In physicochemical terms, solutions may be prepared from any combination of a solid, liquid, and gas, the three states of matter. For example, a solid solute may be dissolved in another solid, a liquid, or a gas, and the same being true for a liquid solute and for a gas; nine types of homogeneous mixtures are possible. In pharmacy, however, interest in solutions is for the most part limited to preparations of a solid, a liquid, and less frequently a gas solute in a liquid solvent.

In pharmaceutical terms, solutions are “liquid preparations that contain one or more chemical substances dissolved in a suitable solvent or mixture of mutually miscible solvents” (1). Because of a particular pharmaceutical solution’s use, it may be classified as oral, otic, ophthalmic, or topical. Still other solutions, because of their composition or use, may be classified as other dosage forms. For example, aqueous solutions containing a sugar are classified as syrups (even though some syrups may contain some alcohol), sweetened hydroalcoholic (combinations of water and ethanol) solutions are termed elixirs, and solutions of aromatic materials are termed spirits if the solvent is alcoholic or aromatic waters if the solvent is aqueous. Solutions prepared by extracting active constituents from crude drugs are termed tinctures or fluidextracts, depending on their method of preparation and concentration. Tinctures may also be solutions of chemical substances dissolved in alcohol or in a hydroalcoholic solvent. Certain solutions prepared to be sterile and pyrogen-free and intended for parenteral administration are classified as injections. Although other examples could be cited, it is apparent that a solution, as a distinct type of pharmaceutical preparation, is much further defined than the physicochemical definition of the term solution.

Oral solutions, syrups, elixirs, spirits, and tinctures are prepared and used for the specific effects of the medicinal agents they carry. In these preparations, the medicinal agents are intended to provide systemic effects. The fact that they are administered in solution form usually means that they are soluble in aqueous systems and their absorption from the gastrointestinal tract into the systemic circulation may be expected to occur more rapidly than from suspension or solid dosage forms of the same medicinal agent.

Solutes other than the medicinal agent are usually present in orally administered solutions. These additional agents are frequently

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**OBJECTIVES**

After reading this chapter, the student will be able to:

1. Define the various types of oral and topical liquid dosage forms
2. List the advantages and disadvantages of using liquid dosage forms in extemporaneous compounded prescriptions and in patient therapy
3. Compare and contrast liquid dosage forms to solid oral dosage forms
4. Define solubility and describe how different factors increase or decrease solute solubility in a given solvent
5. Evaluate and select a proper solvent and delivery system for a given solute, purpose, and/or patient population
included to provide color, flavor, sweetness, or stability. In formulating or compounding a pharmaceutical solution, the pharmacist must use information on the solubility and stability of each solute with regard to the solvent or solvent system. Combinations of medicinal or pharmaceutical agents that will result in chemical and/or physical interactions affecting the therapeutic quality or pharmaceutical stability of the product must be avoided.

For single-solute solutions and especially for multiple-solute solutions, the pharmacist must be aware of the solubility characteristics of the solutes and the features of the common pharmaceutical solvents. Each chemical agent has its own solubility in a given solvent. For many medicinal agents, their solubilities in the usual solvents are stated in the United States Pharmacopeia–National Formulary (USP–NF) as well as in other reference books.

**SOLUBILITY**

Attractive forces between atoms lead to the formation of molecules and ions. The intermolecular forces, which are developed between like molecules, are responsible for the physical state (solid, liquid, or gas) of the substance under given conditions, such as temperature and pressure. Under ordinary conditions, most organic compounds, and thus most drug substances, form molecular solids.

When molecules interact, attractive and repulsive forces are in effect. The attractive forces cause the molecules to cohere, whereas the repulsive forces prevent molecular interpenetration and destruction. When the attractive and repulsive forces are equal, the potential energy between two molecules is minimal and the system is most stable.

Dipolar molecules frequently tend to align themselves with other dipolar molecules so that the negative pole of one molecule points toward the positive pole of the other. Large groups of molecules may be associated through these weak attractions, known as dipole–dipole or van der Waals forces. Other attractions also occur between polar and nonpolar molecules and ions. These include ion–dipole forces and hydrogen bonding. The latter is of particular interest. Because of small size and large electrostatic field, the hydrogen atom can move in close to an electronegative atom, forming an electrostatic type of association, a hydrogen bond or a hydrogen bridge. Hydrogen bonding involves strongly electronegative atoms such as oxygen, nitrogen, and fluorine. Such a bond exists in water, represented by the dotted lines.

![Water](image)

Hydrogen bonds also exist between some alcohol molecules, esters, carboxylic acids, aldehydes, and polypeptides.

When a solute dissolves, the substance’s intermolecular forces of attraction must be overcome by forces of attraction between the solute and the solvent molecules. This entails breaking the solute–solute forces and the solvent–solvent forces to achieve the solute–solvent attraction.

The solubility of an agent in a particular solvent indicates the maximum concentration to which a solution may be prepared with that agent and that solvent. When a solvent at a given temperature has dissolved all of the solute possible, it is said to be saturated. To emphasize the possible variation in solubility between two chemical agents and, therefore, in the amounts of each required to prepare a saturated solution, two official aqueous saturated solutions are cited as examples, Calcium Hydroxide Topical Solution, USP, and Potassium Iodide Oral Solution, USP. The first solution, prepared by agitating an excess amount of calcium hydroxide with purified water, contains only about 140 mg of dissolved solute per 100 mL of the solution at 25°C, whereas potassium iodide solution contains about 100 g of solute per 100 mL of the solution, more than 700 times as much solute as in the calcium hydroxide topical solution. Thus, the maximum possible concentration to which a pharmacist may prepare a solution varies greatly and depends in part on the chemical constitution of the solute.
Through selection of a different solubilizing agent or a different chemical salt form of the medicinal agent, alteration of the pH of a solution, or substitution in part or in whole of the solvent, a pharmacist can, in certain instances, dissolve greater quantities of a solute than would otherwise be possible. For example, iodine granules are soluble in water only to the extent of 1 g in about 3,000 mL. Using only these two agents, the maximum concentration possible would be approximately 0.03% of iodine. However, through the use of an aqueous solution of potassium iodide or sodium iodide as the solvent, much larger amounts of iodine may be dissolved as the result of the formation of a water-soluble complex with the iodide salt. This reaction is taken advantage of, for example, in Iodine Topical Solution, USP, prepared to contain about 2% iodine and 2.4% sodium iodide.

Temperature is an important factor in determining the solubility of a drug and in preparing its solution. Most chemicals absorb heat when they are dissolved and are said to have a positive heat of solution, resulting in increased solubility with an increase in temperature. A few chemicals have a negative heat of solution and exhibit a decrease in solubility with a rise in temperature. Other factors in addition to temperature affect solubility. These include the various chemical and other physical properties of the solute and the solvent, pressure, the pH of the solution, the state of subdivision of the solute, and the physical agitation applied to the solution as it dissolves. The solubility of a pure chemical substance at a given temperature and pressure is constant; however, its rate of solution, that is, the speed at which it dissolves, depends on the particle size of the substance and the extent of agitation. The finer the powder, the greater the surface area, which comes in contact with the solvent, and the more rapid the dissolving process. Also, the greater the agitation, the more unsaturated solvent passes over the drug and the faster the formation of the solution.

The solubility of a substance in a given solvent may be determined by preparing a saturated solution of it at a specific temperature and by determining by chemical analysis the amount of chemical dissolved in a given weight of solution. The amount of solvent required to dissolve the amount of solute can be determined by a simple calculation. The solubility may then be expressed as grams of solute dissolving in milliliters of solvent; for example, “1 g of sodium chloride dissolves in 2.8 mL of water.” When the exact solubility has not been determined, general expressions of relative solubility may be used. These terms are defined in the USP and presented in Table 13.1 (1).

Many of the important organic medicinal agents are either weak acids or weak bases, and their solubility depends on a large measure on the pH of the solvent. These drugs react either with strong acids or strong bases to form water-soluble salts. For instance, the weak bases, including many of the alkaloids (atropine, codeine, and morphine), antihistamines (diphenhydramine and promethazine), local anesthetics (cocaine, procaine, and tetracaine), and other important drugs, are not very water soluble, but they are soluble in dilute solutions of acids. Pharmaceutical manufacturers have prepared many acid salts of these organic bases to enable the preparation of aqueous solutions. However, if the pH of the aqueous solution of these salts is changed by the addition of alkali, the free base may separate from solution unless it has adequate solubility in water. Organic medicinals that are weak acids include the barbiturate drugs (e.g., phenobarbital) and the sulfonamides (e.g., sulfadiazine and sulfacetamide). These and other weak acids form water-soluble salts in basic solution and may separate from solution by a lowering of the pH. Table 13.2 presents the comparative solubilities of some typical examples of weak acids and weak bases and their salts.

<table>
<thead>
<tr>
<th>Table 13.1</th>
<th>RELATIVE TERMS OF SOLUBILITY (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DESCRIPTIVE TERM</strong></td>
<td><strong>PARTS OF SOLVENT REQUIRED FOR 1 PART OF SOLUTE</strong></td>
</tr>
<tr>
<td>Very soluble</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Freely soluble</td>
<td>1–10</td>
</tr>
<tr>
<td>Soluble</td>
<td>10–30</td>
</tr>
<tr>
<td>Sparingly soluble</td>
<td>30–100</td>
</tr>
<tr>
<td>Slightly soluble</td>
<td>100–1,000</td>
</tr>
<tr>
<td>Very slightly soluble or insoluble</td>
<td>&gt;1,000</td>
</tr>
</tbody>
</table>

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Although there are no exact rules for unerringly predicting the solubility of a chemical agent in a particular liquid, experienced pharmaceutical chemists can estimate the general solubility of a chemical compound based on its molecular structure and functional groups. The information gathered on a great number of individual chemical compounds has led to the characterization of the solubilities of groups of compounds, and though there may be an occasional inaccuracy with respect to an individual member of a group of compounds, the generalizations nonetheless are useful. As demonstrated by the data in Table 13.2 and other similar data, salts of organic compounds are more soluble in water than are the corresponding organic bases. Conversely, the organic bases are more soluble in organic solvents, including alcohol, than are the corresponding salt forms. Perhaps the most widely written guideline for the prediction of solubility is “like dissolves like,” meaning a solvent having a chemical structure most similar to that of the intended solute will be most likely to dissolve it. Thus, organic compounds are more soluble in organic solvents than in water. Organic compounds may, however, be somewhat water soluble if they contain polar groups capable of forming hydrogen bonds with water. In fact, the greater the number of polar groups present, the greater will likely be the organic compound’s solubility in water. Organic compounds include OH, CHO, COH, CHO, CH₂OH, COOH, NO₂, CO, NH₂, and SO₃H. The introduction of halogen atoms into a molecule tends to decrease water solubility because of an increase in the molecular weight of the compound without a proportionate increase in polarity. An increase in the molecular weight of an organic compound without a change in polarity reduces solubility in water. Table 13.3 demonstrates some of these generalities with specific chemical examples.

### Table 13.2 WATER AND ALCOHOL SOLUBILITIES OF SOME WEAK ACIDS, WEAK BASES, AND THEIR SALTS

<table>
<thead>
<tr>
<th>DRUG</th>
<th>WATER</th>
<th>ALCOHOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>455.0</td>
<td>2</td>
</tr>
<tr>
<td>Atropine sulfate</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>Codeine</td>
<td>120.0</td>
<td>2</td>
</tr>
<tr>
<td>Codeine sulfate</td>
<td>30.0</td>
<td>1,280</td>
</tr>
<tr>
<td>Codeine phosphate</td>
<td>2.5</td>
<td>325</td>
</tr>
<tr>
<td>Morphine</td>
<td>5,000.0</td>
<td>210</td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>16.0</td>
<td>565</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>1,000.0</td>
<td>8</td>
</tr>
<tr>
<td>Phenobarbital sodium</td>
<td>1.0</td>
<td>10</td>
</tr>
<tr>
<td>Procaine</td>
<td>200.0</td>
<td>Soluble</td>
</tr>
<tr>
<td>Procaine hydrochloride</td>
<td>1.0</td>
<td>15</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>13,000.0</td>
<td>Sparingly soluble</td>
</tr>
<tr>
<td>Sodium sulfadiazine</td>
<td>2.0</td>
<td>Slightly soluble</td>
</tr>
</tbody>
</table>

### Table 13.3 SOLUBILITIES OF SELECTED ORGANIC COMPOUNDS IN WATER AS A DEMONSTRATION OF CHEMICAL STRUCTURE-SOLUBILITY RELATIONSHIP

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>FORMULA</th>
<th>MILLILITERS OF WATER REQUIRED TO DISSOLVE 1 G OF COMPOUND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>C₆H₆</td>
<td>1,430.0</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>C₆H₅COOH</td>
<td>275.0</td>
</tr>
<tr>
<td>Benzy alcohol</td>
<td>C₆H₅CH₂OH</td>
<td>25.0</td>
</tr>
<tr>
<td>Phenol</td>
<td>C₆H₅OH</td>
<td>15.0</td>
</tr>
<tr>
<td>Pyrocatechol</td>
<td>C₆H₄(OH)₂</td>
<td>2.3</td>
</tr>
<tr>
<td>Pyrogallol</td>
<td>C₆H₄(OH)₃</td>
<td>1.7</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>CCl₄</td>
<td>2,000.0</td>
</tr>
<tr>
<td>Chloroform</td>
<td>CHCl₃</td>
<td>200.0</td>
</tr>
<tr>
<td>Methylene chloride</td>
<td>CH₂Cl₂</td>
<td>50.0</td>
</tr>
</tbody>
</table>
As with organic compounds, the pharmacist is aware of some general patterns of solubility that apply to inorganic compounds. For instance, most salts of monovalent cations, for example, sodium, potassium, and ammonium, are water soluble, whereas divalent cations, for example, calcium, magnesium, and barium, usually form watersoluble compounds with nitrate, acetate, and chloride anions but not with carbonate, phosphate, or hydroxide anions. To be sure, certain combinations of anion and cation seem to be similar in makeup but do not have similar solubility characteristics. For instance, magnesium sulfate (Epsom salt) is soluble, but calcium sulfate is only slightly soluble; barium sulfate is very insoluble (1 g dissolves in about 400,000 mL of water) and is used as an opaque medium for x-ray observation of the intestinal tract, but barium sulfide and barium sulfite are more soluble, and their oral use can result in poisoning; and mercurous chloride (HgCl) is insoluble and was formerly used as a cathartic, but mercuric chloride (HgCl₂) is soluble in water and is a deadly poison if taken internally. In many instances, solubilities of drugs and their differentiation from other drugs are critical to the pharmacist for avoidance of compounding failures or therapeutic disasters.

The ability of a solvent to dissolve organic as well as inorganic solutes depends on its effectiveness in overcoming the electronic forces that hold the atoms of the solute together and the corresponding lack of solute on the part of the atoms themselves to resist the solvent action. During dissolution, the molecules of the solvent and the solute become uniformly mixed, and cohesive forces of the atoms are replaced by new forces as a result of the attraction of the solute and solvent molecules for one another.

The student may find the following general rules of solubility useful.

**Inorganic Molecules**

1. **If both the cation and anion of an ionic compound are monovalent, the solute–solute attractive forces are usually easily overcome, and, therefore, these compounds are generally water soluble (e.g., NaCl, LiBr, KI, NH₄NO₃, and NaNO₂).**
2. **If only one of the two ions in an ionic compound is monovalent, the solute–solute interactions are also usually easily overcome and the compounds are water soluble (e.g., BaCl₂, MgI₂, Na₂SO₄, and Na₃PO₄).**
3. **If both the cation and anion are multivalent, the solute–solute interaction may be too great to be overcome by the solute–solvent interaction, and the compound may have poor water solubility (e.g., CaSO₄, BaSO₄, and BiPO₄; exceptions: ZnSO₄, FeSO₄).**
4. **Common salts of alkali metals (e.g., Na, K, Li, Cs, and Rb) are usually water soluble (exception: Li₂CO₃).**
5. **Ammonium and quaternary ammonium salts are water soluble.**
6. **Nitrates, nitrites, acetates, chlorates, and lactates are generally water soluble (exceptions: silver and mercurous acetate).**
7. **Sulfates, sulfites, and thiosulfates are generally water soluble (exceptions: calcium and barium salts).**
8. **Chlorides, bromides, and iodides are water soluble (exceptions: salts of silver and mercurous ions).**
9. **Acid salts corresponding to an insoluble salt will be more water soluble than the original salt.**
10. **Hydroxides and oxides of compounds other than alkali metal cations and the ammonium ion are generally water insoluble.**
11. **Sulfides are water insoluble except for their alkali metal salts.**
12. **Phosphates, carbonates, silicates, borates, and hypochlorites are water insoluble except for their alkali metal salts and ammonium salts.**

**Organic Molecules**

1. **Molecules having one polar functional group are usually soluble to total chain lengths of five carbons.**
2. **Molecules having branched chains are more soluble than the corresponding straight-chain compound.**
3. Water solubility decreases with an increase in molecular weight.
4. Increased structural similarity between solute and solvent is accompanied by increased solubility.

It is the pharmacist’s knowledge of the chemical characteristics of drugs that permits the selection of the proper solvent for a particular solute. However, in addition to the factors of solubility, the selection is based on such additional characteristics as clarity, low toxicity, viscosity, compatibility with other formulative ingredients, chemical inertness, palatability, odor, color, and economy. In most instances, especially for solutions to be taken orally, used intranasally, used ophthalmically, or injected, water is the preferred solvent because it comes closer to meeting these criteria than other solvents. When water is used as the primary solvent, commonly an auxiliary solvent is also employed to augment the solvent action of water or to contribute to a product’s chemical or physical stability. Alcohol, glycerin, and propylene glycol, perhaps the most widely used auxiliary solvents, have been quite effective in contributing to the desired characteristics of pharmaceutical solutions and in maintaining their stability.

Other solvents, such as acetone, ethyl oxide, and isopropyl alcohol, are too toxic to be permitted in pharmaceutical preparations to be taken internally, but they are useful as reagent solvents in organic chemistry and in the preparatory stages of drug development, as in the extraction or removal of active constituents from medicinal plants. For purposes such as this, certain solvents are officially recognized in the compendia. A number of fixed oils, such as corn oil, cottonseed oil, peanut oil, and sesame oil, are useful solvents, particularly in the preparation of oleaginous injections, and are recognized in the official compendia for this purpose.

**SOME SOLVENTS FOR LIQUID PREPARATIONS**

The following agents find use as solvents in the preparation of solutions.

**Alcohol, USP: Ethyl Alcohol, Ethanol, C₂H₅OH**

Next to water, alcohol is the most useful solvent in pharmacy. It is used as a primary solvent for many organic compounds. Together with water, it forms a hydroalcoholic mixture that dissolves both alcohol-soluble and water-soluble substances, a feature especially useful in the extraction of active constituents from crude drugs. By varying the proportion of the two agents, the active constituents may be selectively dissolved and extracted or allowed to remain behind, according to their particular solubility characteristics in the menstruum. Alcohol, USP, is 94.9% to 96.0% C₂H₅OH by volume (i.e., v/v) when determined at 15.56°C, the US government’s standard temperature for alcohol determinations. Dehydrated Alcohol, USP, also called absolute alcohol, contains not less than 99.5% C₂H₅OH by volume and is used when an essentially water-free alcohol is desired.

