CHAPTER 86

Solutions, Emulsions, Suspensions and Extracts

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The dosage forms described in this chapter may be prepared by dissolving the active ingredient(s) in an aqueous or nonaqueous solvent, by suspending the drug (if it is insoluble in pharmaceutically or therapeutically acceptable solvents) in an appropriate medium or by incorporating the medicinal agent into one of the two phases of an oil and water system. Such solutions, suspensions and emulsions are further defined in subsequent paragraphs but some, with similar properties, are considered elsewhere. These dosage forms are useful for a number of reasons. They can be formulated for different routes of administration: oral use, introduction into body cavities or applied externally. The dose easily can be adjusted by dilution, and the oral liquid form readily can be administered to children or people unable to swallow tablets or capsules. Extracts eliminate the need to isolate the drug in pure form, allow several ingredients to be administered from a single source (eg, pancreatic extract) and permit the preliminary study of drugs from natural sources. Occasionally, solutions of drugs such as potassium chloride are used to minimize adverse effects in the gastrointestinal tract.

The preparation of these dosage forms involves several considerations on the part of the pharmacist: purpose of the drug, internal or external use, concentration of the drug, selection of the liquid vehicle, physical and chemical stability of the drug, preservation of the preparation and use of appropriate excipients such as buffers, solubilizers, suspending agents, emulsifying agents, viscosity controlling agents, colors and flavors. Oral preparations require that consideration be given to improving patient compliance by making an acceptable product; consequently, color, odor and taste must be considered. These organoleptic factors are described in Chapter 80. The viscosity of a product also must be considered in order that it has the proper palatability for an oral preparation and to have the appropriate suspending properties if it is an emulsion or suspension. The theory pertaining to these systems is provided in Chapters 21 and 22. The theory of solutions, which involves solubility, ionization, pH control through the use of buffers and solubilization, is discussed in Chapters 16 and 17. Because of the complexity of some manufactured products, compounding may be carried out with the aid of linear programming models in order to obtain the optimal product. Chapters (87 to 89) should be consulted for information on the preparation and characteristics of those liquid preparations that are intended for ophthalmic or parenteral use.

Much has been written during the past decade about the biopharmaceutical properties of, in particular, the solid dosage forms. In assessing the bioavailability of drugs in tablets and capsules, many researchers first have studied the absorption of drugs administered in solution. Since drugs are absorbed in their dissolved state, frequently it is found that the absorption rate of oral dosage forms decreases in the following order: aqueous solution > aqueous suspension > tablet or capsule. The bioavailability of a medicament, for oral ingestion and absorption, should be such that eventually all of the drug is absorbed as it passes through the gastrointestinal tract, regardless of the dosage form. Some formulation factors which may influence the bioavailability and pharmacokinetics of drugs in solution include concentration of the drug, volume of liquid administered, pH, buffer capacity and viscosity. Emulsions and suspensions are more complex systems and consequently the extent of absorption and pharmacokinetic parameters may be affected by a number of additional formulation factors such as surfactants, type of viscosity agent, particle size and particle-size distribution, polymorphism and solubility of drug in the oil phase. Specific examples are provided in Chapter 19. There are a number of reasons for formulating drugs in forms in which the drug is not in the molecular state. These are improved stability, improved taste, low water solubility, palatability and ease of administration. It becomes apparent, then, that each dosage form will have advantages and disadvantages.

Liquid preparations may be dispensed in one of three ways. The pharmacist may dispense the product in its original container, buy the product in bulk and repackage it at the time a prescription is presented by the patient or compound the solution, suspension or emulsion in the dispensary. Compounding may involve nothing more than mixing marketed products in the manner indicated on the prescription or, in specific instances, may require the incorporation of active ingredients in a logical and pharmaceutically acceptable manner into the aqueous or nonaqueous solvents which will form the bulk of the product.

The pharmacist, in the first instance, depends on the pharmaceutical manufacturer to produce a product that is effective, elegant and stable when stored under reasonably adverse conditions. Most manufacturers attempt to guarantee efficacy by evaluating their products in a scientifically acceptable manner but, in some instances, such efficacy is relative. For example, cough mixtures marketed by two different manufacturers may contain the same active ingredients and it becomes difficult to assess the relative merits of the two products. In such instances the commercial advantage gained by one over the other may be based on product acceptability and preference which includes such factors as color, odor, taste, pourability, uniformity and packaging. Two additional important factors which must be considered in formulations are the stability of active and other ingredients, and the prevention of microbial contamination.

The stability of the active ingredient in the final product is of prime concern to the formulator. In general, drug substances are less stable in aqueous media than in the solid dosage form and it is important, therefore, to properly stabilize and preserve, in particular those solutions, suspensions and emulsions that contain water. Certain simple chemical reactions can occur in these products. These may involve an ingredient-ingredient interaction which implies a poor formulation, a container-product interaction which may alter product pH and thus, for pH-sensitive ingredients, be responsible for the subsequent formation of precipitates or a direct reaction with water, ie, hydrolysis. The stability of pharmaceutical products is discussed in Chapter 38.

The more complicated reactions usually involve oxygen. Vitamins, essential oils and almost all fats and oils can be oxidized. Formulators usually use the word *autoxidation*

when the ingredient(s) in the product react with oxygen but without drastic external interference. Such reactions first must be initiated by heat, light (including ultraviolet radiant energy), peroxides or other labile compounds or heavy metals such as copper or iron. This initiation step results in the formation of a free radical (R*) which then reacts with oxygen.

$$R^* + O_2 \rightarrow RO_2^* \text{ (peroxy radical)}$$

$$RO_2^* + RH \rightarrow ROOH + R^*$$

The free radical thus is regenerated and reacts with more oxygen. This propagation step is followed by the termination reactions.

$$RO_2^* + RO_2^* \rightarrow \text{inactive product}$$

$$RO_2^* + R^* \rightarrow \text{inactive product}$$

$$R^* + R^* \rightarrow \text{inactive product}$$

The effect of trace metals can be minimized by using citric acid or EDTA ie, sequestering agents. Antioxidants, however, may retard or delay oxidation by reacting with the free radicals formed in the product. Examples of antioxidants are the propyl, octyl and dodecyl esters of gallic acid, butylated hydroxyanisole (BHA) and the tocopherols or vitamin E. For a more detailed approach to the prevention of oxidative deterioration in pharmaceuticals, the information provided by Connors *et al*[1] should be consulted. A description of many antioxidants is given in Chapter 80.

The problem of drug stability has been well-defined by pharmaceutical scientists, but during the past few years a secondary and, in some respects, more serious problem has confronted the manufacturer of liquid preparations. Such pharmaceutically diverse products as baby lotions and milk of magnesia have been recalled from the market because of microbial contamination. In a survey of retail packages of liquid antacid preparations containing magnesium hydroxide, it was found that 30.5% of the finished bottles were contaminated with *Pseudomonas aeruginosa*. The aerobic plate count ranged from less than 100 to 9,300,000 organisms/g. Kurup and Wan[2] describe many preparations that are not preserved adequately and thus are not able to resist microbial contamination. Other examples could be cited but the range of microorganisms which can contaminate the liquid preparation includes the *Salmonella* sp, *E coli*, certain *Pseudomonas* sp, including *P aeruginosa*, and *Staphylococcus aureus*. Bruch[3] describes the types of microorganisms found in various products and attempts to evaluate the hazards associated with the use of nonsterile pharmaceuticals. Coates[4] in a series of papers describes various interactions which must be considered when preservatives are selected.

The USP recommends that certain classes of products be tested for microbial count and for specified indicator microbial contaminants, eg, natural plant, animal and some mineral products, for freedom from *Salmonella* sp; oral solutions and suspensions, for freedom from *E coli*; articles applied topically, for freedom from *P aeruginosa* and *S aureus* and articles for rectal, urethral or vaginal administration, for yeasts and molds.

Products may become contaminated for a number of reasons.

The raw materials used in the manufacture of solutions, suspensions and emulsions are excellent growth media for bacteria. Water, in particular, must be handled with care but substances such as gums, dispersing agents, surfactants, sugars and flavors can be the carriers of bacteria which ultimately contaminate the product.

Equipment. Bacteria grow well in the nooks and crevices of pharmaceutical equipment (and in the simple equipment used in the dispensary). Such equipment should be cleaned thoroughly prior to use.

