presence of the two terminal hydroxyl groups in the polyalkylene glycols makes possible the formation of both ether and ester derivatives, several of which are marketed products.

**Uses**—Because of their vapor pressure, solubility, solvent power, hygroscopicity, viscosity and lubricating characteristics, the polyalkylene glycols or their derivatives function in many applications as effective replacements for glycerin and water-insoluble oils. They find considerable use as plasticizers, lubricants, conditioners and finishing agents for processing textiles and rubber. They also are important as emulsifying agents and as dispersants for such diverse substances as dyes, oils, resins, insecticides and various types of pharmaceuticals. In addition, they are employed frequently as ingredients in ointment bases and in a variety of cosmetic preparations.

## Polyethylene Glycols

Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, Carbowaxes (*Union Carbide*); Atpeg (*Zeneca*)

$$H—[OCH_2CH_2—]_nOH$$

Polyethylene glycols [25322-68-3].

**Preparation**—Ethylene glycol is reacted with ethylene oxide in the presence of NaOH at temperatures in the range of 120° to 135° under pressure of about 4 atm.

**Description**—*Polyethylene glycols 200, 300, 400* and *600* are clear, viscous liquids at room temperature. *Polyethylene glycols 900, 1000, 1450, 3350, 4500* and *8000* are white, waxy solids. The glycols do not hydrolyze or deteriorate under typical conditions. As their molecular weight increases, their water solubility, vapor pressure, hygroscopicity and solubility in organic solvents decrease; at the same time, freezing or melting range, specific gravity, flash point and viscosity increase. If these compounds ignite, small fires should be extinguished with carbon dioxide or dry-chemical extinguishers and large fires with "alcohol"-type foam extinguishers.

**Solubility**—All members of this class dissolve in water to form clear solutions and are soluble in many organic solvents.

**Uses**—These possess a wide range of solubilities and compatibilities, which make them useful in pharmaceutical and cosmetic preparations. Their blandness renders them highly acceptable for hair dressings, hand lotions, sun-tan creams, leg lotions, shaving creams and skin creams (eg, a peroxide ointment which is stable may be prepared using these compounds, while oil-type bases inactivate the peroxide). Their use in washable ointments is discussed under *Ointments* (page 1585). They also are used in making suppositories, hormone creams, etc. See *Polyethylene Glycol Ointment* (below) and *Glycol Ethers* (above). The liquid polyethylene glycol 400 and the solid polyethylene glycol 3350, used in the proportion specified (or a permissible variation thereof) in the official Polyethylene Glycol Ointment, provide a water-soluble ointment base used in the formulation of many dermatological preparations. The solid, waxy, water-soluble glycols often are used to increase the viscosity of liquid polyethylene glycols and to stiffen ointment and suppository bases. In addition, they are used to compensate for the melting point-lowering effect of other agents, ie, chloral hydrate, etc, on such bases.

**Polyethylene Glycol Ointment USP**—*Preparation:* Heat polyethylene glycol 3350 (400 g) and polyethylene glycol 400 (600 g) on a water bath to 65°. Allow to cool, and stir until congealed. If a firmer preparation is desired, replace up to 100 g of polyethylene glycol 400 with an equal amount of polyethylene glycol 3350. If 6 to 25% of an aqueous solution is to be incorporated in this ointment, replace 50 g of polyethylene glycol 3350 by 50 g of stearyl alcohol. *Uses:* A water-soluble ointment base.

## Polyoxyl 40 Stearate

Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, octadecanoate; Myrj (*Zeneca*)

$$RCOO(C_2H_4O)_nH$$

($RCOO$ is the stearate moiety; $n$ is approximately 40)

Polyethylene glycol monostearate [9004-99-3]; a mixture of monostearate and distearate esters of mixed polyoxyethylene diols and corresponding free glycols, the average polymer length being equivalent to about 40 oxyethylene units. *Polyoxyethylene 50 Stearate* is a similar mixture in which the average polymer length is equivalent to about 50 oxyethylene units.

**Preparation**—One method consists of heating the corresponding polyethylene glycol with an equimolar portion of stearic acid.

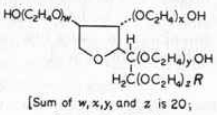
**Description**—White to light-tan waxy solid; odorless or has a faint fat-like odor; congeals between 37 and 47°.

**Solubility**—Soluble in water, alcohol, ether or acetone; insoluble in mineral or vegetable oils.

**Uses**—Contains ester and alcohol functions that impart both lyophilic and hydrophilic characteristics to make it useful as a surfactant and emulsifier. It is an ingredient of some water-soluble ointment and cream bases.

## Polysorbates

Sorbitan esters, poly(oxy-1,2-ethanediyl) derivs, Tweens (*Zeneca*)




[Sum of $w, x, y,$ and $z$ is 20; $R$ is $(C_{11}H_{23})COO$ ]

Sorbitan esters, polyoxyethylene derivatives; fatty acid esters of sorbitol and its anhydrides copolymerized with a varying number of moles of ethylene oxide. The NF recognizes: *Polysorbate 20* (*structure given above*), a laurate ester; *Polysorbate 40*, a palmitate ester; *Polysorbate 60*, a mixture of stearate and palmitate esters; and *Polysorbate 80*, an oleate ester.

**Preparation**—These important nonionic surfactants (page 239) are prepared starting with sorbitol by (1) elimination of water- forming sorbitan (a cyclic sorbitol anhydride); (2) partial esterification of the sorbitan with a fatty acid such as oleic or stearic acid yielding a hexitan ester known commercially as a *Span* and (3) chemical addition of ethylene oxide yielding a *Tween* (the polyoxyethylene derivative).

**Description**—*Polysorbate 80:* Lemon- to amber-colored, oily liquid; faint, characteristic odor; warm, somewhat bitter taste; specific gravity 1.07 to 1.09; pH (1:20 aqueous solution) 6 to 8.

**Solubility**—*Polysorbate 80:* Very soluble in water, producing an odorless and nearly colorless solution; soluble in alcohol, cottonseed oil, corn oil, ethyl acetate, methanol or toluene; insoluble in mineral oil.

**Uses**—Because of their hydrophilic and lyophilic characteristics, these nonionic surfactants are very useful as emulsifying agents forming O/W emulsions in pharmaceuticals, cosmetics and other types of products. Polysorbate 80 is an ingredient in *Coal Tar Ointment* and *Solution*. See *Glycol Ethers* (page 1403).

### Other Water-Soluble Ointment Base Component

**Polyethylene Glycol 400 Monostearate USP XVI**—An ether, alcohol and ester. Semitransparent, whitish, odorless or nearly odorless mass; melts from 30 to 34°. Freely soluble in carbon tetrachloride, chloroform, ether or petroleum benzin; slightly soluble in alcohol; insoluble in water. *Uses:* A nonionic surface-active agent in the preparation of creams, lotions, ointments and similar pharmaceutical preparations, which are readily soluble in water.

# Pharmaceutical Solvents

The remarkable growth of the solvent industry is attested by the more than 300 solvents now being produced on an industrial scale. Chemically, these include a great variety of organic compounds, ranging from hydrocarbons through alcohols, esters, ethers and acids to nitroparaffins. Their main applications are in industry and the synthesis of organic chemicals. Comparatively few, however, are used as solvents in pharmacy, because of their toxicity, volatility, instability and/or flammability. Those commonly used as pharmaceutical solvents are described in this section.

## Acetone

2-Propanone; Dimethyl Ketone

$CH_3COCH_3$

Acetone [67-64-1] $C_3H_6O$ (58.08).

*Caution—It is very flammable. Do not use where it may be ignited.*

**Preparation**—Formerly obtained exclusively from the destructive distillation of wood. The distillate, consisting principally of methanol, acetic acid and acetone was neutralized with lime and the acetone was separated from the methyl alcohol by fractional distillation. Additional quantities were obtained by pyrolysis of the calcium acetate formed in the neutralization of the distillate.

It now is obtained largely as a by-product of the butyl alcohol industry. This alcohol is formed in the fermentation of carbohydrates such as corn starch, molasses, etc, by the action of the bacterium *Clostridium acetobutylicum* (Weizmann fermentation) and it is always one of the products formed in the process. It also is obtained by the catalytic oxidation of isopropyl alcohol, which is prepared from propylene resulting from the "cracking" of crude petroleum.

**Description**—Transparent, colorless, mobile, volatile, flammable liquid with a characteristic odor; specific gravity not more than 0.789; distils between 55.5 and 57°; congeals about −95°; aqueous solution neutral to litmus.

**Solubility**—Miscible with water, alcohol, ether, chloroform or most volatile oils.

**Uses**—An *antiseptic* in concentrations above 80%. In combination with alcohol it is used as an antiseptic *cleansing* solution. It is employed as a menstruum in the preparation of oleoresins in place of ether. It is used as a *solvent* for dissolving fatty bodies, resins, pyroxylin, mercurials, etc, and also in the manufacture of many organic compounds such as chloroform, chlorobutanol and ascorbic acid.

## Alcohol

Ethanol; Spiritus Vini Rectificatus; S. V. R.; Spirit of Wine; Methylcarbinol

Ethyl alcohol [64-17-5]; contains 92.3 to 93.8%, by weight (94.9 to 96.0%, by volume), at 15.56° (60°F) of $C_2H_5OH$ (46.07).

**Preparation**—Has been made for centuries by fermentation of certain carbohydrates in the presence of *zymase*, an enzyme present in yeast cells. Usable carbohydrate-containing materials include molasses, sugar cane, fruit juices, corn, barley, wheat, potato, wood and waste sulfite liquors. As yeast is capable of fermenting only D-glucose, D-fructose, D-mannose and D-galactose it is essential that more complex carbohydrates, such as starch, be converted to one or more of these simple sugars before they can be fermented. This is accomplished variously, commonly by enzyme- or acid-catalyzed hydrolysis.

The net reaction that occurs when a hexose, glucose for example, is fermented to alcohol may be represented as

$$C_6H_{12}O_6 \rightarrow 2C_2H_5OH + 2CO_2$$

but the mechanism of the process is very complex. The fermented liquid, containing about 15% of alcohol, is distilled to obtain a distillate containing 94.9% of $C_2H_5OH$, by volume. To produce *absolute alcohol*, the 95% product is dehydrated by various processes.

It may be produced also by hydration of ethylene, abundant supplies of which are available from natural and coke oven gases, from waste gases of the petroleum industry and other sources. In another synthesis acetylene is hydrated catalytically to acetaldehyde, which then is hydrogenated catalytically to ethyl alcohol.

**Description**—Transparent, colorless, mobile, volatile liquid; slight but characteristic odor; burning taste; boils at 78° but volatilizes even at a low temperature, and is flammable; when pure, it is neutral towards all indicators; specific gravity at 15.56° (the US Government standard temperature for Alcohol) not above 0.816, indicating not less than 92.3% of $C_2H_5OH$ by weight or 94.9% by volume.

**Solubility**—Miscible with water, acetone, chloroform, ether or many other organic solvents.

**Incompatibilities**—This and preparations containing a high percentage of alcohol will precipitate many inorganic salts from an aqueous solution. *Acacia* generally is precipitated from a hydroalcoholic medium when the alcohol content is greater than about 35%.

Strong *oxidizing agents* such as *chlorine, nitric acid, permanganate* or *chromate* in acid solution react, in some cases violently, with it to produce oxidation products.

*Alkalies* cause a darkening in color due to the small amount of aldehyde usually present in it.

**Uses**—In pharmacy principally for its solvent powers (page 204). It also is used as the starting point in the manufacture of many important compounds, like ether, chloroform, etc. It also is used as a fuel, chiefly in the denatured form.

It is a CNS depressant. Consequently, it occasionally has been administered intravenously for preoperative and postoperative sedation in patients in whom other measures are ineffective or contraindicated. The dose employed is 1 to 1.5 mL/kg. Its intravenous use is a specialized procedure and should be employed only by one experienced in the technique of such use.

It is used widely and abused by lay persons as a sedative. It has, however, no medically approved use for this purpose. Moreover, alcohol potentiates the CNS effects of numerous sedative and depressant drugs. Hence, it should not be used by patients taking certain prescription drugs or OTC medications (see page 1822).

Externally, it has a number of medical uses. It is a solvent for the toxicodendrol causing *ivy poisoning*, and should be used to wash the skin thoroughly soon after contact. In a concentration of 25% it is employed for bathing the skin for the purpose of *cooling* and *reducing fevers*. In high concentrations it is a *rubefacient* and an ingredient of many liniments. In a concentration of 50% it is used to prevent sweating in *astringent* and *anhidrotic* lotions. It also is employed to cleanse and harden the skin and is helpful in preventing *bedsores* in bedridden patients. In a concentration of 60 to 90% it is germicidal. At optimum concentration (70% by weight) it is a good *antiseptic* for the skin (*local anti-infective*) and also for instruments. It also is used as a *solvent* to cleanse the skin splashed with phenol. High concentrations of it often are injected into nerves and ganglia for the *relief of pain*, accomplishing this by causing nerve degeneration.

## Denatured Alcohol

An act of Congress June 7, 1906, authorizes the withdrawal of alcohol from bond without the payment of internal revenue tax, for the purpose of denaturation and use in the arts and industries. This is ethyl alcohol to which have been added such denaturing materials as to render the alcohol unfit for use as an intoxicating beverage. It is divided into two classes, namely, *completely denatured alcohol* and *specially denatured alcohol*, prepared in accordance with approved formulas prescribed in Federal Industrial Alcohol Regulations 3.

Information regarding the use of alcohol and permit requirements may be obtained from the Regional Director, Bureau of Alcohol, Tobacco and

Firearms, in any of the following offices: Cincinnati, OH; Philadelphia, PA; Chicago, IL; New York, NY; Atlanta, GA; Dallas, TX and San Francisco, CA. Federal regulation provides that completely and specially denatured alcohols may be purchased by properly qualified persons from duly established denaturing plants or bonded dealers. No permit is required for the purchase and use of completely denatured alcohol unless the purchaser intends to recover the alcohol.

**Completely Denatured Alcohol**—This term applies to ethyl alcohol to which has been added materials (methyl isobutyl ketone, pyronate, gasoline, acetaldol, kerosene, etc) of such nature that the products may be sold and used within certain limitations without permit and bond.

**Specially Denatured Alcohol**—This alcohol is intended for use in a greater number of specified arts and industries than completely denatured alcohol and the character of the denaturant or denaturants used is such that specially denatured alcohol may be sold, possessed and used only by those persons or firms that hold basic permits and are covered by bond.

Formulas for products using specially denatured alcohol must be approved prior to use by the Regional Director, Bureau of Alcohol, Tobacco and Firearms in any of the regional offices listed above.

**Uses**—Approximately 50 specially denatured alcohol formulas containing combinations of more than 90 different denaturants are available to fill the needs of qualified users. Large amounts of specially denaturated alcohols are used as raw materials in the production of acetaldehyde, synthetic rubber, vinegar and ethyl chloride as well as in the manufacture of proprietary solvents and cleaning solutions. Ether and chloroform can be made from suitably denatured alcohols and formulas for the manufacture of Iodine Tincture, Green Soap Tincture and Rubbing Alcohol are set forth in the regulations.

Specially denatured alcohols also are used as solvents for surface coatings, plastics, inks, toilet preparations and external pharmaceuticals. Large quantities are used in the processing of such food and drug products as pectin, vitamins, hormones, antibiotics, alkaloids and blood products. Other uses include supplemental motor fuel, rocket and jet fuel, antifreeze solutions, refrigerants and cutting oils. Few products are manufactured today that do not require the use of alcohol at some stage of production. Specially denatured alcohol may not be used in the manufacture of foods or internal medicines where any of the alcohol remains in the finished product.

## Diluted Alcohol

Diluted Ethanol

A mixture of alcohol and water containing 41.0 to 42.0%, by weight (48.4 to 49.5%, by volume), at 15.56°, of $C_2H_5OH$ (46.07).

**Preparation**—

| | |
|---|---|
| **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°, the volume of the mixture will be about 970 mL.

When equal volumes of alcohol and water are mixed together, a rise in temperature and a contraction of about 3% in volume take place. In small operations the contraction generally is disregarded; in larger operations it is very important. If 50 gal of official alcohol are mixed with 50 gal of water, the product will not be 100 gal of diluted alcohol, but only 96¼ gal, a contraction of 3¾ gal. US *Proof Spirit* differs from this and is stronger; it contains 50%, by volume, of absolute alcohol at 15.56° (60°F). This corresponds to 42.5% by weight, and has a specific gravity of 0.9341 at the same temperature. If spirits have a specific gravity lower than that of "proof spirit" (0.9341), they are said to be "*above proof*"; if greater, "*below proof*."

It also may be prepared from the following:

| | |
|---|---|
| **Alcohol** | **408 g** |
| **Purified Water** | **500 g** |

**Rules for Dilution**—The following rules are applied when making an alcohol of any required lower percentage from an alcohol of any given higher percentage:

**I. By Volume**—Designate the volume percentage of the stronger alcohol by $V$, and that of the weaker alcohol by $v$.

*Rule*—Mix $v$ volumes of the stronger alcohol with purified water to make $V$ volumes of product. Allow the mixture to stand until full contraction has taken place, and until it has cooled, then make up the deficiency in the $V$ volumes by adding more purified water.

*Example*—An alcohol of 30% by volume is to be made from an alcohol of 94.9% by volume.—Take 30 volumes of the 94.9% alcohol, and add enough purified water to produce 94.9 volumes at room temperature.

**II. By Weight**—Designate the weight-percentage of the stronger alcohol by $W$, and that of the weaker alcohol by $w$.

*Rule*—Mix $w$ parts by weight of the stronger alcohol with purified water to make $W$ parts by weight of product.

*Example*—An alcohol of 50% by weight is to be made from an alcohol of 92.3% by weight.—Take 50 parts by weight of the 92.3% alcohol, and add enough purified water to produce 92.3 parts by weight.

**Description**—As for *Alcohol*, except its specific gravity is 0.935 to 0.937 at 15.56°, indicating that the strength of $C_2H_5OH$ corresponds to that given in the official definition.

**Uses**—A menstruum in making tinctures, fluidextracts, extracts, etc. Its properties already have been described fully in connection with the various preparations. Its value consists not only in its *antiseptic* properties, but also in its possessing the *solvent* powers of both water and alcohol. See *Alcohol*.

## Nonbeverage Alcohol

This is tax-paid alcohol or distilled spirits used in the manufacture, by approved formula, of such medicines, medicinal preparations, food products, flavors or flavoring extracts as are unfit for beverage purposes. Internal Revenue Service Regulations provide that qualified holders of Special Tax Stamps who use tax paid alcohol or distilled spirits in the types of products listed above, may file a claim for *alcohol tax drawback* or refund of a considerable part of the tax paid.

**Amylene Hydrate**—see RPS-18, page 1316.

**Chloroform**—page 1409.

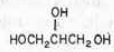
**Coconut Oil**—see RPS-18, page 1317.

**Ether**—see RPS-18, page 1041.

**Ethyl Acetate**—see RPS-18, page 1294.

## Glycerin

1,2,3-Propanetriol; Glycerol



Glycerol [56-81-5] $C_3H_8O_3$ (92.09).

Chemically, it is the simplest trihydric alcohol. It is worthy of special note because the two terminal alcohol groups are primary, whereas the middle one is secondary. Thus this becomes the first polyhydric alcohol which can yield both an aldose (*glyceraldehyde*) and a ketose (*dihydroxyacetone*).

**Preparation**—

1. By saponification of fats and oils in the manufacture of soap.
2. By hydrolysis of fats and oils through pressure and superheated steam.
3. By fermentation of beet sugar molasses in the presence of large amounts of sodium sulfite. Under these conditions a reaction takes place expressed as

$$\underset{\text{Glucose}}{C_6H_{12}O_6} \rightarrow \underset{\text{Glycerin}}{C_3H_5(OH)_3} + \underset{\text{Acetaldehyde}}{CH_3CHO} + CO_2$$

4. Glycerin is now prepared in large quantities from propylene, a petroleum product. This hydrocarbon is chlorinated at about 400° to form allyl chloride, which is converted to allyl alcohol. Treatment of the unsaturated alcohol with hypochlorous acid [HOCl] yields the chlorohydrin derivative. Extraction of HCl with soda lime yields 2,3-epoxypropanol which undergoes hydration to glycerin.

**Description**—Clear, colorless, syrupy liquid with a sweet taste and not more than a slight, characteristic odor, which is neither harsh nor disagreeable; when exposed to moist air it absorbs water and also such gases as $H_2S$ and $SO_2$; solutions are neutral; specific gravity not below 1.249 (not less than 95% $C_3H_5(OH)_3$); boils at about 290° under 1 atm, with decomposition, but can be distilled intact in a vacuum.

**Solubility**—Miscible with water, alcohol or methanol; 1 g in about 12 mL ethyl acetate or about 15 mL acetone; insoluble in chloroform, ether or fixed and volatile oils.

**Incompatibilities**—An explosion may occur if it is triturated with strong *oxidizing agents* such as *chromium trioxide, potassium chlorate* or *potassium permanganate*. In dilute solutions the reactions proceed at a slower rate forming several oxidation products. Iron is an occasional contaminant of it and may be the cause of a darkening in color in mixtures containing *phenols, salicylates, tannin*, etc.

With *boric acid* or *sodium borate*, it forms a complex, generally spoken of as glyceroboric acid, which is a much stronger acid than boric acid.

**Uses**—One of the most valuable products known to pharmacy by virtue of its *solvent* property. It is useful as a *humectant* in keeping substances moist, owing to its hygroscopicity. Its agreeable taste and high viscosity

adapt it for many purposes. Some modern ice collars and ice bags contain it and water hermetically sealed within vulcanized rubber bags. The latter are sterilized by dipping in a germicidal solution and are stored in the refrigerator until needed. It also has some therapeutic uses. In pure anhydrous form, it is used in the eye to reduce corneal edema and to facilitate ophthalmoscopic examination. It is used orally as an evacuant and, in 50 to 75% solution, as a systemic osmotic agent.

**Isopropyl Alcohol**—page 1267.

### Methyl Alcohol

Methanol; Wood Alcohol

$CH_3OH$

Methanol [67-56-1] $CH_4O$ (32.04).

*Caution—It is poisonous.*

**Preparation**—By the catalytic reduction of carbon monoxide or carbon dioxide with hydrogen. A zinc oxide-chromium oxide catalyst is used commonly.

**Description**—Clear, colorless liquid; characteristic odor; flammable; specific gravity not more than 0.790; distils within a range of 1° between 63.5 and 65.7°.

**Solubility**—Miscible with water, alcohol, ether, benzene or most other organic solvents.

**Uses**—*A pharmaceutic aid* (solvent). It is toxic. Ingestion may result in blindness; vapors also may cause toxic reactions.

### Methyl Isobutyl Ketone

2-Pentanone, 4-methyl-,

$(CH_3)_2CHCH_2COCH_3$

[108-10-1]; contains not less than 99% of $C_6H_{12}O$ (100.16).

**Description**—Transparent, colorless, mobile, volatile liquid; faint, ketonic and camphoraceous odor, distils between 114 and 117°.

**Solubility**—Slightly soluble in water; miscible with alcohol, ether or benzene.

**Uses**—A *denaturant* for rubbing alcohol and also a *solvent* for gums, resins, nitrocellulose, etc. It may be irritating to the eyes and mucous membranes, and, in high concentrations, narcotic.

### Monoethanolamine

Ethanol, 2-amino-, Ethanolamine; Ethylolamine

$HOCH_2CH_2NH_2$

[141-43-5] $C_2H_7NO$ (61.08).

**Preparation**—This alkanolamine is prepared conveniently by treating ethylene oxide with ammonia.

**Description**—Clear, colorless, moderately viscous liquid; distinctly ammoniacal odor; affected by light; specific gravity 1.013 to 1.016; distils between 167 and 173°.

**Solubility**—Miscible in all proportions with water, acetone, alcohol, glycerin or chloroform; immiscible with ether, solvent hexane or fixed oils; dissolves many essential oils.