Alcohol has been well recognized as a solvent and excipient in the formulation of oral pharmaceutical products. Certain drugs are insoluble in water and must be dissolved in an alternative vehicle. Alcohol is often preferred because of its miscibility with water and its ability to dissolve many water-insoluble ingredients, including drug substances, flavorants, and antimicrobial preservatives. Alcohol is frequently used with other solvents, such as glycols and glycerin, to reduce the amount of alcohol required. It is also used in liquid products as an antimicrobial preservative alone or with parabens, benzoates, sorbates, and other agents.

However, aside from its pharmaceutical advantages as a solvent and a preservative, concern has been expressed over the undesired pharmacologic and potential toxic effects of alcohol when ingested in pharmaceutical products, particularly by children. Thus, the U.S. Food and Drug Administration (FDA) has proposed that insofar as possible manufacturers of over-the-counter (OTC) oral drug products restrict the use of alcohol and include appropriate warnings in the labeling. For OTC oral products intended for children under 6 years of age,
the recommended alcohol content limit is 0.5%; for products intended for children 6 to 12 years of age, the recommended limit is 5%; and for products recommended for children over 12 years of age and for adults, the recommended limit is 10%.

**Diluted Alcohol, NF**

Diluted Alcohol, NF, is prepared by mixing equal volumes of Alcohol, USP, and Purified Water, USP. The final volume of such mixtures is not the sum of the individual volumes of the two components because the liquids contract upon mixing; the final volume is generally about 3% less than what would otherwise be expected. Thus, when 50 mL of each component is combined, the resulting product measures approximately 97 mL. It is for this reason that the strength of Diluted Alcohol, NF, is not exactly half that of the more concentrated alcohol but slightly greater, approximately 49%. Diluted alcohol is a useful hydroalcoholic solvent in various pharmaceutical processes and preparations.

**Rubbing Alcohol**

Rubbing alcohol contains about 70% ethyl alcohol by volume, the remainder consisting of water, denaturants with or without color additives and perfume oils, and stabilizers. Each 100 mL must contain not less than 355 mg of sucrose octaacetate or 1.4 mg of denatonium benzoate, bitter substances that discourage accidental or abusive oral ingestion. According to the Internal Revenue Service, U.S. Treasury Department, the denaturant employed in rubbing alcohol is formula 23-H, which is composed of 8 parts by volume of acetone, 1.5 parts by volume of methyl isobutyl ketone, and 100 parts by volume of ethyl alcohol. The use of this denaturant mixture makes the separation of ethyl alcohol from the denaturants virtually impossible with ordinary distillation apparatus. This discourages the illegal removal for use as a beverage of the alcoholic content of rubbing alcohol.

The product is volatile and flammable and should be stored in a tight container remote from fire. It is employed as a rubefacient externally and as a soothing rub for bedridden patients, a germicide for instruments, and a skin cleanser prior to injection. It is also used as a vehicle for topical preparations. Synonym: alcohol rubbing compound.

**Glycerin, USP (Glycerol), CH$_{2}$OH·CHOH·CH$_{2}$OH**

Glycerin is a clear syrupy liquid with a sweet taste. It is miscible with both water and alcohol. As a solvent, it is comparable with alcohol, but because of its viscosity, solutes are slowly soluble in it unless it is rendered less viscous by heating. Glycerin has preservative qualities and is often used as a stabilizer and as an auxiliary solvent in conjunction with water or alcohol. It is used in many internal preparations.

**Isopropyl Rubbing Alcohol**

Isopropyl rubbing alcohol is about 70% by volume isopropyl alcohol, the remainder consisting of water with or without color additives, stabilizers, and perfume oils. It is used externally as a rubefacient and soothing rub and as a vehicle for topical products. This preparation and a commercially available 91% isopropyl alcohol solution are commonly employed by diabetic patients in preparing needles and syringes for hypodermic injections of insulin and for disinfecting the skin.

**Propylene Glycol, USP, CH$_{3}$CH(OH)CH$_{2}$OH**

Propylene glycol, a viscous liquid, is miscible with water and alcohol. It is a useful solvent with a wide range of applications and is frequently substituted for glycerin in modern pharmaceutical formulations.

**Purified Water, USP, H$_{2}$O**

Naturally occurring water exerts its solvent effect on most substances it contacts and, thus, is impure, containing varying amounts of dissolved inorganic salts, usually sodium, potassium, calcium, magnesium, and iron; chlorides; sulfates; and bicarbonates, along with dissolved and undissolved organic matter and microorganisms. Water found in
most cities and towns where water is purified for drinking usually contains less than 0.1% of total solids, determined by evaporating a 100-mL sample to dryness and weighing the residue (which weighs <100 mg). Drinking water must meet the U.S. Public Health Service regulations with respect to bacteriologic purity. Acceptable drinking water should be clear, colorless, odorless, and neutral or only slightly acidic or alkaline, the deviation from neutral being due to the nature of the dissolved solids and gases (carbon dioxide contributing to the acidity and ammonia to the alkalinity of water).

Ordinary drinking water from the tap is not acceptable for the manufacture of most aqueous pharmaceutical preparations or for the extemporaneous compounding of prescriptions because of the possible chemical incompatibilities between dissolved solids and the medicinal agents being added. Signs of such incompatibilities are precipitation, discoloration, and occasionally effervescence. Its use is permitted in washing, in extraction of crude vegetable drugs, in preparation of certain products for external use, and when the difference between tap water and purified water is of no consequence. Naturally, when large volumes of water are required to clean pharmaceutical machinery and equipment, tap water may be economically employed so long as a residue of solids is prevented by using purified water as the final rinse or by wiping the water dry with a meticulously clean cloth.

Purified Water, USP, is obtained by distillation, ion exchange treatment, reverse osmosis, or other suitable process. It is prepared from water complying with the federal Environmental Protection Agency with respect to drinking water. Purified Water, USP, has fewer solid impurities than ordinary drinking water. When evaporated to dryness, it must not yield more than 0.001% of residue (1 mg of solids per 100 mL of water). Thus, purified water has only 1% as much dissolved solids as tap water. Purified Water, USP, is intended for use in the preparation of aqueous dosage forms except those intended for parenteral administration (injections). Water for Injection, USP; Bacteriostatic Water for Injection, USP, or Sterile Water for Injection, USP, is used for injections. These are discussed in Chapter 15.

The main methods used in the preparation of purified water are distillation, ion exchange, and reverse osmosis; these methods are described briefly next.

**Distillation Method**

Many stills in various sizes and styles with capacities ranging from about 0.5 to 100 gallons of distillate per hour are available to prepare purified water. Generally, the first portion of aqueous distillate (about the first 10% to 20%) must be discarded because it contains many foreign volatile substances usually found in urban drinking water, the usual starting material. Also, the last portion of water (about 10% of the original volume of water) remaining in the distillation apparatus must be discarded and not subjected to further distillation because distillation to dryness would undoubtedly result in decomposition of the remaining solid impurities to volatile substances that would distill and contaminate the previously collected portion of distillate.

**Ion Exchange Method**

On a large or small scale, ion exchange for the preparation of purified water offers a number of advantages over distillation. For one thing, the requirement of heat is eliminated and with it, the costly and troublesome maintenance frequently encountered in the operation of the more complex distillation apparatus. Because of the simpler equipment and the nature of the method, ion exchange permits ease of operation, minimal maintenance, and a more mobile facility. Many pharmacies and small laboratories that purchase large volumes of distilled water from commercial suppliers for use in their work would no doubt benefit financially and in convenience through the installation of an ion exchange demineralizer in the work area.

The ion exchange equipment in use today generally passes water through a column of cation and anion exchangers consisting of water-insoluble synthetic polymerized phenolic, carboxylic, amino, or sulfonated resins of high molecular weight. These resins...
are mainly of two types: (a) the cations, or acid exchangers, which permit the exchange of the cations in solution (in the tap water) with hydrogen ion from the resin, and (b) the anions, or base exchange resins, which permit the removal of anions. These two processes are successively or simultaneously employed to remove cations and anions from water. The processes are indicated as follows, with M⁺ indicating the metal or cation (as Na⁺) and the X⁻ indicating the anion (as Cl⁻).

Cation exchange:

\[
H^- \text{ resin} + M^+ + X^- + H_2O \rightarrow M^- \text{ resin} + H^+ + X^- + H_2O \quad \text{(pure)}
\]

Anion exchange:

\[
\text{Resin} - NH_2 + H^+ + X^- + H_2O \rightarrow \text{Resin} - NH_2 - HX + H_2O \quad \text{(pure)}
\]

Water purified in this manner, referred to as demineralized or deionized water, may be used in any pharmaceutical preparation or prescription calling for distilled water.

**Reverse Osmosis**

Reverse osmosis is one of the processes referred to in the industry as cross-flow (or tangential flow) membrane filtration (2). In this process, a pressurized stream of water is passed parallel to the inner side of a filter membrane core. A portion of the feed water, or influent, permeates the membrane as filtrate, while the balance of the water sweeps tangentially along the membrane to exit the system without being filtered. The filtered portion is called the permeate because it has permeated the membrane. The water that has passed through the system is called the concentrate because it contains the concentrated contaminants rejected by the membrane. Whereas in osmosis the flow through a semipermeable membrane is from a less concentrated solution to a more concentrated solution, the flow in this cross-flow system is from a more concentrated to a less concentrated solution, thus the term reverse osmosis. Depending on their pore size, cross-flow filter membranes can remove particles defined in the range of microfiltration (0.1 to 2 μm, e.g., bacteria), ultrafiltration (0.01 to 0.1 μm, e.g., virus), nanofiltration (0.001 to 0.01 μm, e.g., organic compounds in the molecular weight range of 300 to 1,000), and reverse osmosis (particles <0.001 μm). Reverse osmosis removes virtually all viruses, bacteria, pyrogens, and organic molecules and 90% to 99% of ions (2).

**PREPARATION OF SOLUTIONS**

Most pharmaceutical solutions are unsaturated with solute. Thus, the amounts of solute to be dissolved are usually well below the capacity of the volume of solvent employed. The strengths of pharmaceutical preparations are usually expressed in terms of percent strength, although for very dilute preparations, expressions of ratio strength may be used. These expressions and examples are shown in Table 13.4.

The symbol % used without qualification (as with w/v, v/v, or w/w) means percent weight in volume for solutions or suspensions of solids in liquids, percent weight in volume for solutions of gases in liquids, percent volume in volume for solutions of liquids in liquids, and weight in weight for mixtures of solids and semisolids.

Some chemical agents in a given solvent require an extended time to dissolve. To hasten dissolution, a pharmacist may employ one of several techniques, such as applying heat, reducing the particle size of the solute, using a solubilizing agent, and/or subjecting the ingredients to vigorous agitation. Most chemical agents are more soluble at elevated temperatures than at room temperature or below because an endothermic reaction between the solute and the solvent uses the energy of the heat to enhance dissolution. However, elevated temperatures cannot be maintained for pharmaceuticals, and the net effect of heat is simply an increase in the rate of solution rather than an increase in solubility. An increased rate is satisfactory to the pharmacist because most solutions are unsaturated anyway and do not require a concentration of solute above the normal capacity of the solvent at room temperature. Pharmacists are reluctant to use heat to
facilitate solution, and when they do, they are careful not to exceed the minimally required temperature, for many medicinal agents are destroyed at elevated temperatures and the advantage of rapid solution may be completely offset by drug deterioration. If volatile solutes are to be dissolved or if the solvent is volatile (as is alcohol), the heat would encourage the loss of these agents to the atmosphere and must therefore be avoided. Pharmacists are aware that certain chemical agents, particularly calcium salts, undergo exothermic reactions as they dissolve and give off heat. For such materials, the use of heat would actually discourage the formation of a solution. The best pharmaceutical example of this type of chemical is calcium hydroxide, which is used in the preparation of Calcium Hydroxide Topical Solution, USP. Calcium hydroxide is soluble in water to the extent of 140 mg/100 mL of solution at 25°C (about 77°F) and 170 mg/100 mL of solution at 15°C (about 59°F). Obviously, the temperature at which the solution is prepared or stored can affect the concentration of the resultant solution.

In addition to or instead of raising the temperature of the solvent to increase the rate of solution, a pharmacist may choose to decrease the particle size of the solute. This may be accomplished by comminution (grinding a solid to a fine state of subdivision) with a mortar and pestle on a small scale or industrial micronizer on a larger scale. The reduced particle size increases the surface area of the solute. If the powder is placed in a suitable vessel (e.g., a beaker, graduated cylinder, bottle) with a portion of the solvent and is stirred or shaken, as suited to the container, the rate of solution may be increased by the continued circulation of fresh solvent to the drug’s surface and the constant removal of newly formed solution from the drug’s surface.

Most solutions are prepared by simple mixing of the solutes with the solvent. On an industrial scale, solutions are prepared in large mixing vessels with ports for mechanical stirrers (Fig. 13.1). When heat is desired, thermostatically controlled mixing tanks may be used.

### Table 13.4 COMMON METHODS OF EXPRESSING THE STRENGTHS OF PHARMACEUTICAL PREPARATIONS

<table>
<thead>
<tr>
<th>EXPRESSION</th>
<th>ABBREVIATED EXPRESSION</th>
<th>MEANING AND EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent weight in volume</td>
<td>% w/v</td>
<td>Grams of constituent in 100 mL of preparation (e.g., 1% w/v = 1 g constituent in 100 mL preparation)</td>
</tr>
<tr>
<td>Percent volume in volume</td>
<td>% v/v</td>
<td>Milliliters of constituent in 100 mL of preparation (e.g., 1% v/v = 1 mL constituent in 100 mL preparation)</td>
</tr>
<tr>
<td>Percent weight in weight</td>
<td>% w/w</td>
<td>Grams of constituent in 100 g of preparation (e.g., 1% w/w = 1 g constituent in 100 g preparation)</td>
</tr>
<tr>
<td>Ratio of strength to weight in volume</td>
<td>:=— w/v</td>
<td>Grams of constituent in stated milliliters of preparation (e.g., 1:1,000 w/v = 1 g constituent in 1,000 mL preparation)</td>
</tr>
<tr>
<td>Ratio of strength to volume in volume</td>
<td>:=— v/v</td>
<td>Milliliters of constituent in milliliters of preparation (e.g., 1:1,000 v/v = 1 mL constituent in 1,000 mL preparation)</td>
</tr>
<tr>
<td>Ratio of strength to weight in weight</td>
<td>:=— w/w</td>
<td>Grams of constituent in stated number of grams of preparation (e.g., 1:1,000 w/w = 1 g constituent in 1,000 g preparation)</td>
</tr>
</tbody>
</table>

**FIGURE 13.1** Large-scale pharmaceutical mixing vessels. (Courtesy of Schering Laboratories.)
ORAL SOLUTIONS AND PREPARATIONS FOR ORAL SOLUTION

Most solutions intended for oral administration contain flavorants and colorants to make the medication more attractive and palatable. When needed, they may also contain stabilizers to maintain the chemical and physical stability of the medicinal agents and preservatives to prevent the growth of microorganisms in the solution. The formulation pharmacist must be wary of chemical interactions between the various components of a solution that may alter the preparation’s stability and/or potency. For instance, esters of \( \beta \)-hydroxybenzoic acid (methyl-, ethyl-, propyl-, and butylparabens), frequently used preservatives in oral preparations, have a tendency to partition into certain flavoring oils. This partitioning effect could reduce the effective concentration of the preservatives in the aqueous medium of a pharmaceutical product below the level needed for preservative action.

Liquid pharmaceuticals for oral administration are usually formulated such that the patient receives the usual dose of the medication in a conveniently administered volume, as 5 (one teaspoonful), 10, or 15 mL (one tablespoonful). A few solutions have unusually large doses, for example, Magnesium Citrate Oral Solution, USP, with a usual adult dose of 200 mL. On the other hand, many solutions for children are given by drop with a calibrated dropper usually furnished by the manufacturer in the product package.

Dry Mixtures for Solution

A number of medicinal agents, particularly certain antibiotics, for example, penicillin V, have insufficient stability in aqueous solution to meet extended shelf-life periods. Thus, commercial manufacturers of these products provide them to the pharmacist in dry powder or granule form for reconstitution with a prescribed amount of purified water immediately before dispensing to the patient. The dry powder mixture contains all of the formulative components, including drug, flavorant, colorant, buffers, and others, except for the solvent. Once reconstituted by the pharmacist, the solution remains stable when stored in the refrigerator for the labeled period, usually 7 to 14 days, depending on the preparation. This is a sufficient period for the patient to complete the regimen usually prescribed. However, in case the medication remains after the patient completes the course of therapy, the patient should be instructed to discard the remaining portion, which would be unfit for use at a later time.

Examples of dry powder mixtures intended for reconstitution to oral solutions are the following:

- Cloxacillin Sodium for Oral Solution, USP (Teva), an anti-infective antibiotic
- Penicillin V Potassium for Oral Solution, USP (Veetids, Geneva), an anti-infective antibiotic
- Potassium Chloride for Oral Solution, USP (K-LOR, Abbott), a potassium supplement

Oral Solutions

The pharmacist may be called on to dispense a commercially prepared oral solution; dilute the concentration of a solution, as in the preparation of a pediatric form of an adult product; prepare a solution by reconstituting a dry powder mixture; or extemporaneously compound an oral solution from bulk ingredients.