Environment and personnel can contribute to product contamination. Hands and hair are the most important carriers of contaminants. General cleanliness thus is vital. Head coverings must be used by those involved in the manufacturing process and face masks should be used by those individuals suffering from colds, coughs, hay fever and other allergic manifestations.

Packaging should be selected so that it will not contaminate the product and also will protect it from the environment.

Finally, consumer use may result in the introduction of microorganisms as a source of contamination, and this is of particular concern if the organism is pathogenic. The consumer should be instructed in the proper technique in order to minimize contamination, and the manufacturer should ensure, through the use of suitable challenge tests, that the product is preserved appropriately and will reduce a severe microbial challenge.

Most factors cited above relate to good manufacturing practice. However, the formulator should add a preservative to the product and decrease the probability of product contamination. If the product contains water, which is an important requirement for microbial growth, it almost is mandatory to include a preservative in the formulation. Nearly all products described in this chapter contain water and, thus, with certain exceptions, eg, aqueous acids, will support microbial growth. Microbes will grow in an aqueous solution, and in the aqueous phase of multiphase systems such as emulsions and suspensions. It must be stressed that the addition of an appropriate preservative in no way replaces good manufacturing practice but merely provides further assurance that the product will retain its pharmaceutically acceptable characteristics until it is used by the patient and for sometime thereafter.

The major criteria that should be considered in selecting a preservative are as follows: it should be effective against a wide spectrum of microorganisms, stable for its shelf life, nontoxic, nonsensitizing, compatible with the ingredients in the dosage form inexpensive and essentially relatively free of taste and odor.

In addition to the above discussion, there are a number of specific factors which should be taken into account when a preservative is selected:

1. The site of use, eg, external, internal or ophthalmic.
2. The pH of the liquid, as it may affect both the ionization of the preservative and its stability.
3. The solvent, as this will affect the solubility of the preservative.
4. Partitioning into the oil phase of an emulsion, thereby reducing the concentration in the aqueous phase where preservative action takes place.
5. Adsorption onto the solid phase of a suspension, thereby reducing the concentration in the aqueous phase.
6. Processing and packaging variables such as heat, order of addition of the ingredients, stirring or container materials.
7. Type of dosage form, eg, solution, emulsion or suspension.

Preservatives[5,6] may be grouped into a number of classes depending upon their molecular structure and only a few will be discussed. The reader should consult Chapter 80 or selected texts in the bibliography for further description.

Alcohols—Ethanol is useful as a preservative when it is used as a solvent; however, it does need a relatively high concentration, somewhat greater than 10%, to be effective. Too high a concentration may result in incompatibilities in suspension and emulsion systems. Propylene glycol also is used as a solvent in oral solutions and topical preparations, and it can function as a preservative in the range of 15 to 30%. It is not volatile like ethanol and is used frequently not only in solutions but also in suspensions and emulsions. Other alcohols used in lower concentrations, about 1%, for preservative action, include chlorobutanol and phenylethyl alcohol.

Acids—Benzoic acid has a low solubility in water, about 0.34% at 25°. The concentration range used for inhibitory action varies from 0.1% to 0.5%. Only the nonionized form is effective and therefore its use is restricted to preparations with a pH below 4.5. Sorbic acid also has a low solubility in water, 0.3% at 30°. Suitable concentrations for preservative action are in the range of 0.05 to 2%. Its preservative action is due to the nonionized form; consequently, it is only effective in acid media. Because of the double bond in its structure, it is subject to oxidation.

Esters—Parabens are esters of *p*-hydroxybenzoic acid and include the methyl, ethyl, propyl and butyl derivatives. The solubility in water decreases as the molecular weight increases from 0.25% for the methyl ester to 0.02% for the butyl ester. These compounds are used widely in pharmaceutical products and are effective and stable over a pH range of 4 to 8. They are employed at concentrations up to about 0.2%. Frequently, two esters are used in combination in the same preparation. This achieves a higher total concentration, and the mixture tends to be active against a wider range of microorganisms. Their activity is reduced in the presence of nonionic surface active agents due to binding. In alkaline solutions, ionization takes place and this reduces their activity; in addition, hydrolytic decomposition of the ester group occurs with a loss of activity.

Quaternary Ammonium Compounds—Benzalkonium chloride is a mixture consisting principally of the homologs $C_{12}H_{25}$ and $C_{14}H_{29}$. This preservative is used at a relatively low concentration, 0.002 to 0.02%, depending on the nature of the pharmaceutical product. This class of compounds has an optimal activity over the pH range of 4 to 10 and is quite stable at room temperature. Because of the cationic nature of this type of preservative, it is incompatible with many anionic compounds such as surfactants and can bind to nonionic surfactants. It is used generally in preparations for external use or those solutions which come in contact with mucous membranes.

It now should be obvious that when the pharmacist dispenses or compounds the various liquid preparations responsibility is assumed along, with the manufacturer, for the maintenance of product stability. The USP includes a section on stability considerations in dispensing, which should be studied in detail. Certain points are self-evident. Stock should be rotated and replaced if expiration dates on the label so indicate. Products should be stored in the manner indicated in the compendium; eg, in a cool place or a tight, light-resistant container. Further, products should be checked for evidence of instability. With respect to solutions, elixirs and syrups, color change, precipitation and evidence of microbial or chemical gas formation are major signs of instability. Emulsions may cream but if they break (ie, there is a separation of an oil phase) the product is considered to be unstable. Sedimentation and caking are primary indications of instability in suspensions. The presence of large particles may mean that excessive crystal growth has occurred.

The USP states that if the product must be repackaged, care and the container specified by the compendium must be used. For example, a suitably opaque plastic container should be used if a light-resistant container is specified. If a product is diluted, or where two products are mixed, the pharmacist should use his or her knowledge to guard against incompatibility and instability. Oral antibiotic preparations constituted into liquid form should never be mixed with other products. If the chemical stability of extemporaneously prepared liquid preparations is unknown, their use should be minimized and every care taken to insure that product characteristics will not change during the time it must be used by the patient.

Because of the number of excipients and additives in these preparations, it is recommended that all the ingredients be listed on the container to reduce the risks which confront hypersensitive patients when these products are administered. Finally, the pharmacist should inform the patient regarding the appropriate use of the product, the proper storage conditions and the time after which it should be discarded.

Solutions

Aqueous Solutions

A solution is a homogeneous mixture that is prepared by dissolving a solid, liquid or gas in another liquid and represents a group of preparations in which the molecules of the solute or dissolved substance are dispersed among those of the solvent. Solutions also may be classified on the basis of physical or chemical properties, method of preparation, use, physical state, number of ingredients and particle size. The narrower definition in this subsection limits the solvent to water and excludes those preparations that are sweet and/or viscid in character and nonaqueous solutions. This section includes, therefore, those pharmaceutical forms that are designated as *Water*, *Aromatic Waters*, *Aqueous Acids*, *Solutions*, *Douches*, *Enemas*, *Gargles*, *Mouthwashes*, *Juices*, *Nasal Solutions*, *Otic Solutions* and *Irrigation Solutions*.

Water

The major ingredient in most of the dosage forms described herein is water. It is used both as a vehicle and as a solvent for the desired flavoring or medicinal ingredients. Its tastelessness, freedom from irritating qualities and lack of pharmacological activity make it ideal for such purposes. There is, however, a tendency to assume that its purity is constant and that it can be stored, handled and used with a minimum of care. While it is true that municipal supplies must comply with Environmental Protection Agency (EPA) regulations (or comparable regulations in other countries), drinking water *must* be repurified before it can be used in pharmaceuticals. For further information on water, see Chapter 23.

Five of the six solvent waters described in the USP are used in the preparation of parenterals, irrigations or inhalations. *Purified Water* must be used for all other pharmaceutical operations, dosage forms and, as needed, in all USP tests and assays. It must meet rigid specifications for chemical purity. Such water may be prepared by distillation, by use of ion-exchange resins or by reverse osmosis.

A wide variety of commercially available stills are used to produce distilled water. The end use of the product dictates the size of the still and extent of pretreatment of the drinking water introduced into the system. A description of stills is provided in Chapter 87. Such water may be sterile provided the condenser is sterile, but to be called sterile it must be subjected to a satisfactory sterilization process. However, it has been shown that *P aeruginosa* (and other microorganisms) can grow in the distilled water produced in hospitals. The implications of this are obvious. Sterile water may be sterile at the time of production but may lose this characteristic if it is stored improperly. Hickman *et al*,[7] by regrouping the components of conventional distillation equipment, have described a method for the continuous supply of sterile, ultrapure water. Quality-control procedures for monitoring the microbiological quality of water should be performed in the pharmaceutical manufacturer's production facilities.