**Uses**—A *solvent* for fats, oils and many other substances, it is a pharmaceutical necessity for *Thimerosal Solution* (page 1271). It combines with fatty acids to form soaps which find application in various types of emulsions such as lotions, creams, etc.

**Petroleum Benzin**—see RPS-18, page 1317.

### Propylene Glycol

$CH_3CH(OH)CH_2OH$

1,2-Propanediol [57-55-6] $C_3H_8O_2$ (76.10).

**Preparation**—Propylene is converted successively to its chlorohydrin (with HOCl), epoxide (with $Na_2CO_3$) and glycol (with water in presence of protons).

**Description**—Clear, colorless, viscous and practically odorless liquid; slightly acrid taste; specific gravity 1.035 to 1.037; completely distils between 184 and 189°; absorbs moisture from moist air.

**Solubility**—Miscible with water, alcohol, acetone or chloroform; soluble in ether; dissolves many volatile oils; immiscible with fixed oils.

**Uses**—A *solvent, preservative* and *humectant.* See *Hydrophilic Ointment* (page 1402).

### Trolamine

Ethanol, 2,2′,2″-nitrilotris-, Triethanolamine

2,2′,2″-Nitrilotriethanol [102-71-6] $N(C_2H_4OH)_3$ (149.19); a mixture of alkanolamines consisting largely of triethanolamine, containing some diethanolamine [$NH(C_2H_4OH)_2$ = 105.14] and monoethanolamine [$NH_2C_2H_4OH$ = 61.08].

**Preparation**—Along with some mono- and diethanolamine, by the action of ammonia on ethylene oxide.

**Description**—Colorless to pale yellow, viscous, hygroscopic liquid; slight odor of ammonia; aqueous solution is very alkaline; melts about 21°; specific gravity 1.120 to 1.128; a strong base and readily combines even with weak acids to form salts.

**Solubility**—Miscible with water or alcohol; soluble in chloroform; slightly soluble in ether or benzene.

**Uses**—In combination with a fatty acid, eg, oleic acid (see *Benzyl Benzoate Lotion*, page 1519), as an *emulsifier.* See *Monoethanolamine.*

**Water**—page 1392.

### Other Pharmaceutical Solvents

**Alcohol, Dehydrated, BP, PhI** [Dehydrated Ethanol; Absolute Alcohol]—Transparent, colorless, mobile, volatile liquid; characteristic odor; burning taste; specific gravity not more than 0.798 at 15.56°; hygroscopic, flammable and boils about 78°C. Miscible with water, ether or chloroform. *Uses:* A pharmaceutical solvent; also used by injection for relief of pain (see *Alcohol*, page 1404).

# Miscellaneous Pharmaceutical Necessities

The agents listed in this section comprise a heterogeneous group of substances with both pharmaceutical and industrial applications. Pharmaceutically, some of these agents are used as diluents, enteric coatings, excipients, filtering agents and as ingredients in products considered in other chapters. Industrially, some of these agents are used in various chemical processes, in the synthesis of other chemicals and in the manufacture of fertilizers, explosives, etc.

### Acetic Acid

Acetic acid; a solution containing 36 to 37%, by weight, of $C_2H_4O_2$ (60.05).

**Preparation**—By diluting with distilled water an acid of higher concentration, such as the 80% product, or more commonly glacial acetic acid, using 350 mL of the latter for the preparation of each 1000 mL of acetic acid.

**Description**—Clear, colorless liquid, having a strong characteristic odor and a sharply acid taste; specific gravity about 1.045; congeals about −14°; acid to litmus.

**Solubility**—Miscible with water, alcohol or glycerin.

**Uses**—In pharmacy as a *solvent* and *menstruum*, and for making diluted acetic acid. It also is used as a starting point in the manufacture of many other organic compounds, eg, acetates, acetanilid, sulfonamides, etc. It is official primarily as a *pharmaceutic necessity* for the preparation of *Aluminum Subacetate Solution* (RPS- 17, page 778).

### Diluted Acetic Acid

Dilute Acetic Acid

A solution containing, in each 100 mL, 5.7 to 6.3 g of $C_2H_4O_2$.

**Preparation**—

| | |
|---|---|
| **Acetic Acid** | **158 mL** |
| **Purified Water,** a sufficient quantity, | |
| To make | **1000 mL** |

Mix the ingredients.

*Note*—This acid also may be prepared by diluting 58 mL of glacial acetic acid with sufficient purified water to make 1000 mL.

**Description**—Essentially the same properties, solubility, purity and identification reactions as *Acetic Acid*, but its specific gravity is about 1.008 and it congeals about −2°.

**Uses**—*Bactericidal* to many types of microorganisms and occasionally is used in 1% solution for surgical dressings of the skin. A 1% solution is *spermatocidal*. It also is used in vaginal douches for the management of *Trichomonas*, *Candida* and *Hemophilus* infections.

### Glacial Acetic Acid

Concentrated Acetic Acid; Crystallizable Acetic Acid; Ethanolic Acid; Vinegar Acid

$CH_3COOH$

Glacial acetic acid [64-19-7] $C_2H_4O_2$ (60.05).

**Preparation**—This acid is termed "glacial" because of its solid, glassy appearance when congealed. In one process it is produced by distillation of weaker acids to which has been added a water-entraining substance such as ethylene dichloride. In this method, referred to as "azeotropic distillation," the ethylene dichloride distils out with the water before the acid distils over, thereby effecting concentration of the latter.

In another process the aqueous acid is mixed with triethanol-amine and heated. The acid combines with the triethanolamine to form a triethanolamine acetate. The water is driven off first; then, at a higher temperature, the triethanolamine compound decomposes to yield this acid.

A greater part of the acid now available is made synthetically from acetylene. When acetylene is passed into this acid containing a metallic catalyst such as mercuric oxide, ethylidene diacetate is produced which yields, upon heating, acetic anhydride and acetaldehyde. Hydration of the former and air oxidation of the latter yield this acid.

**Description**—Clear, colorless liquid; pungent, characteristic odor; when well-diluted with water, it has an acid taste; boils about 118°; congeals at a temperature not lower than 15.6°, corresponding to a minimum of 99.4% of $CH_3COOH$; specific gravity about 1.05.

**Solubility**—Miscible with water, alcohol, acetone, ether or glycerin; insoluble in carbon tetrachloride or chloroform.

**Uses**—A *caustic* and *vesicant* when applied externally and is often sold under various disguises as a *corn solvent*. It is an excellent *solvent* for fixed and volatile oils and many other organic compounds. It is used primarily as an *acidifying agent*.

**Almond Oil**—RPS-16, page 720.

### Aluminum

Aluminim Al (26.98); the free metal in the form of finely divided powder. It may contain oleic acid or stearic acid as a lubricant. It contains not less than 95% of Al, and not more than 5% of *Acid-insoluble substances*, including any added fatty acid.

**Description**—Very fine, free-flowing, silvery powder free from gritty or discolored particles.

**Solubility**—Insoluble in water or alcohol; soluble in hydrochloric and sulfuric acids or in solutions of fixed alkali hydroxides.

**Uses**—A *protective*. An ingredient in *Aluminum Paste* (RPS-14, page 772).

### Aluminum Monostearate

Aluminum, dihydroxy(octadecanoato-*O*-)-,

Dihydroxy(stearato)aluminum [7047-84-9]; a compound of aluminum with a mixture of solid organic acids obtained from fats, and consists chiefly of variable proportions of aluminum monostearate and aluminum monopalmitate. It contains the equivalent of 14.5 to 16.5% of $Al_2O_3$ (101.96).

**Preparation**—By interaction of a hydroalcoholic solution of potassium stearate with an aqueous solution of potassium alum, the precipitate being purified to remove free stearic acid and some aluminum distearate simultaneously produced.

**Description**—Fine, white to yellowish white, bulky powder; faint, characteristic odor.

**Solubility**—Insoluble in water, alcohol or ether.

**Uses**—A *pharmaceutical necessity* used in the preparation of *Sterile Procaine Penicillin G with Aluminum Stearate Suspension* (see RPS-18, page 1288).

### Strong Ammonia Solution

Stronger Ammonia Water; Stronger Ammonium Hydroxide Solution; Spirit of Hartshorn

Ammonia [1336-21-6]; a solution of $NH_3$ (17.03), containing 27.0 to 31.0% (*w/w*) of $NH_3$. Upon exposure to air it loses ammonia rapidly.

*Caution—Use care in handling it because of the caustic nature of the Solution and the irritating properties of its vapor. Cool the container well before opening, and cover the closure with a cloth or similar material while opening. Do not taste it, and avoid inhalation of its vapor.*

**Preparation**—Ammonia is obtained commercially chiefly by synthesis from its constituent elements, nitrogen and hydrogen, combined under high pressure and at high temperature in the presence of a catalyst.

**Description**—Colorless, transparent liquid; exceedingly pungent, characteristic odor; even when well-diluted it is strongly alkaline to litmus; specific gravity about 0.90.

**Solubility**—Miscible with alcohol.

**Uses**—Only for chemical and pharmaceutical purposes. It is used primarily in making ammonia water by dilution and as a chemical reagent. It is too strong for internal administration. It is an ingredient in *Aromatic Ammonia Spirit* (page 873).

### Bismuth Subnitrate

Basic Bismuth Nitrate; Bismuth Oxynitrate; Spanish White; Bismuth Paint; Bismuthyl Nitrate

Bismuth hydroxide nitrate oxide [1304-85-4] $Bi_5O(OH)_9(NO_3)_4$ (1461.99); a basic salt which, dried at 105° for 2 hr, yields upon ignition not less than 79% of $Bi_2O_3$ (465.96).

**Preparation**—A solution of bismuth nitrate is added to boiling water to produce the subnitrate by hydrolysis.

**Description**—White, slightly hygroscopic powder; suspension in distilled water is faintly acid to litmus (pH about 5).

**Solubility**—Practically insoluble in water or organic solvents; dissolves readily in an excess of hydrochloric or nitric acid.

**Incompatibilities**—Slowly hydrolyzed in *water* with liberation of nitric acid; thus, it possesses the incompatibilities of the acid. *Reducing agents* darken it with the production of metallic bismuth.

**Uses**—A *pharmaceutical necessity* in the preparation of milk of bismuth. It also is used as an *astringent*, *adsorbent* and *protective*; however, its value as a protective is questionable. This agent, like other insoluble bismuth salts, is used topically in lotions and ointments.

**Barium Hydroxide Lime**—see RPS-18, page 1318.

### Boric Acid

Boric acid ($H_3BO_3$); Boracic Acid; Orthoboric Acid

Boric acid [10043-35-3] $H_3BO_3$ (61.83).

**Preparation**—Lagoons of the volcanic districts of Tuscany formerly furnished the greater part of this acid and borax of commerce. Borax is now found native in California and some of the other western states; calcium and magnesium borates are found there also. It is produced from native borax, or from the other borates, by reacting with hydrochloric or sulfuric acid.

**Description**—Colorless scales of a somewhat pearly luster, or crystals, but more commonly a white powder slightly unctuous to the touch; odorless and stable in the air; volatilizes with steam.

**Solubility**—1 g in 18 mL water, 18 mL alcohol, 4 mL glycerin, 4 mL boiling water or 6 mL boiling alcohol.

**Uses**—A buffer, and it is this use that is recognized officially. It is a very weak *germicide* (*local anti-infective*). Its nonirritating properties make its solutions suitable for application to such delicate structures as the cornea of the eye. Aqueous solutions are employed as an eye wash, mouth wash and for irrigation of the bladder. A 2.2% solution is isotonic with lacrimal fluid. Solutions, even if they are made isotonic, will hemolyze red blood cells. It also is employed as a dusting powder, when diluted with some inert material. It can be absorbed through irritated skin, eg, infants with diaper rash.

Although it is not absorbed significantly from intact skin, it is absorbed from damaged skin and fatal poisoning, particularly in infants, has occurred with topical application to burns, denuded areas, granulation tissue and serous cavities. *Serious poisoning can result from oral ingestion* of as little as 5 g. Symptoms of poisoning are nausea, vomiting, abdominal pain, diarrhea, headache and visual disturbance. Toxic alopecia has been reported from the chronic ingestion of a mouth wash containing it. The kidney may be injured and death may result. Its use as a preservative in beverages and foods is prohibited by national and state legislation. *There is always present the danger of confusing it with dextrose when compounding milk formulas for infants. Fatal accidents have occurred.* For this reason boric acid in bulk is colored, so that it cannot be confused with dextrose.

It is used to prevent discoloration of physostigmine solutions.

**Dose**—*Topically*, as required.

### Calcium Hydroxide

Slaked Lime; Calcium Hydrate

Calcium hydroxide [1305-62-0] $Ca(OH)_2$ (74.09).

**Preparation**—By reacting freshly prepared calcium oxide with water.

**Description**—White powder; alkaline, slightly bitter taste; absorbs carbon dioxide from the air forming calcium carbonate; solutions exhibit a strong alkaline reaction.

**Solubility**—1 g in 630 mL water or 1300 mL boiling water; soluble in glycerin or syrup; insoluble in alcohol; the solubility in water is decreased by the presence of fixed alkali hydroxides.

**Uses**—In the preparation of *Calcium Hydroxide Solution.*

### Calcium Hydroxide Topical Solution

Calcium Hydroxide Solution; Lime Water

A solution containing, in each 100 mL, not less than 140 mg of $Ca(OH)_2$ (74.09).

*Note*—The solubility of calcium hydroxide varies with the temperature at which the solution is stored, being about 170 mg/100 mL at 15°, and less at a higher temperature. The official concentration is based upon a temperature of 25°.

**Preparation**—

| | |
|---|---|
| **Calcium Hydroxide** | **3 g** |
| **Purified Water** | **1000 mL** |

Add the calcium hydroxide to 1000 mL of cool, purified water, and agitate the mixture vigorously and repeatedly during 1 hr. Allow the excess of calcium hydroxide to settle. Dispense only the clear, supernatant liquid.

The undissolved portion of the mixture is not suitable for preparing additional quantities of the solution.

The object of keeping lime water over undissolved calcium hydroxide is to insure a saturated solution.

**Description**—Clear, colorless liquid; alkaline taste; strong alkaline reaction; absorbs carbon dioxide from the air, a film of calcium carbonate forming on the surface of the liquid; when heated, it becomes turbid, owing to the separation of calcium hydroxide, which is less soluble in hot than in cold water.

**Uses**—Too dilute to be effective as a gastric antacid. It is employed *topically* as a *protective* in various types of lotions. In some lotion formulations it is used with olive oil or oleic acid to form calcium oleate that functions as an emulsifying agent. The USP classes it as an *astringent.*

**Dose**—*Topically*, in astringent solutions and lotions as required (see *Calamine Lotion*, page 872).

## Calcium Pantothenate, Racemic—page 1125.

### Calcium Stearate

Octadecanoic acid, calcium salt

Calcium stearate [1592-23-0]; a compound of calcium with a mixture of solid organic acids obtained from fats and consists chiefly of variable proportions of stearic and palmitic acids [calcium stearate, $C_{36}H_{70}CaO_4$ = 607.03; calcium palmitate, $C_{32}H_{62}CaO_4$ = 550.92]; contains the equivalent of 9 to 10.5% of CaO (calcium oxide).

**Preparation**—By precipitation from interaction of solutions of calcium chloride and the sodium salts of the mixed fatty acids (stearic and palmitic).

**Description**—Fine, white to yellowish white, bulky powder; slight, characteristic odor; unctuous and free from grittiness.

**Solubility**—Insoluble in water, alcohol or ether.

**Uses**—A *lubricant* in the manufacture of compressed tablets. It also is used as a conditioning agent in food and pharmaceutical products. Its virtually nontoxic nature and unctuous properties makes it ideal for these purposes.

### Calcium Sulfate

Sulfuric acid, calcium salt (1:1); Gypsum; Terra Alba

Calcium sulfate (1:1) [7778-18-9] $CaSO_4$ (136.14); *dihydrate* [10101-41-4] (172.17).

**Preparation**—From natural sources or by precipitation from interaction of solutions of calcium chloride and a soluble sulfate.

**Description**—Fine, white to slightly yellow-white, odorless powder.

**Solubility**—Dissolves in diluted HCl; slightly soluble in water.

**Uses**—A *diluent* in the manufacture of compressed tablets. It is sufficiently inert that few undesirable reactions occur in tablets made with this substance. It also is used for making plaster casts and supports.

### Carnauba Wax

Obtained from the leaves of *Copernicia cerifera* Mart (Fam *Palmae*).

**Preparation**—Consists chiefly of *myricyl cerotate* with smaller quantities of *myricyl alcohol*, *ceryl alcohol* and *cerotic acid*. It is obtained by treating the leaf buds and leaves of *Copernicia cerifera*, the so-called *Brazilian Wax Palm*, with hot water.

**Description**—Light-brown to pale-yellow, moderately coarse powder; characteristic bland odor; free from rancidity; specific gravity about 0.99; melts about 84°.

**Solubility**—Insoluble in water; freely soluble in warm benzene; soluble in warm chloroform or toluene; slightly soluble in boiling alcohol.

**Uses**—A pharmaceutic aid used as a *polishing agent* in the manufacture of coated tablets.

### Microcrystalline Cellulose

Cellulose [9004-34-6]; purified, partially depolymerized cellulose prepared by treating alpha cellulose, obtained as a pulp from fibrous plant material, with mineral acids.

**Preparation**—Cellulose is subjected to the hydrolytic action of 2.5 *N* HCl at the boiling temperature of about 105° for 15 min, whereby amorphous cellulosic material is removed and aggregates of crystalline cellulose are formed. These are collected by filtration, washed with water and aqueous ammonia and disintegrated into small fragments, often termed cellulose crystallites, by vigorous mechanical means such as a blendor. US Pat 3,141,875.

**Description**—Fine, white, odorless, crystalline powder; consists of free-flowing, nonfibrous particles.

**Solubility**—Insoluble in water, dilute acids or most organic solvents; slightly soluble in NaOH solution (1 in 20).

**Uses**—A tablet diluent and disintegrant. It can be compressed into self-binding tablets which disintegrate rapidly when placed in water.

**Microcrystalline Cellulose and Sodium Carboxymethylcellulose**—A colloid-forming, attrited mixture of microcrystalline cellulose and sodium carboxymethylcellulose. *Description and Solubility:* Tasteless, odorless, white to off-white, coarse to fine powder; pH (dispersion) 6 to 8; swells in water, producing, when dispersed, a white, opaque dispersion or gel. Insoluble in organic solvents or dilute acids. *Uses:* Pharmaceutic aid (suspending agent). *Grades Available* (amounts of sodium carboxymethylcellulose producing viscosities in the concentrations designated): 8.5%, 120 cps in 2.1% solution; 11%, 120 cps in 1.2% solution; 11%, 65 cps in 1.2% solution.

## Powdered Cellulose—page 1397.

### Cellulose Acetate Phthalate

Cellulose, acetate, 1,2-benzenedicarboxylate

Cellulose acetate phthalate [9004-38-0]; a reaction product of the phthalic anhydride and a partial acetate ester of cellulose. When dried at 105° for 2 hr, it contains 19 to 23.5% of acetyl ($C_2H_3O$) groups and 30 to 36.0% of phthalyl (*o*-carboxybenzoyl, $C_8H_5O_3$) groups.

**Preparation**—Cellulose is esterified by treatment with acetic and phthalic acid anhydrides.

**Description**—Free-flowing, white powder; may have a slight odor of acetic acid.

**Solubility**—Insoluble in water or alcohol; soluble in acetone or dioxane.

**Uses**—An *enteric tablet-coating material.* Coatings of this substance disintegrate due to the hydrolytic effect of the intestinal esterases, even when the intestinal contents are acid. *In vitro* studies indicate that cellulose acetate phthalate will withstand the action of artificial gastric juices for long periods of time, but will disintegrate readily in artificial intestinal juices.

## Cherry Juice—see RPS-18, page 1320.

### Carbon Tetrachloride

Methane, tetrachloro-, Tetrachloromethane

Carbon tetrachloride [56-23-5] $CCl_4$ (153.82).

**Preparation**—One method consists of catalytic chlorination of carbon disulfide.

**Description**—Clear, colorless liquid; characteristic odor resembling that of chloroform; specific gravity 1.588 to 1.590; boils about 77°.

**Solubility**—Soluble in about 2000 volumes water; miscible with alcohol, acetone, ether, chloroform or benzene.

**Uses**—Officially recognized as a *pharmaceutical necessity* (solvent). Formerly it was used as a cheap *anthelmintic* for the treatment of *hookworm* infections but it causes severe injury to the liver if absorbed.

### Chloroform

Methane, trichloro-,

Trichloromethane [67-66-3] $CHCl_3$ (119.38); contains 99 to 99.5% of $CHCl_3$, the remainder consisting of alcohol.

*Caution—Care should be taken not to vaporize it in the presence of a flame, because of the production of harmful gases* (hydrogen chloride and phosgene).

**Preparation**—Made by the reduction of carbon tetrachloride with water and iron and by the controlled chlorination of methane.

The pure compound readily decomposes on keeping, particularly if exposed to moisture and sunlight, resulting in formation of phosgene (carbonyl chloride [$COCl_2$]) and other products. The presence of a small amount of alcohol greatly retards or prevents this decomposition; hence, the requirement that it contain 0.5 to 1% of alcohol. The alcohol combines with any phosgene forming ethyl carbonate, which is nontoxic.

**Description**—Clear, colorless, mobile liquid; characteristic, ethereal odor; burning, sweet taste; not flammable but its heated vapors burn with a green flame; affected by light and moisture; specific gravity 1.474 to 1.478, indicating 99 to 99.5% of $CHCl_3$; boils about 61°; not affected by acids, but is decomposed by alkali hydroxide into alkali chloride and sodium formate.

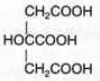
**Solubility**—Soluble in 210 volumes of water; miscible with alcohol, ether, benzene, solvent hexane, acetone or fixed and volatile oils.

**Uses**—An obsolete *inhalation anesthetic*. Although it possesses advantages of nonflammability and great potency, it rarely is used due to the serious toxic effects it produces on the heart and liver. Internally, it has been used, in small doses, as a *carminative*. Externally, it is an *irritant* and when used in liniments it may produce blisters.

It is categorized as a pharmaceutic aid. It is used as a *preservative* during the aqueous percolation of vegetable drugs to prevent bacterial decomposition in the process of manufacture. In most instances it is evaporated before the product is finished. It is an excellent solvent for alkaloids and many other organic chemicals and is used in the manufacture of these products and in chemical analyses.

### Citric Acid

1,2,3-Propanetricarboxylic acid, 2-hydroxy-,



Citric acid [77-92-9] $C_6H_8O_7$ (192.12); *monohydrate* [5949-29-1] (210.14).

**Preparation**—Found in many plants. It formerly was obtained solely from the juice of limes and lemons and from pineapple wastes. Since about 1925 the acid has been produced largely by fermentation of sucrose solution, including molasses, by fungi belonging to the *Aspergillus niger* group, theoretically according to the following reaction

$$\underset{\text{Sucrose}}{C_{12}H_{22}O_{11}} + \underset{\text{Oxygen}}{3O_2} \rightarrow \underset{\text{Citric Acid}}{2H_3C_6H_5O_7} + \underset{\text{Water}}{3H_2O}$$

but in practice there are deviations from this stoichiometric relationship.

**Description**—Colorless, translucent crystals, or a white, granular to fine crystalline powder; odorless; strongly acid taste; the hydrous form effloresces in moderately dry air, but is slightly deliquescent in moist air; loses its water of crystallization at about 50°; dilute aqueous solutions are subject to molding (fermentation), oxalic acid being one of the fermentation products.

**Solubility**—1 g in 0.5 mL water, 2 mL alcohol or about 30 mL ether; freely soluble in methanol.

**Uses**—In the preparation of *Anticoagulant Citrate Dextrose Solution, Anticoagulant Citrate Phosphate Dextrose Solution, Citric Acid Syrup* and *effervescent salts*. It also has been used to dissolve urinary bladder calculi, and as a mild astringent.

### Cocoa Butter

Cacao Butter; Theobroma Oil; Oil of Theobroma

The fat obtained from the roasted seed of *Theobroma cacao* Linné (Fam *Sterculiaceae*).