In each instance, the pharmacist should be sufficiently knowledgeable about the dispensed product to expertly advise the patient of the proper use, dosage, method of administration, and storage of the product. Knowledge of the solubility and stability characteristics of the medicinal agents and the solvents employed in the commercial products is useful to the pharmacist for informing the patient of the advisability of mixing the solution with juice, milk, or other beverage upon administration. Information regarding the solvents used in each commercial product appears on the product label and in the accompanying package insert. Table 13.5 presents examples of some oral solutions. Some solutions of special
### Table 13.5 EXAMPLES OF ORAL SOLUTIONS BY CATEGORY

<table>
<thead>
<tr>
<th>ORAL SOLUTION</th>
<th>REPRESENTATIVE COMMERCIAL PRODUCTS</th>
<th>CONCENTRATION OF COMMERCIAL PRODUCT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram oxalate</td>
<td>Lexapro (Forest)</td>
<td>1 mg/mL</td>
<td>For major depressive disorder</td>
</tr>
<tr>
<td>Fluoxetine HCl</td>
<td>Prozac Liquid (Distal)</td>
<td>20 mg fluoxetine/5 mL</td>
<td>For depression, obsessive–compulsive disorder</td>
</tr>
<tr>
<td>Nortriptyline HCl</td>
<td>Pamelor Oral Solution (Mallinckrodt)</td>
<td>10 mg nortriptyline/5 mL</td>
<td>Tricyclic antidepressant</td>
</tr>
<tr>
<td><strong>Antinauseant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ondansetron HCl</td>
<td>Zofran Oral Solution (GlaxoSmithKline)</td>
<td>4 mg/5 mL</td>
<td>For prevention of nausea and vomiting due to cancer-related therapies</td>
</tr>
<tr>
<td><strong>Antiperistaltic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenoxylate HCl, atropine Sulfate</td>
<td>Lomotil Liquid (Pfizer)</td>
<td>2.5 mg diphenoxylate HCl, 0.025 mg atropine sulfate/5 mL</td>
<td>For diarrhea. Diphenoxylate is related structurally and pharmacologically to the opioid meperidine. Atropine sulfate in subtherapeutic amounts discourages (by virtue of side effects) deliberate overdosage.</td>
</tr>
<tr>
<td>Loperamide HCl</td>
<td>Imodium A-D Liquid (Ortho-McNeil)</td>
<td>1 mg loperamide HCl/5 mL</td>
<td>For diarrhea in adults and children aged 6 years and older. Structurally related to haloperidol</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haloperidol Oral Solution</td>
<td>2 mg haloperidol/mL</td>
<td>Primarily for severe neuropsychiatric conditions when oral medication is preferred and tablets and capsules are impractical. Concentrated solutions used by adding desired amount of concentrate by calibrated dropper to soup or a beverage</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Perphenazine Oral Solution</td>
<td>16 mg perphenazine/5 mL</td>
<td></td>
</tr>
<tr>
<td>Thiothixene HCl</td>
<td>Navane concentrate (Roerig)</td>
<td>Equivalent of 5 mg thiothixene/mL</td>
<td></td>
</tr>
<tr>
<td><strong>Antiretroviral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Emtriva (Gilead)</td>
<td>10 mg/mL</td>
<td>Indicated, in combination with other antiretrovirals, for the treatment of HIV-1 infections</td>
</tr>
<tr>
<td><strong>Bronchodilator</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>Theophylline Oral Solution (Roxane)</td>
<td>80 mg theophylline/15 mL</td>
<td>Alcohol-free solution for the treatment of bronchial asthma and reversible bronchospasm associated with chronic bronchitis and emphysema</td>
</tr>
<tr>
<td><strong>Cathartics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium Citrate, USP</td>
<td></td>
<td></td>
<td>Discussed in text</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>ORAL SOLUTION</th>
<th>REPRESENTATIVE COMMERCIAL PRODUCTS</th>
<th>CONCENTRATION OF COMMERCIAL PRODUCT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium phosphate</td>
<td>Phospho-Soda (Fleet)</td>
<td>2.4 g monobasic sodium phosphate, 0.9 g dibasic sodium phosphate/5 mL</td>
<td>Works as a laxative within 1 hour taken before meals or overnight taken at bedtime. Usual dose is 10–20 mL, best diluted in half glass of water and followed with full glass of water.</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone sodium phosphate</td>
<td>Pediapred Oral Solution (USB)</td>
<td>5 mg prednisolone (as sodium phosphate)/5 mL</td>
<td>Synthetic adrenocortical steroid with mainly glucocorticoid properties indicated for endocrine, rheumatic, collagen, allergic, and other disorders</td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memantine HCl</td>
<td>Namenda Oral Solution (Forest)</td>
<td>2 mg/mL</td>
<td>Treatment of moderate to severe dementia of the Alzheimer type</td>
</tr>
<tr>
<td>Dental Caries Protectant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium fluoride</td>
<td>Pediaflor Drops (Ross)</td>
<td>0.5 mg/mL</td>
<td>Prophylaxis of dental caries; for use when community water supply is inadequately fluoridated</td>
</tr>
<tr>
<td>Electrolyte Replenisher</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>Kaochlor 10% Liquid (Pharmacia)</td>
<td>20 mEq KCl/15 mL in flavored aqueous vehicle</td>
<td>For hypopotassemia (low blood level of potassium). Condition may be prompted by severe or chronic diarrhea, low dietary intake of potassium, increased renal excretion of potassium, or other causes. Solution is diluted with water or fruit juice.</td>
</tr>
<tr>
<td>Fecal Softener</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docusate sodium</td>
<td>Colace Syrup (Purdue)</td>
<td>10 mg docusate sodium/mL</td>
<td>Usually 50–200 mg measured by calibrated dropper, mixed with milk, fruit juice, or other liquid to mask the taste. Softens fecal mass by lowering the surface tension, permitting normal bowel habits, particularly in geriatric, pediatric, cardiac, obstetric, and surgical patients. Taken for several days or until the bowel movements are normal</td>
</tr>
<tr>
<td>Hematinic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>Fer-In-Sol Drops (Mead Johnson Nutritional)</td>
<td>15 mg/0.6 mL</td>
<td>For prevention and treatment of iron deficiency anemias. Usual prophylactic dose 0.3 or 0.6 mL, measured by calibrated dropper, mixed with water or juice. Dosage form intended primarily for infants and children</td>
</tr>
<tr>
<td>Histamine H2 Antagonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cimetidine HCl</td>
<td>Tagamet HCl Liquid (GlaxoSmithKline Consumer)</td>
<td>300 mg/5 mL</td>
<td>For peptic ulcer disease, pathologic hypersecretory conditions, for example, Zollinger-Ellison syndrome</td>
</tr>
<tr>
<td>Immunosuppressant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Sandimmune Oral Solution (Novartis)</td>
<td>100 mg/mL</td>
<td>For prophylaxis of organ rejection</td>
</tr>
</tbody>
</table>
pharmaceutical interest are described later in this chapter.

Oral Rehydration Solutions

Rapid fluid loss associated with diarrhea can lead to dehydration and ultimately death in some patients, particularly infants. More than 5 million children younger than 4 years of age die of diarrhea each year worldwide (4). Diarrhea is characterized by an increased frequency of loose, watery stools, and because of the rapid fluid loss, dehydration can be an outcome. During diarrhea, the small intestine secretes far more than the normal amount of fluid and electrolytes, and this simply exceeds the ability of the large intestine to reabsorb it. This fluid loss, which occurs mostly from the body’s extracellular fluid compartment, can lead to a progressive loss of blood volume culminating in hypovolemic shock.

Diarrhea is a normal physiologic body response to rid itself of a noxious or toxic substance, such as rotavirus or Escherichia coli. Thus, the treatment approach is to allow the diarrhea to proceed and not to terminate it too quickly but promptly replace the lost fluid and electrolytes to prevent dehydration. The loss of fluid during diarrhea is accompanied by depletion of sodium, potassium, and bicarbonate ions; if severe, the loss can result in acidosis, hyperpnea, and vomiting as well as hypovolemic shock. If continuous, bouts of vomiting and diarrhea can cause malnutrition as well. Consequently, the goal is to replace lost fecal water with an oral rehydration solution and use nutritional foods, such as soybean formula and bran.

Oral rehydration solutions are usually effective in treatment of patients with mild volume depletion, 5% to 10% of body weight. These are available OTC and are relatively inexpensive, and their use has diminished the incidence of complications associated with parenterally administered electrolyte solutions. Therapy with these solutions is based on the observation that glucose is actively absorbed from the small intestine, even during bouts of diarrhea. This active transport of glucose is advantageous because it is coupled with sodium absorption. Almost in domino fashion, sodium absorption promotes anion absorption, which in turn promotes water absorption to short-circuit dehydration. To produce maximal absorption of sodium and water, studies have demonstrated that the optimal concentrations of glucose and sodium in an isotonic solution are 110 mM (2%) glucose and 60 mEq/L of sodium ion, respectively. Bicarbonate and/or citrate ions are also included in these solutions to help correct the metabolic acidosis caused by diarrhea and dehydration.

A liter of typical oral rehydration solution contains 45 mEq Na⁺, 20 mEq K⁺, 35 mEq Cl⁻, 30 mEq citrate, and 25 g dextrose. These formulations are available in liquid or powder packet form for reconstitution. It is important that the user add the specific amount of water needed to prepare the powder forms. Furthermore, these products should not be mixed with or given with other electrolyte-containing liquids, such as milk or fruit juices.

<table>
<thead>
<tr>
<th>ORAL SOLUTION</th>
<th>REPRESENTATIVE COMMERCIAL PRODUCTS</th>
<th>CONCENTRATION OF COMMERCIAL PRODUCT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid Agonist Analgesic Methadone HCl</td>
<td>Methadone HCl (Roxane)</td>
<td>1 or 2 mg/mL</td>
<td>For relief of severe pain; detoxification, maintenance treatment of opioid addiction</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Ergocalciferol</td>
<td>Calciferol Drops (Schwartz)</td>
<td>8,000 U/mL</td>
</tr>
</tbody>
</table>
Otherwise, there is no method to calculate how much electrolyte the patient actually received. Commercial ready-to-use oral electrolyte solutions to prevent dehydration or achieve rehydration include Pedialyte Solution (Ross) and Rehydralyte Solution (Ross). These products also contain dextrose or glucose. Infalyte Oral Solution (Bristol-Myers Squibb) contains electrolytes in a syrup of rice solids. The rice-based formula produces a lower osmotic effect than the dextrose- or glucose-based formulas and is thought to be more effective in reducing stool output and shortening the duration of diarrhea. The success of the commercial solutions is based on the physiologic design of the formulation.

**Oral Colonic Lavage Solution**

Traditionally, preparation of the bowel for procedures such as a colonoscopy consisted of administration of a clear liquid diet for 24 to 48 hours preceding the procedure, administration of an oral laxative such as magnesium citrate or bisacodyl the night before, and a cleansing enema administered 2 to 4 hours prior to the procedure. Typically, to circumvent hospitalization of the patient the night before the procedure, patients were allowed to perform this regimen at home. However, while the results have been satisfactory, that is, the bowel is cleared for the procedure, poor compliance with and acceptance of this regimen can cause problems during the procedure. Furthermore, additive effects of malnutrition and poor oral intake prior to the procedure can cause more patient problems.

Consequently, an alternative method to prepare the gastrointestinal tract has been devised. This procedure requires less time and dietary restriction and obviates the cleansing enemas. This method entails oral administration of a balanced solution of electrolytes with polyethylene glycol (PEG-3350-Electrolyte Solution), that is, Colyte (Alaven Pharmaceuticals). Before dispensing it to the patient, the pharmacist reconstitutes this powder with water, creating an iso-osmotic solution having a mildly salty taste. The PEG acts as an osmotic agent in the gastrointestinal tract, and the balanced electrolyte concentration results in virtually no net absorption or secretion of ions. Thus, a large volume of this solution can be administered without a significant change in water or electrolyte balance.

The formulation of this oral colonic lavage solution is as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-3350</td>
<td>240.00 g</td>
</tr>
<tr>
<td>Sodium sulfate</td>
<td>22.72 g</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>6.72 g</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>5.84 g</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>2.98 g</td>
</tr>
</tbody>
</table>

In 4,000 mL disposable container

The recommended adult dose of this product is 4 L of solution before the gastrointestinal procedure. The patient is instructed to drink 240 mL of solution every 10 minutes until about 4 L is consumed. The patient is advised to drink each portion quickly rather than sipping it continuously. Usually, the first bowel movement will occur within 1 hour. Several regimens are used, and one method is to schedule patients for a midmorning procedure, allowing the patient 3 hours for drinking and a 1-hour waiting period to complete bowel evacuation.

To date, this approach to bowel evacuation has been associated with a low incidence of side effects (primarily nausea, transient abdominal fullness, bloating, and occasionally cramps and vomiting). Ideally, the patient should not have taken any food 3 to 4 hours before beginning to take the solution. In no case should solid foods be taken by the patient for at least 2 hours before the solution is administered. No foods except clear liquids are permitted after this product is administered and prior to the examination. The product must be stored in the refrigerator after reconstitution, and this aids somewhat in decreasing the salty taste of the product.

PEG-ES solutions are employed for unlaabeled use in the management of acute iron overdose in children.

**Magnesium Citrate Oral Solution**

Magnesium citrate oral solution is a colorless to slightly yellow clear effervescent liquid having a sweet, acidulous taste and a lemon
flavor. It is commonly referred to as citrate or as citrate of magnesia. It is required to contain an amount of magnesium citrate equivalent to 1.55 to 1.9 g of magnesium oxide in each 100 mL.

The solution is prepared by reacting official magnesium carbonate with an excess of citric acid (Equation 13.1), flavoring and sweetening the solution with lemon oil and syrup, filtering with talc, and then carbonating it by the addition of either potassium or sodium bicarbonate (Equation 13.2). The solution may be further carbonated by the use of carbon dioxide under pressure:

\[
\text{(MgCO}_3\text{)}_4 \text{Mg(OH)}_2 + 5\text{H}_2\text{C}_6\text{H}_4\text{O}_7 \rightarrow 5\text{MgHC}_6\text{H}_5\text{O}_7 + 4\text{CO}_2 + 6\text{H}_2\text{O}
\]

(Equation 13.1)

\[
3\text{KHCO}_3 + \text{H}_2\text{C}_6\text{H}_4\text{O}_7 \rightarrow \text{K}_3\text{C}_6\text{H}_6\text{O}_7 + 3\text{CO}_2 + 3\text{H}_2\text{O}
\]

(Equation 13.2)

The solution provides an excellent medium for the growth of molds, and any mold spores present during the manufacture of the solution must be killed if the preparation is to remain stable. For this reason, during the preparation of the solution, the liquid is heated to boiling (prior to carbonation); boiled water is employed to bring the solution to its proper volume; and boiling water is used to rinse the final container. The final solution may be sterilized.

The solution is employed as a saline cathartic, with the citric acid, lemon oil, syrup, carbonation, and the low temperature of the refrigerated solution all contributing to the patient’s acceptance of the large volume of medication. For many patients, it is a pleasant way of taking an otherwise bitter saline cathartic.

### Sodium Citrate and Citric Acid Oral Solution

This official solution contains sodium citrate 100 mg and citric acid 67 mg in each milliliter of aqueous solution. The solution is administered orally in doses of 10 to 30 mL as frequently as four times daily as a systemic alkalinizer. Systemic alkalinization is useful for patients for whom long-term maintenance of an alkaline urine is desirable, such as those with uric acid and cystine calculi of the urinary tract. The solution is also a useful adjuvant when administered with uricosuric agents in gout therapy because urates tend to crystallize out of an acid urine.

### SYRUPS

Syrups are concentrated aqueous preparations of a sugar or sugar substitute with or without flavoring agents and medicinal substances. Syrups containing flavoring agents but not medicinal substances are called nonmedicated or flavored vehicles (syrups). Some official, previously official, and commercially available nonmedicated syrups are presented in Table 13.6. These syrups are intended to serve as pleasant-tasting vehicles for medicinal substances to be added in the extemporaneous compounding of prescriptions or in the preparation of a standard formula for a medicated syrup, which is a syrup containing a therapeutic agent. Due to the inability of some children and elderly people to swallow solid dosage forms, it is fairly common today for a pharmacist to be asked to prepare an oral liquid dosage form of a medication available in the pharmacy only as tablets or capsules. In these instances, drug solubility, stability, and bioavailability must be considered case by case (5,6). The liquid dosage form selected for compounding may be a solution or a suspension, depending on the chemical and physical characteristics of the particular drug and its solid dosage form. Vehicles are commercially available for this purpose (6).

Medicated syrups are commercially prepared from the starting materials, that is, by combining each of the individual components of the syrup, such as sucrose, purified water, flavoring agents, coloring agents, the therapeutic agent, and other necessary and desirable ingredients. Naturally, medicated syrups are employed in therapeutics for the value of the medicinal agent present in the syrup.

Syrups provide a pleasant means of administering a liquid form of a disagreeable-tasting drug. They are particularly effective in the
Syrup administration of drugs to youngsters, since their pleasant taste usually dissipates any reluctance on the part of the child to take the medicine. The fact that syrups contain little or no alcohol adds to their favor among parents.

Any water-soluble drug that is stable in aqueous solution may be added to a flavored syrup. However, care must be exercised to ensure compatibility between the drug substance and the other formulative components of the syrup. Also, certain flavored syrups have an acidic medium, whereas others may be neutral or slightly basic, and the proper selection must be made to ensure the stability of any added medicinal agent. Perhaps the most frequently found types of medications administered as medicated syrups are antitussive agents and antihistamines. This is not to imply that other types of drugs are not formulated into syrups; a variety of medicinal substances can be found in syrup form and among the many commercial products. Examples of medicated syrups are presented in Table 13.7.

**Components of Syrups**

Most syrups contain the following components in addition to the purified water and any medicinal agents present: (a) the sugar,
**Table 13.7 EXAMPLES OF MEDICATED SYRUPS BY CATEGORY**