The major impurities in water are calcium, iron, magnesium, manganese, silica and sodium. The cations usually are combined with the bicarbonate, sulfate or chloride anions. "Hard" waters are those that contain calcium and magnesium cations. Bicarbonates are the major impurity in "alkaline" waters.

Ion-exchange (deionization, demineralization) processes will remove most of the major impurities in water efficiently and economically. A cation exchanger, H_2R, first converts bicarbonates, sulfates and chlorides to their respective acids, eg,

$$\left.\begin{matrix} CaSO_4 \\ MgSO_4 \\ Na_2SO_4 \end{matrix}\right| + H_2R \rightarrow \left|\begin{matrix} Ca \\ Mg \\ Na_2 \end{matrix}\right| R + H_2SO_4$$

$$\left.\begin{matrix} Ca(HCO_3)_2 \\ Mg(HCO_3)_2 \\ 2NaHCO_3 \end{matrix}\right| + H_2R \rightarrow \left|\begin{matrix} Ca \\ Mg \\ Na_2 \end{matrix}\right| R + 2H_2CO_3$$

Carbonic acid decomposes to carbon dioxide (which is removed by aeration in the decarbonator) and water.

The anion exchanger may contain either a weakly basic or a strongly basic anion resin. These adsorb sulfuric, hydrochloric and nitric acids. Chemical reactions may involve complete adsorption or an exchange with some other anion.

$$H_2SO_4 + A \rightarrow A \cdot H_2SO_4$$

If the resin contains a hydroxyl group, water is formed during the purification process.

$$H_2SO_4 + 2AOH \rightarrow A_2SO_4 + 2H_2O$$

Weakly dissociated carbonic and silicic acids can be removed only by strongly basic anion resins.

$$H_2SiO_3 + 2AOH \rightarrow A_2SiO_2 + 2H_2O$$

Unit capacity varies with the nature of the installation, but it is possible to process as much as 15,000 gal of water/min.

Deionization processes do not necessarily produce *Purified Water* which will comply with EPA requirements for drinking water. Resin columns retain phosphates and organic debris. Either alone or in combination, these substances can act as growth media for microorganisms. Observations have shown that deionized water containing 90 organisms/mL contained, after 24-hour storage, 10^6 organisms/mL. Columns can be cleaned partially of pseudomonads by recharging, but a 0.25% solution of formaldehyde will destroy most bacteria. The column must be washed thoroughly and checked for the absence of aldehyde (with a Schiffs Reagent) before it can be used to generate deionized water.

Ultraviolet radiant energy (240–280 nm), heat or filtration can be used to limit the growth, kill or remove microorganisms in water. The latter method employs membrane filters and can be used to remove bacteria from heat-labile materials as described under membrane filters in Chapter 84.

The phenomenon of osmosis involves the passage of water from a dilute solution across a semipermeable membrane to a more concentrated solution. Flow of water can be stopped by applying pressure, equal to the osmotic pressure, to the concentrated solution. The flow of water can be reversed by applying a pressure, greater than the osmotic pressure. The process of reverse osmosis utilizes the latter principle; by applying pressure, greater than the osmotic pressure, to the concentrated solution, eg, tap water, pure water may be obtained (see *Reverse Osmosis* in Chapter 37).

Cellulose acetate is used in the manufacture of semipermeable membranes for purifying water by reverse osmosis. This polymer has functional groups that can hydrogen-bond to water or other substances such as alcohol. The water molecules which enter the polymer are transported from one bonding site to the next under pressure. Because of the thin layer of pure water strongly adsorbed at the surface of the membrane, salts, to a large extent, are repelled from the surface, the higher-valent ions being repelled to a greater extent, thus causing a separation of ions from the water. Organic molecules are rejected on the basis of a sieve mechanism related to their size and shape. Small organic molecules, with a molecular weight smaller than approximately 200, will pass through the membrane material. Since there are few organic molecules with a molecular weight of less than 200 in the municipal water supply, reverse osmosis usually is sufficient for the removal of organic material. The pore sizes of the selectively permeable reverse-osmosis membranes are between 5 and 100 A. Viruses and bacteria larger than 100 A are rejected if no imperfections exist in the membrane. The membranes may and do develop openings which permit the passage of microorganisms. Because of the semistatic conditions, bacteria can grow both upstream and downstream of the membrane. Improvements in membranes are being made continually in type and manufacturing process such as the use of polyamide materials. It is expected that the preparation of water with negligible or no bacteria present will be achieved by this process.

The selection of water-treatment equipment depends upon the quality of water to be tested, the quality of water required and the specific pharmaceutical purpose of the water. Frequently, two or more methods are used to produce the water desired, for example, filtration and distillation, or filtration, reverse osmosis and ion exchange.

Aromatic Waters

Aromatic waters, known also as medicated waters, are clear, saturated aqueous solutions of volatile oils or other aromatic or volatile substances. Their odors and tastes are similar to those of the drugs or volatile substances from which they are prepared. They are used principally as flavored or perfumed vehicles. Aromatic Waters may be prepared by distillation or solution of the aromatic substance with or without the use of a dispersing agent such as talc. Peppermint Water USP and Stronger Rose Water USP are examples of aromatic waters.

Other methods have been suggested for preparing aromatic waters based on the use of soluble concentrates or on incorporation of solubilizing agents such as polysorbate 20.

Concentrated waters eg, peppermint, dill, cinnamon and caraway, may be prepared as follows:

Dissolve 20 mL of the volatile oil in 600 mL of 90% ethanol. Add sufficient purified water in successive small portions to produce 1000 mL. Shake vigorously after each addition. Add 50 g of sterilized purified talc, shake occasionally for several hours and filter.

The aromatic water is prepared by diluting the concentrate with 39 times its volume of water.

The chemical composition of many of the volatile oils is known and suitable synthetic substances may be used in preparing pharmaceuticals and cosmetics. Similarly, many synthetic aromatic substances have a characteristic odor; eg, geranyl phenyl acetate has a honey odor. Such substances, either alone or in combination, can be used in nonofficial preparations. Additional information regarding the appropriate preparation of aromatic waters is provided in RPS-18, Chapter 83, and RPS-17, Chapter 84.

The principal difficulty experienced in compounding prescriptions containing aromatic waters is due to a "salting out" action of certain ingredients, such as very soluble salts, on the volatile principle of the aromatic water. A replacement of part of the aromatic water with purified water is permissible when no other function is being served than that of a vehicle.

Preservation—Aromatic waters will deteriorate with time and should, therefore, be made in small quantities and protected from intense light, excessive heat and stored in airtight, light-resistant containers.

Aqueous Acids

The official inorganic acids and certain organic acids, although of minor significance as therapeutic agents, are of great importance in chemical and pharmaceutical manufacturing. This is especially true of acetic, hydrochloric and nitric acids.

Percentage Strengths—Many of the more important inorganic acids are available commercially in the form of concentrated aqueous solutions. The percentage strength varies from one acid to another and depends on the solubility and stability of the solute in water and on the manufacturing process. Thus, the official Hydrochloric Acid contains from 36.5 to 38% by weight of HCl, whereas Nitric Acid contains from 69 to 71% by weight of HNO_3.

Because the strengths of these concentrated acids are stated in terms of % by weight, it is essential that specific gravities also be provided if one is to be able to calculate conveniently the amount of absolute acid contained in a unit volume of the solution as purchased. The mathematical relationship involved is given by the equation $M = V \times S \times F$, where M is the mass in g of absolute acid contained in V mL of solution having a specific gravity S and a fractional percentage strength F. As an example, Hydrochloric Acid containing 36.93% by weight of HCl has a specific gravity of 1.1875. Therefore, the amount of absolute HCl supplied by 100 mL of this solution is given by:

$$M = 100 \times 1.1875 \times 0.3693 = 43.85 \text{ g HCl}$$

Incompatibilities—Although many of the reactions characteristic of acids offer opportunities for incompatibilities, only a few are of sufficient importance to require more than casual mention. Acids and acid salts decompose carbonates with liberation of carbon dioxide and, in a closed container, sufficient pressure may be developed to produce an explosion. Inorganic acids react with salts of organic acids to produce the free organic acid and a salt of the inorganic acid. If in-

soluble, the organic acid will be precipitated. Thus, salicylic acid and benzoic acid are precipitated from solutions of salicylates and benzoates. Boric acid likewise is precipitated from concentrated solutions of borates. By a similar reaction, certain soluble organic compounds are converted into an insoluble form. Phenobarbital sodium, for example, is converted into phenobarbital which will precipitate in aqueous solution.