**Preparation**—By grinding the kernels of the "chocolate bean" and expressing the oil in powerful, horizontal hydraulic presses. The yield is about 40%. It also has been prepared by dissolving the oil from the unroasted beans by the use of a volatile solvent.

**Constituents**—Chemically, it is a mixture of stearin, palmitin, olein, laurin, linolein and traces of other glycerides.

**Description**—Yellowish, white solid; faint, agreeable odor; bland (if obtained by extraction) or chocolate-like (if obtained by pressing) taste; usually brittle below 25°; specific gravity 0.858 to 0.864 at 100°/25°; refractive index 1.454 to 1.458 at 40°.

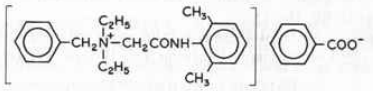
**Solubility**—Slightly soluble in alcohol; soluble in boiling dehydrated alcohol; freely soluble in ether or chloroform.

**Uses**—Valuable in pharmacy for making suppositories by virtue of its low fusing point and its property of becoming solid at a temperature just below the melting point. See *Suppositories* (page 1591). In addition to this use, it is an excellent emollient application to the skin when inflamed; it also is used in various skin creams, especially the so-called "*skin foods*." It also is used in massage.

## Titanium Dioxide—page 884.

### Denatonium Benzoate

Benzenemethanaminium *N*-[2-[(2,6-dimethylphenyl)amino]-2-oxoethyl]-*N*,*N*-diethyl-, benzoate;



Benzyldiethyl [(2,6-xylylcarbamoyl)methyl]ammonium benzoate [3734-33-6] $C_{28}H_{34}N_2O_3$ (446.59).

**Preparation**—2-(Diethylamino)-2′,6′-xylidide is quaternized by reaction with benzyl chloride. The quaternary chloride is then treated with methanolic potassium hydroxide to form the quaternary base which, after filtering off the KCl, is reacted with benzoic acid. The starting xylidide may be prepared by condensing 2,6- xylidine with chloroacetyl chloride and condensing the resulting chloroacetoxylidide with diethylamine. US Pat 3,080,327.

**Description**—White, odorless, crystalline powder; an intensely bitter taste; melts about 168°.

**Solubility**—1 g in 20 mL water, 2.4 mL alcohol, 2.9 mL chloroform or 5000 mL ether.

**Uses**—A *denaturant* for ethyl alcohol.

### Dextrin

British Gum; Starch Gum; Leiocom

Dextrin [9004-53-9] $(C_6H_{10}O_5)_n$.

**Preparation**—By the incomplete hydrolysis of starch with dilute acid, or by heating dry starch.

**Description**—White or yellow, amorphous powder (*white:* practically odorless; *yellow:* characteristic odor); dextrorotatory; $[\alpha]_D^{20}$ generally above 200°; does not reduce Fehling's solution; gives a reddish color with iodine.

**Solubility**—Soluble in 3 parts of boiling water, forming a gummy solution; less soluble in cold water.

**Uses**—An *excipient* and *emulsifier*.

### Dextrose

Anhydrous Dextrose; Dextrose Monohydrate; Glucose; D(+)-Glucose; α-D(+)-Glucopyranose; Medicinal Glucose; Purified Glucose; Grape Sugar; Bread Sugar; Cerelose; Starch Sugar; Corn Sugar

D-Glucose monohydrate [5996-10-1] $C_6H_{12}O_6.H_2O$ (198.17); *anhydrous* [50-99-7] (180.16). A sugar usually obtained by the hydrolysis of starch. For the structure, see page 384.

**Preparation**—See *Liquid Glucose* (page 1410).

**Description**—Colorless crystals or a white, crystalline or granular powder; odorless; sweet taste; specific rotation (anhydrous) +52.5 to +53°; anhydrous dextrose melts at 146°; dextrose slowly reduces alkaline cupric tartrate TS in the cold and rapidly on heating, producing a red precipitate of cuprous oxide (difference from *sucrose*).

**Solubility**—1 g in 1 mL of water or 100 mL of alcohol; more soluble in boiling water or boiling alcohol.

**Uses**—See *Dextrose Injection* (page 916). It also is used, instead of lactose, as a supplement to milk for infant feeding.

### Dichlorodifluoromethane

Methane, dichlorodifluoro-,

$CCl_2F_2$

Dichlorodifluoromethane [75-71-8] $CCl_2F_2$ (120.91).

**Preparation**—Carbon tetrachloride is reacted with antimony trifluoride in the presence of antimony pentafluoride.

**Description**—Clear, colorless gas; faint, ethereal odor; vapor pressure at 25° about 4883 torr.

**Uses**—A *propellant* (No 12, see page 1678).

### Dichlorotetrafluoroethane

Ethane, 1,2-dichloro-1,1,2,2-tetrafluoro-,

$CClF_2CClF_2$

1,2-Dichlorotetrafluoroethane [76-14-2] $C_2Cl_2F_4$ (170.92).

**Preparation**—By reacting 1,1,2-trichloro-1,2,2-trifluoroethane with antimony trifluorodichloride [$SbF_3Cl_2$], whereupon one of the 1-chlorine atoms is replaced by fluorine. The starting trichlorofluoroethane may be prepared from hexachloroethane by treatment with $SbF_3Cl_2$ (Henne AL: *Org Reactions II:* 65, 1944).

**Description**—Clear, colorless gas; faint, ethereal odor; vapor pressure at 25° about 1620 torr; usually contains 6 to 10% of its isomer, $CFCl_2$—$CF_3$.

**Uses**—A *propellant* (No 114 and 114a, see page 1678).

### Edetic Acid

Glycine, *N,N'*-1,2-ethanediylbis[*N*-(carboxymethyl)-,

$(HOOCCH_2)_2NCH_2CH_2N(CH_2COOH)_2$

(Ethylenedinitrilo)tetraacetic acid [60-00-4] $C_{10}H_{16}N_2O_8$ (292.24).

**Preparation**—Ethylenediamine is condensed with sodium monochloroacetate with the aid of sodium carbonate. An aqueous solution of the reactants is heated to about 90° for 10 hr, then cooled and acidified with HCl whereupon the acid precipitates. US Pat 2,130,505.

**Description**—White, crystalline powder; melts with decomposition above 220°.

**Solubility**—Very slightly soluble in water; soluble in solutions of alkali hydroxides.

**Uses**—A *pharmaceutic aid* (metal complexing agent). The acid, rather than any salt, is the form most potent in removing calcium from solution. It may be added to shed blood to prevent clotting. It also is used in pharmaceutical analysis and the removal or inactivation of unwanted ions in solution. Salts of the acid are known as edetates. See *Edetate Calcium Disodium* (page 935) and *Edetate Disodium* (page 935).

### Ethylcellulose

Cellulose ethyl ether [9004-57-3]; an ethyl ether of cellulose containing 44 to 51% of ethoxy groups. The *medium-type* viscosity grade contains less than 46.5% ethoxy groups; the *standard-type* viscosity grade contains 46.5% or more ethoxy groups.

**Preparation**—By the same general procedure described on page 1306 for *Methylcellulose* except that ethyl chloride or ethyl sulfate is employed as the alkylating agent. The 45 to 50% of ethoxy groups in the official ethylcellulose corresponds to from 2.25 to 2.61 ethoxy groups/$C_6H_{10}O_5$ unit, thus representing from 75 to 87% of the maximum theoretical ethoxylation, which is 3 ethoxy groups/$C_6H_{10}O_5$ unit.

**Description**—Free-flowing, white to light tan powder; forms films that have a refractive index of about 1.47; aqueous suspensions are neutral to litmus.

**Solubility**—The medium-type is freely soluble in tetrahydrofuran, methyl acetate, chloroform or mixtures of aromatic hydrocarbons with alcohol; the standard-type is freely soluble in alcohol, methanol, toluene, chloroform or ethyl acetate; both types are insoluble in water, glycerin or propylene glycol.

**Uses**—A *pharmaceutic aid* as a tablet binder and for film-coating tablets and drug particles.

**Gelatin**—page 1397.

### Liquid Glucose

Glucose; Starch Syrup; Corn Syrup

A product obtained by the incomplete hydrolysis of starch. It consists chiefly of dextrose [D(+)-glucose, $C_6H_{12}O_6$ = 180.16] dextrins, maltose and water.

**Preparation**—Commercially by the action of very weak $H_2SO_4$ or HCl on starch.

One of the processes for its manufacture is as follows: The starch, usually from corn, is mixed with 5 times its weight of water containing less than 1% of HCl, the mixture is heated to about 45° and then transferred to a suitable reaction vessel into which steam is passed under pressure until the temperature reaches 120°. The temperature is maintained at this point for about 1 hr, or until tests show complete disappearance of starch. The mass is then heated to volatilize most of the hydrochloric acid, sodium carbonate or calcium carbonate is added to neutralize the remaining traces of acid, the liquid is filtered, then decolorized in charcoal or bone-black filters, as is done in sugar refining and finally concentrated in vacuum to the desired consistency.

When made by the above process, it contains about 30 to 40% of dextrose mixed with about an equal proportion of dextrin, together with small amounts of other carbohydrates, notably maltose. By varying the conditions of hydrolysis, the relative proportions of the sugars also vary.

If the crystallizable dextrose is desired, the conversion temperature is higher and the time of conversion longer. The term "glucose," as customarily used in the chemical or pharmaceutical literature, usually refers to dextrose, the crystallizable product.

The name "grape sugar" sometimes is applied to the solid commercial form of dextrose because the principal sugar of the grape is dextrose, although the fruit has never been used as a source of the commercial supply.

**Description**—Colorless or yellowish, thick, syrupy liquid; odorless, or nearly so; sweet taste; differs from sucrose in that it readily reduces hot alkaline cupric tartrate TS, producing a red precipitate of cuprous oxide.

**Solubility**—Miscible with water; sparingly soluble in alcohol.

**Uses**—As an ingredient of *Cocoa Syrup* (page 1393), as a tablet binder and coating agent, and as a diluent in pilular extracts; it has replaced glycerin in many pharmaceutical preparations. It is sometimes given *per rectum* as a *food* in cases where feeding by stomach is impossible. It should not be used in the place of dextrose for intravenous injection.

### Hydrochloric Acid

Chlorhydric Acid; Muriatic Acid; Spirit of Salt

Hydrochloric acid [7647-01-0] HCl (36.46); contains 36.5 to 38.0%, by weight, of HCl.

**Preparation**—By the interaction of NaCl and $H_2SO_4$ or by combining chlorine with hydrogen. It is obtained as a byproduct in the manufacture of sodium carbonate from NaCl by the Leblanc process in which common salt is decomposed with $H_2SO_4$. HCl is also a byproduct in the electrolytic production of NaOH from NaCl.

**Description**—Colorless, fuming liquid; pungent odor; fumes and odor disappear when it is diluted with 2 volumes of water; strongly acid to litmus even when highly diluted; specific gravity about 1.18.

**Solubility**—Miscible with water or alcohol.

**Uses**—Officially classified as a pharmaceutic aid that is used as an acidifying agent. It is used in preparing *Diluted Hydrochloric Acid* (see RPS-18, page 783).

### Hypophosphorous Acid

Phosphinic acid

Hypophosphorous acid [6303-21-5] $HPH_2O_2$ (66.00); contains 30 to 32% by weight, of $H_3PO_2$.

**Preparation**—By reacting barium or calcium hypophosphite with sulfuric acid or by treating sodium hypophosphite with an ion-exchange resin.

**Description**—Colorless or slightly yellow, odorless liquid; solution is acid to litmus even when highly diluted; specific gravity about 1.13.

**Solubility**—Miscible with water or alcohol.

**Incompatibilities**—Oxidized on exposure to air and by nearly all *oxidizing agents*. *Mercury, silver* and *bismuth salts* are reduced partially to the metallic state as evidenced by a darkening in color. *Ferric compounds* are changed to ferrous.

**Uses**—An *antioxidant* in pharmaceutical preparations.

### Isopropyl Myristate

Tetradecanoic acid, 1-methylethyl ester

$CH_3(CH_2)_{12}COOCH(CH_3)_2$

Isopropyl myristate [110-27-0] $C_{17}H_{34}O_2$ (270.45).

**Preparation**—By reacting myristoyl chloride with 2-propanol with the aid of a suitable dehydrochlorinating agent.

**Description**—Liquid of low viscosity; practically colorless and odorless; congeals about 5° and decomposes at 208°; withstands oxidation and does not become rancid readily.

**Solubility**—Soluble in alcohol, acetone, chloroform, ethyl acetate, toluene, mineral oil, castor oil or cottonseed oil; practically insoluble in water, glycerin or propylene glycol; dissolves many waxes, cholesterol or lanolin.

**Uses**—*Pharmaceutic aid* used in cosmetics and topical medicinal preparations as an emollient, lubricant and to enhance absorption through the skin.

**Kaolin**—page 907.

### Lactic Acid

Propanoic acid, 2-hydroxy-, 2-Hydroxypropionic Acid; Propanoloic Acid; Milk Acid

$CH_3CH(OH)COOH$

Lactic acid [50-21-5] $C_3H_6O_3$ (90.08); a mixture of lactic acid and lactic acid lactate ($C_6H_{10}O_5$) equivalent to a total of 85 to 90%, by weight, of $C_3H_6O_3$.

Discovered by Scheele in 1780, it is the acid formed in the souring of milk, hence the name *lactic*, from the Latin name for milk. It results from the decomposition of the lactose (milk sugar) in milk.

**Preparation**—A solution of glucose or of starch previously hydrolyzed with diluted sulfuric acid is inoculated, after the addition of suitable nitrogen compounds and mineral salts, with *Bacillus lactis*. Calcium carbonate is added to neutralize the lactic acid as soon as it is formed, otherwise the fermentation stops when the amount of acid exceeds 0.5%. When fermentation is complete, as indicated by failure of the liquid to give a test for glucose, the solution is filtered, concentrated and allowed to stand. The calcium lactate that crystallizes is decomposed with dilute sulfuric acid and filtered with charcoal. The lactic acid in the filtrate is extracted with ethyl or isopropyl ether, the ether is distilled off and the aqueous solution of the acid concentrated under reduced pressure.

**Description**—Colorless or yellowish, nearly odorless, syrupy liquid; acid to litmus; absorbs water on exposure to moist air; when a dilute solution is concentrated to above 50%, lactic acid lactate begins to form; in the official acid the latter amounts to about 12 to 15%; specific gravity about 1.20; decomposes when distilled under normal pressure but may be distilled without decomposition under reduced pressure.

**Solubility**—Miscible with water, alcohol or ether; insoluble in chloroform.

**Uses**—In the preparation of *Sodium Lactate Injection* (page 933). It also is used in babies' milk formulas, as an acidulant in food preparations, and in 1 to 2% concentration in some spermatocidal jellies. A 10% solution is used as a bactericidal agent on the skin of neonates. It is corrosive to tissues on prolonged contact. A 16.7% solution in flexible collodion is used to remove warts and small cutaneous tumors.

### Lactose

D-Glucose, 4-*O*-β-D-galactopyranosyl-, Milk Sugar

Lactose [63-42-3] $C_{12}H_{22}O_{11}$ (342.30); *monohydrate* [10039-26-6] (360.31); a sugar obtained from milk.

For the structural formula, see page 385.

**Preparation**—From skim milk, to which is added diluted HCl to precipitate the casein. After removal of the casein by filtration, the reaction of the whey is adjusted to a pH of about 6.2 by addition of lime and the remaining albuminous matter is coagulated by heating; this is filtered out and the liquid set aside to crystallize. Animal charcoal is used to decolorize the solution in a manner similar to that used in purifying sucrose.

Another form of lactose, known as β-lactose, also is available on the market. It differs in that the D-glucose moiety is β instead of α. It is reported that this variety is sweeter and more soluble than ordinary lactose and for that reason is preferable in pharmaceutical manufacturing where lactose is used. Chemically, β-lactose does not appear to differ from ordinary α-lactose. It is manufactured in the same way as α-lactose up to the point of crystallization, then the solution is heated to a temperature above 93.5°, this being the temperature at which the α form is converted to the β variety. The β form occurs only as an anhydrous sugar whereas the α variety may be obtained either in the anhydrous form or as a monohydrate.

**Description**—White or creamy white, hard, crystalline masses or powder; odorless; faintly sweet taste; stable in air, but readily absorbs odors; pH (1 in 10 solution) 4.0 to 6.5; specific rotation +54.8 to +55.5°.

**Solubility**—1 g in 5 mL water or 2.6 mL boiling water; very slightly soluble in alcohol; insoluble in chloroform or ether.

**Uses**—A *diluent* largely used in medicine and pharmacy. It is generally an ingredient of the medium used in penicillin production. It is used extensively as an addition to milk for infant feeding.

### Magnesium Chloride

Magnesium chloride hexahydrate [7791-18-6] $MgCl_2.6H_2O$ (203.30); *anhydrous* [7786-30-3] (95.21).

**Preparation**—By treating magnesite or other suitable magnesium minerals with HCl.

**Description**—Colorless, odorless, deliquescent flakes or crystals, which lose water when heated to 100° and loose HCl when heated to 110°; pH (1 in 20 solution in carbon dioxide-free water) 4.5 to 7.

**Solubility**—Very soluble in water; freely soluble in alcohol.

**Uses**—*Electrolyte replenisher; pharmaceutical necessity* for hemodialysis and peritoneal dialysis fluids.

### Magnesium Stearate

Octadecanoic acid, magnesium salt

Magnesium stearate [557-04-0]. A compound of magnesium with a mixture of solid organic acids obtained from fats, and consists chiefly of variable proportions of magnesium stearate and magnesium palmitate. It contains the equivalent of 6.8 to 8.0% of MgO (40.30).

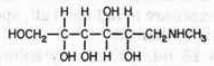
**Description**—Fine, white, bulky powder; faint, characteristic odor; unctuous, adheres readily to the skin and free from grittiness.

**Solubility**—Insoluble in water, alcohol or ether.

**Uses**—A *pharmaceutical necessity (lubricant)* in the manufacture of compressed tablets.

### Meglumine

D-Glucitol, 1-deoxy-1-(methylamino)-,



1-Deoxy-1-(methylamino)-D-glucitol [6284-40-8] $C_7H_{17}NO_5$ (195.21).

**Preparation**—By treating glucose with hydrogen and methylamine under pressure and in the presence of Raney nickel.

**Description**—White to faintly yellowish white, odorless crystals or powder; melts about 130°.

**Solubility**—Freely soluble in water; sparingly soluble in alcohol.

**Uses**—In forming salts of certain pharmaceuticals, surface-active agents and dyes. See *Diatrizoate Meglumine Injections* (page 1375), *Iodipamide Meglumine Injection* (page 1368) and *Iothalamate Meglumine Injection* (page 1378).

### Light Mineral Oil

Light Liquid Petrolatum NF XII; Light Liquid Paraffin; Light White Mineral Oil

A mixture of liquid hydrocarbons obtained from petroleum. It may contain a suitable stabilizer.

**Description**—Colorless, transparent, oily liquid, free, or nearly free, from fluorescence; odorless and tasteless when cold, and develops not more than a faint odor of petroleum when heated; specific gravity 0.818 to 0.880; kinematic viscosity not more than 33.5 centistokes at 40°.

**Solubility**—Insoluble in water or alcohol; miscible with most fixed oils, but not with castor oil; soluble in volatile oils.

**Uses**—Officially recognized as a *vehicle*. Once it was used widely as a vehicle for nose and throat medications; such uses are now considered dangerous because of the possibility of lipoid pneumonia. It sometimes is used to cleanse dry and inflamed skin areas and to facilitate removal of dermatological preparations from the skin. It should never be used for internal administration because of "leakage." See *Mineral Oil* (page 889).

### Nitric Acid

Nitric acid [7697-37-2] $HNO_3$ (63.01); contains about 70%, by weight, of $HNO_3$.

**Preparation**—May be prepared by treatment of sodium nitrate (Chile saltpeter) with sulfuric acid, but usually produced by catalytic oxidation of ammonia.

**Description**—Highly corrosive fuming liquid; characteristic, highly irritating odor; stains animal tissues yellow; boils about 120°; specific gravity about 1.41.

**Solubility**—Miscible with water.

**Uses**—*Pharmaceutic aid* (acidifying agent).

### Nitrogen

Nitrogen [7727-37-9] $N_2$ (28.01); contains not less than 99%, by volume, of $N_2$.

**Preparation**—By the fractional distillation of liquified air.

**Uses**—A diluent for medicinal gases. Pharmaceutically, is employed to replace air in the containers of substances which would be affected adversely by air oxidation. Examples include its use with fixed oils, certain vitamin preparations and a variety of injectable products. It also is used as a propellant.

**Persic Oil**—see RPS-18, page 1323.

### Phenol

Carbolic Acid

$C_6H_5OH$

Phenol [108-95-2] $C_6H_6O$ (94.11).

**Preparation**—For many years made only by distilling crude carbolic acid from coal tar and separating and purifying the distillate by repeated crystallizations, it now is prepared synthetically.

A more recent process uses chlorobenzene as the starting point in the manufacture. The chlorobenzene is produced in a vapor phase reaction, with benzene, HCl and oxygen over a copper catalyst, followed by hydrolysis with steam to yield HCl and phenol (which is recovered).

**Description**—Colorless to light pink, interlaced, or separate, needle-shaped crystals, or a white or light pink, crystalline mass; characteristic odor; when undiluted, it whitens and cauterizes the skin and mucous membranes; when gently heated, phenol melts, forming a highly refractive liquid; liquefied by the addition of 10% of water; vapor is flammable; gradually darkens on exposure to light and air; specific gravity 1.07; boils at 182°; congeals not lower than 39°.

**Solubility**—1 g in 15 mL water; very soluble in alcohol, glycerin, chloroform, ether or fixed and volatile oils; sparingly soluble in mineral oil.

**Incompatibilities**—Produces a liquid or soft mass when triturated with *camphor, menthol, acetanilid, acetophenetidin, aminopyrine, antipyrine, ethyl aminobenzoate, methenamine, phenyl salicylate, resorcinol, terpin hydrate, thymol* and several other substances including some *alkaloids*. It also softens *cocoa butter* in suppository mixtures.

It is soluble in about 15 parts of water; stronger solutions may be obtained by using as much glycerin as phenol. Only the crystallized form is soluble in fixed oils and liquid petroleum, the liquefied form is not all soluble due to its content of water. *Albumin* and *gelatin* are precipitated by it. *Collodion* is coagulated by the precipitation of pyroxylin. Traces of *iron* in various chemicals such as *alum, borax*, etc, may produce a green color.

**Uses**—A *caustic, disinfectant, topical anesthetic* and pharmaceutical necessity as a *preservative* for injections, etc. At one time widely used as a germicide and still the standard against which other antiseptics are compared, it has few legitimate uses in modern medicine. Nevertheless, it is still used in several proprietary antiseptic mouthwashes, hemorrhoidal preparations and burn remedies. In full strength, a few drops of the liquefied form may be used to cauterize small wounds, dog bites, snake bites, etc. It commonly is employed as an *antipruritic*, either in the form of phenolated calamine lotion (1%), phenol ointment (2%) or a simple aqueous solution (0.5 to 1%). It has been used for sclerosing hemorrhoids, but more effective and safer drugs are available. A 5% solution in glycerin is used in simple earache. Crude carbolic acid is an effective, economical agent for disinfecting excrement. It is of some therapeutic value as a *fungicide*, but more effective and less toxic agents are available. If accidentally spilled, it should be removed promptly from the skin by swabbing with alcohol.