<table>
<thead>
<tr>
<th>SYRUP</th>
<th>REPRESENTATIVE COMMERCIAL PRODUCTS</th>
<th>CONCENTRATION OF COMMERCIAL PRODUCT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analgesic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meperidine HCl</td>
<td>Demerol Syrup (Sanofi-Synthelabo)</td>
<td>50 mg/5 mL</td>
<td>Opioid analgesic for the relief of moderate to severe pain, adjunct to general anesthesia</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dicyclomine HCl</td>
<td>Bentyl (Axcan Scandipharm)</td>
<td>10 mg/5 mL</td>
<td>Adjunctive therapy in the treatment of peptic ulcer</td>
</tr>
<tr>
<td>Oxybutynin chloride</td>
<td>Various</td>
<td>5 mg/5 mL</td>
<td>Relief of symptoms with voiding in patients with uninhibited neurogenic and reflex neurogenic bladder</td>
</tr>
<tr>
<td><strong>Antiemetics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine HCl</td>
<td>Thorazine Syrup (GlaxoSmithKline)</td>
<td>10 mg HCl/5 mL</td>
<td>Control of nausea and vomiting</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>Children’s Dramamine Liquid (Pharmacia)</td>
<td>12.5 mg/5 mL</td>
<td>Control of nausea, vomiting, motion sickness</td>
</tr>
<tr>
<td>Promethazine HCl</td>
<td>Various</td>
<td>5 mg/5 mL</td>
<td>Control of nausea and vomiting</td>
</tr>
<tr>
<td><strong>Anticonvulsant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>Depakene Syrup (Abbott)</td>
<td>250 mg as sodium salt/5 mL</td>
<td>Sole or adjunctive therapy in simple (petit mal), complex absence seizure disorders</td>
</tr>
<tr>
<td><strong>Antihistamines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpheniramine maleate</td>
<td>Chlor-Trimeton Allergy Syrup (Schering-Plough)</td>
<td>2 mg/5 mL</td>
<td>For prevention, treatment of allergic reactions</td>
</tr>
<tr>
<td>Desloratadine</td>
<td>Clarinex Syrup (Schering)</td>
<td>0.5 mg/1 mL</td>
<td>For relief of nasal and nonnasal symptoms of allergic rhinitis and urticaria</td>
</tr>
<tr>
<td>Hydroxyzine HCl</td>
<td>Atarax Syrup (Roerig)</td>
<td>10 mg/5 mL</td>
<td></td>
</tr>
<tr>
<td><strong>Antipsychotic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram hydrobromide</td>
<td>Celexa (Forest)</td>
<td>10 mg/5 mL</td>
<td>For depression</td>
</tr>
<tr>
<td>Lithium citrate</td>
<td>Various</td>
<td>8 mEq/5 mL</td>
<td>Management of psychotic disorders</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal (Janssen)</td>
<td>1 mg/mL</td>
<td>For treatment of schizophrenia</td>
</tr>
<tr>
<td><strong>Antitussives</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>Benylin Adult Cough Formula (Warner-Lambert)</td>
<td>15 mg/5 mL</td>
<td>For relief of cough</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Benadryl Allergy Liquid Medication (McNeil)</td>
<td>12.5 mg/5 mL</td>
<td>For control of coughs due to colds or allergy</td>
</tr>
<tr>
<td><strong>Antiviral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amantadine HCl</td>
<td>Symmetrel Syrup (Endo)</td>
<td>50 mg/5 mL</td>
<td>Prevention of respiratory infections caused by A2 (Asian) viral strains. Treatment of idiopathic Parkinson disease</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>SYRUP</th>
<th>REPRESENTATIVE COMMERCIAL PRODUCTS</th>
<th>CONCENTRATION OF COMMERCIAL PRODUCT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>Epivir Oral Solution (GlaxoSmithKline)</td>
<td>10 mg/mL</td>
<td>Treatment of HIV</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Norvir (Abbott)</td>
<td>80 mg/mL</td>
<td>Treatment of HIV</td>
</tr>
<tr>
<td><strong>Bronchodilators</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol sulfate</td>
<td>Proventil Syrup (Schering)</td>
<td>2 mg/5 mL</td>
<td>Relief of bronchospasm of obstructive airway disease; prevention of exercise-induced bronchospasm</td>
</tr>
<tr>
<td>Metaproterenol sulfate</td>
<td>Alupent Syrup (Boehringer Ingelheim)</td>
<td>10 mg/5 mL</td>
<td></td>
</tr>
<tr>
<td><strong>Cathartic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactulose</td>
<td>Chronulac Syrup (Hoechst)</td>
<td>10 g/15 mL</td>
<td>15–30 mL qd as laxative</td>
</tr>
<tr>
<td><strong>Cholinergic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyridostigmine bromide</td>
<td>Mestinon Syrup (ICN Pharmaceuticals)</td>
<td>60 mg/5 mL</td>
<td>Treatment of myasthenia gravis</td>
</tr>
<tr>
<td><strong>Decongestant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudoephedrine hydrochloride</td>
<td>Sudafed Children’s Nondrowsy (Pfizer Consumer)</td>
<td>15 mg/5 mL</td>
<td>Temporary relief of nasal congestion of common cold, hay fever, upper respiratory allergies, sinusitis</td>
</tr>
<tr>
<td><strong>Emetic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipecac</td>
<td>Various</td>
<td>21 mg ether-soluble alkaloids of ipecac/15 mL</td>
<td>To induce vomiting in poisoning. Dose of 15 mL may be repeated in 20 min if vomiting does not occur. If after the second dose vomiting does not occur, the stomach should be emptied by gastric lavage.</td>
</tr>
<tr>
<td><strong>Expectorant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guaifenesin</td>
<td>Guaifenesin Syrup (Roxane)</td>
<td>100 mg/5 mL</td>
<td>For symptomatic relief of respiratory conditions associated with cough and bronchial congestion</td>
</tr>
<tr>
<td><strong>Fecal softener</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docusate sodium</td>
<td>Colace Syrup (Purdue)</td>
<td>20 mg/5 mL</td>
<td>Stool softener by surface action</td>
</tr>
<tr>
<td><strong>Gastrointestinal stimulant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Various</td>
<td>5 mg/5 mL</td>
<td>Relief of symptoms of diabetic gastroparesis (gastric stasis) and gastroesophageal reflux</td>
</tr>
<tr>
<td>H2 receptor antagonist</td>
<td>Zantac Syrup (GlaxoSmithKline)</td>
<td>15 mg/mL</td>
<td>Treatment of duodenal ulcers and GERD</td>
</tr>
<tr>
<td><strong>Hemostatic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminocaproic acid</td>
<td>Amicar Syrup (Xanodyne)</td>
<td>1.25 g/5 mL</td>
<td>Treatment of excessive bleeding from systemic hyperfibrinolysis, urinary fibrinolysis</td>
</tr>
<tr>
<td><strong>Hypnotic Sedative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>Chloral Hydrate Syrup (Pharmaceutical Associates)</td>
<td>250 mg/5 mL</td>
<td>Sedative at 250 mg; hypnotic to induce sleep at 500 mg. Alcoholic beverages should be avoided. Usually diluted with water or some other beverage</td>
</tr>
</tbody>
</table>

*A usual single dose unless otherwise stated.*
usually sucrose, or sugar substitute used to provide sweetness and viscosity; (b) antimicrobial preservatives; (c) flavorants; and (d) colorants. Also, many types of syrups, especially those prepared commercially, contain special solvents (including alcohol), solubilizing agents, thickeners, or stabilizers.

Sucrose- and Nonsucrose-Based Syrups

Sucrose is the sugar most frequently employed in syrups, although in special circumstances, it may be replaced in whole or in part by other sugars or substances such as sorbitol, glycerin, and propylene glycol. In some instances, all glycogenetic substances (materials converted to glucose in the body), including the agents mentioned earlier, are replaced by nonglycogenetic substances, such as methylcellulose or hydroxyethylcellulose. These two materials are not hydrolyzed and absorbed into the blood stream, and their use results in an excellent syrup-like vehicle for medications intended for use by diabetic patients and others whose diet must be controlled and restricted to nonglycogenetic substances. The viscosity resulting from the use of these cellulose derivatives is much like that of a sucrose syrup. The addition of one or more artificial sweeteners usually produces an excellent facsimile of a true syrup.

The characteristic body that the sucrose and alternative agents seek to impart to the syrup is essentially the result of attaining the proper viscosity. This quality, together with the sweetness and flavorants, results in a type of pharmaceutical preparation that masks the taste of added medicinal agents. When the syrup is swallowed, only a portion of the dissolved drug actually makes contact with the taste buds, the remainder of the drug being carried past them and down the throat in the viscous syrup. This type of physical concealment of the taste is not possible for a solution of a drug in an unthickened, mobile aqueous preparation. In the case of antitussive syrups, the thick, sweet syrup has a soothing effect on the irritated tissues of the throat as it passes over them.

Most syrups contain a high proportion of sucrose, usually 60% to 80%, not only because of the desirable sweetness and viscosity of such solutions but also because of their inherent stability in contrast to the unstable character of dilute sucrose solutions. The aqueous sugar medium of dilute sucrose solutions is an efficient nutrient medium for the growth of microorganisms, particularly yeasts and molds. On the other hand, concentrated sugar solutions are quite resistant to microbial growth because of the unavailability of the water required for the growth of microorganisms. This aspect of syrups is best demonstrated by the simplest of all syrups, Syrup, NF, also called simple syrup. It is prepared by dissolving 85 g of sucrose in enough purified water to make 100 mL of syrup. The resulting preparation generally requires no additional preservation if it is to be used soon; in the official syrup, preservatives are added if the syrup is to be stored. When properly prepared and maintained, the syrup is inherently stable and resistant to the growth of microorganisms. An examination of this syrup reveals its concentrated nature and the relative absence of water for microbial growth. Syrup has a specific gravity of about 1.313, which means that each 100 mL of syrup weighs 131.3 g. Because 85 g of sucrose is present, the difference between 85 and 131.3 g, or 46.3 g, represents the weight of the purified water. Thus, 46.3 g, or mL, of purified water is used to dissolve 85 g of sucrose. The solubility of sucrose in water is 1 g in 0.5 mL of water; therefore, to dissolve 85 g of sucrose, about 42.5 mL of water would be required. Thus, only a very slight excess of water (about 3.8 mL per 100 mL of syrup) is employed in the preparation of syrup. Although not enough to be particularly amenable to the growth of microorganisms, the slight excess of water permits the syrup to remain physically stable in varying temperatures. If the syrup were completely saturated with sucrose, in cool storage, some sucrose might crystallize from solution and, by acting as nuclei, initiate a type of chain reaction that would result in separation of an amount of sucrose disproportionate to its solubility at the storage temperature. The syrup would then be very much unsaturated and probably suitable for microbial growth. As formulated, the official
syrup is stable and resistant to crystallization and microbial growth. However, many of the other official syrups and a host of commercial syrups are not intended to be as nearly saturated as Syrup, NF, and therefore must employ added preservative agents to prevent microbial growth and to ensure their stability during their period of use and storage.

As noted earlier, sucrose-based syrup may be substituted in whole or in part by other agents in the preparation of medicated syrups. A solution of a polyol, such as sorbitol, or a mixture of polyols, such as sorbitol and glycerin, is commonly used. Sorbitol Solution, USP, which contains 64% by weight of the polyhydric alcohol sorbitol, is employed as shown in the following example formulations for medicated syrups (7):

### Antihistamine Syrup
- Chlorpheniramine maleate: 0.4 g
- Glycerin: 25.0 mL
- Syrup: 83.0 mL
- Sorbitol solution: 282.0 mL
- Alcohol: 60.0 mL
- Color and flavor: qs
- Purified water, to make: 1,000.0 mL

### Ferrous Sulfate Syrup
- Ferrous sulfate: 135.0 g
- Citric acid: 12.0 g
- Sorbitol solution: 350.0 mL
- Glycerin: 50.0 mL
- Sodium benzoate: 1.0 g
- Flavor: qs
- Purified water, to make: 1,000.0 mL

### Acetaminophen Syrup
- Acetaminophen: 24.0 g
- Benzoic acid: 1.0 g
- Disodium calcium EDTA: 1.0 g
- Propylene glycol: 150.0 mL
- Alcohol: 150.0 mL
- Saccharin sodium: 1.8 g
- Purified water: 200.0 mL
- Flavor: qs
- Sorbitol solution, to make: 1,000.0 mL

### Cough and Cold Syrup
- Dextromethorphan hydrobromide: 2.0 g
- Guaifenesin: 10.0 g
- Chlorpheniramine maleate: 0.2 g
- Phenylephrine hydrochloride: 1.0 g
- Sodium benzoate: 1.0 g
- Saccharin sodium: 1.9 g
- Citric acid: 1.0 g
- Sodium chloride: 5.2 g
- Alcohol: 50.0 mL
- Sorbitol solution: 324.0 mL
- Syrup: 132.0 mL
- Liquid glucose: 44.0 mL
- Glycerin: 50.0 mL
- Color: qs
- Flavor: qs
- Purified water, to make: 1,000.0 mL

All materials used in the extemporaneous compounding and manufacturing of pharmaceuticals should be of USP–NF quality and obtained from FDA-approved sources.

### Antimicrobial Preservative
The amount of a preservative required to protect a syrup against microbial growth varies with the proportion of water available for growth, the nature and inherent preservative activity of some formulative materials (e.g., many flavoring oils that are inherently sterile and possess antimicrobial activity), and the capability of the preservative itself. Among the preservatives commonly used in syrups with the usually effective concentrations are benzoic acid 0.1% to 0.2%, sodium benzoate 0.1% to 0.2%, and various combinations of methylparabens, propylparabens, and butylparabens totaling about 0.1%. Frequently, alcohol is used in syrups to assist in dissolving the alcohol-soluble ingredients, but normally, it is not present in the final product in amounts that would be considered to be adequate for preservation (15% to 20%). See Physical Pharmacy Capsule 13.1, Preservation of Syrups.
Preservation of Syrups

Syrups can be preserved by (a) storage at low temperature; (b) adding preservatives such as glycerin, benzoic acid, sodium benzoate, methylparaben, or alcohol in the formulation; or (c) the maintenance of a high concentration of sucrose as a part of the formulation. High sucrose concentrations will usually protect an oral liquid dosage form from growth of most microorganisms. A problem arises, however, when pharmacists must add other ingredients to syrups that can result in a decrease in the sucrose concentration. This may cause a loss of the preservative effectiveness of the sucrose. This can be overcome, however, by calculating the quantity of a preservative (such as alcohol) to add to the formula to maintain the preservative effectiveness of the final product.

**EXAMPLE**

- Rx active drug 5 mL volume occupied
- Other drug solids 3 mL volume occupied
- Glycerin 15 mL
- Sucrose 25 g
- Ethanol 95% q.s.
- Purified water q.s. 100 mL

How much alcohol would be required to preserve this prescription? We will use the free-water method to calculate the quantity of alcohol required.

Simple syrup contains 85 g sucrose per 100 mL of solution, which weighs 131.3 g (specific gravity, 1.313). It takes 46.3 mL of water to prepare the solution (131.3 − 85 = 46.3), and the sucrose occupies a volume of (100 − 46.3 = 53.7) 53.7 mL.

1. Because this solution is preserved, 85 g of sucrose preserves 46.3 mL of water, and 1 g of sucrose preserves 0.54 mL of water. With 25 g of sucrose present, the amount of water preserved is
   \[25 \times 0.54 = 13.5 \text{ mL}\]

2. Because 85 g of sucrose occupies a volume of 53.7 mL, 1 g of sucrose will occupy a volume of 0.63 mL. The volume occupied by the sucrose in this prescription is
   \[25 \times 0.63 = 15.75 \text{ mL}\]

3. The active drug and other solids occupy 8 mL (5 + 3) volume.
4. Each mL of glycerin can preserve an equivalent quantity of volume (2 × 15 = 30), so 30 mL would be preserved.
5. The volume taken care of so far is 13.5 + 15.75 + 8 + 30 = 67.25 mL. The quantity of free water remaining is
   \[100 − 67.25 = 32.75 \text{ mL}\]

6. Because it requires about 18% alcohol to preserve the water,
   \[0.18 \times 32.75 = 5.9 \text{ mL of alcohol (100\%)}\]

   would be required.
7. If 95% ethanol is used, 5.9/0.95 = 6.21 mL would be required.

To prepare the prescription, about 6.21 mL of 95% ethanol can be added with sufficient purified water to make 100 mL of the final solution.
**Flavorant**

Most syrups are flavored with synthetic flavorants or with naturally occurring materials, such as volatile oils (e.g., orange oil), vanillin, and others, to render the syrup pleasant tasting. Because syrups are aqueous preparations, these flavorants must be water soluble. However, sometimes a small amount of alcohol is added to a syrup to ensure the continued solution of a poorly water-soluble flavorant. Commercial flavoring systems (FLAVORx) may also be considered and used.

**Colorant**

To enhance the appeal of the syrup, a coloring agent that correlates with the flavorant employed (i.e., green with mint, brown with chocolate) is used. Generally, the colorant is water soluble, nonreactive with the other syrup components, and color stable at the pH range and under the intensity of light that the syrup is likely to encounter during its shelf life.

**Preparation of Syrups**

Syrups are most frequently prepared by one of four general methods, depending on the physical and chemical characteristics of the ingredients. Broadly stated, these methods are (a) solution of the ingredients with the aid of heat, (b) solution of the ingredients by agitation without the use of heat or the simple admixture of liquid components, (c) addition of sucrose to a prepared medicated liquid or to a flavored liquid, and (d) percolation of either the source of the medicating substance or the sucrose. Sometimes a syrup is prepared by more than one of these methods, and the selection may simply be a matter of preference on the part of the pharmacist. Many of the official syrups have no officially designated method of preparation.

**Solution with the Aid of Heat**

Syrups are prepared by this method when it is desired to prepare the syrup as quickly as possible and when the syrup’s components are not damaged or volatilized by heat. In this method, the sugar is generally added to the purified water, and heat is applied until the sugar is dissolved. Then, other heat-stable components are added to the hot syrup, the mixture is allowed to cool, and its volume is adjusted to the proper level by the addition of purified water. If heat-labile agents or volatile substances, such as volatile flavoring oils and alcohol, are to be added, they are generally added to the syrup after the sugar is dissolved by heat, and the solution is rapidly cooled to room temperature.

The use of heat facilitates rapid solution of the sugar and certain other components of syrups; however, caution must be exercised against becoming impatient and using excessive heat. Sucrose, a disaccharide, may be hydrolyzed into monosaccharides, dextrose (glucose), and fructose (levulose). This hydrolytic reaction is inversion, and the combination of the two monosaccharide products is invert sugar. When heat is applied in the preparation of a sucrose syrup, some inversion of the sucrose is almost certain. The speed of inversion is greatly increased by the presence of acids, the hydrogen ion acting as a catalyst to the reaction. Should inversion occur, the sweetness of the syrup is altered because invert sugar is sweeter than sucrose, and the normally colorless syrup darkens because of the effect of heat on the levulose portion of the invert sugar. When the syrup is greatly overheated, it becomes amber colored as the sucrose caramelizes. Syrups so decomposed are more susceptible to fermentation and to microbial growth than the stable, undecomposed syrups. Because of the prospect of decomposition by heat, syrups cannot be sterilized by autoclaving. The use of boiled purified water in the preparation of a syrup can enhance its permanency, and the addition of preservative agents, when permitted, can protect it during its shelf life. Storage in a tight container is a requirement for all syrups.

**Solution by Agitation Without the Aid of Heat**

To avoid heat-induced inversion of sucrose, a syrup may be prepared without heat by agitation. On a small scale, sucrose and other
Formulative agents may be dissolved in purified water by placing the ingredients in a vessel larger than the volume of syrup to be prepared, permitting thorough agitation of the mixture. This process is more time consuming than the use of heat, but the product has maximum stability. Huge glass-lined or stainless steel tanks with mechanical stirrers or agitators are employed in large-scale preparation of syrups.

Sometimes, simple syrup or some other nonmedicated syrup, rather than sucrose, is employed as the sweetening agent and vehicle. In that case, other liquids that are soluble in the syrup or miscible with it may be added and thoroughly mixed to form a uniform product. When solid agents are to be added to a syrup, it is best to dissolve them in minimal amount of purified water and incorporate the resulting solution into the syrup. When solid substances are added directly to a syrup, they dissolve slowly because the viscous nature of the syrup does not permit the solid substance to distribute readily throughout the syrup to the available solvent and also because a limited amount of available water is present in concentrated syrups.

**Addition of Sucrose to a Medicated Liquid or to a Flavored Liquid**

Occasionally, a medicated liquid, such as a tincture or fluidextract, is employed as the source of medication in the preparation of a syrup. Many such tinctures and fluidextracts contain alcohol-soluble constituents and are prepared with alcoholic or hydroalcoholic vehicles. If the alcohol-soluble components are desired medicinal agents, some means of rendering them water soluble is employed. However, if the alcohol-soluble components are undesirable or unnecessary components of the corresponding syrup, they are generally removed by mixing the tincture or fluidextract with water, allowing the mixture to stand until separation of the water-insoluble agents is complete, and filtering them from the mixture. The filtrate is the medicated liquid to which the sucrose is added in preparation of the syrup. If the tincture or fluidextract is miscible with aqueous preparations, it may be added directly to simple syrup or to a flavored syrup.

**Percolation**

In the percolation method, either sucrose may be percolated to prepare the syrup or the source of the medicinal component may be percolated to form an extractive to which sucrose or syrup may be added. This latter method really is two separate procedures: first the preparation of the extractive of the drug and then the preparation of the syrup.

An example of a syrup prepared by percolation is ipecac syrup, which is prepared by adding glycerin and syrup to an extractive of powdered ipecac obtained by percolation. The drug ipecac, which consists of the dried rhizome and roots of *Cephaëlis ipecacuanha*, contains the medicinally active alkaloids emetine, cephaline, and psychotrine. These alkaloids are extracted from the powdered ipecac by percolation with a hydroalcoholic solvent.