The ability of acids to combine with alkaloids and other organic compounds containing a basic nitrogen atom is used in preparing soluble salts of these substances.

It should be borne in mind that certain solutions, syrups, elixirs and other pharmaceutical preparations, may contain free acid, which causes these preparations to exhibit the incompatibilities characteristic of the acid.

Acids also possess the incompatibilities of the anions which they contain and, in the case of organic acids, these are frequently of prime importance. These are discussed under the specific anions.

Diluted Acids—The diluted acids in the USP are aqueous solutions of acids, of a suitable strength (usually 10% *w/v* but Diluted Acetic Acid is 6% *w/v*) for internal administration or for the manufacture of other preparations.

The strengths of the official undiluted acids are expressed as percentages *w/w*, whereas the strengths of the official diluted acids are expressed as percent *w/v*. It, therefore, becomes necessary to consider the specific gravities of the concentrated acids when calculating the volume required to make a given quantity of diluted acid. The following equation will give the number of mL required to make 1000 mL of diluted acid:

$$\frac{\text{Strength of diluted acid} \times 1000}{\text{Strength of undiluted acid} \times \text{sp gr of undiluted acid}}$$

Thus, if one wishes to make 1000 mL of Diluted Hydrochloric Acid USP using Hydrochloric Acid which assays 37.5% HCl (sp gr 1.18), the amount required is

$$\frac{10 \times 1000}{37.5 \times 1.18} = 226 \text{ mL}$$

Diluted Hydrochloric Acid USP has been used in the treatment of achlorhydria. However, it may irritate the mucous membrane of the mouth and attack the enamel of the teeth. The usual dose is 5 mL, well-diluted with water. In the treatment of achlorhydria no attempt is made to administer more than a relief-producing dose.

Solutions

A solution, in the present context, is a liquid preparation that contains one or more soluble chemical substances dissolved in water. The solute usually is nonvolatile. Solutions are used for the specific therapeutic effect of the solute, either internally or externally. Although the emphasis here is on the aqueous solution, certain preparations of this type such as syrups, infusions and decoctions have distinctive characteristics and, therefore, are described later in the chapter.

Solvents, solubility and general methods for the incorporation of a solute in a solvent are discussed in Chapter 16. Solutions are usually bottled automatically with equipment of the type shown in Fig. 1.

Preparation—A specific method of preparation is given in the compendia for most solutions. These procedures fall into three main categories.

Simple Solutions—Solutions of this type are prepared by dissolving the solute in most of the solvent, mixing until dissolved, then adding sufficient solvent to bring the solution up to the proper volume. The solvent may contain other ingredients which stabilize or solubilize the active ingredient. Calcium Hydroxide Topical Solution USP (Lime Water), Sodium Phosphates Oral Solution USP and Strong Iodine Solution USP are examples.

Calcium Hydroxide Topical Solution contains, in each 100 mL, not less than 140 mg of $Ca(OH)_2$. The solution is prepared by agitating vigorously 3 g of calcium hydroxide with 1000 mL of cool, purified water. Excess calcium hydroxide is allowed to settle out and the clear, supernatant liquid dispensed.

An increase in solvent temperature usually implies an increase in solute solubility. This rule does not apply, however, to the solubility of calcium hydroxide in water, which decreases with increasing temperature. The official solution is prepared at 25°.

Solutions containing hydroxides react with the carbon dioxide in the atmosphere.

$$OH^- + CO_2 \rightarrow HCO_3^-$$

$$OH^- + HCO_3^- \rightarrow CO_3^{2-} + H_2O$$

Calcium Hydroxide Topical Solution, therefore, should be preserved in well-filled, tight containers, at a temperature not exceeding 25°.

Strong Iodine Solution contains, in each 100 mL, 4.5–5.5 g of iodine, and 9.5–10.5 g of potassium iodide. It is prepared by dissolving 50 g of iodine in 100 mL of purified water containing 100 g of potassium iodide. Sufficient purified water then is added to make 1000 mL of solution.

One g of iodine dissolves in 2950 mL of water. However, solutions of iodides dissolve large quantities of iodine. Strong Iodine Solution is, therefore, a solution of polyiodides in excess iodide.

$$I^- + nI_2 \rightarrow I^-_{(2n+1)}$$

Doubly charged anions may be found also

$$2I^- + nI_2 \rightarrow I^{2-}_{(2n+2)}$$

Strong Iodine Solution is used in the treatment of iodide deficiency disorders such as endemic goiter.

Several antibiotics (eg, cloxacillin sodium, nafcillin sodium and vancomycin), because they are relatively unstable in aqueous solution, are prepared by manufacturers as dry powders or granules in combination with suitable buffers, colors, diluents, dispersants, flavors and/or preservatives. These preparations, Cloxacillin Sodium for Oral Solution, Nafcillin for Oral Solution and Vancomycin Hydrochloride for Oral Solution meet the requirements of the USP. Upon dispensing to the patient, the pharmacist adds the appropriate amount of water. The products are stable for up to 14 days when refrigerated. This period usually provides sufficient time for the patient to complete the administration of all the medication.

Solution by Chemical Reaction—These solutions are prepared by reacting two or more solutes with each other in a suitable solvent. An example is Aluminum Subacetate Topical Solution USP.

Aluminum sulfate (145 g) is dissolved in 600 mL of cold water. The solution is filtered, and precipitated calcium carbonate (70 g) is added, in several portions, with constant stirring. Acetic acid (160 mL) is added slowly and the mixture set aside for 24 hr. The product is filtered and the magma on the Büchner filter washed with cold water until the total filtrate measures 1000 mL.

The solution contains pentaquohydroxo- and tetraquodihydroxoaluminum (III) acetates and sulfates dissolved in an aqueous medium saturated with calcium sulfate. The solution contains a small amount of acetic acid. It is stabilized by the addition of not more than 0.9% boric acid.

The reactions involved in the preparation of the solution are given below. The hexaquo aluminum cations first are converted to the nonirritating $[Al(H_2O)_5(OH)]^{2+}$ and $[Al(H_2O)_4(OH)_2]^+$ cations.

$$[Al(H_2O)_6]^{3+} + CO_3^{2-} \rightarrow [Al(H_2O)_5(OH)]^{2+} + HCO_3^-$$

$$[Al(H_2O)_6]^{3+} + HCO_3^- \rightarrow [Al(H_2O)_5(OH)]^{2+} + H_2O + CO_2$$

As the concentration of the hexaquo cations decreases, secondary reactions involving carbonate and bicarbonate occur.

$$[Al(H_2O)_5(OH)]^{2+} + CO_3^{2-} \rightarrow [Al(H_2O)_4(OH)_2]^+ + HCO_3^-$$

$$[Al(H_2O)_5(OH)]^{2+} + HCO_3^- \rightarrow [Al(H_2O)_4(OH)_2]^+ + H_2CO_3$$

The pH of the solution now favors the precipitation of dissolved calcium ions as the insoluble sulfate. Acetic acid now is added. The bicarbonate which is formed in the final stages of the procedure is removed as carbon dioxide.

Aluminum Subacetate Topical Solution is used in the preparation of Aluminum Acetate Topical Solution USP (Burow's Solution). The latter solution contains 15 mL of glacial acetic acid, 545 mL of Aluminum Subacetate Topical Solution and sufficient water to make 1000 mL. It is defined as a solution of aluminum acetate in approximately 5%, by weight, of acetic acid in water. It is stabilized by the addition of not more than 0.6% boric acid.