**Liquefied Phenol** [Liquefied Carbolic Acid is phenol maintained in a liquid condition by the presence of 10.0% of water. It contains not less than 89.0%, by weight, of $C_6H_6O$. *Note—When it is to be mixed with a fixed oil, mineral oil or white petrolatum, use the crystalline Phenol, not Liquefied Phenol. Preparation:* Melt phenol (a convenient quantity) by placing the unstoppered container in a steam bath and applying heat gradually. Transfer the liquid to a tared vessel, weigh, add 1 g of purified water for each 9 g of phenol, and mix thoroughly. *Description:* Colorless liquid, which may develop a red tint upon exposure to air and light; characteristic, somewhat aromatic odor; when undiluted it cauterizes and whitens the skin and mucous membranes; specific gravity about 1.065; when it is subjected to distillation, the boiling temperature does not rise above 182°, which is the boiling temperature of phenol; partially solidifies at about 15°. *Solubility:* Miscible with alcohol, ether or glycerin; a mixture of liquefied phenol and an equal volume of glycerin is miscible with water. *Uses:* A formulation which facilitates the dispensing of concentrated phenol. Its therapeutic uses are described above under *Phenol*. It is a *pharmaceutical necessity for Phenolated Calamine Lotion* (page 872).

**Phenyl Salicylate**—see RPS-15, page 1269.

### Phosphoric Acid

Orthophosphoric Acid; Syrupy Phosphoric Acid; Concentrated Phosphoric Acid

Phosphoric acid [7664-38-2] $H_3PO_4$ (98.00); contains 85 to 88%, by weight, of $H_3PO_4$.

**Preparation**—Phosphorus is converted to phosphorus pentoxide [$P_2O_5$] by exposing it to a current of warm air, then the $P_2O_5$ is treated with water to form phosphoric acid. The conversion of the phosphorus to the pentoxide takes place while the phosphorus, distilling from the phosphorus manufacturing operation, is in the vapor state.

**Description**—Colorless, odorless liquid of a syrupy consistency; specific gravity about 1.71.

**Solubility**—Miscible with water or alcohol, with the evolution of heat.

**Uses**—To make the diluted acid and as a weak acid in various pharmaceutical preparations. Industrially, it is used in dental cements and in beverages as an acidulant.

**Diluted Phosphoric Acid** [Dilute Phosphoric Acid] contains, in each 100 mL, 9.5 to 10.5 g of $H_3PO_4$ (98.00). *Preparation:* Mix phosphoric acid (69 mL) and purified water (qs) to make 1000 mL. *Description and Solubility:* Clear, colorless, odorless liquid; specific gravity about 1.057. Miscible with water or alcohol. *Uses:* A *pharmaceutical necessity*. It also has been employed in *lead poisoning* and in other conditions in which it is desired to administer large amounts of phosphate and at the same time produce a mild acidosis. It has been given in the dose of 60 mL a day (5 mL/hour) under carefully controlled conditions.

### Potassium Metaphosphate

Metaphosphoric acid ($HPO_3$), potassium salt

Potassium metaphosphate [7790-53-6] $KPO_3$ (118.07); a straight-chain polyphosphate, having a high degree of polymerization; contains the equivalent of 59 to 61% of $P_2O_5$.

**Preparation**—By thermal dehydration of monopotassium phosphate ($KH_2PO_4$).

**Description**—White, odorless powder.

**Solubility**—Insoluble in water; soluble in dilute solutions of sodium salts.

**Uses**—*Pharmaceutic aid* (buffering agent).

### Monobasic Potassium Phosphate

Phosphoric acid, monopotassium salt; Potassium Biphosphate; Potassium Acid Phosphate; Potassium Dihydrogen Phosphate; Sørensen's Potassium Phosphate

Monopotassium phosphate [7778-77-0] $KH_2PO_4$ (136.09).

**Preparation**—$H_3PO_4$ is reacted with an equimolar quantity of KOH and the solution is evaporated to crystallization.

**Description**—Colorless crystals or a white, granular or crystalline powder; odorless and stable in air; pH (1 in 100 solution) about 4.5.

**Solubility**—Freely soluble in water; practically insoluble in alcohol.

**Uses**—A component of various buffer solutions. Medicinally, it has been used as a urinary acidifier.

## Pumice

Pumex

A substance of volcanic origin, consisting chiefly of complex silicates of aluminum, potassium and sodium.

**Description**—Very light, hard rough, porous, grayish masses or a gritty, grayish powder of several grades of fineness; odorless, tasteless and stable in the air.

Three powders are available:

*Pumice Flour* or *Superfine Pumice*—Not less than 97% passes through a No 200 standard mesh sieve.

*Fine Pumice*—Not less than 95% passes through a No 150 standard mesh sieve, and not more than 75% passes through a No 200 standard mesh sieve.

*Coarse Pumice*—Not less than 95% passes through a No 60 standard mesh sieve, and not more than 5% passes through a No 200 standard mesh sieve.

**Solubility**—Insoluble in water and is not attacked by acids or alkali hydroxide solutions.

**Uses**—A *filtering* and *distributing medium* for pharmaceutical preparations. Because of its grittiness the powdered form is used in certain types of soaps and cleaning powders and also as a *dental abrasive.*

## Pyroxylin

Cellulose, nitrate; Soluble Guncotton

Pyroxylin [9004-70-0]; a product obtained by the action of a mixture of nitric and sulfuric acids on cotton, and consists chiefly of cellulose tetranitrate [$(C_{12}H_{16}N_4O_{18})_n$].

*Note—The commercially available form is moistened with about 30% of alcohol or other suitable solvent. The alcohol or solvent must be allowed to evaporate to yield the dried substance described in the Pharmacopeia.*

**Preparation**—Shönbein, in 1846, found that nitric acid acts on cotton and produces a soluble compound. It subsequently was proved that this substance belongs to a series of closely related nitrates in which the nitric acid radical replaces the hydroxyl of the cellulose formula. This usually is indicated by taking the double empirical formula for cellulose $C_{12}H_{20}O_{10}$ and indicating replacement of four of the OH groups thus

$$\underset{\text{Cellulose}}{C_{12}H_{20}O_{10}} + 4HNO_3 \rightarrow \underset{\text{Cellulose Tetranitrate}}{C_{12}H_{16}O_6(NO_3)_4} + 4H_2O$$

The compound used in preparing collodion is a varying mixture of the di-, tri-, tetra- and pentanitrates, but is mainly tetranitrate. The hexanitrate is the true explosive guncotton, and is insoluble in ether, alcohol, acetone or water.

**Description**—Light yellow, matted mass of filaments, resembling raw cotton in appearance, but harsh to the touch; *exceedingly flammable* burning, when unconfined, very rapidly and with a luminous flame; when kept in well-closed bottles and exposed to light, it is decomposed with the evolution of nitrous vapors, leaving a carbonaceous residue.

**Solubility**—Insoluble in water; dissolves slowly but completely in 25 parts of a mixture of 3 volumes of ether and 1 volume of alcohol; soluble in acetone or glacial acetic acid and precipitated from these solutions by water.

**Uses**—A *pharmaceutical necessity* for *Collodion* (RPS-16, page 717).

## Rosin

Resina; Colophony; Georgia Pine Rosin; Yellow Pine Rosin

A solid resin obtained from *Pinus palustris* Miller, and from other species of *Pinus* Linné (Fam *Pinaceae*).

**Constituents**—American rosin contains *sylvic acid* [$C_{20}H_{30}O_2$], α-, β- and γ-*abietic acids* [$C_{20}H_{30}O_2$], γ-*pinic acid* (from which α- and β-pinic acids are gradually formed) and *resene.* Some authorities also include *pimaric acid* [$C_{30}H_{20}O_2$] as a constituent. French rosin is called *galipot.*

**Description**—Sharply angular, translucent, amber-colored fragments, frequently covered with a yellow dust; fracture brittle at ordinary temperatures, shiny and shallow-conchoidal; odor and taste are slightly terebinthinate; easily fusible and burns with a dense, yellowish smoke, specific gravity 1.07 to 1.09.

**Solubility**—Insoluble in water; soluble in alcohol, ether, benzene, glacial acetic acid, chloroform, carbon disulfide, dilute solutions of sodium hydroxide and potassium hydroxide or some volatile and fixed oils.

**Uses**—A pharmaceutical necessity for *Zinc-Eugenol Cement* (see RPS-18, page 1328). Formerly, and to some extent still, used as a component of plasters, cerates and ointments, to which it adds adhesive qualities.

## Purified Siliceous Earth

Purified Kieselguhr; Purified Infusorial Earth; Diatomaceous Earth; Diatomite

A form of silica [$SiO_2$] [7631-86-9] consisting of the frustules and fragments of diatoms, purified by boiling with acid, washing and calcining.

**Occurrence and Preparation**—Large deposits of this substance are found in Virginia, Maryland, Nevada, Oregon and California, usually in the form of masses of rocks, hundreds of feet in thickness. Under the microscope it is seen to consist largely of the minute siliceous frustules of diatoms. It must be purified carefully in a manner similar to that directed for *Talc* (page 1415), and thoroughly calcined. The latter treatment destroys the bacteria which are present in large quantities in the native earth.

**Description**—Very fine, white, light-gray or pale-buff mixture of amorphous powder and lesser amounts of crystalline polymorphs, including quartz and cristobalite; gritty, readily absorbs moisture and retains about four times its weight of water without becoming fluid.

**Solubility**—Insoluble in water, acids or dilute solutions of alkali hydroxides.

**Uses**—Introduced into the USP as a distributing and *filtering medium* for aromatic waters; also suitable for filtration of elixirs. Like talc, it does not absorb active constituents.

## Sarsparilla—see RPS-18, page 1329.

## Colloidal Silicon Dioxide

Silica [7631-86-9] $SiO_2$ (60.08); a submicroscopic fumed silica prepared by the vapor-phase hydrolysis of a silicon compound.

**Description**—Light, white, nongritty powder of extremely fine particle size (about 15 nm).

**Solubility**—Insoluble in water or acids (except hydrofluoric); dissolved by hot solutions of alkali hydroxides.

**Uses**—A *tablet moisture adsorber, glidant* and as a *suspending* and *thickening agent* in pharmaceutical preparations.

## Soda Lime

A mixture of calcium hydroxide and sodium or potassium hydroxide or both.

It may contain an indicator that is inert toward anesthetic gases such as ether, cyclopropane and nitrous oxide, and that changes color when the soda lime no longer can absorb carbon dioxide.

**Description**—White or grayish white granules; if an indicator is added, it may have a color; absorbs carbon dioxide and water on exposure to air.

**Uses**—Neither a therapeutic nor a pharmaceutical agent. It is a *reagent for the absorption of carbon dioxide* in anesthesia machines, oxygen therapy and metabolic tests. Because of the importance of the proper quality for these purposes it has been made official and standardized.

## Sodium Borate

Sodium Tetraborate; Sodium Pyroborate; Sodium Biborate

Borax [1303-96-4] $Na_2B_4O_7.10H_2O$ (381.37); anhydrous [1330-43-4] $Na_2B_4O_7$ (201.22).

**Preparation**—Found in immense quantities in California as a crystalline deposit. The earth, which is strongly impregnated with borax, is lixiviated; the solution is evaporated and crystallized.

Calcium borate, or *cotton balls,* also occurs in the borax deposits of California, and sodium borate is obtained from it by double decomposition with sodium carbonate.

**Description**—Colorless, transparent crystals, or a white, crystalline powder; odorless; the crystals often are coated with white powder due to efflorescence; solution alkaline to litmus and phenolphthalein; pH about 9.5.

**Solubility**—1 g in 16 mL water, 1 mL glycerin or 1 mL boiling water; insoluble in alcohol.

**Incompatibilities**—Precipitates many *metals* as insoluble borates. In aqueous solution it is alkaline and precipitates *aluminum salts* as aluminum hydroxide, *iron salts* as a basic borate and ferric hydroxide and *zinc sulfate* as zinc borate and a basic salt. *Alkaloids* are precipitated from solutions of their salts. Approximately equal weights of *glycerin* and boric acid react to produce a decidedly acid derivative generally called glyceroboric acid. Thus, the addition of glycerin to a mixture containing it overcomes incompatibilities arising from an alkaline reaction.

**Uses**—As a pharmaceutical necessity, it is used as an alkalizing agent and as a buffer for alkaline solutions. Its alkalizing properties provide the basis for its use in denture adhesives and its buffering action for its use in eyewash formulations.

### Sodium Carbonate

Carbonic acid, disodium salt, monohydrate; Monohydrated Sodium Carbonate USP XVII

Disodium carbonate monohydrate [5968-11-6] $Na_2CO_3.H_2O$ (124.00); *anhydrous* [497-19-8] (105.99).

**Preparation**—The initial process for its manufacture was devised by Leblanc, a French apothecary, in 1784, and consists of two steps: first, the conversion of common salt [NaCl] into sodium sulfate by heating it with sulfuric acid and, second, the decomposition of the sulfate by calcium carbonate (limestone) and charcoal (coal) at a high temperature to yield this salt and calcium sulfide. The carbonate then is leached out with water.

It currently is prepared by the electrolysis of sodium chloride, whereby sodium and chlorine are produced, the former reacting with water to produce sodium hydroxide and this solution treated with carbon dioxide to produce the salt. The process is used most extensively in localities where electric power is very cheap.

The monohydrated form is made by crystallizing a concentrated solution of this salt at a temperature above 35° (95°F), and stirring the liquid so as to produce small crystals. It contains about 15% of water of crystallization.

*Soda ash* is a term designating a commercial quality of the anhydrous salt. Its annual production is very large, and it has a wide variety of applications, among which are the manufacture of glass, soap and sodium salts; it also is used for washing fabrics.

*Washing soda*, or *sal soda*, is the salt with 10 molecules of water. It is in the form of colorless crystals which rapidly effloresce in the air.

**Description**—Colorless crystals or a white, crystalline powder; stable in air under ordinary conditions; when exposed to dry air above 50° it effloresces, and at 100° becomes anhydrous; decomposed by weak acids forming the salt of the acid and liberating carbon dioxide; aqueous solution alkaline to indicators (pH about 11.5).

**Solubility**—1 g in 3 mL water or 1.8 mL boiling water; insoluble in alcohol.

**Incompatibilities**—*Acids, acid salts* and *acidic preparations* cause its decomposition. Most *metals* are precipitated as carbonates, hydroxides or basic salts. *Alkaloids* are precipitated from solutions of their salts.

**Uses**—Occasionally, for dermatitides topically as a lotion; it has been used as a mouthwash and a vaginal douche. It is used in the preparation of the sodium salts of many acids. The USP recognizes it as a pharmaceutic aid used as an alkalizing agent.

### Sodium Hydroxide

Caustic Soda, Soda Lye

Sodium hydroxide [1310-73-2] NaOH (40.00); includes not more than 3% of $Na_2CO_3$ (105.99).

*Caution—Exercise great care in handling it, as it rapidly destroys tissues.*

**Preparation**—By treating sodium carbonate with milk of lime, or by the electrolysis of a solution of sodium chloride as explained under *Potassium Hydroxide* (page 877). It now is produced largely by the latter process. See also *Sodium Carbonate*, above.

**Description**—White, or nearly white, fused masses, small pellets, flakes, sticks and other forms; hard and brittle and shows a crystalline fracture; exposed to the air, it rapidly absorbs carbon dioxide and moisture; melts at about 318°; specific gravity 2.13; when dissolved in water or alcohol, or when its solution is treated with an acid, much heat is generated; aqueous solutions, even when highly diluted, are strongly alkaline.

**Solubility**—1 g in 1 mL water; freely soluble in alcohol or glycerin.

**Incompatibilities**—Exposed to air, it absorbs *carbon dioxide* and is converted to sodium carbonate. With *fats* and *fatty acids* it forms soluble soaps; with *resins* it forms insoluble soaps. See *Potassium Hydroxide* (page 877).

**Uses**—Too alkaline to be of medicinal value but occasionally used in veterinary practice as a caustic. It is used extensively in pharmaceutical processes as an alkalizing agent and is generally preferred to potassium hydroxide because it is less deliquescent, and less expensive; in addition, less of it is required since 40 parts of it are equivalent to 56 parts of KOH. It is a pharmaceutical necessity in the preparation of *Glycerin Suppositories* (see RPS-18, page 785).

### Sodium Stearate

Octadecanoic acid, sodium salt

Sodium stearate [822-16-2] $C_{18}H_{35}NaO_2$ (306.47) consists chiefly of sodium stearate and sodium palmitate [$C_{16}H_{31}NaO_2$ = 278.41).

**Preparation**—Stearic acid is reacted with an equimolar portion of NaOH.

**Description**—Fine, white powder, soapy to the touch; usually has a slight, tallow-like odor; affected by light; solutions are alkaline to phenolphthalein TS.

**Solubility**—Slowly soluble in cold water or cold alcohol; readily soluble in hot water or hot alcohol.

**Uses**—Officially, a pharmaceutic aid used as an emulsifying and stiffening agent. It is an ingredient of glycerin suppositories. In dermatological practice it has been used topically in sycosis and other skin diseases.

### Starch

Corn Starch; Wheat Starch; Potato Starch

Starch [9005-25-8]; consists of the granules separated from the mature grain of corn [*Zea mays* Linné (Fam *Gramineae*)] or of wheat [*Triticum aestivum* Linné] (Fam *Gramineae*), or from tubers of the potato [*Solanum tuberosum* Linné (Fam *Solanaceae*)].

**Preparation**—In making starch from corn, the germ is separated mechanically and the cells softened to permit escape of the starch granules. This generally is done by permitting it to become sour and decomposed, stopping the fermentation before the starch is affected. On the small scale, it may be made from wheat flour by making a stiff ball of dough and kneading it while a small stream of water trickles upon it. It is carried off with the water, while the *gluten* remains as a soft, elastic mass; the latter may be purified and used for various purposes to which gluten is applicable. Commercially, its quality largely depends on the purity of the water used in its manufacture. It may be made from potatoes by first grating them, and then washing the soft mass upon a sieve, which separates the cellular substances and permits the starch granules to be carried through. It then must be washed thoroughly by decantation, and the quality of this starch also depends largely on the purity of the water that is used in washing it.

**Description**—Irregular, angular, white masses or fine powder; odorless; slight, characteristic taste. *Corn starch:* Polygonal, rounded or spheroidal granules up to about 35 μm in diameter which usually have a circular or several-rayed central cleft. *Wheat starch:* Simple lenticular granules 20 to 50 μm in diameter and spherical granules 5 to 10 μm in diameter; striations faintly marked and concentric. *Potato starch:* Simple granules, irregularly ovoid or spherical, 30 to 100 μm in diameter, and subspherical granules 10 to 35 μm in diameter; striations well-marked and concentric.

**Solubility**—Insoluble in cold water or alcohol; when it is boiled with about 20 times its weight of hot water for a few minutes and then cooled, a translucent, whitish jelly results; aqueous suspension neutral to litmus.

**Uses**—Has absorbent and demulcent properties. It is used as a dusting powder and in various dermatological preparations; also as a pharmaceutic aid (filler, binder and disintegrant). *Note—Starches obtained from different botanical sources may not have identical properties with respect to their use for specific pharmaceutical purposes, eg, as a tablet-disintegrating agent. Therefore, types should not be interchanged unless performance equivalency has been ascertained.*

Under the title *Pregelatinized Starch* the NF recognizes starch that has been processed chemically or mechanically to rupture all or part of the granules in the presence of water, and subsequently dried. Some types may be modified to render them compressible and flowable.

### Storax

Liquid Storax; Styrax; Sweet Gum; Prepared Storax

A balsam obtained from the trunk of *Liquidambar orientalis* Miller, known in commerce as Levant Storax, or of *Liquidambar styraciflua* Linné, known in commerce as American Storax (Fam *Hamamelidaceae*).

**Constituents**—The following occur in both varieties: *styracin* (*cinnamyl cinnamate*), *styrol* (*phenylethylene*, $C_8H_8$), α- and β-*storesin* (the cinnamic acid ester of an alcohol called *storesinol*), *phenylpropyl cinnamate*, free *cinnamic acid* and *vanillin*. In addition to these, Levant storax contains *ethyl cinnamate, benzyl cinnamate*, free *storesinol, isocinnamic acid, ethylvanillin, styrogenin* and *styrocamphene*. This variety yields from 0.5 to 1% of *volatile oil;* from this have been isolated *styrocamphene, vanillin*, the cinnamic acid esters of *ethyl, phenylpropyl, benzyl* and *cinnamyl alcohols, naphthalene* and *styrol*.

The American variety contains, in addition to the aforementioned substances common to both varieties, *styaresin* (the cinnamic acid ester of the alcohol *styresinol*, an isomer of storesinol) and *styresinolic acid*. It yields up to 7% of a dextrorotatory volatile oil, the composition of which has not been investigated completely; styrol and traces of vanillin have been isolated from it.

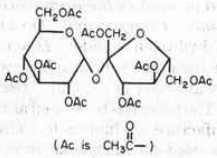
**Description**—Semiliquid, grayish to grayish brown, sticky, opaque mass, depositing on standing a heavy dark brown layer (Levant storax); or a semisolid, sometimes a solid mass, softened by gently warming (American storax); transparent in thin layers; characteristic odor and taste; more dense than water.

**Solubility**—Insoluble in water, but soluble, usually incompletely, in an equal weight of warm alcohol; soluble in acetone, carbon disulfide or ether, some insoluble residue usually remaining.

**Uses**—An *expectorant* but is used chiefly as a local remedy, especially in combination with benzoin; eg, it is an ingredient of *Compound Benzoin Tincture* (page 869). It may be used, like benzoin, to protect fatty substances from rancidity.

### Sucrose Octaacetate

α-D-Glucopyranoside, 1,3,4,6-tetra-*O*-acetyl-β-D-fructofuranosyl-, tetraacetate




Sucrose octaacetate [126-14-7] $C_{28}H_{38}O_{19}$ (678.60).

**Preparation**—Sucrose is subjected to exhaustive acetylation by reaction with acetic anhydride in the presence of a suitable condensing agent such as pyridine.

**Description**—White, practically odorless powder; intensely bitter taste; hygroscopic; melts not lower than 78°.

**Solubility**—1 g in 1100 mL water, 11 mL alcohol, 0.3 mL acetone or 0.6 mL benzene; very soluble in methanol or chloroform; soluble in ether.

**Uses**—A *denaturant* for alcohol.

### Sulfurated Potash

Thiosulfuric acid, dipotassium salt, mixt. with potassium sulfide ($K_2(S_x)$); Liver of Sulfur

Dipotassium thiosulfate mixture with potassium sulfide ($K_2S_x$) [39365-88-3]; a mixture composed chiefly of potassium polysulfides and potassium thiosulfate. It contains not less than 12.8% of S (sulfur) in combination as sulfide.

**Preparation**—By thoroughly mixing 1 part of sublimed sulfur with 2 parts of potassium carbonate and gradually heating the mixture in a covered iron crucible until the mass ceases to swell and is melted completely. It then is poured on a stone or glass slab and, when cold, broken into pieces and preserved in tightly closed bottles. When the heat is regulated properly during its production, the reaction is represented approximately by

$$3K_2CO_3 + 8S \rightarrow 2K_2S_3 + K_2S_2O_3 + 3CO_2$$

As this product rapidly deteriorates on exposure to moisture, oxygen and carbon dioxide, it is important that it be prepared recently to produce satisfactory preparations.

**Description**—Irregular pieces, liver-brown when freshly prepared, changing to a greenish yellow; decomposes upon exposure to air; an odor of hydrogen sulfide and a bitter, acrid, alkaline taste; even weak acids cause the liberation of $H_2S$ from sulfurated potash; 1 in 10 solution light brown in color and alkaline to litmus.

**Solubility**—1 g in about 2 mL water, usually leaving a slight residue; alcohol dissolves only the sulfides.

**Uses**—Extensively in dermatological practice, especially in the official *White Lotion* or *Lotio Alba* (page 873). It is used as an opacifier.

The equation for the reaction of the potassium trisulfide in preparing the lotion is

$$ZnSO_4 + K_2S_3 \rightarrow \underline{ZnS} + 2\underline{S} + K_2SO_4$$

### Talc

Talcum; Purified Talc; French Chalk; Soapstone; Steatite

A native, hydrous magnesium silicate, sometimes containing a small proportion of aluminum silicate.

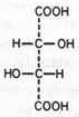
**Occurrence and Preparation**—The native form, called *soapstone* or *French chalk*, is found in various parts of the world. An excellent quality is obtained from deposits in North Carolina. Deposits of a high grade, conforming to the USP requirements, also are found in Manchuria. The native form usually is accompanied by variable amounts of mineral substances. These are separated from it by mechanical means, such as flotation or elutriation. It then is powdered finely, treated with boiling dilute HCl, washed well and dried.