The syrup is categorized as an emetic with a usual dose of 15 mL. This amount of syrup is commonly used in the management of poisoning in children when evacuation of the stomach contents is desirable. About 80% of children given this dose will vomit within half an hour. For a household emetic in the event of poisoning, 1-oz bottles of the syrup are sold without a prescription. Ipecac syrup also has some application as a nauseant expectorant in doses smaller than the emetic dose.

Evidence indicates that many bulimics—most commonly young women in their late teens to early 30s—use the syrup of ipecac to bring on attacks of vomiting in an attempt to lose weight (8). Pharmacists must be aware of this misuse of the syrup of ipecac and warn these individuals because one of the active ingredients in the syrup is emetine. With continual use of the syrup, emetine builds up toxic levels within the body tissues and can do irreversible damage to the heart muscles in 3 to 4 months, resulting in symptoms mimicking a heart attack. Shortness of breath is the most common symptom in patients who misuse the syrup of ipecac, but some persons describe
low blood pressure–related symptoms and irregularities of heartbeat.

ELIXIRS

Elixirs are clear, sweetened hydroalcoholic solutions intended for oral use and are usually flavored to enhance their palatability. Nonmedicated elixirs are employed as vehicles, and medicated elixirs are used for the therapeutic effect of the medicinal substances they contain. Compared with syrups, elixirs are usually less sweet and less viscous because they contain a lower proportion of sugar and consequently are less effective than syrups in masking the taste of medicinal substances. However, because of their hydroalcoholic character, elixirs are better able than aqueous syrups to maintain both water-soluble and alcohol-soluble components in solution. Also, because of their stable characteristics and the ease with which they are prepared (by simple solution), from a manufacturing standpoint, elixirs are preferred to syrups.

The proportion of alcohol in elixirs varies widely because the individual components of the elixirs have different water and alcohol solubility characteristics. Each elixir requires a specific blend of alcohol and water to maintain all of the components in solution. Naturally, for elixirs containing agents with poor water solubility, the proportion of alcohol required is greater than for elixirs prepared from components having good water solubility. In addition to alcohol and water, other solvents, such as glycerin and propylene glycol, are frequently employed in elixirs as adjunctive solvents.

Although many elixirs are sweetened with sucrose or with a sucrose syrup, some use sorbitol, glycerin, and/or artificial sweeteners. Elixirs having a high alcoholic content usually use an artificial sweetener, such as saccharin, which is required only in small amounts, rather than sucrose, which is only slightly soluble in alcohol and requires greater quantities for equivalent sweetness.

All elixirs contain flavorings to increase their palatability, and most elixirs have coloring agents to enhance their appearance.

Elixirs containing more than 10% to 12% of alcohol are usually self-preserving and do not require the addition of an antimicrobial agent.

Although the USP monographs for medicated elixirs provide standards, they do not generally provide official formulas. Formulations are left up to the individual manufacturers. Example formulations for some medicated elixirs are as follows (7):

**Phenobarbital Elixir**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>4.0 g</td>
</tr>
<tr>
<td>Orange oil</td>
<td>0.25 mL</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>100.0 mL</td>
</tr>
<tr>
<td>Alcohol</td>
<td>200.0 mL</td>
</tr>
<tr>
<td>Sorbitol solution</td>
<td>600.0 mL</td>
</tr>
<tr>
<td>Color</td>
<td>q.s.</td>
</tr>
<tr>
<td>Purified water, to make</td>
<td>1,000.0 mL</td>
</tr>
</tbody>
</table>

**Theophylline Elixir**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline</td>
<td>5.3 g</td>
</tr>
<tr>
<td>Citric acid</td>
<td>10.0 g</td>
</tr>
<tr>
<td>Liquid glucose</td>
<td>44.0 g</td>
</tr>
<tr>
<td>Syrup</td>
<td>132.0 mL</td>
</tr>
<tr>
<td>Glycerin</td>
<td>50.0 mL</td>
</tr>
<tr>
<td>Sorbitol solution</td>
<td>324.0 mL</td>
</tr>
<tr>
<td>Alcohol</td>
<td>200.0 mL</td>
</tr>
<tr>
<td>Saccharin sodium</td>
<td>5.0 g</td>
</tr>
<tr>
<td>Lemon oil</td>
<td>0.5 g</td>
</tr>
<tr>
<td>FD&amp;C Yellow No. 5</td>
<td>0.1 g</td>
</tr>
<tr>
<td>Purified water, to make</td>
<td>1,000.0 mL</td>
</tr>
</tbody>
</table>

Medicated elixirs are formulated so that a patient receives the usual adult dose of the drug in a convenient measure of elixir. For most elixirs, one or two teaspoonfuls (5 or 10 mL) provides the usual adult dose of the drug. One advantage of elixirs over their counterpart drugs in solid dosage forms is the flexibility and ease of dosage administration to patients who have difficulty swallowing solid forms.

A disadvantage of elixirs for children and for adults who choose to avoid alcohol is their alcoholic content. The reader may wish to refer to the discussion of alcohol as a solvent earlier in this chapter for FDA-recommended limits on alcohol content for OTC oral products.
Because of their usual content of volatile oils and alcohol, elixirs should be stored in tight, light-resistant containers and protected from excessive heat.

**Preparation of Elixirs**

Elixirs are usually prepared by simple solution with agitation and/or by admixture of two or more liquid ingredients. Alcohol-soluble and water-soluble components are generally dissolved separately in alcohol and in purified water, respectively. Then the aqueous solution is added to the alcoholic solution, rather than the reverse, to maintain the highest possible alcoholic strength at all times so that minimal separation of the alcohol-soluble components occurs. When the two solutions are completely mixed, the mixture is made to the volume with the specified solvent or vehicle. Frequently, the final mixture will be cloudy, principally because of separation of some of the flavoring oils by the reduced alcoholic concentration. If this occurs, the elixir is usually permitted to stand for a prescribed number of hours to ensure saturation of the hydroalcoholic solvent and to permit the oil globules to coalesce so that they may be more easily removed by filtration. Talc, a frequent filter aid in the preparation of elixirs, absorbs the excessive amounts of oils and therefore assists in their removal from the solution. The presence of glycerin, syrup, sorbitol, and propylene glycol in elixirs generally contributes to the solvent effect of the hydroalcoholic vehicle, assists in the dissolution of the solute, and enhances the stability of the preparation. However, the presence of these materials adds to the viscosity of the elixir and slows the rate of filtration.

**Nonmedicated Elixirs**

Nonmedicated elixirs may be useful to the pharmacist in the extemporaneous filling of prescriptions involving (a) the addition of a therapeutic agent to a pleasant-tasting vehicle and (b) dilution of an existing medicated elixir. In selecting a liquid vehicle for a drug substance, the pharmacist should be concerned with the solubility and stability of the drug substance in water and alcohol. If a hydroalcoholic vehicle is selected, the proportion of alcohol should be only slightly above the amount needed to effect and maintain the drug’s solution. When a pharmacist is called on to dilute an existing medicated elixir, the nonmedicated elixir he or she selects as the diluent should have approximately the same alcoholic concentration as the elixir being diluted. Also, the flavor and color characteristics of the diluent should not be in conflict with those of the medicated elixir, and all components should be chemically and physically compatible.

In years past, when pharmacists were called on more frequently than today to compound prescriptions, the three most commonly used nonmedicated elixirs were aromatic elixir, compound benzaldehyde elixir, and isoalcoholic elixir.

**Medicated Elixirs**

As noted previously, medicated elixirs are employed for the therapeutic benefit of the medicinal agent. Most official and commercial elixirs contain a single therapeutic agent. The main advantage of having only a single therapeutic agent is that the dosage of that single drug may be increased or decreased by simply taking more or less of the elixir, whereas when two or more therapeutic agents are present in the same preparation, it is impossible to increase or decrease the dose of one without an automatic and corresponding adjustment in the dose of the other, which may not be desired. Thus, for patients required to take more than a single medication, many physicians prefer them to take separate preparations of each drug so that if an adjustment in the dosage of one is desired, it may be accomplished without the concomitant adjustment of the other. Table 13.8 presents some examples of medicated elixirs. Some of these are briefly discussed next.

**Antihistamine Elixirs**

As indicated in Table 13.8, antihistamines are useful primarily in the symptomatic relief of certain allergic disorders. They suppress symptoms caused by histamine, one of the
Table 13.8 EXAMPLES OF MEDICATED ELIXIRS BY CATEGORY

<table>
<thead>
<tr>
<th>ELIXIR</th>
<th>REPRESENTATIVE COMMERCIAL PRODUCTS</th>
<th>USUAL ADULT DOSE/VOLUME OF COMMERCIAL ELIXIR</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenocortical Steroid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Dexamethasone Elixir</td>
<td>500 mg/5 mL</td>
<td>Synthetic analog of hydrocortisone, about 30 times more potent. Commercial elixir is packaged with a calibrated dropper for accurate measurement of small doses; intended primarily for children; also has utility for adults with trouble swallowing tablets. Used for many indications: rheumatoid arthritis, skin diseases, allergies, inflammatory conditions. Commercial product contains 5% alcohol.</td>
</tr>
<tr>
<td>Analgesic, Antipyretic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Children’s Tylenol Elixir (McNeil)</td>
<td>160 mg/5 mL</td>
<td>Reduction of pain and lowering of fever particularly in patients sensitive to or unable to take aspirin. Elixir is especially useful for pediatric patients and is alcohol-free.</td>
</tr>
<tr>
<td>Anticholinergic, Antispasmodic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyoscyamine sulfate</td>
<td>Alaven</td>
<td>0.125 mg/5 mL</td>
<td>Used to control gastric secretion, visceral spasm, hypermotility, abdominal cramps. Commercial product contains 20% alcohol.</td>
</tr>
<tr>
<td>Antihistamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine HCl</td>
<td>Diphenhydramine HCl Elixir</td>
<td>12.5 mg/5 mL</td>
<td>Antihistamines are used for a variety of allergic reactions, for example, perennial and seasonal allergic rhinitis, vasomotor rhinitis, allergic skin manifestations of urticaria, reactions to insect bites. Commercial product contains 5.6% alcohol.</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluphenazine HCl</td>
<td>Fluphenazine HCl Elixir (Pharmaceutical Associates)</td>
<td>2.5 mg/5 mL</td>
<td>Management of psychotic disorders</td>
</tr>
<tr>
<td>Cardiotonic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>Various</td>
<td>50 mg/mL</td>
<td>Among other effects, increases the force of myocardial contraction. Used in congestive heart failure, atrial fibrillation, other cardiac conditions. Commercial product contains 10% alcohol.</td>
</tr>
<tr>
<td>Sedatives, Hypnotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butobarbital sodium</td>
<td>Butisol Sodium Elixir (Medpointe)</td>
<td>30 mg/5 mL</td>
<td>In low dosage, sedatives; in higher dosage, hypnotics. Butobarbital sodium elixir contains 7% alcohol; phenobarbital elixir contains 14% alcohol.</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Various</td>
<td>20 mg/5 mL</td>
<td></td>
</tr>
</tbody>
</table>
chemical agents released during the antigen–
antibody reaction of the allergic response.
Although only minor differences exist in
the properties of most antihistamines, one
or another may be preferred by a prescriber
because of experience in managing a specific
type of allergic reaction. A prescriber’s pref-
erence may also be based on the incidence
of adverse effects that may be expected to
occur. The incidence and severity of these
effects do vary somewhat with the drug and
the dose. The most common untoward effect
is sedation, and patients taking antihista-
mines should be warned against engaging in
activities requiring mental alertness, such as
driving an automobile or tractor or operating
machinery. Other common adverse effects
include dryness of the nose, throat, and
mouth; dizziness; and disturbed concentra-
tion. Among the most sedating antihistamines
are diphenhydramine and doxylamine. In
fact, diphenhydramine is used as a sleep aid
in numerous OTC products for its ability to
cause drowsiness.

Most antihistaminic agents are basic
amines. By forming salts through interac-
tion with acid, the compounds are rendered
water soluble. These salt forms are used in
elixirs, so the elixirs of the antihistamines are
not required to contain a large proportion of
alcohol. Because the acid salts of the antihis-
tamines are used, the pH of these elixirs is on
the acid side and must remain so if the drugs
are to remain freely soluble in water. A phar-
macist should keep this in mind when using
one of these elixirs to compound a prescrip-
tion with other components.

**Barbiturate Sedative and Hypnotic
Elixirs**
The barbiturates are sedative and hypnotic
agents that are used to produce various
degrees of central nervous system depression.
As the dose of these drugs is increased, the
effects go from sedation to hypnosis to respi-
ratory depression, the last being the cause of
death in fatal barbiturate overdose.

Barbiturates are administered in small
doses in the daytime as sedatives to reduce
restlessness and emotional tension. The
appropriate dose for this purpose is the
amount that alleviates anxiety or tension but
does not produce drowsiness or lethargy.
Greater doses of the barbiturates may be
given before bedtime as hypnotics to relieve
insomnia.

Barbiturates have been classified accord-
ing to the duration of their hypnotic effects,
that is, long-acting, intermediate-acting,
short-acting, or ultrashort-acting agents.
The long-acting barbiturates, including pheno-
obarbital, are considered most useful in
maintaining daytime sedation and in treating
some convulsive states and least useful
as hypnotics. The intermediate-acting
barbiturates include amobarbital; they are
used primarily for short-term daytime seda-
tion and are effective in treating insomnia.
The barbiturates classified as short-acting
include secobarbital; they are used similarly
to the intermediate-acting barbiturates. The
ultra–short-acting barbiturates, including
thiopental, are given intravenously to induce
anesthesia.

The most common untoward effects in
patients taking barbiturates are drowsiness
and lethargy. Large doses may produce resid-
ual sedation resembling the hangover follow-
ing alcohol intoxication. Prolonged use of
barbiturates may lead to psychic or physical
dependence. This dependence, in susceptible
individuals, leads to compulsive abuse of the
drug with severe withdrawal symptoms fol-
lowing abstinence. In heavy chronic users,
abrupt withdrawal may lead to convulsions,
delirium, and occasionally to coma and death.

Some pharmaceutical aspects of phenobarbi-
tal elixir are presented below.

**Phenobarbital Elixir**
Phenobarbital elixir is formulated to contain
phenobarbital 0.4%, which provides about 20
mg of drug per teaspoonful (5 mL) of elixir.
The elixir is commonly flavored with orange
oil, colored red with an FDA-approved colo-
rant, and sweetened with syrup. The official
elixir contains about 14% alcohol, which is
used to dissolve the phenobarbital. However,
this amount is almost the very minimum
required to keep the phenobarbital in solu-
tion. Therefore, glycerin is often added to
enhance the solubility of phenobarbital.
Phenobarbital is a long-acting barbiturate with a duration of action of about 4 to 6 hours, a usual adult dose as a sedative of about 30 mg and a hypnotic dose of about 100 mg. The strength of the elixir permits convenient adjustment of dosage to achieve the proper degree of sedation in the treatment of infants, children, and certain adults. The elixir is commercially available from a variety of manufacturers under its nonproprietary name.

**Digoxin Elixir**

No official method of preparation is indicated for Digoxin Elixir, USP; however, it is required to contain 4.5 to 5.25 mg of digoxin per 100 mL of elixir, or about 0.25 mg/5 mL teaspoonful. The usual oral adult dose of digoxin as a cardiotonic agent is about 1.5 mg on initial therapy and about 0.5 mg for maintenance therapy.

Digoxin is a cardiotonic glycoside obtained from the leaves of *Digitalis lanata*. It is a white crystalline powder that is insoluble in water but soluble in dilute alcohol solutions. The official elixir contains about 10% alcohol. Digoxin is poisonous, and its dose must be carefully determined and administered to each individual patient. Adults generally take digoxin tablets rather than the elixir, which must be measured by the highly variable household teaspoon. The elixir is generally employed for children, and the commercial product available for this purpose is packaged with a calibrated dropper to facilitate accurate dosing.

Digoxin is one of many drugs available in more than a single dosage form. The prescriber frequently has the choice of a solid dosage form—a tablet or capsule—or a liquid. The advantages of each have been noted previously, but it is important to point out again that drugs administered in different dosage forms may exhibit different bioavailability characteristics, with varying patterns of drug release and rates and extents of absorption. Such differences have been noted for digoxin between tablets from different manufacturers and between tablets and oral liquid forms. Figure 13.2 shows the differences noted in one study of the serum digoxin levels following administration of 0.5 mg of digoxin by oral tablet and oral solution having an elixir-like vehicle. It can be readily observed that the serum digoxin levels following administration of the oral solution were considerably greater than from the oral tablet.

A patient taking a drug known to exhibit bioavailability problems and whose therapeutic dosage regimen has been successfully established with a particular drug product should not be changed to another product.

**TINCTURES**

Tinctures are alcoholic or hydroalcoholic solutions prepared from vegetable materials or from chemical substances. They vary in method of preparation, strength of the active ingredient, alcoholic content, and intended use in medicine or pharmacy. When they are prepared from chemical substances (e.g., iodine, thimerosal), tinctures are prepared by simple solution of the chemical agent in the solvent.
Depending on the preparation, tinctures contain alcohol in amounts ranging from approximately 15% to 80%. The alcohol content protects against microbial growth and keeps the alcohol-soluble extractives in solution. In addition to alcohol, other solvents, such as glycerin, may be employed. The solvent mix of each tincture is important in maintaining the integrity of the product. Tinctures cannot be mixed successfully with liquids too diverse in solvent character because the solute may precipitate. For example, compound benzoin tincture, prepared with alcohol as the sole menstruum, contains alcohol-soluble principles that are immediately precipitated from solution upon addition of water.

Because of the alcoholic content, tinctures must be tightly stoppered and not exposed to excessive temperatures. Also, because many of the constituents found in tinctures undergo a photochemical change upon exposure to light, many tinctures must be stored in light-resistant containers and protected from sunlight.

Medicated tinctures taken orally include Paregoric, USP, or camphorated tincture of opium. Usually, patients requiring oral medication nowadays prefer to take a tablet or capsule or a pleasant-tasting elixir or syrup. Tinctures have a rather high alcoholic content, and some physicians and patients alike prefer other forms of medication. Opium Tincture, USP, or laudanum, is much more potent than paregoric, and the two should not be confused. Opium Tincture contains 10% opium (which equates to 1% morphine) and camphorated tincture of opium contains 0.4% opium (which equates to 0.04% morphine). Any prescription for either one should be carefully evaluated and the dose checked and confirmed.

**PROPER ADMINISTRATION AND USE OF LIQUID PERORAL DOSAGE FORMS**

Most of the dosage forms discussed in this chapter are to be administered by mouth. Conveniently, these can be measured in a teaspoon or tablespoon, depending on the desired dosage. Preferably, however, these medicines should be measured out in calibrated devices for administration. These devices ensure that the correct dose will be received, and household flatware can vary dramatically in the volume delivered. Even though these are liquids, it is recommended that the patient follow the administration of the liquid dosage form with a glassful of water.