Solution by Extraction—Drugs or pharmaceutical necessities of vegetable or animal origin often are extracted with water or with water containing other substances. Preparations of this type may be classified

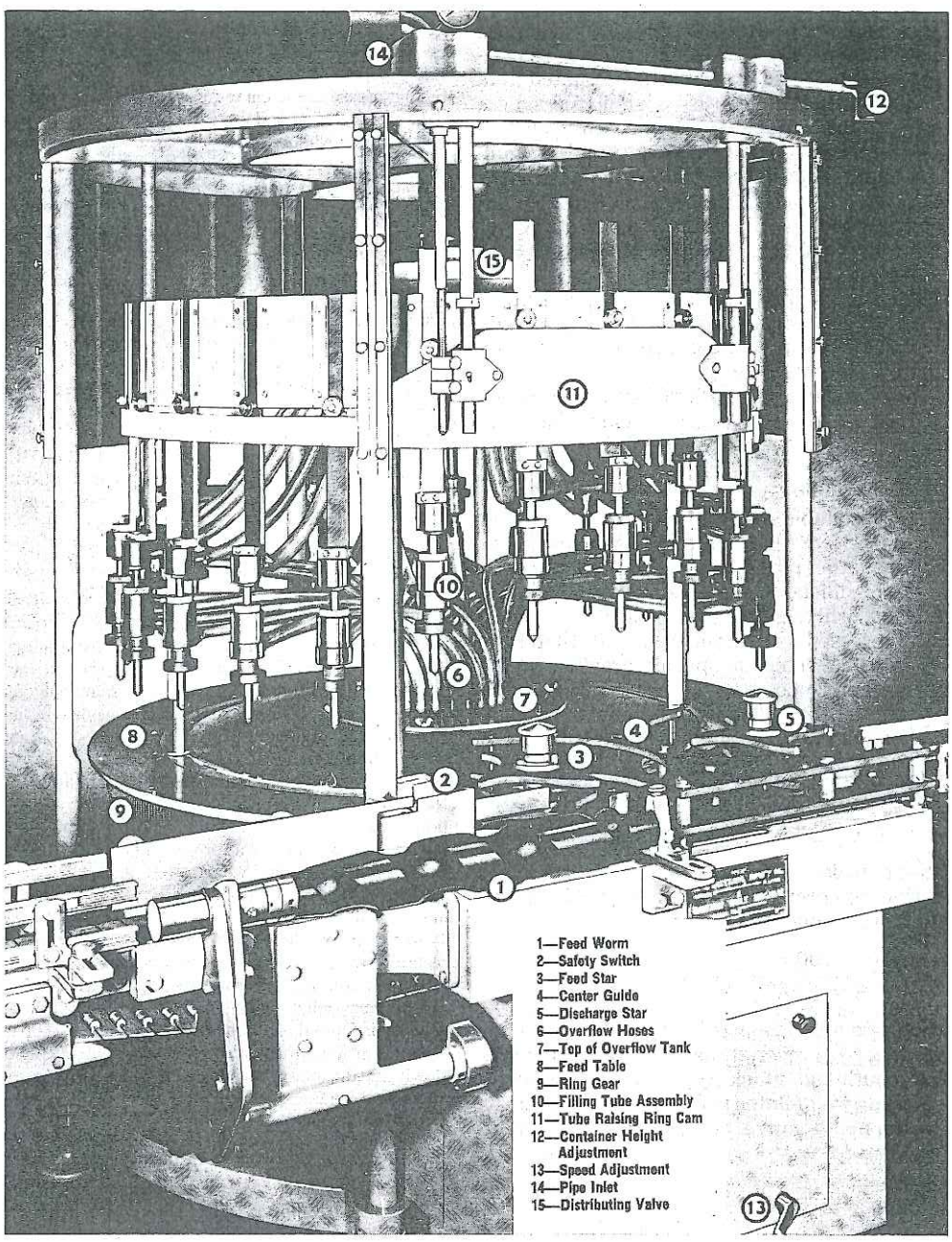


Fig 1. A rotary gravity bottle filler (courtesy, US Bottlers).

as solutions but, more often, are classified as extracts and are described at the end of this chapter.

Douches

A douche is an aqueous solution directed against a part or into a cavity of the body. It functions as a cleansing or antiseptic agent. An *eye douche*, used to remove foreign particles and discharges from the eyes, is directed gently at an oblique angle and allowed to run from the inner to the outer corner of the eye. *Pharyngeal douches* are used to prepare the interior of the throat for an operation and cleanse it in suppurative conditions. Similarly, there are *nasal douches* and *vaginal douches*. Douches usually are directed to the appropriate body part by using bulb syringes (Chapter 107).

Douches most frequently are dispensed in the form of a powder with directions for dissolving in a specified quantity of water (usually warm). However, tablets for preparing solutions are available (eg, Dobell's Solution Tablets) or the solution may be prepared by the pharmacist. If powders or tablets are supplied, they must be free from insoluble material, in order to produce a clear solution. Tablets are produced by the usual processes (see Chapter 92) but any lubricants or diluents used must be readily soluble in water. Boric acid may be used as a lubricant and sodium chloride normally is used as a diluent. Tablets deteriorate on exposure to moist air and should be stored in airtight containers.

Douches are not official as a class of preparations but several substances in the compendia frequently are employed as such in weak solutions, eg, benzalkonium chloride is used in various douches and Compound Sodium Borate Solution NFXI (Dobell's Solution) has been used as a nasal or pharyngeal douche. A sodium bicarbonate vaginal douche has been used to improve the postcoital test.

Vaginal douches are the most common type of douche and are used for cleansing the vagina and hygienic purposes. Liquid concentrates or powders, which may be prepared in bulk or as single-use packages, should be diluted or dissolved in the appropriate amount of warm water prior to use. The

ingredients used in vaginal douches include antimicrobial agents such as benzalkonium chloride, the parabens or chlorothymol, anesthetics or antipruritics such as phenol or menthol. Astringents such as zinc sulfate or potassium alum, surface-active agents such as sodium lauryl sulfate and chemicals to alter the pH such as sodium bicarbonate or citric acid also are used.

Enemas

These preparations are rectal injections employed to evacuate the bowel (evacuation enemas), influence the general system by absorption or to affect locally the seat of disease. The latter two are called retention enemas. They may possess anthelmintic, nutritive, sedative or stimulating properties, or they may contain radiopaque substances for roentgenographic examination of the lower bowel.

Sodium chloride, sodium bicarbonate, sodium monohydrogen phosphate and sodium dihydrogen phosphate are used in enemas to evacuate the bowel. These substances may be used alone, in combination with each other or in combination with irritants such as soap. Enema of Soap BPC 1963 is prepared by dissolving 50 g of soft soap in sufficient purified water to make 1000 mL of enema. Sodium Phosphate Enema USP contains 6 g of dibasic sodium phosphate heptahydrate and 16 g of monobasic sodium phosphate monohydrate in each 100 mL. Evacuation enemas usually are given at body temperature in quantities of 1 to 2 pt injected slowly with a syringe.

An official retention enema used for systemic purposes is aminophylline. Retention enemas are to be retained in the intestine and should not be used in larger quantities than 150 mL for an adult. Usually, the volume is considerably smaller, such as a few mL. *Microenema* is a term used to describe these small-volume preparations. Vehicles for retention microenemas have been formulated with small quantities of ethanol and propylene glycol, and no significant difference in irritation, as compared with water, was found. A number of other drugs such as valproic acid, indomethacin and metronidazole have been formulated as microenemas for the purpose of absorption. The absorption of large molecular weight drugs, such as insulin, is under current investigation.

Sulfasalazine rectal enema has been administered for the treatment of ulcerative colitis and may be prepared by dispersing the tablets (1-g strength) in 250 mL water. An enema in the form of a suspension is 5-aminosalicylic acid, 168 g; NaH_2PO_4, 1.6 g; Na_2HPO_4, 17.9 g; NaCl, 36 g; sodium ascorbate, 2 g; tragacanth, 16 g; methylparaben, 8 g; propylparaben, 2 g; propylene glycol, 100 mL; and distilled water to make 4000 mL. It has been prepared by Montgomery *et al*[8] and shown to be stable for 90 days at both room and refrigerator temperatures. Barium sulfate enema contains 120 g of barium sulfate, 100 mL of acacia mucilage and sufficient starch enema to make 500 mL. An enema containing 30 to 50 g of sodium polystyrene sulfonate has been prepared using 100 mL of sorbitol solution.

Starch enema may be used either by itself or as a vehicle for other forms of medication. A thin paste is made by triturating 30 g of powdered starch with 200 mL of cold water. Sufficient boiling water is added to make 1000 mL of enema. The preparation then is reheated to obtain a transparent liquid.