**Description**—Very fine, white, or grayish white crystalline powder; unctuous to the touch, adhering readily to the skin, and free from grittiness.

**Uses**—Officially, as a dusting powder and pharmaceutic aid; in both categories it has many specific uses. Its medicinal use as a dusting powder depends on its desiccant and lubricant effects. When perfumed, and sometimes medicated, it is used extensively for toilet purposes under the name *talcum powder;* for such use it should be in the form of an impalpable powder. When used as a filtration medium for clarifying liquids a coarser powder is preferred to minimize passage through the pores of the filter paper; for this purpose it may be used for all classes of preparations with no danger of adsorption or retention of active principles. It is used as a lubricant in the manufacture of tablets, and as a dusting powder when making handmade suppositories. Although it is used as a lubricant for putting on and removing rubber gloves, it should not be used on surgical gloves because even small amounts deposited in organs or healing wounds may cause granuloma formation.

### Tartaric Acid

Butanedioic acid, [*R*-(*R**,*R**)] 2,3-dihydroxy-,




L-(+)-Tartaric acid [87-69-4] $C_4H_6O_6$ (150.09).

**Preparation**—From *argol*, the crude cream of tartar (potassium bitartrate) deposited on the sides of wine casks during the fermentation of grapes, by conversion to calcium tartrate which is hydrolyzed to tartaric acid and calcium sulfate.

**Description**—Large, colorless or translucent crystals, or a white granular to fine crystalline powder; odorless; acid taste; stable in the air; solutions acid to litmus; dextrorotatory.

**Solubility**—1 g in 0.8 mL water, 0.5 mL boiling water, 3 mL alcohol or 250 mL ether; freely soluble in methanol.

**Uses**—Chiefly, as the acid ingredient of preparations in which it is neutralized by a bicarbonate, as in effervescent salts, and the free acid is completely absent or present only in small amounts in the finished product. It also is used as a buffering agent.

### Trichloromonofluoromethane

Methane, trichlorofluoro-,

$CFCl_3$

Trichlorofluoromethane [75-69-4] $CCl_3F$ (137.37).

**Preparation**—Carbon tetrachloride is reacted with antimony trifluoride in the presence of a small quantity of antimony pentachloride. The reaction produces a mixture of $CCl_3F$ and $CCl_2F_2$ which is readily separable by fractional distillation.

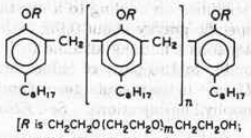
**Description**—Clear, colorless gas; faint, ethereal odor; vapor pressure at 25° is about 796 torr; boils about 24°.

**Solubility**—Practically insoluble in water; soluble in alcohol, ether or other organic solvents.

**Uses**—A *propellant* (No 11, see page 1696).

### Tyloxapol

Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane; (*Various Mfrs*)




[*R* is $CH_2CH_2O(CH_2CH_2O)_mCH_2CH_2OH$; *m* is 6 to 8; *n* is not more than 5]

*p*-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde [25301-02-4].

**Preparation**—*p*-(1,1,3,3-Tetramethylbutyl)phenol and formaldehyde are condensed by heating in the presence of an acidic catalyst and the polymeric phenol thus obtained is reacted with ethylene oxide at elevated temperature under pressure in the presence of NaOH. US Pat. 2,454,541.

**Description**—Amber, viscous liquid; may show a slight turbidity; slight aromatic odor; specific gravity about 1.072; stable at sterilization temperature and in the presence of acids, bases and salts; oxidized by metals; pH (5% aqueous solution) 4 to 7.

**Solubility**—Slowly but freely soluble in water; soluble in many organic solvents, including acetic acid, benzene, carbon tetrachloride, carbon disulfide, chloroform or toluene.

**Uses**—A nonionic detergent that depresses both surface tension and interfacial tension. It also is used in contact-lens-cleaner formulations.

**Zinc-Eugenol Cement**—see RPS-18, page 1328.

### Iso-Alcoholic Elixir

#### Iso-Elixir

| | |
|---|---|
| **Low-Alcoholic Elixir** | |
| **High-Alcoholic Elixir** | of each a calculated volume |

Mix the ingredients.

#### Low-Alcoholic Elixir

| | |
|---|---|
| **Compound Orange Spirit** | **10 mL** |
| **Alcohol** | **100 mL** |
| **Glycerin** | **200 mL** |
| **Sucrose** | **320 g** |
| **Purified Water,** a sufficient quantity, To make | **1000 mL** |

**Alcohol Content**—8 to 10%.

#### High-Alcoholic Elixir

| | |
|---|---|
| **Compound Orange Spirit** | **4 mL** |
| **Saccharin** | **3 g** |
| **Glycerin** | **200 mL** |
| **Alcohol,** a sufficient quantity, To make | **1000 mL** |

**Alcohol Content**—73 to 78%.

**Uses**—Intended as a general *vehicle* for various medicaments that require solvents of different alcohol strengths. When it is specified in a prescription, the proportion of its two ingredients to be used is that which will produce a solution of the required alcohol strength.

The alcohol strength of the elixir to be used with a single liquid galenical in a prescription is approximately the same as that of the galenical. When galenicals of different alcohol strengths are used in the same prescription, the elixir to be used is to be of such alcohol strength as to secure the best solution possible. This generally will be found to be the average of the alcohol strengths of the several ingredients.

For nonextractive substances, the lowest alcohol strength of the elixir that will yield a perfect solution should be chosen.

### Other Miscellaneous Pharmaceutical Necessities

**Bucrylate** [Propenoic acid, 2-cyano-, 2-methylpropyl ester; Isobutyl 2-cyanoacrylate [1069-55-2] $C_8H_{11}NO_2$ (153.18); (*Ethicon*)]—*Preparation:* One method reacts isobutyl 2-chloroacrylate with sodium cyanide. *Uses:* Surgical aid (tissue adhesive).

**Ceresin** [Ozokerite; Earth Wax; Cerosin; Mineral Wax; Fossil Wax]—A hard, white odorless solid resembling spermaceti when purified, occurring naturally in deposits in the Carpathian Mountains, especially in Galicia. It is a mixture of natural complex paraffin hydrocarbons. Melts between 61 and 78°; specific gravity 0.91 to 0.92; stable toward oxidizing agents. Soluble in 30% alcohol, benzene, chloroform, petroleum, benzin or hot oils. *Uses:* Substitute for beeswax; in dentistry, for impression waxes.

**Ethylenediamine Hydrate BP, PhI** [$H_2NCH_2CH_2NH_2.H_2O$]—Clear, colorless or slightly yellow liquid with an ammoniacal odor and characteristic alkaline taste; solidifies on cooling to a crystalline mass (mp 10°); boils 118 to 119°; specific gravity about 0.96; hygroscopic and absorbs $CO_2$ from the air; aqueous solutions alkaline to litmus. Miscible with water or alcohol; soluble in 130 parts of chloroform; slightly soluble in benzene or ether. *Uses:* In the manufacture of aminophylline and in the preparation of aminophylline injections. See *Ethylenediamine* (page 1381).

**Ferric Oxide, Red**—Contains not less than 90% $Fe_2O_3$. It is made by heating native ferric oxide or hydroxide at a temperature which will yield a product of the desired color. The color is governed by the temperature and time of heating, the presence and kind of other metals and the particle size of the oxide. A dark-colored oxide is favored by prolonged heating at high temperature and the presence of manganese. A light-colored oxide is favored by the presence of aluminum and by finer particle size. *Uses:* Imparting color to neocalamine and cosmetics.

**Ferric Oxide, Yellow**—Contains not less than 97.5% $Fe_2O_3$. It is prepared by heating ferrous hydroxide or ferrous carbonate in air at a low temperature. *Uses:* As for *Red Ferric Oxide* (above).

**Honey NF XII** [Mel; Clarified Honey; Strained Honey]—The saccharine secretion deposited in the honeycomb by the bee, *Apis mellifera* Linné (Fam *Apidae*). It must be free from foreign substances such as parts of insects, leaves, etc, but may contain pollen grains. *History:* Honey is one of the oldest of food and medicinal products. During the 16th and 17th centuries it was recommended as a cure for almost everything. *Constituents: Invert sugar* (62 to 83%), *sucrose* (0 to 8%) and *dextrin* (0.26 to 7%). *Description:* Thick, syrupy liquid of a light yellowish to reddish brown color; translucent when fresh, but frequently becomes opaque and granular through crystallization of dextrose; characteristic odor and a sweet, faintly acrid taste. *Uses:* A sweetening agent and pharmaceutic necessity.

**Hydriodic Acid, Diluted**—Contains, in each 100 mL 9.5 to 10.5 g of HI (127.91), and 600 mg to 1 g of $HPH_2O_2$ (66.00). The latter is added to prevent the formation of free iodine. *Caution: Diluted Hydriodic Acid must not be dispensed or used in the preparation of other products if they contain free iodine. Preparation:* On a large scale, by the interaction of iodine and hydrogen sulfide. *Description* and *Solubility:* Colorless or not more than pale-yellow, odorless liquid; specific gravity about 1.1. Miscible with water or alcohol. *Uses:* In *Hydriodic Acid Syrup* (page 1393). The latter has been used as an expectorant. It also is used in the manufacture of inorganic iodides and disinfectants. The 57% acid also is used for analytical purposes, such as methoxyl determinations.

**Lime** [Calx; Calcium Oxide; Quicklime; Burnt Lime; Calx Usta; CaO (56.08)]—*Preparation:* By calcining *limestone* (a native calcium carbonate) in kilns with strong heat. *Description and Solubility:* Hard, white or grayish white masses or granules, or a white or grayish white powder; odorless; solution strongly alkaline. 1 g is soluble in about 840 mL water and 1740 mL boiling water; soluble in glycerin or syrup; insoluble in alcohol. *Uses:* In making mortar, whitewash, and various chemicals and products. It is an ingredient in *Sulfurated Lime Solution* (RPS-16, page 1187). In the USP, calcium hydroxide has replaced it, as it is more stable and more readily available of a quality suitable for medicinal use than the lime usually obtainable. Unless protected from air, lime soon becomes unfit for use, due to the action of carbon dioxide and moisture in the air. See *Calcium Hydroxide* (page 1408).

**Peach Oil**—An oil resembling almond oil obtained from *Persica vulgaris* (Fam *Rosaceae*). See *Persic Oil* (RPS-18, page 1323).

**Polacrilin Potassium** [Methacrylic acid polymer with divinylbenzene, potassium salt [39394-76-5]; Amberlite IRP-88 (*Rohm & Haas*)]—Prepared by polymerizing methacrylic acid with divinylbenzene and the resulting resin is neutralized with KOH. Dry, buff-colored, odorless, tasteless, free-flowing powder; stable in light, air, and heat; insoluble in water. *Uses: Pharmaceutic aid* (tablet disintegrant).

**Poloxalene** [Glycols, polymers, polyethylene-polypropylene [9003-11-6]—Polypropylene glycol is reacted with ethylene oxide. *Uses: Pharmaceutic aid* (surfactant).

**Raspberry Juice**—The liquid expressed from the fresh ripe fruit of *Rubus idaeus* Linné or of *Rubus strigosus* Michaux (Fam *Rosaceae*); contains not less than 1.5% of acids calculated as citric acid. *Preparation:* Express the juice from the washed, well-drained, fresh, ripe, red raspberries. Dissolve 0.1% of benzoic acid in the expressed juice and allow it to stand at room temperature (possibly for several days) until a small portion of the filtered juice produces a clear solution when mixed with ½ of its volume of alcohol, the solution remaining clear for not less than 30 min. Strain the juice from the mixture or filter it, if necessary. *Description:* Clear liquid with an aromatic, characteristic odor and a characteristic, sour taste; the freshly prepared juice is red to reddish orange; affected by light. *Uses:* In the preparation of *Raspberry Syrup* (see RPS-18, page 1302), a *flavored vehicle.*

**Sodium Glutamate** [Sodium Acid Glutamate [142-47-2] $HOOCCH(NH_2)CH_2CH_2COONa$]—White or nearly white, crystalline powder. Very soluble in water; sparingly soluble in alcohol. *Uses:* Imparts a meat flavor to foods.

**Sodium Thioglycollate** [Sodium Mercaptoacetate; $HSCH_2COONa$]—Hygroscopic crystals which discolor on exposure to air or iron. Freely soluble in water; slightly soluble in alcohol. *Uses:* Reducing agent in Fluid Thioglycollate Medium for sterility testing.

**Suet, Prepared** [Mutton Suet]—Internal fat of the abdomen of the sheep, *Ovis aries* (Fam *Bovidae*), purified by melting and straining. White, solid fat with a slight, characteristic odor and taste when fresh; melts between 45° and 50° and congeals between 37° and 40°; must be preserved in a cool place in tight containers. *Uses:* In ointments and cerates.

**Urea** [Carbamide [57-13-6] $CO(NH_2)_2$(60.06)]—A product of protein metabolism; prepared by hydrolysis of cyanamide or from carbon dioxide by ammonolysis. Colorless to white crystals or white, crystalline powder; almost odorless but may develop a slight odor of ammonia in presence of moisture; melts 132 to 135°. 1 g dissolves in 1.5 mL of water or 10 mL of alcohol; practically insoluble in chloroform or ether. *Uses:* A protein denaturant that promotes hydration of keratin and mild keratolysis in dry and hyperkeratotic skin. It is used in 2 to 20% concentrations in various dry-skin creams.

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CHAPTER 89

# Ophthalmic Preparations

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Ophthalmic preparations are sterile products essentially free from foreign particles, suitably compounded and packaged for instillation into the eye. Ophthalmic preparations include solutions, suspensions, ointments and solid dosage forms. The solutions and suspensions are, for the most part, aqueous. Ophthalmic ointments usually contain a white petrolatum-mineral oil base.

Ophthalmic preparations can be grouped broadly into two divisions of major significance to the pharmacist. These include single or multidose prescription products and the category described as OTC or over-the-counter ophthalmic products. The latter group has been subjected to a searching review and analysis by a body of experts as a part of the FDA's OTC Drug Review process.

The single dominant factor characteristic of all ophthalmic products is the specification of sterility. Any product intended for use in the eye regardless of form, substance or intent must be sterile. This requirement increases the similarity between ophthalmic and parenteral products, however the physiology of the human eye in many respects imposes more rigid formulation requirements. This will be considered in the following discussion.

Preparations intended for the treatment of eye disorders can be traced to antiquity. Egyptian papyri writings describe eye medications. The Greeks and Romans expanded such uses and gave us the term *collyria*. Collyria refer collectively to materials which were dissolved in water, milk or egg white for use as eyedrops. In the Middle Ages collyria included mydriatic substances to dilate the pupils of milady's eyes for cosmetic purposes, thus the term belladonna or "beautiful lady."

From the time of belladonna collyria, ophthalmic technology progressed at a pharmaceutical snail's pace well into modern times. It was not until after the second World War that the concept of sterility became mandatory for ophthalmic solutions. Prior to World War II and continuing into the 1940s very few ophthalmic preparations were available commercially or were described officially. The USP XIV, official in 1950, included only three ophthalmic preparations and all three were ointments.

Preparations to be used in the eye, either solutions or ointments, invariably were compounded in the community or hospital pharmacy and were intended for immediate (prescription) use. Such preparation and prompt use is reflected in the pharmaceutical literature of the times. The stability of ophthalmic preparations is discussed in terms of days or a few months.

One of the most important attributes of ophthalmic products is the requirement of sterility. Even that, however, is a surprisingly recent event. The USP XV in 1955 was the first official compendium to include a sterility requirement for ophthalmic solutions. The FDA in 1953 adopted the position that a nonsterile ophthalmic solution was adulterated. Sterile ophthalmic products were, of course, available prior to the mid 1950s, however the legal requirement of sterility dates only from 1955.

The sterility requirements for ophthalmic ointments appeared first in the USP XVIII, *Third Supplement* (1972). Prior to that date there was no legal requirement for a sterile ophthalmic ointment. This probably was due to the difficulty (at that time) of testing for sterility in such nonaqueous systems and also for the anticipated difficulties in sterilizing and maintaining sterile conditions during the manufacture and filling of ointments on a large scale.

## Anatomy and Physiology of the Eye

The human eye is a challenging subject for topical administration of drugs. The basis of this can be found in the anatomical arrangement of the surface tissues and in the permeability of the cornea. The protective operation of the eyelids and lacrimal system is such that there is rapid removal of material instilled into the eye, unless the material is suitably small in volume and chemically and physiologically compatible with surface tissues. Figures 1[1] and 2[1] include pertinent anatomy of the human eye.

**Eyelids**—The eyelids serve two purposes: mechanical protection of the globe and creation of an optimum milieu for the cornea. The eyelids are lubricated and kept fluid-filled by secretions of the lacrimal glands and specialized cells residing in the bulbar conjunctiva. The antechamber has the shape of a narrow cleft directly over the front of the eyeball, with pocket-like extensions upward and downward. The pockets are called the superior and inferior fornices (vaults), and the entire space, the cul-de-sac. The elliptical opening between the eyelids is called the palpebral fissure.

**Eyeball**—The wall of the human eyeball (bulbus, globe) is composed of three concentric layers.

1. The outer fibrous layer.
2. A middle vascular layer—the uvea or uveal tract, consisting of the choroid, the ciliary body and the iris.
3. A nervous layer—the retina.

The outer layer is tough, pliable but only slightly stretchable. In its front portion—the portion facing the outside world—the fine structure of the outer layer is so regular and the water content so carefully adjusted that it acts as a clear transparent window (the cornea). It is devoid of blood vessels. Over the remaining two-thirds the fibrous coat is opaque (the "white" of the eye) and is called the sclera. It contains the microcirculation which nourishes the tissues of this anterior segment and is usually white except when irritated and vessel dilatation occurs.

The eyeball houses an optical apparatus that causes inverted reduced images of the outside world to form on the retina, which is a thin translucent membrane. The optical apparatus consists, in sequence, of the precorneal film, the cornea, the aqueous humor, the pupil, the crystalline lens, the vitreous humor and the retina. The aqueous and vitreous humors are layers of clear fluid or gel-like material interposed between the solid structures. The pupil, a round centric hole in a contractile membranous partition (called the iris), acts as the variable aperture of the system. The crystalline lens is a refractive element with variable power controlled and supported by a muscle incorporated in the ciliary body. The choroid is the metabolic support for the retina.

The optical function of the eye calls for stability of its dimensions, which is provided partly by the fibrous outer coat;

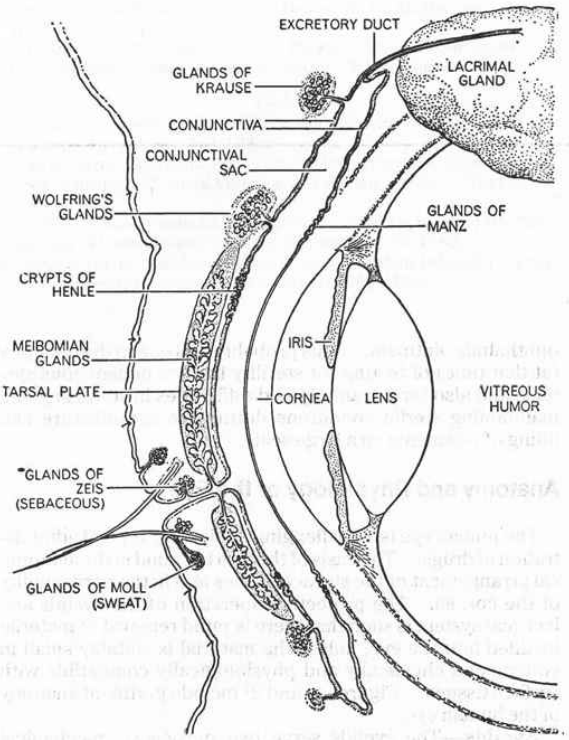



**Fig 1.** The eye: vertical section.[1]

more effective as a stabilizing factor is the intraocular pressure, which is in excess of the pressure prevailing in the surrounding tissues. This intraocular pressure is the result of a steady production of specific fluid, the aqueous humor, which originates from the ciliary processes and leaves the eye by an intricate system of outflow channels. The resistance

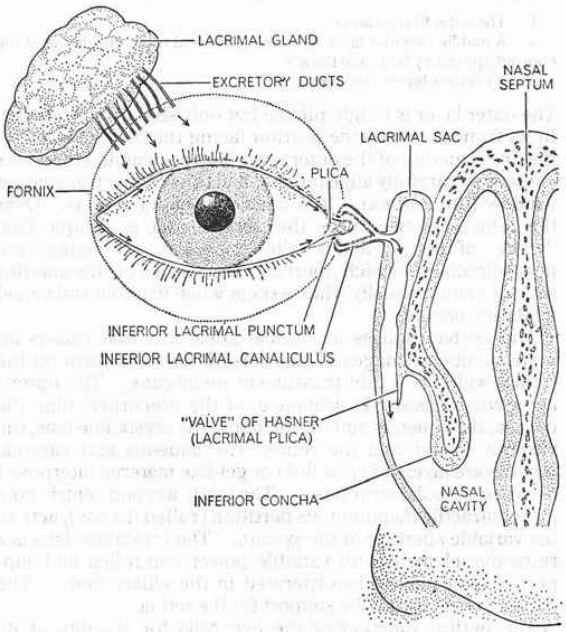



**Fig 2.** Nasolacrimal duct.[1]

encountered during this passage and the rate of aqueous production are the principal factors determining the level of the intraocular pressure. In addition to this hydromechanical function, the aqueous humor acts as a carrier of nutrients, substrates and metabolites for the avascular tissues of the eye.

The bones of the skull join to form an approximately pyramid-shaped housing for the eyeball, called the orbit.

**Conjunctiva**—The conjunctival membrane covers the outer surface of the white portion of the eye and the inner aspect of the eyelids. In most places it is attached loosely and thereby permits free movement of the eyeball. This makes possible subconjunctival injections. Except for the cornea the conjunctiva is the most exposed portion of the eye.

**Lacrimal System**—The conjunctival and corneal surfaces are covered and lubricated by a film of fluid secreted by the conjunctival and lacrimal glands. The secretion of the lacrimal gland, the tears, is delivered through a number of fine ducts into the conjunctival fornix. The secretion is a clear, watery fluid containing numerous salts, glucose, other organic compounds, approximately 0.7% protein and the enzyme, lysozyme. Small accessory lacrimal glands are situated in the conjunctival fornices. Their secretion suffices for lubrication and cleansing under ordinary conditions and for maintaining a thin fluid film covering the cornea and conjunctiva (the precorneal film). The mucin-protein layer of the film is especially important in maintaining the stability of the film. The main lacrimal gland is called into play only on special occasions. The sebaceous glands of the eyelids secrete an oily fluid which helps to prevent overflowing of tears at the lid margin and reduces evaporation from the exposed surfaces of the eye by spreading over the tear film.

Spontaneous blinking replenishes the fluid film by pushing a thin layer of fluid ahead of the lid margins as they come together. The excess fluid is directed into the lacrimal lake—a small triangular area lying in the angle bound by the innermost portions of the lids. The skin of the eyelids is the thinnest in the body and folds easily, thus permitting rapid opening and closing of the palpebral fissures. The movement of the eyelids includes a narrowing of the palpebral fissures in a zipper-like action from the lateral canthus toward the medial canthus (canthi: the corners where the eyelids meet). This aids the transport or movement of fluid toward the lacrimal lake.

Tears are drained from the lacrimal lake by two small tubes—the lacrimal canaliculi—which lead into the upper part of the nasolacrimal duct, the roomy beginning of which is called the lacrimal sac. The drainage of tears into the nose does not depend merely on gravity. Fluid enters and passes along the lacrimal canaliculi by capillary attraction aided by aspiration caused by contraction of muscle embedded in the eyelids. When the lids close, as in blinking, contraction of the muscle causes dilatation of the upper part of the lacrimal sac and compression of its lower portion. Tears are thus aspirated into the sac, and any which have collected in its lower part are forced down the nasolacrimal duct toward its opening into the nose. As the lids open, the muscle relaxes. The upper part of the sac then collapses and forces fluid into the lower part, which at the same time is released from compression. Thus, the act of blinking exerts a suction-force-pump action in removing tears from the lacrimal lake and emptying them into the nasal cavity. Lacrimation is induced reflexly by stimulation of nerve endings of the cornea or conjunctiva. The reflex is abolished by anesthetization of the surface of the eye and by disorders affecting its nerve components.