The pharmacist must be careful in the selection of liquid products, given the patient’s history and other concurrent medicines. For example, some syrups contain sucrose or another sugar, and the pharmacist must recall that such syrups would not be suitable for use in an oral prescription intended for a diabetic patient. Similarly, a product that is formulated as an elixir or syrup containing alcohol would not be suitable for a patient who receives concurrent medicines that possess an Antabuse-like activity; the patient may get violently ill from the concurrent ingestion of alcohol. Metronidazole and chlorpropamide have been implicated to cause this reaction when mixed with alcohol. Furthermore, if the patient is receiving another drug that causes drowsiness, the pharmacist must consult the prescribing physician to determine whether the prescribed elixir could be harmful to the patient.

**TOPICAL SOLUTIONS AND TINCTURES**

Generally, the topical solutions employ an aqueous vehicle, whereas the topical tinctures characteristically employ an alcoholic vehicle. As required, cosolvents or adjuncts to enhance stability or the solubility of the solute are employed.

Most topical solutions and tinctures are prepared by simple dissolving. However, certain solutions are prepared by chemical reaction; these, in particular, are discussed later in this section. Of the tinctures for topical use, one, compound benzoin tincture, is prepared by maceration of the natural components in the solvent; the others are prepared by simple solution.

Because of the nature of the active constituents or the solvents, many topical solutions and tinctures are self-preserved. Those that are not may contain suitable preservatives. Topical solutions and tinctures should be
packaged in containers that make them convenient to use. Those that are used in small volume, such as the anti-infectives, are usually packaged in glass or plastic bottles with an applicator tip as a part of the cap assembly or in plastic squeeze bottles that deliver the medication in drops. Many of the anti-infective solutions and tinctures contain a dye to delineate the area of application to the skin. In contrast to aqueous solutions, when the alcoholic tinctures are applied to abraded or broken skin, they sting.

**Sprays**

Sprays may be defined as aqueous or oleaginous solutions in the form of coarse droplets or as finely divided solids to be applied topically, most usually to the nasopharyngeal tract or to the skin. Many commercial sprays are used intranasally to relieve nasal congestion and inflammation and to combat infection and contain antihistamines, sympathomimetic agents, and antibiotic substances. Because of the noninvasive nature and quickness with which nasal sprays can deliver medication systemically, in the future, several drugs that typically have been administered by other routes may be taken nasally. Most notably, insulin and glucagon may be administered in this fashion. It has been demonstrated that the administration of glucagon via a nasal spray can relieve hypoglycemic symptoms within 7 minutes, a definite advantage over conventional emergency intravenous glucose or intramuscular glucagon.

Other sprays that are employed against sunburn and heat burn contain local anesthetics, antiseptics, skin protectants, and antipruritics. Throat sprays containing antiseptics, deodorants, and flavorants may be effectively employed to relieve conditions such as halitosis, sore throat, and laryngitis. Other sprays treat athlete’s foot and other fungal infections. Numerous other medicinal and cosmetic uses of sprays are commonly available in pharmacies.

To break up a solution into small particles so that it may be effectively sprayed or to facilitate the spraying of a powder, several mechanical devices are commonly employed. The plastic spray bottle, gently squeezed to issue a spray of its contents, is familiar to most. It is commonly used for nasal decongestant sprays as well as cosmetically, especially for body deodorant products. Recently, one-way pump sprays have been developed to deliver medication into the nose. These sprays are used for both prescription, such as Nasalide (Syntex), and nonprescription, such as Nostrilla (Boehringer Ingelheim), medicines. The advantage of these over conventional sprays is that the design prevents drawback contamination of nasal fluids into the bottle after administration, a definite advantage for someone trying to cope with viruses associated with the common cold. Pharmacists are familiar with medicinal atomizers, which emit medication in the form of fine droplets (Fig. 13.3). One type of atomizer has a rubber bulb at the end of the apparatus, which when squeezed causes a flow of air, some of which enters the glass reservoir and some of which exits from the opposite end of the system. The air forced into the reservoir causes the liquid to rise in a small dip tube, forcing the solution up and into the stream of air exiting the system. The air and the solution are forced through a jet opening, and the liquid is broken up into a spray, the droplets being carried by the airstream. In other similar apparatus, the stream of air caused by the depression of the bulb does not enter the reservoir of solution but passes swiftly over it, creating a pressure change and sucking the liquid into the dip tube and into the airstream, in which it exits the system. Examples of solutions and tinctures intended for application to the skin are presented in Tables 13.9 and 13.10. As shown.

**Figure 13.3** A common type of atomizer for spray administration of liquid medication. This model has an adjustable tip for directing the spray upward or downward to reach the otherwise inaccessible areas of the throat. (Courtesy of DeVilbiss Co.)
<table>
<thead>
<tr>
<th>SOLUTION</th>
<th>CORRESPONDING COMMERCIAL SOLUTION</th>
<th>ACTIVE CONSTITUENT IN COMMERCIAL PRODUCT</th>
<th>VEHICLE</th>
<th>CATEGORY AND COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum acetate</td>
<td>—</td>
<td>5%</td>
<td>Aqueous</td>
<td>Astringent</td>
</tr>
<tr>
<td>Aluminum subacetate</td>
<td>—</td>
<td>~2.45% aluminum oxide, 5.8% acetic acid</td>
<td>Aqueous</td>
<td>Astringent</td>
</tr>
<tr>
<td>Calcium hydroxide (limewater)</td>
<td>—</td>
<td>0.14%</td>
<td>Aqueous</td>
<td>Astringent</td>
</tr>
<tr>
<td>Chlorhexidine gluconate</td>
<td>Hibiclen Skin Cleanser (Molnlycke)</td>
<td>4%</td>
<td></td>
<td>Skins wound and general skin cleanser, surgical scrub, preoperative skin preparation. Effective for gram-positive and gram-negative bacteria such as Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Clindamycin phosphate</td>
<td>Cleocin T Topical Solution (Pfizer)</td>
<td>1%</td>
<td>Isopropyl alcohol, water</td>
<td>Treatment of acne vulgaris</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>Lotrimin Solution (Schering-Plough)</td>
<td>1%</td>
<td>PEG 400</td>
<td>Antifungal</td>
</tr>
<tr>
<td>Coal tar (liquor carbonis detergents; LCD)</td>
<td>—</td>
<td>20%</td>
<td>Alcohol</td>
<td>Antieczematic; antipsoriatic</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Erymax Topical Solution (Allergan)</td>
<td>2%</td>
<td>Polyethylene glycol/acetone/alcohol</td>
<td>Treatment of acne vulgaris</td>
</tr>
<tr>
<td>Fluocinolone acetonide</td>
<td>Synalar Topical Solution (E. Fougera)</td>
<td>0.01%</td>
<td>Propylene glycol</td>
<td>Adrenocortical steroid (topical anti-inflammatory)</td>
</tr>
<tr>
<td>Fluouracil</td>
<td>Efudex Topical Solution (Valeant Pharmaceuticals)</td>
<td>2.5%</td>
<td>Propylene glycol</td>
<td>Antineoplastic (actinic keratoses)</td>
</tr>
<tr>
<td>Hydrogen peroxide</td>
<td>—</td>
<td>3%</td>
<td>Aqueous</td>
<td>Topical anti-infective</td>
</tr>
<tr>
<td>Hydroquinone</td>
<td>Melanex Topical Solution (Neutrogena Dermatologics)</td>
<td>3%</td>
<td>Water, alcohol, propylene glycol</td>
<td>Temporary bleaching of hyperpigmented skin, for example, chloasma, melasma</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Nizoral A-D (McNeill)</td>
<td>1%</td>
<td>Water</td>
<td>Treatment of dandruff</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>Rogaine Topical Solution (Pfizer Consumer Health)</td>
<td>2.5%</td>
<td>Alcohol, water, propylene glycol</td>
<td>Long-term topical treatment of male pattern baldness by stimulating hair regrowth</td>
</tr>
<tr>
<td>Povidone iodine</td>
<td>Betadine Solution (Purdue)</td>
<td>7.5, 10%</td>
<td>Aqueous</td>
<td>Topical anti-infective</td>
</tr>
<tr>
<td>Tolnaftate</td>
<td>Tinactin Solution (Schering-Plough)</td>
<td>1%</td>
<td>Polyethylene glycol</td>
<td>Topical antifungal</td>
</tr>
<tr>
<td>Undecylenic acid</td>
<td>Gordochom Solution (Gordon Laboratories)</td>
<td>25%</td>
<td>Oil base</td>
<td>Topical antifungal</td>
</tr>
</tbody>
</table>
in these tables, most of these preparations are used as anti-infective agents. All medications intended for external use should be clearly labeled for external use only and kept out of the reach of children. In addition to their listing in Table 13.9, the following topical solutions are discussed because of their particular pharmaceutical interest.

**Aluminum Acetate Topical Solution**

Aluminum acetate is colorless and has a faint acetous odor and a sweetish, astringent taste. It is widely applied topically as an astringent wash or wet dressing after dilution with 10 to 40 parts of water. It is frequently used in various types of dermatologic lotions, creams, and pastes. Commercial premeasured tablets and packets of powders are available for preparation of this solution. Synonym: Burow solution.

**Aluminum Subacetate Topical Solution**

The requirement for the amount of acetic acid differentiates aluminum acetate topical solution from aluminum subacetate topical solution. In the subacetate solution, the ratio of aluminum oxide to acetic acid is 1:2.35, whereas in the acetate solution, the ratio is 1:3.52. Aluminum subacetate topical solution, the stronger of the two, is used in preparation of aluminum acetate topical solution. Aluminum acetate topical solution, diluted first with 20 to 40 parts of water, is used externally as an astringent wash and wet dressing (modified Burow solution).

**Calcium Hydroxide Topical Solution**

Calcium hydroxide topical solution, commonly called limewater, must contain not less than 140 mg of Ca(OH)\(_2\) in each 100 mL of solution. Calcium hydroxide is less soluble in hot than in cold water, and cool purified water is the solvent. The solution is intended to be saturated with solute, and to ensure saturation, an excess of calcium hydroxide, 300 mg for each 100 mL of solution to be prepared, is agitated with the purified water, vigorously and repeatedly, for 1 hour. After this time, the excess calcium hydroxide is allowed to settle to the bottom of the container. This permits the solution to remain saturated should a portion of the dissolved solute at the solution’s surface react with the carbon dioxide of the air to form insoluble calcium carbonate:

\[
\text{Ca(OH)}_2 + \text{CO}_2 \rightarrow \text{CaCO}_3 + \text{H}_2\text{O}
\]

The calcium carbonate settles to the bottom of the container and, by appearance, is indistinguishable from the remaining excess of calcium hydroxide. The calcium hydroxide reserve dissolves as calcium is removed from the solution in the form of the carbonate, and, in this way, it continually maintains the saturation of the solution. After the solution stands for an appreciable length of time, the undissolved material at the bottom of the container is composed of varying proportions of calcium hydroxide and calcium carbonate. Because of the uncertainty of the residue’s composition, one may not prepare additional quantities.
of calcium hydroxide solution by adding more purified water.

The solution should be stored in well-filled, tightly stoppered containers to deter the absorption of carbon dioxide and should be kept in a cool place to maintain an adequate concentration of dissolved solute. Only the clear supernatant liquid is dispensed. This is best accomplished by the use of a siphon with care not to entrain the residue.

The solution is categorized as an astringent. For this purpose, it is generally employed in combination with other ingredients in dermatologic solutions and lotions to be applied topically. Synonyms: limewater, liquor calcis.

Coal Tar Topical Solution

Coal tar topical solution is an alcoholic solution containing 20% coal tar and 5% polysorbate 80. It is prepared by mixing the coal tar with two and a half times its weight of washed sand, adding the polysorbate 80 and most of the alcohol, and then macerating the mixture for 7 days in a closed vessel with frequent agitation followed by filtration and adjustment to the proper volume with alcohol. The final content is 81% to 86% ethyl alcohol.

Coal tar is a nearly black viscous liquid having a characteristic naphthalene-like odor and a sharp, burning taste. It is the tar obtained as a by-product during the destructive distillation of bituminous coal. It is slightly soluble in water and partially soluble in most organic solvents, including alcohol. In the preparation of the official solution, the coal tar is mixed with the sand to distribute it mechanically and create a large surface area of tar exposed to the solvent action of the alcohol. During the maceration, or soaking, the alcohol-soluble components of the tar dissolve, leaving the undissolved portion clinging to the sand. Filtration removes the sand and the insoluble tar components from the solution. The container in which the solution was prepared should be rinsed with alcohol, and the washings should be passed through the filter paper in the adjustment of the final volume of the solution.

In the extemporaneous compounding of prescriptions and in the therapeutic application of this preparation to the skin, the solution is frequently mixed with aqueous preparations or simply diluted with water. Because coal tar is only slightly soluble in water, it would separate from the solution were it not for the polysorbate 80 in the preparation. This agent, commercially available as Tween 80 (ICI Americas) and as other brand name products, is an oily liquid that is a nonionic surfactant. It is quite effective in dispersing the water-insoluble components of coal tar upon admixture with an aqueous preparation.

Coal tar is a local antieczematic used in external treatment of a wide variety of chronic skin conditions after dilution with about nine volumes of water or in combination with other agents in various lotions, ointments, or solutions. Synonyms: liquor carbonis detersgens; liquor picis carbonis; LCD.

Hydrogen Peroxide Topical Solution

Hydrogen peroxide topical solution contains 2.5% to 3.5% (w/v) hydrogen peroxide, or H₂O₂. Suitable preservatives, totaling not more than 0.05%, may be added.

One method of preparation uses the action of either phosphoric or sulfuric acid on barium peroxide:

\[ \text{BaO}_2 + \text{H}_2\text{SO}_4 \rightarrow \text{BaSO}_4 + \text{H}_2\text{O}_2 \]

Another method uses electrolytic oxidation of a cold solution of concentrated sulfuriacid to form persulfuric acid, which when hydrolyzed liberates hydrogen peroxide:

\[ 2\text{H}_2\text{SO}_4 \rightarrow \text{H}_2\text{SO}_8 + \text{H}_2 \]

\[ \text{H}_2\text{SO}_8 + 2\text{H}_2\text{O} \rightarrow 2\text{H}_2\text{SO}_4 + \text{H}_2\text{O}_2 \]

A solution prepared by this method usually contains about 30% hydrogen peroxide and is capable of liberating 100 times its volume of oxygen. A solution of this strength is commonly referred to as 100-volume peroxide. The dilute solution, which contains about 3% hydrogen peroxide and liberates 10 times its volume of oxygen, may be prepared from the concentrated solution.
The solution is a clear, colorless liquid that may be odorless or have the odor of ozone. It usually deteriorates upon long standing, forming oxygen and water. Preservative agents, such as acetanilide, have been found to retard decomposition. Decomposition is enhanced by light and by heat, and for this reason, the solution should be preserved in tight, light-resistant containers, preferably at a temperature not exceeding 35°C (95°F). The solution is also decomposed by practically all organic matter and other reducing agents and reacts with oxidizing agents to liberate oxygen and water; metals, alkalis, and other agents can catalyze its decomposition.

Hydrogen peroxide solution is categorized as a local anti-infective for use topically on the skin and mucous membranes. Its germicidal activity is based on the release of nascent oxygen on contact with the tissues. However, because of the short duration of this release, the chief value of the preparation in the reduction of infection is probably its ability to cleanse wounds by mechanical action through the bubbling and frothing caused by the release of oxygen. It is also used to disinfect aseptic working environments. Synonym: peroxide.

Chlorhexidine Gluconate Solution

Since 1957, chlorhexidine gluconate has been employed extensively as a broad-spectrum antiseptic in clinical and veterinary medicine. Its spectrum encompasses gram-positive and gram-negative bacteria, including Pseudomonas aeruginosa. In a concentration of 4% (Hibiclens, Molynlycke Health Care Inc.), it is used as a surgical scrub, hand wash, and skin wound and general skin cleanser. Procedures are established for all of these purposes to maximize the effectiveness of the chlorhexidine. Experience has demonstrated that irritation, dermatitis, and photosensitivity associated with topical use of chlorhexidine are rare.

In 1987, the FDA and the Council of Dental Therapeutics of the American Dental Association approved chlorhexidine gluconate 0.12% (Peridex, Procter & Gamble) as the first prescription-only antiplaque, anti-gingivitis drug with antimicrobial activity. Microbiologic sampling of plaque has shown a reduction of aerobic and anaerobic bacteria ranging from 54% to 97% through 6 months of use when it is used as a mouth rinse. The oral rinse should be used twice daily for 30 seconds, morning and night, after tooth brushing. Usually a 15-mL dose of undiluted solution is used and expectorated after rinsing. The most common side effect of chlorhexidine is the formation of an extrinsic yellow-brown stain on the teeth and tongue after only a few days of use. The amount of stain depends on the concentration of chlorhexidine and individual susceptibility. Increased consumption of tannin-containing substances, such as tea, red wine, and port wine, will increase the level of discoloration. The developed stain can be periodically removed with dental prophylaxis.

Povidone Iodine Topical Solution

The agent povidone iodine is a chemical complex of iodine with polyvinylpyrrolidone, the latter agent being a polymer having an average molecular weight of about 40,000. The povidone iodine complex contains approximately 10% available iodine and slowly releases it when applied to the skin.

The preparation is employed topically as a surgical scrub and nonirritating antiseptic solution, with its effectiveness directly attributable to the presence and release of iodine from the complex. Commercial product: Betadine Solution (Purdue).

Thimerosal Topical Solution

Thimerosal is a water-soluble organic mercury antibacterial agent used topically for its bacteriostatic and mild fungistatic properties. It is used mainly to disinfect skin prior to surgery and as a first aid application to wounds and abrasions. It has been applied to the eye, nose, throat, and urethra in dilutions of 1:5,000. It is also used as a preservative for various pharmaceutical preparations, including many vaccines and other biologic products.
Thimerosal topical solution contains 0.1% thimerosal. Also present are ethylenediamine solution and sodium borate to maintain the alkalinity (usually pH 9.8 to 10.3) required for the solution’s stability. Monoethanolamine is used as an additional stabilizer. The solution is affected by light and must be maintained in light-resistant containers. Commercial product: Merthiolate Solution (Lilly).

**Medicated Soaps and Shampoo Solutions**

Medicated soaps and shampoos are liquid or solid preparations intended for topical application to the skin or scalp followed by subsequent rinsing with water. They are solution, emulsion, or surface-active products that readily form emulsions or foams upon the addition of water followed by rubbing. Incorporation of active pharmaceutical ingredients (APIs) in the soaps and shampoos combines the cleansing/degreasing abilities of the vehicle and facilitates the topical application of the API to affected areas of the body. The surface-active properties of the vehicle facilitate contact of the API with the skin or scalp. Medicated soap and shampoo formulations frequently contain antimicrobial agents to protect against bacteria, yeast, and mold contamination.

**VAGINAL AND RECTAL SOLUTIONS**

**Vaginal Douches**

Solutions may be prepared from powders as indicated earlier or from liquid solutions or liquid concentrates. In using liquid concentrates, the patient is instructed to add the prescribed amount of concentrate (usually a teaspoonful or capful) to a certain amount of warm water (frequently a quart). The resultant solution contains the appropriate amount of chemical agents in proper strength. The agents are similar to the ones described for douche powders. Examples are shown in Figure 13.4.