Gargles

Gargles are aqueous solutions frequently containing antiseptics, antibiotics and/or anesthetics used for treating the pharynx and nasopharynx by forcing air from the lungs through the gargle which is held in the throat; subsequently, the gargle is expectorated. Many gargles must be diluted with water prior to use. Although mouthwashes are considered as a separate class of pharmaceuticals, many are used as gargles, either as is, or diluted with water.

A gargle/mouthwash containing the antibiotic tyrothricin has been shown to provide levels of gramicidin, a component of tyrothricin, in saliva when used as a gargle rather than a mouthwash. Higher saliva levels of gramicidin were obtained when a lozenge formulation was employed. Rapid relief of pharyngeal and oral pain was obtained when Cepacaine solution, which contains a topical anesthetic, was used as a gargle.

Potassium Chlorate and Phenol Gargle is official in the PC. It contains potassium chlorate, 30 g, patent blue V (Color Index No 42051) commercial food grade (0.01 g), liquified phenol (15 mL) and water for preparations qs to 1000 mL. It should be diluted with 10 volumes of warm water before use. The product should be labeled so that it cannot be mistaken for preparations intended for internal administration.

A flavored solution containing 7.5% povidone-iodine and 35% alcohol (*Isodine*) is available commercially as a mouthwash or gargle after suitable dilution.

Mouthwashes

A mouthwash can be used for two purposes, therapeutic and cosmetic. Therapeutic rinses or washes can be formulated to reduce plaque, gingivitis, dental caries and stomatitis. Cosmetic mouthwashes may be formulated to reduce bad breath through the use of antimicrobial and/or flavoring agents.

Recent information indicates that mouthwashes are being used as a dosage form for a number of specific problems in the oral cavity; for example, mouthwashes containing a combination of antihistamines, hydrocortisone, nystatin and tetracycline have been prepared from commercially available suspensions, powders, syrups or solutions for the treatment of stomatitis, a painful side effect of cancer therapy. Other drugs include allopurinol, also used for the treatment of stomatitis, pilocarpine for xerostoma (dry mouth), tranexamic acid for the prevention of bleeding after oral surgery, amphotericin B for oral candidiasis, chlorhexidine gluconate for plaque control and hexetidine as an antibactericidal and antifungal agent.

Mouthwashes may be used for a number of other purposes; for example, cetylpyridinum chloride and dibucaine hydrochloride mouthwashes provide satisfactory relief of pain in patients with ulcerative lesions of the mouth, mouthwashes or creams containing carbenoxolone are highly effective dosage forms for the treatment of orofacial herpes simplex infections and undetected oral cancer has been recognized using toluidine blue in the form of a mouth rinse.

Mouthwashes generally contain four groups of excipients as suggested by Tricca.[9]

Alcohols—Alcohol is often present in the range of 10–20%. It enhances the flavor, provides a certain sharpness to the taste, aids in masking the unpleasant taste of active ingredients, functions as a solubilizing agent for some flavoring agents and may function as a preservative. Humectants such as glycerin and sorbitol, may form 5–20% of the mouthwash. These agents increase the viscosity of the preparation and provide a certain *body* or *mouth feel* to the product. They enhance the sweetness of the product and, along with the ethanol, improve the preservative qualities of the product.

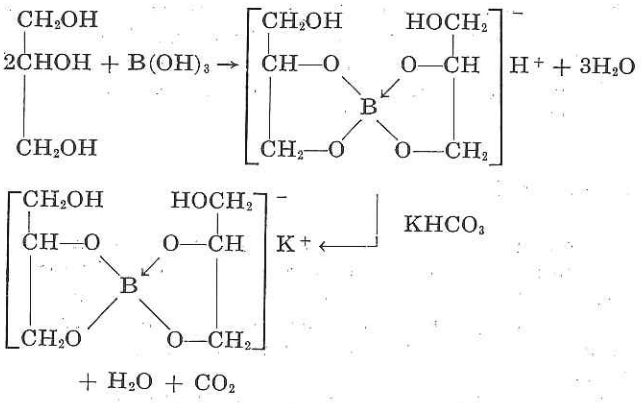
Surfactants, usually of the nonionic class such as polyoxyethylene/polyoxypropylene block copolymers or polyoxyethylene derivatives of sorbitol fatty acid esters may be used. The concentration range is 0.1–0.5%. An anionic surfactant occasionally used is sodium lauryl sulfate. Surfactants are used because they aid in the solubilization of flavors and in the removal of debris by providing foaming action. Cationic surfactants such as cetylpyridinium chloride are used for their antimicrobial properties, but these tend to impart a bitter taste.

Flavors are used in conjunction with alcohol and humectants to overcome disagreeable tastes, and at the same time they must be safe to use. The principle flavoring agents are peppermint, spearmint, cinnamon, wintergreen oils, menthol

or methyl salicylate. Other flavoring agents may be used singly or in combination.

Coloring agents also are used in these products.

The products of commerce (eg, Cepacol, Listerine, Micrin or Scope) vary widely in composition. Antiseptic Solution and Mouthwash are described in NF XII. The latter wash contains sodium borate, glycerin and potassium bicarbonate. The reactions which take place when these substances are dissolved in water are given below.



Compound Sodium Chloride Mouthwash and Zinc Sulphate Mouthwash are described in the BP and the PC, respectively. The former wash contains sodium chloride, sodium bicarbonate, concentrated peppermint emulsion and double-strength chloroform water. Extemporaneously compounded preparations include allopurinol at a strength of about 0.1% prepared from tablets in a suspending vehicle of 0.5% methylcellulose sweetened and flavored. Modifications of this preparation have been shown to have considerable stability.

Juices

A juice is prepared from fresh ripe fruit, is aqueous in character and is used in making syrups which are employed as vehicles. The freshly expressed juice is preserved with benzoic acid and allowed to stand at room temperature for several days, until the pectins which naturally are present are destroyed by enzymatic action, as indicated by the filtered juice yielding a clear solution with alcohol. Pectins, if allowed to remain, would cause precipitation in the final syrup.

Cherry Juice (RPS-18 page 1320) is described in the USP XXI and Raspberry Juice in USP XVIII. Concentrated Raspberry Juice PC is prepared from the clarified juice of raspberries. Pectinase is stirred into pulped raspberries and the mixture allowed to stand for 12 hours. The pulp is pressed, the juice clarified and sufficient sucrose added to adjust the weight at 20° to 1.050 to 1.060 g per mL. The juice then is concentrated to one-sixth of its original volume. Sufficient sulfurous acid or sodium metabisulfite is added as a preservative.

Artificial flavors now have replaced many of the natural fruit juices. Although they lack the flavor of the natural juice, they are more stable and easier to incorporate into the final pharmaceutical form. Commercial juices such as orange, apple, grape and mixed vegetables have been used recently to prepare extemporaneous preparations of cholestyramine and nizatidine.

Information on cranberry juice indicates that it may be effective in controlling some urinary tract infections and urolithiosis.

Nasal Solutions

Nasal solutions are usually aqueous solutions designed to be administered to the nasal passages in drops or sprays. While many of the drugs are administered for their local sympathomimetic effect such as Ephedrine Sulfate or Naphazoline Hydrochloride Nasal Solution USP, to reduce nasal congestion, a few other official preparations, Lypressin Nasal Solution USP and Oxytocin Nasal Solution USP, are administered in spray form for their systemic effect for the treatment of diabetes insipidus and *milk letdown* prior to breast feeding, respectively. The current route of administration of peptides and proteins is limited to parenteral injection because of inactivation within the gastrointestinal tract. As a result, there is considerable research on intranasal delivery of these drugs such as analogs of enkephalins or luteinizing hormone releasing hormone and insulin. Other drugs which are absorbed poorly from the GI tract such as gentamicin sulfate, are being administered in the form of nasal solutions, in order to obtain appropriate blood levels.

Nasal solutions are prepared so that they are similar in many respects to nasal secretions, so that normal ciliary action is maintained. Thus, the aqueous nasal solutions usually are isotonic and slightly buffered to maintain a pH of 5.5 to 6.5. In addition, antimicrobial preservatives, similar to those used in ophthalmic preparations, and appropriate drug stabilizers, if required, are included in the formulation.

Commercial nasal preparations, in addition to the drugs listed above also include antibiotics, antihistamines and drugs for asthma prophylaxis.