The normal cul-de-sac usually is free of pathogenic organisms and often found sterile. The sterility may be due partly to the action of lysozyme in the tears, which normally destroys saprophytic organisms but has little action against pathogens. More effective in producing sterility may be the fact that the secretions, which are normally sterile as they leave the glands, constantly wash the bacteria, dust, etc, down in the nose. In certain diseases the lacrimal gland, like other glandular structures in the body, undergoes involution, with the result that

the lacrimal fluid becomes scanty. Furthermore, changes in the conjunctival glands may lead to alteration in the character of the secretion so that quality as well as quantity of tears may be abnormal. This may lead to symptoms of dryness, burning and general discomfort, and may interfere with visual acuity.

**Precorneal Film**—The cornea must be wet to be an optically adequate surface; when dry, it loses both its regular gloss and its transparency. The precorneal film, part of the tear fluid, provides this important moist surface. Its character depends on the condition of the corneal epithelium. The film, compatible with both aqueous and lipid ophthalmic preparations, is composed of a thin outer lipid layer, a thicker middle aqueous layer and a thin inner mucoid layer. It is renewed during each blink and when blinking is suppressed, either by drugs or by mechanical means, it dries in patches. It seems to be unaffected by the addition of concentrations of up to 2% sodium chloride to conjunctival fluid. A pH below 4 or above 9 causes derangement of the film. The film affects the movement of contact lenses and forms more easily on glass than on plastic prostheses.

**Cornea**—The cornea, from 0.5 to 1 mm thick, consists mainly of the following structures (from the front backwards):

1. Corneal epithelium.
2. Substantia propria (stroma).
3. Corneal endothelium.

The cornea is transparent to ordinary diffuse light, largely because of a special laminar arrangement of the cells and fibers and because of the absence of blood vessels. Cloudiness of the cornea may be due to any one of several factors including excess pressure in the eyeball as in glaucoma; scar tissue due to injury, infection or deficiency of oxygen or excess hydration such as may occur during the wearing of improperly fitted contact lenses. A wound of the cornea usually heals as an opaque patch which can be a permanent impairment of vision unless it is located in the periphery of the cornea.

The chief refraction of light for the eye occurs at the outer surface of the cornea where the index of refraction changes from that of air (1.00) to that of precorneal substance (1.38). Any alteration in its shape or transparency interferes with the formation of a clear image; therefore, any pathological process, however slight, may interfere seriously with the resolving power or visual acuity of the eye.

The normal cornea possesses no blood vessels except at the corneoscleral junction. The cornea, therefore, must derive its nutrition by diffusion and must have certain permeability characteristics; it also receives nourishment from the fluid circulating through the chambers of the eye and from the air. The fact that the normal cornea is devoid of blood vessels is an important feature in surgical grafting. The corneal nerves do not supply all forms of sensation to the cornea. Pain and cold are well supplied. The pain fibers have a very low threshold, which makes the cornea one of the most sensitive areas on the surface of the body. It now is agreed generally that the cornea possesses a true sense of touch; nerve endings supplying the sensation of heat are lacking.

The corneal epithelium provides an efficient barrier against bacterial invasion. Unless its continuity has been broken by an abrasion (a traumatic opening or defect in the epithelium) pathogenic bacteria, as a rule, cannot gain a foothold. Trauma, therefore, plays an important part in most of the infectious diseases of the cornea which occur exogenously. Any foreign body that either scratches the cornea or lodges and becomes imbedded in the cornea is of serious moment because of the role it may play in permitting pathogenic bacteria to gain a foothold.

A means of detecting abrasions on the corneal surface is afforded by staining the cornea with sodium fluorescein. If there is an abrasion on the epithelium, the underlying layer stains a brilliant green, so that even pinpoint abrasions show up quite clearly. Abrasion may occur during tonometry, that is, during the measurement of ocular tension (pressure) with a tonometer. Care must be used in applying the device to the cornea to avoid abrasion of the cornea. Corneal abrasions sometimes result from wearing contact lenses. Every corneal abrasion is subject to infection.

## Bioavailability

**Physical Consideration**—Under normal conditions the human tear volume averages about 7 μL.[2] The estimated maximum volume of the cul-de-sac is about 30 μL with drainage capacity far exceeding lacrimation rate. The outflow capacity accommodates the sudden large volume resulting from the instillation of an eyedrop. Most commercial eyedrops range from 50 to 75 μL in volume, however, much in excess of 50 μL probably is unable to enter the cul-de-sac.

Within the rabbit cul-de-sac, the drainage rate has been shown to be proportional to the instilled drop volume. Multiple drops administered at intervals produced higher drug concentrations. Ideally, a high concentration of drug in a minimum drop volume is desirable. Patton[3] has shown that approximately equal tear-film concentrations result from the instillation of 5 μL of $1.61 \times 10^{-2}$ *M* pilocarpine nitrate or from 25 μL of $1.0 \times 10^{-2}$ *M* solution. The 5 μL contains only 38% as much pilocarpine, yet its bioavailability is greater due to decreased drainage loss.

There is a practical limit or limits to the concept of minimum dosage volume. There is a difficulty in designing and producing a dropper configuration which will deliver small volumes reproducibly. Also, the patient often cannot detect the administration of such a small volume. This sensation or lack of sensation is particularly apparent at the 5.0–7.5-μL dose-volume range.

The concept of dosage-volume drainage and cul-de-sac capacity directly effects the prescribing and administering of separate ophthalmic preparations. The first drug administered may be diluted significantly by the administration of the second. On this basis combination drug products for use in ophthalmology have considerable merit.

**Corneal Absorption**——Drugs administered by instillation must penetrate the eye and do so primarily through the cornea. Corneal absorption is much more effective than scleral or conjunctival absorption where removal by blood vessels into the general circulation occurs.

Many ophthalmic drugs are weak bases and are applied to the eye as aqueous solutions of their salts. The free base and the salt will be in an equilibrium which will depend on the pH and on the individual characteristics of the drug molecule. To aid in maintaining storage stability and solubility, the medication may be acidic at the moment of instillation but, usually, the neutralizing action of the lacrimal fluid will convert it rapidly to the physiological pH range (approximately pH 7.4), at which there will be enough free base present to begin penetration of the corneal epithelium. Once inside the epithelium the undissociated free base dissociates immediately to a degree. The dissociated moiety then will tend to penetrate the stroma because it is water-soluble. At the junction of the stroma and endothelium the same process that took place at the outer surface of the epithelium must occur again. Finally, the dissociated drug leaves the endothelium for the aqueous humor. Here it can readily diffuse to the iris and the ciliary body, the site of its pharmacological action.

The cornea can be penetrated by ions to a small, but measurable, degree. Under comparable conditions, the permeabilities are similar for all ions of small molecular weight, which suggests that the passage is through extracellular spaces. The diameter of the largest particles which can pass across the cellular layers seems to be in the range 10–25 Å. An instilled drug is subject to protein binding in the tear fluid and metabolic degradation by enzymes such as lysozyme, in addition to the losses by simple overflow and lacrimal drainage.

Since the cornea is a membrane including both hydrophilic and lipophilic layers, most effective penetration is obtained with drugs having both lipid and hydrophilic properties. Highly water soluble drugs penetrate less readily. As an

example highly water soluble steroid phosphate esters penetrate the cornea poorly. Better penetration is achieved with the poorly soluble but more lipophilic steroid alcohol; still greater absorption is seen with the steroid acetate form.

In 1976 Lee and Robinson[4] and in 1990, Lee[5] presented a summary of the factors controlling precorneal pilocarpine disposition and pilocarpine bioavailability in the rabbit eye. Combining experimental work and computer simulation the investigators discussed the mechanisms competing with corneal absorption of pilocarpine. Included were solution drainage, drug-induced vasodilation, nonconjunctival loss including uptake by the nictitating membrane, conjunctival absorption, induced lacrimation and normal tear turnover. Subject to experimental conditions the relative effectiveness of the factors involved in precorneal drug removal are drainage ≃ vasodilation > nonconjunctival loss > induced lacrimation ≃ conjunctival absorption > normal tear turnover.

The authors discuss the implications of the mechanisms of precorneal drug loss in the design of ocular drug-delivery systems including the effect of instilled drug volume on aqueous humor concentration and the amount of drug available for systemic absorption. On an absolute basis a smaller volume allows more drug to be absorbed. For a given instilled concentration the opposite is true; however, a smaller volume instilled remains more efficient, ie, the fraction of dose absorbed is greater. Lang[6] discusses the transcorneal route of absorption of a drug into the eye as that route most effective in bringing a given drug to the anterior portion of the eye. This route of absorption is enhanced by the water-lipid gradient found in the cornea. As previously mentioned, the cornea is composed of three general layers: the lipid-rich epithelium, the lipid-poor stroma and the lipid-rich endothelium. Differential studies on the relative lipid contents of these three layers have shown that the corneal epithelium and the corneal endothelium both contain approximately 100 times as much lipid as the corneal stroma. This, coupled with the physiological pH of 7.2 ± 0.2 and its effect on ionizable drug molecules plays the most significant role in corneal penetration.

Ophthalmic ointments generally produce greater bioavailability than the equivalent aqueous solution. Because of the greater contact time drug levels are prolonged and total drug absorption is increased.

### *Types of Ophthalmic Products*

**Administration**—The instillation of eyedrops remains one of the less precise, yet one of the more accepted means of topical drug delivery. The method of administration is cumbersome at best, particularly for the elderly, patients with poor vision who have difficulty seeing without eyeglasses and patients with other physical handicaps. Perhaps, surprisingly, the majority of patients become quite adept at routine instillation.

The pharmacist should advise each patient to keep the following points in mind to aid in the instillation of eyedrops or ointments:

**How to Use Eyedrops**

1. Wash hands.
2. With one hand, gently pull lower eyelid down.
3. If dropper is separate, squeeze rubber bulb once while dropper is in bottle to bring liquid into dropper.
4. Holding dropper above eye, drop medicine inside lower lid while looking up; do not touch dropper to eye or fingers.
5. Release lower lid. Try to keep eye open and not blink for at least 30 seconds.
6. If dropper is separate, replace on bottle and tighten cap.

- If dropper is separate, always hold it with tip down.
- Never touch dropper to any surface.
- Never rinse dropper.
- When dropper is at top of bottle, avoid contaminating cap when removed.
- When dropper is a permanent fixture on the bottle, ie, when supplied by a pharmaceutical manufacturer to the pharmacist, the same rules apply to avoid contamination.
- Never use eye drops that have changed color.
- If you have more than one bottle of the same kind of drops, open only one bottle at a time.
- If you are using more than one kind of drop at the same time, wait several minutes before use of other drops.
- It may be helpful in use of the medicine to practice use by positioning yourself in front of a mirror.
- After instillation of drops, do not close eyes tightly and try not to blink more often than usual, as this removes the medicine from the place on the eye where it will be effective.

**How to Use Ophthalmic Ointments**

1. Wash hands.
2. Remove cap from tube.
3. With one hand, gently pull lower eyelid down.
4. While looking up, squeeze a small amount of ointment (about ¼ to ½ in) inside lower lid. Be careful not to touch tip of tube to eye, eyelid, fingers, etc.
5. Close eye gently and roll eyeball in all directions while eye is closed. Temporary blurring may occur.
6. The closed eyelid may be rubbed very gently by a finger to distribute the drug throughout the fornix.
7. Replace cap on tube.

- Take care to avoid contaminating cap when removed.
- When opening ointment tube for the first time, squeeze out the first ¼" of ointment and discard as it may be too dry.
- Never touch tip of tube to any surface.
- If you have more than one tube of the same ointment, open only one at a time.
- If you are using more than one kind of ointment at the same time, wait about 10 minutes before use of another ointment.
- To improve flow of ointment, hold tube in hand several minutes to warm before use.
- It may be helpful in use of the ointment to practice use by positioning yourself in front of a mirror.

**Ophthalmic Solutions**—This is by far the most common means of administering a drug to the eye. The USP describes 59 ophthalmic solutions. By definition, all ingredients are completely in solution, uniformity is not a problem and there is little physical interference with vision. The principal disadvantage of solutions is the relatively brief contact time between the medication and absorbing surfaces. Contact time may be increased to some extent by the inclusion of a viscosity increasing agent such as methylcellulose. Inclusions of this sort are permitted by the USP. A viscosity in the range of 15 to 25 cps is considered optimum for drug retention and visual comfort.

**Ophthalmic Suspensions**—Suspensions are dispersions of finely divided, relatively insoluble drug substances in an aqueous vehicle containing suitable suspending and dispersing agents. There are 29 listed in the USP. The vehicle is, among other things, a saturated solution of the drug substance. Because of a tendency of particles to be retained in the cul-de-sac, the contact time and duration of action of a suspension probably exceeds that of a solution. The drug is absorbed from solution and the solution concentration is replenished from retained particles. Each of these actions is a function of particle size, with solubility rate being favored by smaller size and retention favored by a larger size; thus, optimum activity should result from an optimum particle size.

For aqueous suspensions the parameters of intrinsic solubility and dissolution rate must be considered. The intrinsic solubility determines the amount of drug actually in solution and available for immediate absorption upon instillation of the dose. As the intrinsic solubility of the drug increases, the concentration of the drug in the saturated solution surrounding the suspended drug particle also increases. For this reason, any comparison of different drugs in suspension systems should include their relative intrinsic solubilities. The observed differences in their biological activities may be ascribed wholly or in part to the differences in this physical parameter. As the drug penetrates the cornea and the initial saturated solution becomes depleted, the particles must dissolve to provide a further supply of the drug. The requirement here is that the particles must undergo significant disso-

lution within the residence time of the dose in the eye if any benefit is to be gained from their presence in the dosing system.

For a drug whose dissolution rate is rapid, the dissolution requirement may present few problems, but for a slowly soluble substance the dissolution rate becomes critical. If the dissolution rate is not sufficiently rapid to supply significant additional dissolved drug, there is the possibility that the slowly soluble substance in suspension provides no more drug to the aqueous humor than does a more dilute suspension or a saturated solution of the substance in a similar vehicle. Obviously, the particle size of the suspended drug affects the surface area available for dissolution. Particle size also plays an important part in the irritation potential of the dosing system. This consideration is important, as irritation produces excessive tearing and rapid drainage of the instilled dose. It has been recommended that particles be less than 10 μm in size to minimize irritation to the eye. It should be kept in mind, however, that in any suspension system the effects of prolonged storage and changes in storage temperature may cause the smallest particles to dissolve and the largest particles to become larger. In summary, aqueous suspensions should, in general, give a more extended effect than aqueous solutions.

The pharmacist should be aware of two potential difficulties inherent in suspension dosage forms. In the first instance dosage uniformity nearly always requires brisk shaking to distribute the suspended drug. Adequate shaking is a function of the suitability of the suspension formulation but also, and most importantly, patient compliance. Studies have demonstrated that a significant number of patients may not shake the container at all, others may contribute a few trivial shakes. The pharmacist should stress the need of vigorous shaking whenever an ophthalmic suspension is dispensed.

A second and infrequent characteristic of suspensions is the phenomenon of polymorphism or the ability of a substance to exist in several different crystalline forms. A change in crystal structure may occur during storage resulting in an increase (or decrease) in crystal size and alteration in the suspension characteristics causing solubility changes reflected in increased or decreased bioavailability.

The pharmacist should be aware of the procedures used by pharmaceutical manufacturers in the preparation of commercial sterile ophthalmic suspensions and ointments, when called upon to compound such preprations extemporaneously.[7]

**Ophthalmic Ointments**—Despite disadvantages, ophthalmic ointments remain a popular and frequently prescribed dosage form. There are 58 ophthalmic ointments listed in the USP. Dosage variability probably is greater than with solutions (although probably not with suspensions). Ointments will interfere with vision unless use is limited to bedtime instillation.

Ointments do offer the advantage of longer contact time and greater total drug bioavailability, albeit with slower onset and time to peak absorption. The relationship describing the availability of finely divided solids dispersed in an ointment base was given by Higuchi[8] where the amount of solid (drug) released in unit time is a function of concentration, solubility in the ointment base and diffusivity of the drug in the base.

Special precautions must be taken in the preparation of ophthalmic ointments. They are manufactured from sterilized ingredients under rigidly aseptic conditions and meet the requirements of the official sterility tests. Terminal sterilization of the finished ointment in tubes is accomplished occasionally using a validated dose of gamma radiation. If the specific ingredients used in the formulation do not lend themselves to routine sterilization techniques, other ingredients that meet the sterility requirements described under the official sterility tests, along with aseptic manufacture, may be employed. Ophthalmic ointments must contain a suitable substance or mixture of substances to prevent growth of, or to destroy, microorganisms introduced accidentally when the container is opened during use. The antimicrobial agents currently used are chlorobutanol, the parabens or one of the organic mercurials. The medicinal agent is added to the ointment base either as a solution or as a micronized powder. The finished ointment must be free from large particles. Most ophthalmic ointments are prepared with a base of white petrolatum and mineral oil, often with anhydrous lanolin. Some contain a polyethylene-mineral oil gel. Whichever base is selected, it must be nonirritating to the eye, permit diffusion of the drug throughout the secretions bathing the eye and retain the activity of the medicament for a reasonable period of time under proper storage conditions.

It is obligatory that ophthalmic ointments not contain particulate matter that may be harmful to eye tissues. Hence, in preparing such ointments special precautions must be taken to exclude or to minimize contamination with foreign particulate matter, eg, metal particles fragmented from equipment used in preparing ointments and also to reduce the particle size of the active ingredient(s) to impalpability. The official compendium provides tests designed to limit to a level considered to be unobjectionable the number and size of discrete particles that may occur in ophthalmic ointments. In these tests the extruded contents of 10 tubes of ointment, previously melted in flat-bottom Petri dishes and then allowed to solidify, are scanned under a low-power microscope fitted with a micrometer eyepiece for metal particles 50 μm or larger in any dimension. The requirements are met if the total number of metal particles in all 10 tubes does not exceed 50 and if not more than one tube is found to contain eight such particles.

Testing for sterility of products such as ophthalmic ointments has been facilitated greatly by the use of sterile, bacteria-retaining membranes (those having a nominal porosity of 0.45 or 0.22 μm are used commonly). For ointments soluble in isopropyl myristate (the solvent used in the official test for sterility) a sample of the ointment is dissolved in the sterile test solvent. For ointments insoluble in isopropyl myristate the sample is suspended in a suitable aqueous vehicle that may contain a dispersing agent and tested by the conventional *General Procedure* (see the USP for details).

For a long time the technology available for manufacture of ophthalmic ointments was considered inadequate to produce sterile products; indeed, it was believed by some to be impossible to operate a tube-filling machine so as to maintain sterility even in a sterile room. In recent years technological advances have made it possible to manufacture sterile ophthalmic ointment units. Major improvements have been achieved in the area of filtration technology. Membrane filters have improved the reliability of both sterile filtration procedures and sterility-testing methods. Use of laminar flow of HEPA-filtered air in appropriately designed rooms and hoods has been a major factor in the successful aseptic operation of the roller mill and of devices for filling tubes with ointment. While the ideal method of sterilization is one in which the finished ointment is sterilized in its final container, at present it does not appear feasible to do so by any method with the possible exception of the use of ionizing radiation.

As previously noted, the official compendium directs that ophthalmic ointments be prepared from previously sterilized ingredients, under rigidly aseptic conditions. This is the procedure followed in commercial manufacture as well as in extemporaneous preparation of ophthalmic ointments. In extemporaneous compounding the following information may be helpful: petrolatum vehicles and many medicaments may be sterilized by being heated in a hot air oven and utensils required for compounding may be sterilized by autoclaving. A sterile disposable syringe without a needle may be used to transfer the finished ointment, if it is semifluid, to the presterilized ointment tube, or sterile aluminum foil or powder paper may be used for the same purpose. Probability of microbial contamination may be reduced greatly by carrying out selected steps of the procedure in a laminar-flow hood.

**Ocular Inserts**—The use of solid dosage forms in the eye actually dates from the *lamellae* of the British Pharmacopeia of the 1940s. These drug-impregnated wafers were designed to dissolve on insertion beneath the eyelid. Other

slowly soluble or erodible matrices were investigated from time to time. Each is characterized by a form of enhanced-pulse drug activity. That is, the bioavailability curve of the drug instilled in aqueous solutions was greatly enhanced both in peak absorption and in duration. Drug side effects were enhanced concomitantly as well.

More recently, ocular inserts have been developed in which the drug is delivered based on diffusional mechanisms. Such a device delivers an ophthalmic drug at a constant known rate, minimizing side effects by avoiding excessive absorption peaks. The delivery of pilocarpine by such a device is a well-known commercial product (*Ocusert*, Alza).

Ocular inserts are plagued with some of the same manipulative disadvantages as conventional eyedrops. The insert must be placed in the eye in a manner similar to the insertion of a contact lens. Additionally, the insert, exhausted of its drug content, must be removed from the eye. Such manipulations can be difficult for the elderly patient. Nonetheless, such therapeutic inserts represent a notable scientific contribution to ophthalmic therapy.

**Intraocular Solutions**—Ophthalmic solutions intended for intraocular use are relatively recent additions to the armamentarium of the ophthalmologist-surgeon. Surgical procedures such as cataract removal require two types of intraocular solutions. During surgery the operating site is rinsed frequently with an irrigating solution. Late in the surgical procedure the surgeon may choose to constrict the iris by the use of a miotic solution such as carbachol or acetylcholine chloride. Drugs such as the latter usually are used in a unit-dose, minimum-volume form. Irrigating solutions, in contrast, may be used over a period of hours during surgery and are available in volumes ranging from 15 to 500 mL.

The formulation of intraocular ophthalmic products presents requirements that differ depending on the type of product. Medicated solutions such as carbachol or acetylcholine are formulated best in relatively simple isotonic vehicles. Preservatives should not be used and buffers should be avoided if possible. The product pH should be adjusted as close to the physiological range as possible. Needless to say, the product should be sterile and particle-free.

Intraocular irrigating solutions present a considerable formulation challenge distinct from the active ingredient solutions described above. Intraocular irrigating solutions are in contact with the delicate internal structures of the eye throughout the course of various surgeries, ie, for time periods measured in hours. The requirements of tonicity, pH, sterility and clarity are obvious; additionally, however, such irrigating solutions require a balanced ionic structure to prevent or minimize deleterious effects on structures such as the corneal endothelium. Edelhauser[9] has shown that isotonic sodium chloride can be toxic to corneal epithelial, endothial, iris and conjunctival cells. The same cells in contrast are unchanged after exposure to Ringer's Solution containing glutathione, bicarbonate and adenosine.

The question of particulate matter in intraocular irrigating solutions is particularly important. In view of the volumes used for irrigations in the surgically opened eye, any particulates could physically block the trabecular meshwork and canals of Schlemm. The latter are vital in the outflow of aqueous humor and help maintain proper intraocular pressure in the intact eye.

### *Other Modes of Administration*

**Packs**—These sometimes are used to give prolonged contact of the solution with the eye. A cotton pledget is saturated with an ophthalmic solution and this pledget is inserted into the superior or inferior fornix. Packs may be used to produce maximal mydriasis. In this case the cotton pledgets can be, for example, saturated with phenylephrine solution.

**Intracameral Injections**—Injections may be made directly into the anterior chamber (eg, acetylcholine chloride, alpha-chymotrypsin, carbamylcholine chloride, certain antibiotics and steroids) or directly into the vitreous chamber (eg, amphotericin B, gentamicin sulfate and certain steroids). Injections are not made into the posterior chamber.

**Iontophoresis**—This procedure keeps the solution in contact with the cornea by means of an eyecup bearing an electrode. Diffusion of the drug (eg, fluorescein sodium, an antibiotic, etc) is effected by difference of electrical potential.