Powders are used to prepare solutions for vaginal douche, that is, for irrigation cleansing of the vagina. The powders themselves may be prepared and packaged in bulk or as unit packages. A unit package is designed to contain the appropriate amount of powder to prepare the specified volume of douche solution. The bulk powders are used by the teaspoonful or tablespoonful in preparation of the desired solution. The user simply adds the prescribed amount of powder to the appropriate volume of warm water and stirs until dissolved. Among the components of douche powders are the following:

1. Boric acid or sodium borate
2. Astringents, for example, potassium, alum, ammonium alum, and zinc sulfate
3. Antimicrobials, for example, oxyquinoline sulfate and povidone iodine
4. Quaternary ammonium compounds, for example, benzethonium chloride
5. Detergents, for example, sodium lauryl sulfate
6. Oxidizing agents, for example, sodium perborate
7. Salts, for example, sodium citrate and sodium chloride
8. Aromatics, for example, menthol, thymol, eucalyptol, methyl salicylate, and phenol

Douche powders are used for their hygienic effects. A few douche powders containing specific therapeutic anti-infective agents such as those mentioned in the discussion of vaginal suppositories are used against monilial and trichomonal infections.
Retention Enemas

A number of solutions are administered rectally for local effects (e.g., hydrocortisone) or for systemic absorption (e.g., aminophylline). In the case of aminophylline, rectal administration minimizes the undesirable gastrointestinal reactions associated with oral therapy. Clinically effective blood levels of the agents are usually obtained within 30 minutes following rectal instillation. Corticosteroids are administered as retention enemas or continuous drip as adjunctive treatment of some patients with ulcerative colitis.

Evacuation Enemas

Rectal enemas are used to cleanse the bowel. Commercially, many enemas are available in disposable plastic squeeze bottles containing a premeasured amount of enema solution. The agents are solutions of sodium phosphate and sodium biphosphate, glycerin and docusate potassium, and light mineral oil.

Instruction from a pharmacist is advantageous to ensure that the patient correctly uses these products. The patient should be advised to gently insert the tip of the product with steady pressure and be told that it is not absolutely necessary to squeeze all of the contents out of the disposable plastic bottle. The patient should be told that the product will most probably work within 5 to 10 minutes.

TOPICAL TINCTURES

Examples of tinctures for topical application to the skin are presented in Table 13.10. Those of particular pharmaceutical interest are discussed briefly as follows.

Iodine Tincture

Iodine tincture is prepared by dissolving 2% iodine crystals and 2.4% sodium iodide in an amount of alcohol equal to half the volume of tincture to be prepared and diluting the solution to volume with sufficient purified water. The sodium iodide reacts with the iodine to form sodium triiodide:

\[ I_2 + NaI \leftrightarrow NaI_3 \]

This reaction prevents formation of ethyl iodide from the interaction between iodine and alcohol, which would result in the loss of the antibacterial activity of the tincture. An added benefit of the triiodide form of iodine is its water solubility, which is important should the tincture, which contains between 44% and 50% alcohol, be diluted with water during use.

The tincture is a popular local anti-infective agent applied to the skin in general household first aid. The reddish-brown color, which produces a stain on the skin, is useful in delineating the application over the affected skin area. The tincture should be stored in a tight container to prevent loss of alcohol.

Compound Benzoin Tincture

Compound benzoin tincture is prepared by maceration in alcohol of 10% benzoin and lesser amounts of aloe, storax, and Tolu balsam totaling about 24% of starting material. The drug mixture is best macerated in a wide-mouthed container because it is difficult to introduce storax, a sticky semiliquid material, into a narrow-mouthed container. Generally, it is advisable to weigh the storax in the container in which it will be macerated to avoid possible loss through a transfer of the material from one container to another.

The tincture is categorized as a protectant. It is used to protect and toughen skin in the treatment of bedsores, ulcers, cracked nipples, and fissures of the lips and anus. It is also commonly used as an inhalant in bronchitis and other respiratory conditions, 1 teaspoonful commonly being added to a pint of boiling water. The volatile components of the tincture travel with the steam vapor and are inhaled by the patient. Because of the incompatibility of the alcoholic tincture and water, the mixture produces a milky product with some separation of resinous material. Alcohol or acetone may be used as necessary to remove the residue from the vaporizer after use.
Compound tincture of benzoin serves as a delivery vehicle of podophyllum in the treatment of venereal warts. It is important that podophyllum not be systemically absorbed because it can cause peripheral neuropathy characterized by paresthesias, loss of sensation, and loss of deep tendon reflexes in the extremities, in addition to neuropathy of the central nervous system including lethargy, confusion, and coma. Second, the podophyllum is teratogenic and should be administered to a pregnant woman only when the risk–benefit ratio is extremely low. Thus, the nonocclusive compound tincture of benzoin is preferred to the occlusive flexible collodion.

Compound benzoin tincture is best stored in tight, light-resistant containers. Exposure to direct sunlight or to excessive heat should be avoided.

The tincture originated in the fifteenth or sixteenth century and, through the years, probably has acquired more synonyms than any other official preparation. A few of these are friar’s balsam, Turlington drops, Persian balsam, Swedish balsam, Jerusalem balsam, Wade drops, and Turlington balsam of life.

Thimerosal Tincture

The same general remarks about thimerosal topical solution apply to thimerosal tincture except that sodium chloride and sodium borate are absent from the tincture and the vehicle of the tincture is water, acetone, and about 50% alcohol. A number of metals, notably copper, cause decomposition of the tincture, and for this reason, it must be manufactured and stored in glass or suitably resistant containers. Monoethanolamine and ethylenediamine are used as stabilizers in the official solution and tincture and are thought to be effective because of their chelating action on traces of metallic impurities that may be present at the time of preparation or may later gain access to the preparation.

The commercial preparation is colored orange red and has greenish fluorescence. The red stain it leaves on the skin defines the area of application. It is a commonly used household antiseptic for application to abrasions and cuts and also in the preparation of patients for surgery.

**TOPICAL ORAL (DENTAL) SOLUTIONS**

A variety of medicinal substances are employed topically in the mouth for a number of purposes and in a wide range of dosage forms. Among the drugs and preparations included in this group are the following:

- Benzocaine: Topical anesthetic. Indicated for temporary relief of pain, soreness, and irritation in the mouth associated with teething, orthodontic appliances, new or poorly fitting dentures, and canker sores
- Camphorated parachlorophenol: Dental anti-infective. A eutectic liquid composed of 65% camphor and 35% parachlorophenol, used in dentistry for sterilization of deep root canals
- Carbamide peroxide topical solution: Dental anti-infective. Acts as a chemomechanical cleansing and debriding agent through the release of bubbling oxygen. The commercial product (Gly-Oxide Liquid, GlaxoSmithKline) contains 10% carbamide in flavored anhydrous glycerin.
- Cetylpyridinium chloride solution and cetylpyridinium chloride lozenges: Local anti-infective. Commercial counterparts (Cepacol Mouthwash/Gargle and Cepacol Lozenges; Combe) contain 1:2,000 w/v and 1:1,500 w/v of cetylpyridinium chloride, respectively. Used primarily as a freshening mouth cleanser. Lozenges have benzyl alcohol as a local anesthetic in soothing throat irritations.
- Erythrosine sodium topical solution and erythrosine sodium soluble tablets: Diagnostic aid (dental disclosing agent). Solution applied to the teeth to reveal plaque left by inadequate brushing. Tablets chewed for the same purpose and are not to be swallowed
- Eugenol: Dental analgesic. Applied topically to dental cavities and dental...
Section VI • Liquid Dosage Forms

protectives. Eugenol is a pale yellow liquid having an aromatic odor of clove and a spicy taste.

- Lidocaine oral spray: Topical dental anesthetic. Applied through metered spray at 10 mg per spray; 20 mg per quadrant of gingiva and oral mucosa is usually employed (Xylocaine Oral Spray, AstraZeneca).
- Nystatin oral suspension: Antifungal. May be employed for oral fungal infections by retaining in the mouth as long as possible before swallowing.
- Saliva substitutes: Electrolytes in a carboxymethylcellulose base. They are indicated for relief of dry mouth and throat in xerostomia.
- Sodium fluoride oral solution and sodium fluoride tablets: Dental caries prophylactic. Solution applied to the teeth; or when drinking water does not contain adequate fluoride, a dilute solution may be swallowed. Tablets containing sodium fluoride 1.1 or 2.2 mg are chewed or swallowed as required.
- Sodium fluoride and phosphoric acid gel and sodium fluoride and phosphoric acid topical solution: Dental caries prophylactic. Gel and solution applied to the teeth; each contains 1.23% of fluoride ion and 1% of phosphoric acid. Triamcinolone acetonide dental paste—topical anti-inflammatory agent. Applied to the oral mucous membranes as a 0.1% paste.
- Zinc oxide–eugenol mixture: Temporary filling mix.

In addition to these drugs and preparations, a host of other products for oral use are commercially available. Some of these products, such as teething lotions and toothache drops, are medicated, whereas others are used for hygienic purposes, such as dentifrices, denture products, and many of the mouthwashes. Among the variety of products is a like variety of physical forms—solutions, emulsions, ointments, pastes, aerosols, and so on, with the manufacture of each following the general procedures outlined in this text. One type of dosage form for oral use, the lozenge, has not been previously described.

**MISCELLANEOUS SOLUTIONS**

**Aromatic Waters**

Aromatic waters are clear, aqueous solutions saturated with volatile oils or other aromatic or volatile substances. Aromatic waters are no longer in widespread use. In years past, aromatic waters were prepared from a number of volatile substances, including orange flower oil, peppermint oil, rose oil, anise oil, spearmint oil, wintergreen oil, camphor, and chloroform. Naturally, the odors and tastes of aromatic waters are of the volatile substances from which they are prepared.

Most of the aromatic substances in the preparation of aromatic waters have very low solubility in water, and even though the water may be saturated, its concentration of aromatic material is still rather small. Aromatic waters may be used for perfuming and/or flavoring.

**Diluted Acids**

Diluted acids are aqueous solutions prepared by diluting the corresponding concentrated acids with purified water. The strength of a diluted acid is generally expressed on a percent weight-to-volume (% w/v) basis, that is, the weight in grams of solute per 100 mL of solution, whereas the strength of a concentrated acid is generally expressed in terms of percent weight to weight (% w/w), which indicates the number of grams of solute per 100 g of solution. To prepare a diluted acid from a concentrated one, it is necessary first to calculate the amount of solute required in the diluted product. Then the amount of concentrated acid required to supply the needed amount of solute can be determined.

To illustrate, concentrated hydrochloric acid contains not <35 g and not more than 38 g of solute (absolute HCl) per 100 g of acid and therefore is considered to be, on the average, 36.5% w/w in strength. Diluted hydrochloric acid contains 9.5 to 10.5 g of solute per 100 mL of solution and is therefore considered to be approximately 10% w/v in strength. If one wished to prepare 100 mL of the diluted acid from the concentrated acid, one would require 10 g of solute. The amount...
of concentrated HCl required to supply this amount of solute may be calculated by the following proportion:

\[
\frac{36.5 \text{ g (solute)}}{100 \text{ g (conc. acid)}} = \frac{10 \text{ g (solute)}}{x \text{ g (conc. acid)}}
\]

Solving for \(x\):

\[
x = \frac{36.5 \times 1,000}{10} = 365 \text{ g (conc. acid)}
\]

Thus, 36.5 g of concentrated acid is required to supply 10 g of solute needed for the preparation of 100 mL of the diluted acid. Although the required amount of concentrated acid may be accurately weighed, it is a cumbersome task, and as a rule, pharmacists prefer to measure liquids by volume. Therefore, in the preparation of diluted acids, the calculations are generally carried one step further to determine the volume of concentrated acid that corresponds to the calculated weight. Because this additional step requires the use of the concentrated acid’s specific gravity, a brief review of specific gravity seems appropriate.

By definition, specific gravity is a ratio, expressed decimally, of the weight of a substance to the weight of an equal volume of a standard, both substances having the same temperature or the temperature of each being known. Water is used as the standard for liquids and solids and hydrogen or air for gases. In pharmacy, specific gravity calculations mainly involve liquids and solids, and water is an excellent choice for a standard because it is readily available and easily purified.

At 4°C, the density of water is 1 g per cubic centimeter. Because the USP states that 1 mL may be considered the equivalent of 1 cc, in pharmacy, water is assumed to weigh 1 g per milliliter. By the following equation used to calculate specific gravity, a substance having a density the same as water would have a specific gravity of 1.0:

\[
\text{spgr} = \frac{\text{weight of a substance}}{\text{weight of an equal volume of water}}
\]

In solving this equation, the same units of weight must be used in each part of the ratio. These units cancel out, and the ratio is expressed decimally.

Specific gravity indicates the ratio of the weight of a substance to that of an equal volume of water. For example, 10 mL of a liquid weighs 20 g. An equal volume of water weighs 10 g, and the ratio in the equation is 20:10, yielding a specific gravity of 2.0. This indicates that the liquid is twice as heavy as water in equal volume. By the same token, a liquid having a specific gravity of 0.5 is half as heavy as water; a liquid with a specific gravity of 0.8 is eight-tenths as heavy as water and so on.

If both the volume of a liquid and its specific gravity are known, its weight may be calculated. For instance, if concentrated hydrochloric acid has a specific gravity of 1.17, it is that number times as heavy as water, and 100 mL of the acid would weigh 1.17 times as much as 100 mL of water. Because 100 mL of water weighs 100 g, 100 mL of the acid weighs 117 g.

If one knows the weight of a liquid and its specific gravity, the volume of the liquid may be determined. For example, a liquid that is twice as heavy as water has a specific gravity of 2.0 and occupies half the volume that an equal weight of water occupies. If one has 100 g of this liquid and substitutes in the equation as indicated next, the volume of the liquid can be arrived at

\[
2.0 = \frac{100 \text{ g}}{\text{weight of an equal volume of water}}
\]

weight of an equal volume of water

Because 50 g is the weight of an equal volume of water, it follows that the water must measure 50 mL. Since the volume of the water is an equal volume to the other liquid, that liquid must also measure 50 mL.

The volume represented by 27.39 g of the concentrated hydrochloric acid may be similarly determined by dividing the weight of the concentrated acid by its specific gravity and equating the weight of an equal volume of water to the volume of the acid:
Thus, because 23.41 g of water measures 23.41 mL and it is equal in volume to the concentrated acid, the latter also measures 23.41 mL, and this is the amount required to prepare 100 mL of the 10% w/v diluted acid.

Once the aforementioned is thoroughly understood, the following simplified formula can be used to calculate the amount of a concentrated acid required in the preparation of a specific volume of the corresponding diluted acid:

\[
\frac{\text{Percentage strength (w/v) of diluted acid}}{\text{Volume of diluted acid to be prepared}} \times \frac{\text{Percentage strength of concentrated acid (w/w)}}{\text{Specific gravity of concentrated acid}} = \text{volume of concentrated acid to use}
\]

Recalculating the preparation of 100 mL of diluted hydrochloric acid from the concentrated acid gives the following:

\[
\frac{10 \times 100 \text{ mL}}{36.5 \times 1.17} = 23.41 \text{ mL of concentrated acid to use}
\]

Most diluted acids have a strength of 10% w/v, with the exception of diluted acetic acid, which is 6% w/v. The strengths of these acids are commensurate with the concentrations generally used for medicinal or pharmaceutical purposes. The concentrations of the corresponding concentrated acids vary widely from one acid to another, depending on various properties of the solute such as solubility, stability, and ease of preparation. For instance, concentrated sulfuric acid is generally between 95% and 98% w/w, nitric acid between 69% and 71% w/w, and concentrated phosphoric acid between 85% and 88% w/w. As a result, the amounts of each concentrated acid required to prepare the corresponding diluted acid vary widely and must be calculated on an individual basis.

There is very little use of diluted acids in medicine today. However, because of its antibacterial effects, acetic acid finds application as a 1% solution in surgical dressings, as an irrigating solution to the bladder in 0.25% concentration, and as a spermatocidal in some proprietary contraceptive preparations.

**Spirits**

Spirits are alcoholic or hydroalcoholic solutions of volatile substances. Generally, the alcoholic concentration of spirits is rather high, usually over 60%. Because of the greater solubility of aromatic or volatile substances in alcohol than in water, spirits can contain a greater concentration of these materials than the corresponding aromatic waters. When mixed with water or with an aqueous preparation, the volatile substances present in spirits generally separate from the solution and form a milky preparation.

Spirits may be used pharmaceutically as flavoring agents and medicinally for the therapeutic value of the aromatic solute. As flavoring agents, they are used to impart the flavor of their solute to other pharmaceutical preparations. For medicinal purposes, spirits may be taken orally, applied externally, or used by inhalation, depending upon the particular preparation. When taken orally, they are generally mixed with a portion of water to reduce the pungency of the spirit. Depending on the materials, spirits may be prepared by simple solution, solution by maceration, or distillation. The spirits most recently official in the USP–NF are aromatic ammonia spirit, camphor spirit, compound orange spirit, and peppermint spirit.

**NONAQUEOUS SOLUTIONS**

**Liniments**

Liniments are alcoholic or oleaginous solutions or emulsions of various medicinal substances intended to be rubbed on the skin. Liniments with an alcoholic or hydroalcoholic vehicle are useful when rubefacient, counterirritant, or penetrating action is desired; oleaginous liniments are employed primarily when massage is desired. By their nature, oleaginous liniments are less irritating to the skin than alcoholic liniments. Liniments are not applied to skin areas that are broken or bruised because excessive irritation might result. The vehicle for a liniment
should therefore be selected for the type of action desired (rubefacient, counterirritant, or massage) and also on the solubility of the desired components in the various solvents. For oleaginous liniments, the solvent may be a fixed oil such as almond oil, peanut oil, sesame oil, or cottonseed oil or a volatile substance such as wintergreen oil or turpentine, or it may be a combination of fixed and volatile oils.

All liniments should bear a label indicating that they are suitable only for external use and must never be taken internally. Liniments that are emulsions or that contain insoluble matter must be shaken thoroughly before use to ensure even distribution of the dispersed phase, and these preparations should be labeled shake well. Liniments should be stored in tight containers. Depending on their individual ingredients, liniments are prepared in the same manner as solutions, emulsions, or suspensions, as the case may warrant.

Collodions
Collodions are liquid preparations composed of pyroxylin dissolved in a solvent mixture usually composed of alcohol and ether with or without added medicinal substances. Pyroxylin (i.e., nitrocellulose, soluble gun cotton, collodion cotton), obtained by the action of a mixture of nitric and sulfuric acids on cotton, consists chiefly of cellulose tetranitrate. It has the appearance of raw cotton when dry but is harsh to the touch. It is frequently available commercially moistened with about 30% alcohol or other similar solvent.

One part of pyroxylin is slowly but completely soluble in 25 parts of a mixture of 3 volumes of ether and 1 volume of alcohol. It is also soluble in acetone and glacial acetic acid. Pyroxylin is precipitated from solution in these solvents upon the addition of water. Pyroxylin, like collodions, is exceedingly flammable and must be stored away from flame in well-closed containers, protected from light.