A formula for Ephedrine Nasal Drops PC is

Ephedrine Hydrochloride	0.5 g
Chlorobutanol	0.5 g
Sodium Chloride	0.5 g
Water for preparations	to 100 mL

Current studies indicate that nasal sprays are deposited mainly in the atrium and cleared slowly into the pharynx with the patient in an upright position. Drops spread more extensively than the spray and three drops cover most of the walls of the nasal cavity, with the patient in a supine position and head tilted back and turned left and right. It is suggested that drop delivery, with appropriate movement by the patient, leads to extensive coverage of the walls of the nasal cavity.

Otic Solutions

These solutions occasionally are referred to as aural preparations. Other otic preparations often include formulations such as suspensions and ointments for topical application in the ear.

The main classes of drugs used for topical administration to the ear include analgesics, eg, benzocaine; antibiotics, eg, neomycin; and anti-inflammatory agents, eg, cortisone. The USP preparations include Antipyrine and Benzocaine Otic Solution. The Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solutions contain appropriate buffers and dispersants usually in an aqueous solution. The main solvents used in these preparations include glycerin or water. The viscous glycerin vehicle permits the drug to remain in the ear for a long time. Anhydrous glycerin, being hygroscopic, tends to remove moisture from surrounding tissues, thus reducing swelling. Viscous liquids like glycerin or propylene glycol are used either alone or in combination with a surfactant to aid in the removal of cerumen (ear wax). Sodium Bicarbonate Ear-Drops BP may be used if wax is to be removed from the ear. This preparation contains sodium bicarbonate (5 g), glycerin (30 mL) and purified water (a sufficient quantity to make 100 mL).

In order to provide sufficient time for aqueous preparations to act, it is necessary for the patient to remain on his side for a few minutes so the drops do not run out of the ear. Otic preparations are dispensed in a container which permits the administration of drops.

Irrigation Solutions

These solutions are used to wash or bathe surgical incisions, wounds or body tissues. Because they come in contact with exposed tissue, they must meet stringent requirements for Injections of the USP such as sterility, particulate

matter and the requirements of the Pyrogen Test. These products are prepared by dissolving the active ingredient in Water for Injection. They are packaged in single-dose containers, preferably Type I or Type II glass, or suitable plastic containers, and then sterilized. See Chapter 84 for sterilization procedures. A number of irrigations are described in the USP: Acetic Acid Irrigation for bladder irrigation, Dimethyl Sulfoxide Irrigation for relief of internal cystitis, Neomycin and Polymyxin B Sulfates Solution for Irrigation for infection and Sodium Chloride Irrigation for washing wounds.

Extemporaneous formulations frequently are prepared using an isotonic solution of sodium chloride as the solvent. For example, cefazolin or gentamicin in 0.9% sodium chloride are used as anti-infective irrigations, dinoprostone in lactated ringers injection is used by continuous intrauterine irrigation for severe postpartum hemorrhage and 5-fluororacil in 0.9% sodium chloride is employed for bladder irrigation. Alum, either potassium or ammonium, in either sterile water or 0.9% sodium chloride for irrigation has been used for bladder hemorrhage. Amphotericin in sterile water has been used for the treatment of localized infections of the bladder and urinary tract. All the extemporaneous preparations should meet the general requirements noted above for USP irrigations.

Sweet or Other Viscid Aqueous Solutions

Solutions which are sweet or viscid include syrups, honeys, mucilages and jellies. All of these are viscous liquids or semisolids. The basic sweet or viscid substances giving body to these preparations are sugars, polyols or polysaccharides (gums).

Syrups

Syrups are concentrated solutions of sugar such as sucrose in water or other aqueous liquid. When Purified Water alone is used in making the solution of sucrose, the preparation is known as *Syrup*, or *simple syrup*. In addition to sucrose, certain other polyols, such as glycerin or sorbitol, may be added to retard crystallization of sucrose or to increase the solubility of added ingredients. Alcohol often is included as a preservative and also as a solvent for flavors; further resistance to microbial attack can be enhanced by incorporating antimicrobial agents. When the aqueous preparation contains some added-medicinal substance, the syrup is called a *medicated syrup*. A *flavored* syrup is one which usually is not medicated, but which contains various aromatic or pleasantly flavored substances and is intended to be used as a vehicle or flavor for prescriptions, eg, Acacia, Cherry, Cocoa and Orange USP XXI.

Flavored syrups offer unusual opportunities as vehicles in extemporaneous compounding and are accepted readily by both children and adults. Because they contain no, or very little, alcohol they are vehicles of choice for many of the drugs that are prescribed by pediatricians. Their lack of alcohol makes them superior solvents for water-soluble substances. However, sucrose-based medicines continuously administered to children apparently cause an increase in dental caries and gingivitis; consequently, alternate formulations of the drug either unsweetened or sweetened with noncariogenic substances should be considered. A knowledge of the sugar content of liquid medicines is useful for patients who are on a restricted calorie intake; a list has been prepared by Bergen.[10]

Syrups possess remarkable masking properties for bitter or saline drugs. Glycyrrhiza syrup has been recommended for disguising the salty taste of bromides, iodides and chlorides. This has been attributed to its colloidal character and its double sweetness—the immediate sweetness of the sugar and the lingering sweetness of the glycyrrhizin. This syrup is also of value in masking bitterness in preparations containing the B complex vitamins. Acacia Syrup USP XXI (page 1393), because of its colloidal character, is of particular value as a vehicle for masking the disagreeable taste of many medica- ments. Raspberry Syrup BP is one of the most efficient flavoring agents and is especially useful in masking the taste of bitter drugs. Many factors, however, enter into the choice of a suitable flavoring agent. Literature reports are often contradictory and there appears to be no substitute for the taste panel. The literature on this subject has been reviewed by Meer[11] and this reference and Chapter 80 should be consulted for further information on the flavoring of pharmaceuticals and the preparation of a number of official syrups. A series of papers by Schumacher deals with improving the palatability of bulk-compounded products using flavoring and sweetening agents.[12]

In manufacturing syrups the sucrose must be selected carefully and a purified water, free from foreign substances, and clean vessels and containers must be used. The operation must be conducted with care to avoid contamination, if the products are to be stable.

It is important that the concentration of sucrose approach but not quite reach the saturation point. In dilute solutions sucrose provides an excellent nutrient for molds, yeasts and other microorganisms. In concentrations of 65% by weight or more, the solution will retard the growth of such microorganisms. However, a saturated solution may lead to crystal lization of a part of the sucrose under conditions of changing temperature.

When heat is used in the preparation of syrups, there is almost certain to be an inversion of a slight portion of the sucrose. Sucrose solutions are dextrorotary but, as hydrolysis proceeds, the optical rotation decreases and becomes negative when the reaction is complete. This reaction is termed *inversion* because *invert sugar* (dextrose plus levulose) is formed. The speed of inversion is increased greatly by the presence of acids; the hydrogen ion acts as a catalyst in this hydrolytic reaction. Invert sugar is more readily fermentable than sucrose and tends to be darker in color. Nevertheless, its two reducing sugars are of value in retarding the oxidation of other substances.

Invert Syrup is described in the BP. It is prepared by hydrolyzing sucrose with hydrochloric acid and neutralizing the solution with calcium or sodium carbonate. The sucrose in the 66.7% *w/w* solution must be at least 95% inverted. The monograph states that invert syrup, when mixed in suitable proportions with syrup, prevents the deposition of crystals of sucrose under most conditions of storage.

The levulose formed during inversion is sweeter than sucrose and, therefore, the resulting syrup is sweeter than the original syrup. The relative sweetness of levulose, sucrose and dextrose is in the ratio of 173:100:74. Thus, invert sugar is $1/100\,(173 + 74)\frac{1}{2} = 1.23$ times as sweet as sucrose. The levulose formed during the hydrolysis also is responsible for the darkening of syrup. It is sensitive to heat and darkens readily, particularly in solution. When syrup or sucrose is overheated, it caramelizes. See *Caramel* (RPS-18 page 1290). Occasionally, it is appropriate to use a sugar-free liquid preparation; a list of these has been published.[13]

Preparation—Syrups are prepared in various ways, the choice of the proper method depends on the physical and chemical characteristics of the substances entering into the preparation.