**Subconjunctival Injections**—Subconjunctival injections (Fig 3[10]) are used frequently to introduce medications which, if applied topically, either do not penetrate into the anterior segment or penetrate too slowly to attain the concentration required. The drug is injected underneath the conjunctiva and probably passes through the sclera and into the eye by simple diffusion. The most common use of subconjunctival injection is for the administration of antibiotics in infections of the anterior segment of the eye. Subconjunctival injections of mydriatrics and cycloplegics also are used to achieve maximal pupillary dilation or relaxation of the ciliary muscle. If the drug is injected underneath the conjunctiva and the underlying Tenon's capsule in the more posterior portion of the eye, effects on the ciliary body, choroid and retina can be obtained.

**Retrobulbar Injections**—Drugs administered by retrobulbar injection (Fig 1) may enter the globe in essentially the same manner as the medications given subconjunctivally. The orbit is not well-vascularized and the possibility of significant via-blood stream effects from these injections is very remote. In general, such injections are given for the purpose of getting medications (eg, antibiotics, local anesthetics, enzymes with local anesthetics, steroids, vasodilators, etc) into the posterior segment of the globe and to affect the nerves and other structures in that space.

## Preparation

The preparation of ophthalmic solutions, suspensions or ointments by the community pharmacist, or even the hospital pharmacist, is becoming less common. The pharmacist may be called upon to prepare a special concentration, particularly of an antibiotic, in the hospital setting. However, the extemporaneous compounding of ophthalmic prescriptions is becoming rare. In those cases where the pharmacist is called upon to compound an ophthalmic preparation extemporaneously, careful documentation, along with physician consultation, is required. Meticulous attention to detail and the use of a detailed, preapproved preparation plan must be in place prior to compounding.[11] In the view of many, the advantages of commercial preparations such as stability, uniformity and sterility outweigh possible disadvantages such as standardization of dosage. A general discussion concerning the preparation of ophthalmic solutions is found in the USP.

**Vehicles**—Sterile isotonic solutions, properly preserved, are suitable for preparing ophthalmic solutions (see Chapter 36). In most cases, where the concentration of active ingre-

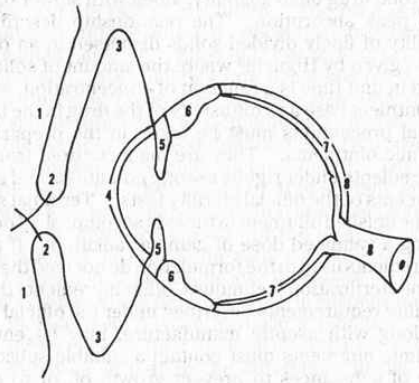



**Fig 3.** Modes of local therapy in ocular inflammation: *Ointment:* 1–5. *Drops:* 3–5. *Parenteral Injections*— subconjunctival: 4–6; deep subtenons: 6–8; retrobulbar: 8.[10]

dient is low, ie, less than 2.5 to 3.0%, the drug can be dissolved directly in the isotonic vehicle. The finished solutions will be hypertonic somewhat but well within the comfort tolerance of the eye.

Typical stock solutions are as follows:

*Isotonic Sodium Chloride Solution*

| | |
|---|---|
| Sodium Chloride USP | 0.9 g |
| Benzalkonium Chloride | 1:10,000 |
| Sterile Distilled Water | qs 100 mL |

*Boric Acid Solution*

| | |
|---|---|
| Boric Acid USP | 1.9 g |
| Benzalkonium Chloride | 1:10,000 |
| Sterile Distilled Water | qs 100 mL |

Boric acid solution at pH 5 is an appropriate vehicle for the following:

| | |
|---|---|
| Cocaine | Tetracaine |
| Neostigmine | Zinc salts |
| Phenacaine | Piperocaine |
| Procaine | |

Boric acid solution with an antioxidant is useful for oxygen sensitive drugs such as epinephrine, phenylephrine or physostigmine. The following solutions are suggested. Phenylmercuric nitrate replaces benzalkonium chloride as the preservative in the first solution.

| | |
|---|---|
| Boric Acid | 1.9 g |
| Sodium Sulfite Anhydrous | 0.1 g |
| Phenylmercuric nitrate | 1:50,000 |
| Sterile Purified Water | qs 100 mL |
| Sodium Acid Phosphate ($NaH_2PO_4$) anhydrous | 0.56 g |
| Disodium Phosphate ($Na_2HPO_4$) anhydrous | 0.284 g |
| Sodium Chloride | 0.5 g |
| Disodium Edetate | 0.1 g |
| Benzalkonium Chloride | 1:10,000 |
| Sterile Purified Water | qs 100 mL |

These vehicles are suitable for salts of

| | |
|---|---|
| Atropine | Homatropine |
| Ephedrine | Pilocarpine |

**Sterilization Procedures**—Those procedures suited best for the extemporaneous preparation of ophthalmic solutions are:

1. Solutions in Final Container
   a. Place the filtered solution in containers that have been washed and rinsed with distilled water.
   b. Seal dropper bottles with regular screw caps. The dropper assembly should be stapled into a paper envelope.
   c. Sterilize 20 minutes at 15 psi (121°).
   d. Do not assemble until ready to use.
2. Dropper Bottles
   a. Wash container thoroughly and rinse with distilled water.
   b. Loosen caps and place bottles in autoclave.
   c. Autoclave 15 minutes at 15 psi (121°).
   d. Partially cool autoclave.
   e. Remove bottles from autoclave and secure caps.
   f. Store sterilized bottles in a clean, dustproof cabinet.
3. Glassware and Equipment
   a. Wrap adapters (containing filter), syringes, glassware, spatulas, etc, in autoclave paper and secure with masking tape.
   b. Place articles in autoclave and sterilize in the manner described in Section 2 above.
   c. Store in separate cabinet until ready to use.
4. Microbiological Filtration
   a. All equipment and glassware as well as stock solutions should be sterile. The prescription should be dispensed in a sterile container.
   b. Unwrap sterile syringe and draw prepared solution into syringe.
   c. Unwrap sterile adapter containing bacterial filter and attach to syringe. These are available as single-filtration, presterilized disposable units and should be utilized whenever possible.
   d. Force solution through filter directly into sterile container (dropper or plastic *Drop-Tainer* (Alcon) type).
   e. By employing an automatic filling outfit, more than one container of the same prescription can be prepared.
   f. Cap container immediately.

The procedures outlined above should be carried out in a clean area equipped with ultraviolet lighting and preferably in a laminar-flow hood.

*Laminar-Flow Principles*—A laminar-flow work area is a particularly convenient means of preparing sterile, particulate-free solutions. Laminar flow is defined as air flow in which the total body of air moves with uniform velocity along parallel lines with a minimum of eddies. Laminar flow minimizes the possibility of airborne microbial contamination by providing air free of viable particles and free of practically all inert particulates. Laminar-flow units are available in a variety of shapes and sizes and in two broad categories, horizontal and vertical laminar flow. It should be noted that laminar flow *per se* is not a guarantee of sterility. Correct procedures and sterile techniques remain necessary. See Chapter 84.

### *General Considerations*

A number of requirements must be considered in the preparation of ophthalmic solutions, suspensions or ointments. These include sterility, clarity, buffer, buffer capacity and pH, tonicity, viscosity, stability, comfort, additives, particle size, packaging and preservatives. Many of these requirements are interrelated and must be considered collectively in the preparation of an ophthalmic product. The buffer system must be considered with tonicity and comfort in mind. Stability can be related to the pH, buffer system and packaging. Sterilization must be considered in terms of stability and packaging.

Ophthalmic solutions are formulated to be sterile, isotonic and buffered for stability and comfort. A viscosity-imparting agent may or may not be present. Solutions must be free from foreign particles. Solution pH must be selected for optimum drug stability. The pH then should be maintained by the inclusion of a buffer system of sufficient capacity to maintain pH throughout the extent of the shelf life of the product.

The proper pH, buffer and buffer capacity often represent a compromise between stability of the drug and comfort in the eye, since optimum patient comfort usually is found at the pH of the tear fluid, or about 7.4, while optimum stability for many drugs is generally lower, perhaps as low as 4.0–5.0. Buffer capacity should be sufficient to maintain pH, but minimized to the point where tear fluid can overcome capacity and readjust to pH to 7.4 immediately after instillation in the eye.

Sterilization represents the major requirement of eye products and the method, or methods, employed depend on the active ingredient and product resistance to heat and to the packaging used. More than one means of sterilization may be used. The sterile solution or suspension usually will contain an antimicrobial preservative to deal with inadvertent contamination during use. The preservative should not be relied upon to produce a sterile product and should not be considered as a substitute for sterile techniques and procedures.

## Sterilization

Common methods of sterilization include moist heat under pressure (autoclave), dry heat, filtration, gas sterilization and ionizing radiation.

**Dangers of Nonsterile Medications**—The possibility of serious ocular infection resulting from the use of contaminated ophthalmic solutions has been documented amply in the literature. Such solutions repeatedly have been the cause of corneal ulcers and loss of eyesight. Contaminated solutions have been found in use in physicians' offices, eye clinics and industrial infirmaries, and dispensed on prescription in community and hospital pharmacies. The microbe most frequently found as a contaminant is the *Staphylococcus* group. *Pseudomonas aeruginosa* is a less frequent contaminant and the solution most often found contaminated is that of sodium fluorescein.

*Pseudomonas aeruginosa* (*B pyocyaneus; Pseudomonas pyocyanea*; Blue pus bacillus)—This is a very dangerous and

opportunistic organism that grows well on most culture media and produces both toxins and antibacterial products. The latter tend to kill off other contaminants and allow the *P aeruginosa* to grow in pure culture. This gram-negative bacillus also grows readily in ophthalmic solutions, which may become the source of extremely serious infections of the cornea. It can cause complete loss of sight in 24–48 hours. In concentrations tolerated by tissues of the eye, it seems that all the antimicrobial agents discussed in the following sections may be ineffective against some strains of this organism.

A sterile ophthalmic solution in a multiple-dose container can be contaminated in a number of ways unless precautions are taken. For example, if a dropper bottle is used, the tip of the dropper while out of the bottle can touch the surface of a table or shelf if laid down, or it can touch the eyelid or eyelash of the patient during administration. If the *Drop-Tainer* (Alcon) type of bottle is used, the dropper tip can touch an eyelash, or the cap while removed to permit administration, or its edge may touch a table or finger and that edge can touch the dropper tip as the cap is replaced.

The solution may contain an effective antimicrobial but the next use of the contaminated solution may occur before enough time has elapsed for all of the organisms to be killed, and living organisms can find their way through an abrasion into the corneal stroma. Once in the corneal stroma, any residual traces of antimicrobial agents are neutralized by tissue components and the organisms find an excellent culture medium for rapid growth and dissemination through the cornea and the anterior segment of the eye.

**Other Organisms**—*Bacillus subtilis* may produce a serious abscess when it infects the vitreous humor. The pathogenic fungus considered of particular importance in eye solutions is *Aspergillus fumigatus*. Other fungi or molds may be harmful by accelerating deterioration of the active drugs.

With regard to viruses, as many as 42 cases of epidemic keratoconjunctivitis were caused by one bottle of virus-contaminated tetracaine solution. Virus contamination is particularly difficult to control because none of the preservatives now available is virucidal. Moreover, viruses are not removable by filtration. However, they are destroyed by autoclaving. The pharmacist and physician have not been made adequately aware of the dangers of transmitting virus infection via contaminated solutions. This is particularly pertinent to the adenoviruses (Types III and VIII) which are now believed to be the causative agents of viral conjunctivitis such as epidemic keratoconjunctivitis.

### *Methods*

**Steam under Pressure**—Terminal sterilization by autoclaving is an acceptable, effective method of sterilization; however, the solution or suspension components must be sufficiently heat-resistant to survive the procedure. If sterilization is carried out in the final container, the container also must be able to survive the heat and pressure. A recent addition to this technique is the so-called air over steam autoclave. This combination allows pressure adjustments to be made during the autoclave cycle. Pressure manipulations permit the autoclave sterilization of materials which, while heat-resistant, tend to deform (ie, polypropylene containers).

**Filtration**—The USP states that sterile membrane filtration under aseptic conditions is the preferred method of sterilization. Membrane filtration offers the substantial advantage of room temperature operation with none of the deleterious effects of exposure to heat or sterilizing gas.

Sterilization by filtration does involve the transfer of the finished sterile product into previously sterilized containers using aseptic techniques. The membrane filtration equipment itself usually is sterilized as an assembly by autoclaving.

The application of filtration procedures to the extemporaneous preparation of sterile ophthalmic solutions has been proposed by several workers. Several types of equipment are available for small-scale work, as described in Chapter 37. Particular interest has been shown in the Swinny adapter fitted on a syringe and in the Millipore *Swinnex* disposable filter units. Empty sterile plastic "squeeze" containers and sterile plastic filtration units can be purchased directly from the manufacturers, eg, Wheaton (polyethylene containers) and Millipore (*Swinnex* filter units). They permit extemporaneous preparation of ophthalmic solutions which have a high probability of being sterile if the work is carried out under aseptic conditions. A supplementary device can permit automatic refilling of the syringe. The filter unit must be replaced after use.

**Gas**—Gas sterilization of heat-sensitive materials may be carried out by exposure to ethylene oxide gas in the presence of moisture. Ethylene oxide gas for sterilization use is available commercially diluted either with carbon dioxide or halogenated hydrocarbons. Ethylene oxide sterilization requires careful consideration of conditions required to effect sterility. Temperature and pressure conditions are quite nominal in contrast to wet or dry heat, however, careful control of exposure time, ethylene oxide concentration and moisture is essential.

Gas sterilization requires the use of specialized but not necessarily elaborate equipment. Gas autoclaves may range from very large walk-in units to small laboratory bench-scale units suitable for small hospitals, laboratories or pharmacies.

In using gas sterilization the possibility of human toxicity must be kept in mind. Care should be taken to restrict exposure to ethylene oxide during the loading, venting and unloading of the sterilizer. Ethylene oxide sterilization produces irritating byproducts which remain as residues in or on the articles sterilized. Residues include ethylene glycol and ethylene chlorohydrin (when in contact with chloride ions) in addition to ethylene oxide itself. To minimize such residues the sterilized articles should be aerated for at least 72 hours, preferably at 40 to 50°.

Ambient aeration time for sterilized polyethylene bottles should be about 48 hours. Ethylene oxide is recommended for the sterilization of solid materials which will not withstand heat sterilization. The FDA has recommended maximum residues in the parts per million range for ethylene oxide, ethylene glycol and ethylene chlorohydrin.

**Radiation**—Sterilization by exposure to ionizing radiation is an acceptable procedure for components of ophthalmic preparations or indeed for the total product as in certain ophthalmic ointments. Sources of radiation are twofold and include linear electron accelerators and radioisotopes. The linear accelerators produce high-energy electrons with very little penetrating power. Radioisotopes, particularly $^{60}Co$, are employed more widely for sterilization. Sterilization by radiation may produce untoward effects such as chemical changes in product components, as well as changes in color or physical characteristics of package components.

## Ophthalmic Preparation Characteristics

**Clarity**—Ophthalmic solutions are by definition free from foreign particles and clarity normally is achieved by filtration. It is, of course, essential that the filtration equipment be clean and well-rinsed so that particulate matter is not contributed to the solution by equipment designed to remove it. Operations performed in clean surroundings, the use of laminar-flow hoods and proper nonshedding garments will contribute collectively to the preparation of brilliantly clear solutions free from foreign particles. In many instances clarity and sterility may be achieved in the same filtration step. It is essential to realize that solution clarity is equally a function of the cleanliness of the intended container and closure. Both container and closure must be thoroughly clean, sterile and nonshedding. That is, the container or closure must not contribute particles to the solution during prolonged contact such as shelf-life storage. This normally is established by thorough stability testing.

**Stability**—The stability of a drug in solution, ie, an ophthalmic product, depends on the chemical nature of the drug substance, product pH, method of preparation (particularly

temperature exposure), solution additives and type of packaging. Until two or three decades ago the stability of ophthalmic solutions was an exceedingly short-term concept; generally, it was the time required for a patient to complete the use of 15 or 30 mL of solution. Now, of course, the stability of ophthalmic products is expressed in terms of years. However, 2- to 3-year stability often is achieved only by virtue of compromise.

Drugs such as pilocarpine and physostigmine are both active and comfortable in the eye at a pH of 6.8; however, at this pH chemical stability (or instability) can be measured in days or months. With either drug, a substantial loss in chemical stability will occur in less than 1 year. On the other hand, at pH 5 both drugs are stable for a period of several years.

In addition to optimal pH, if oxygen sensitivity is a factor, adequate stability may require the inclusion of an antioxidant. Plastic packaging, ie, the low-density polyethylene *Drop-Tainer* (Alcon) that represents a patient convenience, may prove detrimental to stability by permitting oxygen permeation resulting in oxidative decomposition of the drug substance.

The attainment of optimum stability most often imposes a series of compromises on the formulator. The optimum pH may be lower than preferable for product comfort, although this effect may be minimized by adjusting pH with a buffer of minimum capacity. Additives such as chelating agents and antioxidants may be required and convenience packaging may diminish shelf life of the product.

It should be stressed that stability refers to total product stability not just the chemical stability of a single product component. That is an oversimplification. A well-planned stability program will consider and evaluate the chemical stability of the active ingredient, chemical stability of the preservative substance, continuing preservative efficacy against selected test organisms and adequacy of the package as a function of time (ie, does the package protect sterility in addition to various physical measures such as pH, clarity, resuspendability of suspensions and the like). One also must support the thesis that the material on test is representative of all lots of a given product.

**Buffer and pH**—Ideally, ophthalmic preparations should be formulated at a pH equivalent to the tear fluid value of 7.4. Practically, this seldom is achieved. The large majority of active ingredients used in ophthalmology are salts of weak bases and are most stable at an acid pH. This generally can be extended to suspensions of insoluble corticosteroids. Such suspensions usually are most stable at an acid pH.

Optimum pH adjustment generally requires a compromise on the part of the formulator. The pH selected should be optimum for stability. The buffer system selected should have a capacity adequate to maintain pH within the stability range for the duration of the product shelf life. Buffer capacity is the key in this situation.

It generally is accepted that a low (acid) pH *per se* necessarily will not cause stinging or discomfort on instillation. If the overall pH of the tears, after instillation, reverts rapidly to pH 7.4, discomfort is minimal. On the other hand, if the buffer capacity is sufficient to resist adjustment by tear fluid and the overall eye pH remains acid for an appreciable period of time, then stinging and discomfort may result. Consequently, buffer capacity should be adequate for stability, but minimized so far as possible, to allow the overall pH of the tear fluid to be disrupted only momentarily.

**Tonicity**—Tonicity refers to the osmotic pressure exerted by salts in aqueous solution. An ophthalmic solution is isotonic with another solution when the magnitudes of the colligative properties of the solutions are equal. An ophthalmic solution is considered isotonic when its tonicity is equal to that of an 0.9% sodium chloride solution.

The calculation of tonicity at one time was stressed rather heavily. The fledging pharmacist was taught in great detail the requirements of and means of achieving exact tonicity, sometimes to the detriment of other factors such as sterility and stability.

In actuality the eye is much more tolerant of tonicity variations than was at one time suggested. The eye usually can tolerate solutions equivalent to a range of 0.5% to 1.8% sodium chloride. Given a choice, isotonicity always is desirable and particularly is important in intraocular solutions. It need not, however, be an overriding concern when total product stability is to be considered.

The tonicity of ophthalmic (and parenteral) solutions has been investigated intensively over the years. These studies have resulted in the accumulation and publication of a large number of sodium chloride equivalents which are useful in calculating tonicity values. See Chapter 36.

**Viscosity**—The USP permits the use of viscosity-increasing agents to prolong contact time in the eye and thus enhance drug absorption and activity. Substances such as methylcellulose, polyvinyl alcohol and hydroxypropylmethyl cellulose are added frequently to increase viscosity.

Various investigators have studied the effect of increased viscosity on contact time in the eye. In general terms, viscosity increased up to the 15 to 50 cps range significantly improves contact time in the eye. Results tend to plateau beyond the 50-centipose range; higher viscosity values offer no significant advantage and have a tendency to leave a noticeable residue on the lid margins.

**Additives**—The use of various additives in ophthalmic solutions is permissible, however the choices are few in number. An antioxidant, specifically sodium bisulfite or metabisulfite, is permitted in concentrations up to 0.3%, particularly in solutions containing epinephrine salts. Other antioxidants such as ascorbic acid or acetylcysteine also may be used. The antioxidant acts in this case as a stabilizer to minimize oxidation of epinephrine.

The use of surfactants in ophthalmic preparations is restricted similarly. Nonionic surfactants, that class of such compounds which are least toxic to the ophthalmic tissues, are used in low concentrations particularly in steroid suspensions and as aids in achieving solution clarity. Surfactants may be used rarely as cosolvents to increase solubility.

The use of surfactants, particularly in any significant concentration, should be tempered by recognition of the sorption characteristics of these compounds. Nonionic surfactants, in particular, may react by binding with antimicrobial preservative compounds and inactivate much of the preservative system.

Cationic surfactants are used frequently in ophthalmic solutions but almost invariably as antimicrobial preservatives. Benzalkonium chloride is typical of this class of substances. Concentrations are in the range of 0.005 to 0.02%, with toxicity the limiting factor on the concentration used. Because of its large molecular weight the benzalkonium cation is inactivated easily by macromolecules of opposite charge or by sorption. Despite such limitations, benzalkonium chloride is the preservative used in the large majority of commercial ophthalmic solutions and suspensions.

## Packaging

The traditional ophthalmic glass container with accompanying glass dropper has been supplanted almost completely by the low-density polyethylene dropper unit called the *Drop-Tainer* (Alcon). In only a very few instances are glass containers still in use, usually because of stability limitations. Large-volume intraocular solutions of 250 and 500 mL have been packaged in glass, but even these parenteral-type products are beginning to be packaged in specially fabricated polyethylene/polypropylene containers.

One should be ever mindful that plastic packaging, usually low-density polyethylene, is by no means interchangeable with glass. Plastic packaging is permeable to a variety of substances including light and air. The plastic package may contain a variety of extraneous substances such as mold release agents, antioxidants, reaction quenchers and the like, that readily may leach out of the plastic and into the contained solution. Label glues, inks and dyes also may penetrate poly-

ethylene readily. In the opposite sense, volatile materials may permeate from solution into or through plastic containers.

Glass containers remain a convenient package material for extemporaneous preparation of ophthalmic solutions. Type 1 glass should be used. The container should be well-rinsed with sterile distilled water and may be sterilized by autoclaving. Droppers normally are available presterilized and packaged in a convenient blister pack.

Ophthalmic ointments invariably are packaged in metal tubes with an ophthalmic tip. Such tubes are sterilized conveniently by autoclaving or by ethylene oxide. In rare cases of metal reactivity or incompatibility, tubes lined with epoxy or vinyl plastic may be obtained.

Regardless of the form of packaging, some type of tamper-evident feature must be used for consumer protection. The common tamper-evident feature used on most ophthalmic preparations is the moisture- or heat-sensitive shrink band. The band should be identified in such a way that its disruption or absence should constitute a warning that tampering, either accidental or purposeful, has occurred.

The eyecup, an ancillary packaging device, fortunately seems to have gone the way of the community drinking cup. An eyecup should not be used. Its use inevitably will spread or aggravate eye infections. The pharmacist should not fail to discourage such use just as he or she should take the time to instruct the patient in the proper use and care of eye medications. While ophthalmic administration may seem simple enough, it may be a foreign and difficult task for many people. The suggestions and precautions given on page 1566 may be useful in instructing patients.

## Antimicrobial Preservatives

The USP states that ophthalmic solutions may be packaged in multiple-dose containers. Each solution must contain a substance or mixture of substances to prevent the growth of, or to destroy, microorganisms introduced accidentally when the container is opened during use. The preservative is not intended to be used as a means of preparing a sterile solution. Appropriate techniques, discussed elsewhere, are to be employed to prepare a sterile solution.