Collodions are intended for external use. When applied to the skin with a fine camel’s hair brush or glass applicator, the solvent rapidly evaporates, leaving a filmy residue of pyroxylin. This provides an occlusive protective coating to the skin, and when the collodion is medicated, it leaves a thin layer of that medication firmly placed against the skin. Naturally, collodions must be applied to dry tissues to adhere to the skin’s surface. The products must be clearly labeled “for external use only” or with words of similar effect.

Collodion
Collodion is a clear or slightly opalescent viscous liquid prepared by dissolving pyroxylin (4%w/v) in a 3:1 mixture of ether and alcohol. The resulting solution is highly volatile and flammable and should be preserved in a tight container remote from fire at a temperature not exceeding 30°C.

The product is capable of forming a protective film on application to the skin and the volatilization of the solvent. The film is useful in holding the edges of an incised wound together. However, its presence on the skin is uncomfortable because of its inflexible nature. The following product, which is flexible, has a greater appeal when a pliable film is acceptable.

Flexible Collodion
Flexible collodion is prepared by adding 2% camphor and 3% castor oil to collodion. The castor oil renders the product flexible, permitting its comfortable use over skin areas that are normally moved, such as joints, fingers, and toes. The camphor makes the product waterproof. Physicians frequently apply the coating over bandages or stitched incisions to make them waterproof and to protect them from external stress.

Salicylic Acid Collodion
Salicylic acid collodion is a 10% solution of salicylic acid in flexible collodion. It is used for its keratolytic effects, especially in the removal of corns from the toes. Patients who use such products should be advised about their proper use. The product should be applied one drop at a time on the corn or wart, allowing time to dry before the next
drop is added. Because salicylic acid can irritate normal, healthy skin, every attempt must be made to ensure application directly on the corn or wart. A useful preventive measure is to line the adjacent healthy skin with some white petrolatum prior to application of the product. Proper tightening and storage of the product after use are absolutely necessary because of the volatility of the vehicle.

**EXTRACTION METHODS FOR PREPARING SOLUTIONS**

Certain pharmaceutical preparations are prepared by extraction, that is, by withdrawal of desired constituents from crude drugs through the use of selected solvents in which the desired constituents are soluble. Crude drugs are vegetable or animal drugs that have undergone no other processes than collection, cleaning, and drying. Because each crude drug contains a number of constituents that may be soluble in a given solvent, the products of extraction, termed extracts, do not contain just a single constituent but rather varying constituents, depending on the drug used and the conditions of the extraction. Tinctures, fluidextracts, and extracts are the pharmaceutical products most commonly prepared from extracts.

Plant materials are composed of heterogeneous mixtures of constituents, some of which are pharmacologically active and others pharmacologically inactive and considered inert. Among the varied plant constituents are sugars, starches, mucilages, proteins, albumins, pectins, cellulose, gums, inorganic salts, fixed and volatile oils, resins, tannins, coloring materials, and a number of very active constituents such as alkaloids and glycosides. The solvent systems used in extraction are selected on the basis of their capacity to dissolve the maximum amount of desired active constituents and the minimum amount of undesired constituents.

In many instances, the active constituents of a plant drug are of the same general chemical type, have similar solubility characteristics, and can be simultaneously extracted with a single solvent or a single solvent mixture. Extraction concentrates the active constituents of a crude drug and removes from it the extraneous matter. In drug extraction, the solvent or solvent mixture is referred to as the menstruum, and the plant residue, which is exhausted of active constituents, is termed the marc.

The selection of the menstruum to use in the extraction of a crude drug is based primarily on its ability to dissolve the active constituents. Although water and alcohol and to a lesser extent glycerin are probably the most frequently employed solvents in drug extraction, acetic acid and organic solvents like ether may be used for special purposes.

Because of its ready availability, cheapness, and good solvent action for many plant constituents, water has some use in drug extraction, particularly in combination with other solvents. However, as a sole solvent, it has many disadvantages and is infrequently used alone. For one thing, most active plant constituents are complex organic chemical compounds that are less soluble in water than in alcohol. Although water has a great solvent action on such plant constituents as sugars, gums, starches, coloring principles, and tannins, most of these are not particularly desirable components of an extracted preparation. Water also tends to extract plant principles that separate upon standing in the extractive, leaving an undesired residue. Finally, unless preserved, aqueous preparations serve as excellent growth media for molds, yeasts, and bacteria. When water alone is employed as the menstruum, alcohol is frequently added to the extractive or to the final preparation as an antimicrobial preservative.

Hydroalcoholic mixtures are perhaps the most versatile and most widely employed menstrua. They combine the solvent effects of both water and alcohol, and the complete miscibility of these two agents permits flexible combining of the two agents to form solvent mixtures most suited to the extraction of the active principles from a particular drug. A hydroalcoholic menstruum generally provides inherent protection against microbial contamination and helps to prevent the separation of extracted material on standing. Alcohol is used alone as a menstruum only
when necessary because it is more expensive than hydroalcoholic mixtures.

Glycerin, a good solvent for many plant substances, is occasionally employed as a cosolvent with water or alcoholic menstrua because of its ability to extract and then prevent inert materials from precipitating upon standing. It is especially useful in this regard in preventing separation of tannin and tannin oxidation products in extractives. Because glycerin has preservative action, depending on its concentration in the final product, it may contribute to the stability of a pharmaceutical extractive.

**Methods of Extraction**

The principal methods of drug extraction are maceration and percolation. Generally, the method of extraction selected for a given drug depends on several factors, including the nature of the crude drug, its adaptability to each of the various extraction methods, and the interest in obtaining complete or nearly complete extraction of the drug.

Frequently, a combination of maceration and percolation is actually employed in the extraction of a crude drug. The drug is macerated first to soften the plant tissues and to dissolve much of the active constituents, and percolation separates the extractive from the marc.

**Maceration**

The term maceration comes from the Latin *macerrare*, meaning to soak. It is a process in which the properly comminuted drug is permitted to soak in the menstruum until the cellular structure is softened and penetrated by the menstruum and the soluble constituents are dissolved.

In the maceration process, the drug to be extracted is generally placed in a wide-mouthed container with the prescribed menstruum, the vessel is stoppered tightly, and the contents are agitated repeatedly over a period usually ranging from 2 to 14 days. The agitation permits the repeated flow of fresh solvent over the entire surface area of the comminuted drug. An alternative to repeated shaking is to place the drug in a porous cloth bag that is tied and suspended in the upper portion of the menstruum, much the same as a tea bag is suspended in water to make a cup of tea. As the soluble constituents dissolve in the menstruum, they tend to settle to the bottom because of an increase in the specific gravity of the liquid due to its added weight. Occasional dipping of the drug bag may facilitate the speed of the extraction. The extractive is separated from the marc by expressing the bag of drug and washing it with additional fresh menstruum, the washings being added to the extractive. If the maceration is performed with the drug loose, the marc may be removed by straining and/or filtration, with the marc being washed free of extractive by the additional passage of menstruum through the strainer or filter into the total extractive.

For drugs containing little or no cellular material, such as benzoin, aloe, and Tolu, which dissolve almost completely in the menstruum, maceration is the most efficient method of extraction.

Maceration is usually conducted at a temperature of 15°C to 20°C for 3 days or until the soluble matter is dissolved.

**Percolation**

The term *percolation*, from the Latin *per*, meaning through, and *colare*, meaning to strain, may be described generally as a process in which a comminuted drug is extracted of its soluble constituents by the slow passage of a suitable solvent through a column of the drug. The drug is packed in a special extraction apparatus termed a percolator, with the collected extractive called the percolate. Most drug extractions are performed by percolation, a process whereby coffee is routinely prepared.

In the process of percolation, the flow of the menstruum over the drug column is generally downward to the exit orifice, drawn by the force of gravity as well as the weight of the column of liquid. In certain specialized and more sophisticated percolation apparatus, additional pressure on the column is exerted with positive air pressure at the inlet and suction at the outlet or exit.

Percolators for drug extraction vary greatly as to their shape, capacities, composition,
and, most important, utility. Percolators employed in the large-scale industrial preparation of extractives are generally stainless steel or glass-lined metal vessels that vary greatly in size and in operation. Percolators used to extract leaves, for instance, may be 6 to 8 feet in diameter and 12 to 18 feet high. Other vegetable parts like seeds that are greater in density than leaves and would pack too tightly in percolators of such large dimensions are extracted in much smaller percolators. Some special industrial percolators are designed to percolate with hot menstrua; in others, pressure is used to force the menstruum through the drug columns.

Percolation on a small scale generally involves the use of glass percolators of various shapes for extraction of small amounts (perhaps up to 1,000 g) of crude drug. The shapes of percolators in common laboratory and small-scale use are (a) cylindrical, with little, if any, taper except for the lower orifice; (b) roundish, but with a definite taper downward; and (c) conical, or funnel shaped. Each type has a special utility in drug extraction.

The cylindrical percolator is particularly suited to the complete extraction of drugs with a minimal expenditure of menstruum. By the passage of the menstruum over the drug contained in a high, narrow column (rather than in a lower, wider column), each drug particle is more repeatedly exposed to the passing solvent. A funnel-shaped percolator is useful for drugs that swell a great deal during maceration, because the large upper surface permits expansion of the drug column with little risk of a too tightly packed column or breakage of a glass percolator.

**Example Preparations Prepared by Extraction Processes**

**Fluidextracts**

Fluidextracts are liquid preparations of vegetable drugs prepared by percolation. They contain alcohol as a solvent, preservative, or both and are made so that each milliliter contains the therapeutic constituents of 1 g of the standard drug that it represents. Because of their concentrated nature, many fluidextracts are considered too potent to be safely self-administered, and their use per se is almost nonexistent in medical practice. Also, many fluidextracts are simply too bitter tasting or otherwise unpalatable to be accepted by the patient. Therefore, most fluidextracts today are either modified by the addition of flavoring or sweetening agents before use or used as the drug source of other liquid dosage forms, such as syrups.

**Extracts**

Extracts are concentrated preparations of vegetable or animal drugs obtained by removal of the active constituents of the respective drugs with suitable menstrua, evaporation of all or nearly all of the solvent, and adjustment of the residual masses or powders to the prescribed standards.

Extracts are potent preparations, usually between two and six times as potent on a weight basis as the crude drug. They contain primarily the active constituents of the crude drug, with a great portion of the inactive constituents and structural components of the crude drug having been removed. Their function is to provide in small amounts and in convenient, stable physical form the medicinal activity and character of the bulkier plants that they represent. As such, they have use in product formulation.

In the manufacture of most extracts, percolation is employed to remove the active constituents from the drug, with the percolates generally being reduced in volume by distillation under reduced pressure to reduce the degree of heat and to protect the drug substances against thermal decomposition. The extent of removal of the solvent determines the final physical character of the extract. Extracts are made in three forms: (a) semiliquid extracts or those of a syrupy consistency prepared without the intent of removing all or even most of the menstruum, (b) pilular or solid extracts of a plastic consistency prepared with nearly all of the menstruum removed, and (c) powdered extracts prepared to be dry by the removal of all of the menstruum insofar as is feasible or practical. Pilular and powdered extracts differ only by the slight amount of remaining
solvent in the former preparation, but each has its pharmaceutical advantage because of its physical form. For instance, the pilular extract is preferred in compounding a plastic dosage form such as an ointment or paste or one in which a pliable material facilitates compounding, whereas the powdered form is preferred in the compounding of such dosage forms as powders, capsules, and tablets.

**Pharmaceutics Case Study**

**Subjective Information**

You have been given the responsibility of formulating a new oral solution containing a nasal decongestant (phenylephrine) and cough suppressant (dextromethorphan) for treating the symptoms of a cold or influenza. The oral solution should have a reasonably pleasant taste and appearance, be stable and preserved, and contain a suitable dose combination so that one or two teaspoonfuls can be used per administration to a 6- to 12-year-old child.

**Objective Information**

*Phenylephrine hydrochloride* \((C_9H_{13}NO_2\cdot HCl)\), molecular weight 203.67, is the salt form selected for this drug. Phenylephrine hydrochloride occurs as white or nearly white odorless crystals with a bitter taste. It melts at 140°C to 145°C (284°F to 293°F). It is freely soluble in water and in alcohol. It is stable in aqueous solution below pH 7. Above pH 7, degradation occurs apparently involving the side chain, with loss of the secondary amine function; the phenolic group remains intact. The presence of heavy metals, especially copper, can catalyze the decomposition. It has two dissociation constant \((pK_a)\) values, one at 8.77 and one at 9.84.

*Dextromethorphan* \((C_{18}H_{25}NO)\), molecular weight 271.40, is a practically white to slightly yellow odorless crystalline powder that melts at 109.5°C to 112.5°C (229°F to 234.5°F). It is practically insoluble in water. Dextromethorphan hydrobromide \((C_{18}H_{25}NO\cdot HBr\cdot H_2O)\), molecular weight 370.32) occurs as practically white crystals or crystalline powder with a faint odor and a melting range of 124°C to 126°C (255°F to 259°F). It is freely soluble in alcohol. It is stable in aqueous and hydroalcoholic solutions.

**Assessment**

The two drugs should be soluble and stable in a slightly acidic oral solution consisting of water and alcohol. The vehicle should be slightly thickened by a viscosity-increasing additive; it also should be sweetened and flavored. These drugs are bitter, so a flavor that will help mask the bitterness must be selected. The addition of a small amount of menthol may also be considered as a flavor enhancer. An appropriate preservative must be selected.

**Plan**

An aqueous solution consisting of water, alcohol (low concentration, such as 5%), and glycerin (10%) adjusted to a pH in the range of 4 to 5 should be reasonable. Sucrose can be added as a sweetener (40%) and also for its viscosity-enhancing effect. A small amount of sorbitol (10%) will help give a smooth mouth feel and minimize cap lock of the container. Several flavor combinations can work, but raspberry and marshmallow work nicely to cover the bitter tastes of drugs. A blend of 0.05% methylparaben and 0.02% propylparaben can be added as a preservative. The addition of about 0.25% menthol will further enhance the flavoring and also impart an additional aromatic effect.
HPI: Late one evening at the local pharmacy, the pharmacist notices a woman searching aimlessly in the nonprescription medication aisle. In hopes of being able to help this customer, the pharmacist approaches the woman and asks if he can help her find anything. The woman replies, “My husband and I are taking a family vacation to Florida tomorrow, and my son gets sick to his stomach when he flies. I was trying to find something that he could take for motion sickness.” After asking the woman a few questions, the pharmacist discovers that her 5-year-old son is quite finicky and will not take tablets, including chewables. The pharmacist recalls a similar situation from a while back for which he compounded an oral solution of dimenhydrinate (Dramamine), and he asked the woman if this would be a suitable option for her son. The woman expressed much gratitude and asked the pharmacist if he could have the solution ready for her by the morning. The pharmacist said that would be fine, and he obtained the following information about her son, J.M.

PMH: Motion sickness
Recurrent ear infections

SH: None

FH: Mother (−)
Father (+) for hypertension

ALL: NKDA

MEDS: None

PHARMACEUTICAL CARE PLAN

S: Mother states that her “finicky” son will not take oral tablets, including chewables.

O: Dimenhydrinate, a common nonprescription medication used for motion sickness, is no longer available in liquid form.

A: J.M. is a 5-year-old WM who has motion sickness on airplanes, and his family is leaving on vacation in the morning. Because the patient will not take tablets, the pharmacist plans to compound an oral solution of dimenhydrinate. The patient does not have any present medical conditions or a medication history that would contraindicate the use of dimenhydrinate.

P: 1. The pharmacist decides that to make the compound, he must first review information on the solubility and stability of dimenhydrinate. To do so, he consults Remington (9), where he reads that dimenhydrinate is “slightly soluble in water and freely soluble in alcohol and chloroform.”

2. Although the pharmacist has prepared this solution before, he does not remember exactly how he did so. He does, however, remember that in the *US Pharmacist* journal, there is a monthly Contemporary Compounding section, which he thinks may be useful. He scans the journal archives in the pharmacy until he finds the article “Oral Solution Stops Motion Sickness” (10). He secures the appropriate issue and reads the article to review how to prepare the dimenhydrinate solution.

3. Following the methods for preparation outlined in this article, the pharmacist prepares the compound from the following formula:

4. Rx:
5. Dimenhydrinate 12.5 mg/5 mL oral solution
6. Dimenhydrinate 250 mg
7. Glycerin qs
8. Ora-Plus 50 mL
9. Ora-Sweet or Ora-Sweet SF qs 100 mL
10. As the article suggests, the pharmacist packages the solution in a tight, light-resistant container. In addition, he labels the bottle as directed, keep out of the reach of children, may cause drowsiness, and contents should be discarded (6 months from the date of preparation).

11. The pharmacist is working the next morning, so he plans to counsel the woman on her son’s medication at that time. Based on the dimenhydrinate package directions, a 5-year-old child should take one-quarter to one-half of a tablet every 6 to 8 hours, not to exceed one and a half tablets in 24 hours or as directed by a doctor. Each manufactured tablet contains dimenhydrinate 50 mg, and the compounded oral solution contains dimenhydrinate 12.5 mg/5 mL. Thus, the pharmacist should instruct the woman to give J.M. 1 to 2 teaspoonfuls by mouth every 6 to 8 hours, not to exceed 5 teaspoonfuls every 24 hours. Because dimenhydrinate’s onset of action is approximately 30 minutes, the pharmacist recommends that J. M. take the first dose about 30 minutes prior to the flight departure.

12. In addition to dosage information, the pharmacist counsels the mother on the possible side effects. The most common is drowsiness, which should prove useful in this situation. Other adverse effects include a dry mouth and constipation. However, these can be relieved or prevented by drinking plenty of fluid.

13. Finally, the pharmacist reminds the mother that the solution may be stored at room temperature until the expiration date. After that time, any remaining contents should be discarded. The pharmacist also gives the directions from the dimenhydrinate package along with the remaining tablets so that the patient and his family have the important product information that should accompany the medication (9,10).

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Compare and contrast the useful properties of various solvents used in liquid dosage forms.

2. Name medicinal preparations that utilize each of the following solvents: ethyl alcohol, diluted alcohol, rubbing alcohol, glycerin, isopropyl alcohol, propylene glycol, and purified water.

3. Consult the FDA Center for Drug Evaluation and Research’s Data Standards Manual web site and distinguish which dosage forms are liquid formulations.

4. Discuss pertinent patient counseling points regarding each liquid dosage form.

5. Define the following and explain benefits for use and contraindications for use of syrups, elixirs, topical solutions, tinctures, and fluid extracts.

6. Amass a number of extemporaneous compounded prescriptions, which use liquids within their formulation.

7. List specific patient circumstances and therapeutic circumstances where alcoholic liquid dosage forms would be contraindicated.

8. Describe common indications for oral solutions and how these liquid formulations have improved patient medication adherence.
Individual Activities

1. Name a prescription or nonprescription product that utilizes each of the following solvents: Alcohol USP, diluted alcohol, rubbing alcohol, glycerin, isopropyl rubbing alcohol, propylene glycol, and purified water.

2. Identify two advantages of purifying water with the ion exchange method versus the distillation method.
   a. Describe two methods utilized to increase the rate of solute dissolution in a given solvent, and provide an example of each.

3. List the four main components of syrups and the role each play in the final formulation.

REFERENCES