Preservatives are not to be used in solutions intended for intraocular use because of the risk of irritation. Ophthalmic solutions prepared and packaged for a single application, ie, a unit dose, need not contain a preservative because it is not intended for reuse.

The need for proper control of ophthalmic solutions to prevent serious contamination was recognized in the 1930s. The first preservative recommended for use in ophthalmics was chlorobutanol, as an alternative to daily boiling!

The selection of an ophthalmic preservative can be a rather difficult task, in part, because of the relatively small number of suitable candidates. There is, of course, no such thing as an ideal preservative; however, the following criteria may be useful in preservative selection.

1. The agent should have a broad spectrum, and be active against gram-positive and gram-negative organisms as well as fungi. The agent should exert a rapid bactericidal activity particularly against known virulent organisms such as *P aeruginosa* strains.
2. The agent should be stable over a wide range of conditions including autoclaving temperatures and pH range.
3. Compatibility should be established with other preparation components and with package systems.
4. Lack of toxicity and irritation should be established with a reasonable margin of safety.

Preservative substances must be evaluated as a part of the total ophthalmic preparation in the proposed package. Only in this way can the adequacy of the preservative be established. The USP includes a test for preservative effectiveness; additionally, certain manufacturers have developed a panel of test organisms to further challenge and verify preservative activity.

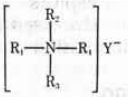
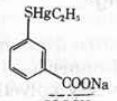
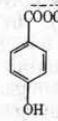
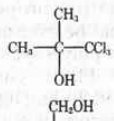
In addition to preservative effectiveness as an immediate measure, its adequacy or stability as a function of time also must be ascertained. This often is done by measuring both chemical stability and preservative effectiveness over a given period of time and under varying conditions.

Many of these test procedures are, of course, not completely pertinent to the preparation of an extemporaneous ophthalmic solution. In such a situation the pharmacist must make selections based upon known conditions and physical and chemical characteristics. In such circumstances it would be prudent to prepare minimum volumes for short-term patient use.

The choice of preservatives suitable for ophthalmic use is surprisingly narrow. The classes of compounds available for such use are described in Table 1.[12] In each case or category there are specific limitations and shortcomings.

**Quaternary Ammonium Compounds**—Benzalkonium chloride is a typical quaternary ammonium compound and is, by far, the most common preservative used in ophthalmic preparations. Over 65% of commercial ophthalmic prod-

**Table 1—Ophthalmic Preservatives[12]**

| Type | Typical structure | Concentration range | Incompatibilities |
|---|---|---|---|
| Quaternary ammonium compounds |  | 0.004%–0.02%<br>0.01% most common | Soaps<br>Anionic materials<br>Salicylates<br>Nitrates |
| Organic mercurials |  | 0.001%–0.01% | Certain halides with phenylmercuric acetate |
| Parahydroxy benzoates |  | Maximum 0.1% | Adsorption by macromolecules; marginal activity |
| Chlorobutanol |  | 0.5% | Stability is pH-dependent; activity concentration is near solubility maximum |
| Aromatic alcohols | | 0.5%–0.9% | Low solubility in water; marginal activity |

ucts are preserved with benzalkonium chloride. Despite this broad use the compound has definite limitations. As a cationic surface-active material of high molecular weight it is not compatible with anionic compounds. It is incompatible with salicylates and nitrates and may be inactivated by high molecular weight nonionic compounds. Conversely, benzalkonium chloride has excellent chemical stability and very good antimicrobial characteristics. Given the alternative it would be preferable to modify a formulation to remove the incompatibility, rather than include a compatible but less effective preservative.

The literature on benzalkonium chloride is somewhat mixed; however, this is not unexpected given the wide variation in test methods and, indeed, the chemical variability of benzalkonium chloride itself. The official substance is defined as a mixture of alkyl benzyldimethylammonium chlorides including all or some of the group ranging from $n$-$C_8H_{17}$ through $n$-$C_{16}H_{33}$. The $n$-$C_{12}H_{25}$ homolog content is not less than 40% on an anhydrous basis.

Reviews[13] of benzalkonium chloride indicate that it is well-suited for use as an ophthalmic preservative. Certain early negative reports have been shown to be quite erroneous; in some cases adverse tissue reactions were attributed to benzalkonium chloride when, in fact, a totally different compound was used as the test material. Although benzalkonium chloride is by far the most common quaternary preservative others occasionally referred to include benzethonium chloride and cetyl pyridinium chloride. All are official compounds. More recently quaternary ammonium compounds have been attached to soluble, reasonably high-molecular-weight polymers. These agents possess good antimicrobial effectiveness with fewer compatibility problems than the official quaternary preservatives. Refer to RPS-14, page 1571 for a summary of quaternary germicides in ophthalmic drugs.

**Organic Mercurials**—It generally is stated that phenylmercuric nitrate or phenylmercuric acetate, in 0.002% concentration, should be used instead of benzalkonium chloride as a preservative for salicylates and nitrates, and in solutions of salts of physostigmine and epinephrine that contain 0.1% of sodium sulfite. The usual range of concentrations employed is 0.002 to 0.004%. Phenylmercuric borate sometimes is used in place of the nitrate or acetate.

Phenylmercuric nitrate has the advantage, over some other organic mercurials, in not being precipitated at a slightly acid pH. As with other mercurials, it is slow in its bactericidal action, and it also produces sensitization reactions. Phenylmercuric ion is incompatible with halides as it forms precipitates.

The effectiveness of phenylmercuric nitrate against *P aeruginosa* is questionable; it has been found that pseudomonal organisms survive after exposure to a concentration of 0.004% for longer than a week.

Development of iatrogenic mercury deposits in the crystalline lens resulting from use of miotic eye drops containing 0.004% phenylmercuric nitrate, 3 times daily, for periods of 3 to 6 years, has been reported. No impairment of vision was found, but the yellowish brown discoloration of the lens capsule is reported to be permanent.

Thimerosal (*Merthiolate*, Lilly) is an organomercurial with bacteriostatic and antifungal activity and is used as an antimicrobial preservative in concentrations of 0.005 to 0.02%. Its action, as with other mercurials, has been reported to be slow.

**Parahydroxybenzoic Acid Esters**—Mixtures of methylparaben and propylparaben sometimes are used as ophthalmic antimicrobial preservatives; the concentration of methylparaben is in the range of 0.1 to 0.2%, while that of propylparaben approaches its solubility in water (approximately 0.04%). They are not considered efficient bacteriostatic agents and are slow in their antimicrobial action. Ocular irritation and stinging have been attributed to their use in ophthalmic preparations. In a review of OTC drugs for use in ophthalmology, the FDA expert panel found the parabens unacceptable as ophthalmic solution preservatives.

**Substituted Alcohols and Phenols**—Chlorobutanol is stated to be effective against both gram-positive and gram-negative organisms, including *P aeruginosa* and some fungi. It broadly is compatible with other ingredients and normally used in a concentration of 0.5%. One of the products of hydrolysis is hydrochloric acid, which causes a decrease in the pH of aqueous solutions. This decomposition occurs rapidly at high temperatures and slowly at room temperature, in unbuffered solutions that were originally neutral or alkaline. Therefore, ophthalmic solutions that contain chlorobutanol should be buffered between pH 5.0 and 5.5. At room temperature it dissolves slowly in water and, although it dissolves more rapidly on heating, loss by vaporization and decomposition is accelerated.

A combination of chlorobutanol and phenylethyl alcohol (0.5% of each) has been reported to be more effective against *P aeruginosa*, *S aureus* and *P vulgaris* than either antimicrobial singly. Also, preliminary solution of the chlorobutanol in phenylethyl alcohol effects solution of the former in water without the use of heat.

## Ophthalmic Preparations for OTC Use

A comprehensive review of over-the-counter ophthalmic preparations recently has been completed by an expert panel approved by the FDA. The panel review extended over the period 1973 through 1979. The finding of this panel, in the form of a tentative final monograph, appeared in the *Federal Register*.[14]

In a comprehensive assessment the panel considered the following conditions amenable to OTC drug therapy.

**Tear Insufficiency**—Rational formulations used to treat tear insufficiency are aqueous solutions containing demulcent agents, tonicity agents and pH and buffering agents. Tear insufficiency includes:

1. Keratoconjunctivitis sicca
2. Sjogren's syndrome
3. Dry eye in the elderly

**Corneal Edema**—Increased water content in the cornea usually is treated with hypertonic solutions of sodium chloride, either 2 or 5%.

**Inflammation and Irritation of the Eye**—

1. Presence of loose foreign material in the eye. Commonly treated with an isotonic eyewash properly buffered and preserved.
2. Irritation from airborne pollutants and chlorinated water. Management consists of avoiding the offending allergens and the use of vasoconstrictors, astringents, demulcents and emollients for symptomatic relief.
3. Allergic conjunctivitis. Treatment by topically applied vasoconstrictors and astringents, demulcents, emollients and cold compresses. Only in mild cases, where edema and congestion are slight, is OTC treatment alone adequate.

In providing such OTC medications the pharmacist should take the opportunity to point out that unsupervised use of these products should be limited to 72 hours, when based on self-diagnosis. If the condition persists or worsens at any time, treatment should be discontinued and a physician consulted at once.

## Contact Lenses

Contact lenses are optical and/or therapeutic ophthalmic devices divisible into four general categories. The rigid, hydrophobic, so-called hard contact lenses, principally PMMA (polymethyl methacrylate); rigid, semihydrophobic; flexible hydrophilic; flexible hydrophobic and rigid-gas-permeable. Each lens class is accompanied by its support solution products and devices. Solutions used with hard contact lenses are rather conventional compositions, usually regarded as OTC products. Conversely, solutions ancillary to the hydrophilic lenses may be classed as new drugs or devices from a regulatory standpoint. Such preparations require great care and considerable pharmaceutical skill to formulate. Lens materials and support products are further classified and identified in Table 2.

**Hard Contact Lens**—Some evidence is available to show that contact lenses were visualized by Leonardo da Vinci in

**Table 2—Contact Lens Classes, Characteristics and Support Products**

| Lens type | Chemical classification | Major characteristics | Typical support products |
|---|---|---|---|
| "Hard," rigid, hydrophobic | PMMA (polymethyl methacrylate) | Negligible gas permeability, low water content, medium wettability | Wetting solutions<br>Soaking solutions<br>Cleaning solutions<br>Combination<br>Artificial tears |
| "Soft," flexible, hydrophilic | HEMA (hydroxyethyl methylmethacrylate) | High water content, low gas permeability, good wettability | Cleaning solutions<br>Disinfection solutions |
| Flexible hydrophobic | Silicone rubber | Good gas permeability<br>Poor wettability | Wetting solutions<br>Cleaning solutions<br>Soaking solutions |
| | Silicone vinylpyrollidone | Good gas permeability<br>Good wettability | |
| Rigid, hydrophilic | CAB (cellulose acetate butyrate) | Good gas permeability<br>Good wettability | Wetting solutions<br>Cleaning solutions<br>Soaking solutions<br>Rewetting solutions |

1508 and later, in 1637, by Rene Descartes. In 1827 the British astronomer, Sir John Herschel, described the mathematics of these devices. He speculated on the possibility of filling a glass contact lens with transparent gelatin to correct for corneal irregularities. Not until 1888 was the original concept executed by the artificial eye maker, Albert Muller. He made a glass protective shell for the cornea of a lagophthalmic patient who had carcinoma of the upper lid. The patient wore the device for 20 years, and corneal clarity was maintained. Other cases were reported in Europe of glass shells placed on the eye as corneal protective devices.

Until the latter part of the 1940s almost all contact lenses had a portion resting directly on, or arching over, the cornea with a supporting flange resting beyond the limbus on the sclera. Thus, they were scleral lenses. However, contact lenses without scleral portions (corneal lenses) were in existence at least as early as 1912, when they were being manufactured by Carl Zeiss.

The glass scleral contact lenses that were made from 1888 to 1938 were fitted by a tedious method of trial and error using a fitting set that might contain more than 1000 lenses. The lenses were heavy and adjustments on them by the fitter were impossible. Their life in the eye was short, because the glass was attacked vigorously by lacrimal fluid; in about 6 months the lenses became too rough to wear or to see through. However, they had the advantage that tears readily wet glass. In 1922 Dallos, in Budapest, perfected a molding technique by which a glass shell could be fabricated to approximate closely the curvature of the globe. With the introduction of the methyl methacrylate plastic molded scleral contact lens in 1938 by Obrig and Muller, the feasibility of using plastic for lens fabrication was demonstrated. Although the optical properties of glass are superior to those of plastic, the relative gain in ruggedness and the reduction in weight to one-third that of glass far offset this disadvantage. Not until PMMA became available was a flush-fitting shell possible. The concept was developed by Ridley, in England, in 1954. The protective effect is very useful in various conditions characterized by corneal epithelial fragility and for cosmetic effects.

The "hard" plastic corneal contact lens was introduced by Tuohy in 1948. This was a major development. He specified a lens of smaller diameter that rested within the limbal area of the cornea. The results were poor. Development of a corneal lens was hindered by the fear of traumatizing the cornea with an appliance that fitted directly onto it. The first corneal lens to have any measure of success was developed in the early 1950s by Dickinson, Sohnges and Neill. Its thickness was about 0.2 mm and was considered to be a fairly thick lens. Thinner lenses, about 0.1 mm, were introduced in the early 1960s.

Scleral bifocal lenses were developed initially in 1936 and the corneal type in 1958. Bifocal contact lenses are more difficult to fit, more costly and, in many cases, more uncomfortable than single-vision lenses.

## Lens-Care Products

**Wetting Solutions**—These are preparations designed to furnish an hydrophilic coating over the characteristically hydrophobic surface of PMMA, silicon, acrylate and other rigid lens surfaces. Typically, wetting solutions include an acceptable viscosity-imparting agent, a surfactant and a preservative. The surface-activity and viscosity effect may be obtained from a single compound. Agents commonly used include cellulose derivatives, polyvinyl pyrollidone, polyvinyl alcohol and polyethylene glycol derivatives. Preservatives include those acceptable for ophthalmic use. Such solutions are sterile.

**Cleaning Solutions**—Cleaning solutions commonly are used to remove surface contaminants—lipids, protein and the like. Cleaning is accomplished by the use of surfactants which preferably are nonionic or amphoteric. Solutions are sterile and properly preserved. Viscosity-imparting agents generally are not included.

Adequate cleaning of hydrophilic lenses is a far more complex and challenging problem than hard-lens cleaning. Because of their permeability characteristics, contaminants penetrate into the lens structure and easily may bind chemically or physically to the HEMA lens material. Contaminants may be surface films or crystals, amorphous aggregates of protein material, cellular debris or insoluble inorganic salts.

Cleaning products generally are specific to the lens material and require FDA approval, with proof of cleaning efficacy and safety. Cleaners are based on surface activity, enzyme action or even abradant action, in which case the abradant material is softer than the lens itself. Adequate cleaning of hydrophilic lens material daily is a necessary prelude to disinfection. Most recently the use of extended-wear lenses has found wide acceptance. Successful use usually depends on the use of an enzyme for cleaning, together with special disinfectants.

**Disinfecting Systems**—Disinfection of the first hydrophilic lens approved by the FDA was accomplished using a heating device which generated steam from a saline solution. The latter was prepared either by the user or available from the manufacturer. Subsequent to the so-called thermal systems, disinfection solutions were developed which met the requirements necessary for FDA approval. Because of the sorption characteristics of hydrophilic lens materials, many of the accepted ophthalmic preservatives are unsatisfactory for use in soft-lens disinfecting systems, including the ubiquitous benzalkonium chloride. Once again, however, the use of a quaternary disinfectant covalently bonded to a soluble, relatively high-molecular-weight polymer has met with some success.

In addition to possessing satisfactory disinfecting activity, such a preparation must be isotonic, in an acceptable pH range, nonreactive (nonbinding) with lens materials and, over a normal use period, induce or bring about no physical, chemical or optical changes in the lens. It is of course sterile and safe for use in the eye even though direct instillation into the eye is not intended.

**Soaking Solutions**—Soaking or storage solutions, as the name suggests, are used to store and hydrate hard lenses but, most importantly, to disinfect such lenses. Disinfection should be rapid and as complete as possible making use, once again, of acceptable ophthalmic preservative substances. Soaking solutions typically contain chlorhexidine (gluconate), benzalkonium or quaternary/polymer compounds enhanced by sodium edetate.

**Artificial Tears**—Solutions intended to rewet hard lenses *in situ* are referred to as rewetting solutions or artificial tears. Such preparations are intended to reinforce the wetting capacity of the normal tear film. Early products of this type tended to be somewhat viscous wetting solutions acceptable for direct installation into the eye. More recent preparations mimic tears more accurately and their viscosity is rather low, thus, user acceptability is improved.

**Guidelines for Safety and Efficacy Testing**—The FDA periodically issues or updates guidelines describing recommended test procedures for contact lens-care products, other than those used with PMMA lenses and, also, for typical OTC products used with hard lenses. The reader is advised to review the most recent guidelines for appropriate protocols for non-PMMA products.

Tests for OTC (hard) lens products are divided into those appropriate for products intended for direct instillation in the eye and those not so intended. Products intended for direct instillation require multiple-application safety tests in the rabbit eye, preservative efficacy tests and sterility testing, in addition to adequate efficacy tests.

Products not intended for direct instillation require short term evaluation in the rabbit eye and, of course, preservative efficacy and sterility testing.

**Soft Contact Lens**—In 1960 Wichterle and Lim introduced a new, soft, hydrophilic gel lens synthesized by copolymerization of HEMA with ethylene glycol dimethacrylate (EGDM). Its hydrophilic nature was in marked contrast to the hydrophobic properties of PMMA; its increased permeability to water, oxygen and other constituents of tears having low molecular weight appears to offer metabolic advantages.

Hydrophilic (gel, hydrogel, soft or flexible) lenses are made of polymerized or copolymerized hydrophilic monomers with a cross-linking agent, such as EGDM. The cross-links add stability to the gel lenses and act to decrease the water saturation. The most widely used monomer is HEMA which may be copolymerized with lesser amounts of polyvinylpyrrolidone (PVP), a more hydrophilic polymer. The copolymer acts to increase the hydration level beyond the maximum 40% potential of homogenous poly-HEMA. Gel lenses of even higher water content can be formed by combining a hydrophilic monomer or polymer (usually PVP) with a relatively hydrophobic monomer (usually methyl methacrylate). Lenses of this type are available with as much as 85% water at equilibrium. In addition, these cross-linked polymers cannot be formed by heat or pressure and thus usually are not harmed by boiling in aqueous solution or by autoclaving.

Hydrophilic lenses are elastic and flexible when hydrated, yet brittle when dry. They can absorb and concentrate tear-film constituents as well as environmental pollutants, vapors, cosmetic ingredients, water impurities and antimicrobial preservatives, as well as active ingredients, in ophthalmic preparations. The refractive index for HEMA is 1.43 when hydrated in normal saline; hydrophilic lenses of greater hydration level have a correspondingly lower refractive index. Depending on the amount of cross-linking and the amount and type of additives, the dimensions can be influenced by such factors as pH, tonicity and molecular or ionic species of dissolved substances.

**Advantages and Disadvantages of Soft Contact Lenses**—Soft contact lenses have the major advantage of wearer comfort and easy adaptability, particularly for the first-time lens wearer. Soft lenses are misplaced or lost less easily and allow an easier transition to eye glasses. The typical vision blurring associated with a transition from hard lenses to eye glasses is absent.

Because of the flexibility of soft contact lenses an accurate fit to the eye is more difficult than is the case with hard lenses. Visual clarity usually is less with soft lenses; indeed, the long-time hard-lens wearer may find visual clarity or acuity of soft lenses unacceptable at first wearing.

Soft lenses require far more care than their hard counterparts. The soft polymers will allow penetration of contaminants deep into the lens body where even simple removal become difficult. Soft lenses may become more or less permanently contaminated by sorption of drug product components, in addition to protein fragments or various other debris.

Even with reasonable care, soft lenses can be expected to have a wearer life substantially shorter than hard lenses. Eye corrective changes requiring refitting and lens replacement may occur well before hard lenses require replacing because of wear.

Despite the obvious practical disparities the popularity of soft contact lenses is immense, and increasing as durability and wearing time are increased. Wearer comfort, easy adaptability and adequacy for most relatively minor visual corrections contribute to soft-lens acceptability and popularity.

### *Therapeutic Uses*

The majority of contact lenses are used for reasons of optical acuity, convenience and/or cosmetic value. However, so far as is known, the first use of such a device, in 1888, was to protect a cornea, and therapeutic usefulness has continued since that time. A major therapeutic advance was made by Ridley, in 1954, using PMMA, at the time that it was replacing glass as the principal material used in making lenses. Currently, there is evidence of contact-lens development of major therapeutic importance in the use of soft lenses in the treatment of very serious pathological conditions. They are of value in several ways, which are interrelated to the extent it is difficult to give an example which illustrates only one point. The several functions can be listed as:

1. As "bandages" (through which one can see) to protect the epithelium of the cornea.
2. While in use as bandages, to permit movement of medicinal fluids through the lens to the eye, as well as under the lens (see below).
3. When so used, to increase the duration of the effect from a given quantity of drug.
4. When so used, to increase the degree of effect from a given amount of drug (see below).

The first two functions have become rather well-established in the past few years; the last two have been of less therapeutic value.

Bullous keratopathy is the most severe form of corneal edema. Its treatment is presented as an example of the first two functions of soft contact lenses. The lens acts basically as a simple bandage, but has the added valuable quality that the ophthalmic solutions, used as drops, can pass through the lenses and act on the eye. The pain of bullous keratopathy usually is relieved dramatically by the use of the lens as a protective shield, as similarly accomplished by the earlier hard scleral lenses. Vision may be improved slightly. The pain results mainly from the lids rubbing on the bullae, rupturing them and exposing corneal nerves. The lenses can be worn fulltime, 24 hours a day for months, except for removal for cleaning. They may need to be cleaned only when protein deposits build up on them. They should be removed and inserted only by a physician. New lenses will be needed as the cornea changes in shape.

Compared with hard lenses, use of the soft lens is much simpler. No moldings of the eye or keratometer readings are needed. The iatrogenic aspects of the hard lens have, to a great extent, been alleviated by the soft lens. Few problems occur on over-wearing the lenses. Usually, no abrasions are found. The eyes are white and usually free of conjunctival infection. As to medicinal agents, because of the concomitant iritis, pupils must be dilated with cycloplegics for the first few days, as by use of atropine. Eyelid hygiene techniques are needed. Antibiotics, such as chloramphenicol drops, are used if secondary infection or blepharitis is present. A 5% hypertonic saline solution may be used to improve vision; the patient can use it as often as it is helpful.

The conditions for which the use of soft lenses is apparently very helpful and well established are

1. Edema
   a. Bullous keratopathy
   b. Aphakic
   c. Secondary to glaucoma
   d. Fuchs' dystrophy
   e. Uveitis, etc
2. Epithelial erosion and defects
   a. Ulcers
   b. Chemical burns
   c. Post-graft
3. Exposure
   a. Neurotropic keratitis
   b. Lid abnormalities
4. Irregular cornea
   a. Scars
   b. Dystrophy
5. Dry eye
   a. Nonprogressive conjunctival cicatrization (Stevens-Johnson syndrome)
   b. Sjögren's syndrome
   c. Trachoma
   d. Pemphigoid

## Summary

The progress in ophthalmic pharmaceutics and in lens care pharmaceutics during the last decade must be considered as striking. Very substantial advances have been made in ophthalmic bioavailability and the factors influencing ophthalmic drug absorption. New approaches and new techniques have confirmed (or refuted) many long held tenets of ophthalmic formulation technology. Continuing studies in the general field of ophthalmic pharmaceutics and pharmacokinetics should continue to advance the frontiers of ophthalmic drug therapy and ophthalmic drug delivery.

In the contact-lens and lens-care field one is confronted with a plethora of new lenses and lens polymers. Wearing time has been lengthened substantially, comfort improved and correctable visual defects increased. By the same token the requirements for lens hygiene also have increased. Advances in this broad field also show no signs of abating.

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