Solution with Heat—This is the usual method of making syrups when the valuable constituent is neither volatile nor injured by heat, and when it is desirable to make the syrup rapidly. The sucrose usually is added to the purified water or aqueous solution and heated until solution is effected, then strained and sufficient purified water added to make the desired weight or volume. If the syrup is made from an infusion, a decoction or an aqueous solution containing organic matter, such as sap from maple trees, it usually is proper to heat the syrup to the boiling point to coagulate albuminous matter; subsequently, this is separated by straining. If the albumin or other impurities were permitted to remain in the syrup, fermentation probably would be induced in warm weather. Saccharometers are very useful in making syrups by the hot process in cases where the proper

specific gravity of the finished syrup is known. They may be floated in the syrup while boiling, and thus the exact degree of concentration determined without waiting to cool the syrup and having to heat it again to concentrate it further. When taking a reading of the specific gravity of the hot syrup, allowance must be made for the variation from the official temperature (specific gravities in the USP are taken at 25°).

Excessive heating of syrups at the boiling temperature is undesirable since more or less inversion of the sucrose occurs with an increased tendency to ferment. Syrups cannot be sterilized in an autoclave without some caramelization. This is indicated by a yellowish or brownish color resulting from the formation of caramel by the action of heat upon sucrose.

The formula and procedure given for Acacia Syrup (page 1393) illustrates this method of preparation.

Agitation without Heat—This process is used in those cases where heat would cause the loss of valuable, volatile constituents. In making quantities up to 2000 mL the sucrose should be added to the aqueous solution in a bottle of about twice the size required for the syrup. This permits active agitation and rapid solution. Stoppering the bottle is important, as it prevents contamination and loss during the process. The bottle should be allowed to lie on its side when not being agitated. Glass-lined tanks with mechanical agitators, especially adapted to dissolving of sucrose, are used for making syrups in large quantities.

This method and that previously described are used for the preparation of a wide variety of preparations that are described popularly as syrups. Most cough syrups, for example, contain sucrose and one or more active ingredients. However, the exact composition of such products is not given on the label. Furthermore, some of these products are listed in the USP but no directions are given for their preparation. For example, Guaifenesin Syrup USP (glyceryl guaiacolate syrup) is official but the only known ingredients are guaifenesin (glyceryl guaiacolate) and ethanol (not less than 3% or more than 4%).

The PC, on the other hand, gives a method for the preparation of Codeine Phosphate Syrup. This contains codeine phosphate (5 g), water for preparations (15 mL), chloroform spirit (25 mL) and sufficient syrup to make 1000 mL. It can be used for the relief of cough. Another syrup for this purpose is Codeine Linctus PC. This is really a medicated syrup which possesses demulcent, expectorant or sedative properties. Unlike the syrup, it is colored and flavored. The formula for Codeine Linctus PC is

Codeine Phosphate	3 g
Compound Tartrazine Solution	10 mL
Benzoic Acid Solution	20 mL
Chloroform Spirit	20 mL
Water for Preparations	20 mL
Lemon Syrup	200 mL
Syrup	to 1000 mL

Dissolve the codeine phosphate in the water, add 500 mL of the syrup and mix. Add the other ingredients and sufficient syrup to produce 1000 mL.

For pediatric use, 200 mL of this linctus is diluted with sufficient syrup to make 1000 mL. If sugar is contraindicated in the diet, Diabetic Codeine Linctus can be used:

Codeine Phosphate	3 g
Citric Acid monohydrate	5 g
Lemon Spirit	1 mL
Compound Tartrazine Solution	10 mL
Benzoic Acid Solution	20 mL
Chloroform Spirit	20 mL
Water for Preparations	20 mL
Sorbitol Solution	to 1000 mL

Dissolve the codeine phosphate and the citric acid in the water, add 750 mL of the sorbitol solution and mix. Add the other ingredients and sufficient sorbitol solution to produce 1000 mL.

Sorbitol Solution is the sweetening agent and contains 70% *w/w* of total solids, consisting mainly of D-sorbitol. It has about half the sweetening power of syrup. In the US the FDA has banned the use of chloroform in medicines and cosmetics because of reported carcinogenicity in animals.

Basic formulations can be varied easily to produce the highly advertised articles of commerce. The prescription-only drug (eg, codeine phosphate or methadone) must, of course, be omitted from the formulation but, in certain countries, such as Canada, a decreased quantity of codeine phosphate is permitted in an OTC cough syrup. In addition to the ingredients cited or listed in the official compendia (eg, tolu, squill or ipecacuanha), many cough syrups contain an antihistamine.

Many other active ingredients (eg, ephedrine sulfate, dicyclomine hydrochloride, chloral hydrate or chlorpromazine hydrochloride) are marketed as syrups. Like cough syrups, these preparations are flavored, colored and recommended in those instances where the patient cannot swallow the solid dosage form.

Addition of a Medicating Liquid to Syrup—This method is resorted to in those cases in which fluidextracts, tinctures or other liquids are added to syrup to medicate it. Syrups made in this way usually develop precipitates since alcohol is often an ingredient of the liquids thus used, and the resinous and oily substances dissolved by the alcohol precipitate when mixed with the syrup, producing unsightly preparations. A modification of this process, frequently adopted, consists of mixing the fluidextract or tincture with the water, allowing the mixture to stand to permit the separation of insoluble constituents, filtering and then dissolving the sucrose in the filtrate. It is obvious that this procedure is not permissible when the precipitated ingredients are the valuable medicinal agents.

The formula and procedure given for Aromatic Eriodictyon Syrup USP XXI (RPS-18 page 1301) illustrate this method of preparation.

Percolation—In this procedure, purified water, or an aqueous solution, is permitted to pass slowly through a bed of crystalline sucrose, thus dissolving it and forming a syrup. A cotton pledget is placed in the neck of the percolator and the water or aqueous solution added. By means of a suitable stopcock the flow is regulated so that drops appear in rapid succession. If necessary, a portion of the liquid is recycled through the percolator to dissolve all the sucrose. Finally, sufficient purified water is passed through the cotton to make the required volume.

To be successful in using this process, care in several particulars must be exercised: (1) the percolator used should be cylindrical or semicylindrical and cone-shaped as it nears the lower orifice; (2) a coarse granular sugar must be used, otherwise it will coalesce into a compact mass, which the liquid cannot permeate; (3) the purified cotton must be introduced with care.

If pressed in too tightly, the cotton will stop the process effectually; if inserted too loosely, the liquid will pass through the cotton rapidly and the filtrate will be weak and turbid (from imperfect filtration); it should be inserted completely within the neck of the percolator, since a protruding end, inside the percolator, up through the sucrose, will permit the last portions of water to pass out at the lower orifice without dissolving all the sucrose. For specific directions see *Syrups* (page 1393). The process of percolation is applied on a commercial scale for the making of official syrups as well as those for confectionary use.

Percolation is the preferred method for the preparation of Syrup USP (page 1301). The sucrose, in this instance, is placed in the percolator. However, a slightly modified approach must be used if a drug of vegetable origin is to be incorporated into the syrup. For example, wild cherry bark is first percolated with water; the collection vessel contains sucrose (800 g) and glycerol (50 mL). When the total volume is 1000 mL, the percolate is agitated to produce Wild Cherry Syrup PC.

Reconstitution—In order to improve stability and minimize microbial contamination, dry syrup formulations can be prepared and Purified Water USP added just prior to dispensing or use. Powder mixtures, wholly granulated products and partially granulated products have been investigated for this purpose by Ryder.[14]

The powder mixture preparation requires less equipment and energy to prepare. Chemical stability problems are minimal, since no heat or solvents are used in the process and a low moisture content can be obtained in the final product; unfortunately, powder mixtures are prone to homogeneity problems. In the case of the wholly granulated product all the ingredients are included in the granulation stage. The drug may be incorporated into the dry product before granulation or dissolved or suspended in the granulating fluid. After formation, the granules are dried and then screened to break down oversize particles. The advantages of granulated over powder mixtures include better appearance, better flow, fewer segregation problems and less dust during processing. Partially granulated mixtures are used to gain some of the advantages of granulation without the disadvantages. Usually the drug, and other fine particles, are included at the granulation stage, perhaps with some diluents to improve flow and reduce segregation and dust. Materials selected for mixing with the dried granules would include thermolabile excipients, such as flavors, and free flowing materials, such as sugars.

Preservation—Syrups should be made in quantities which can be consumed within a few months, except in those cases where special facilities can be employed for their preservation; a low temperature is the best method. Concentration without super-saturation is also a condition favorable to preservation. The USP states that syrups may contain preservatives such as glycerin, methylparaben, benzoic acid and sodium benzoate to prevent bacterial and mold growth. Combinations of alkyl esters of *p*-hydroxybenzoic acid are effective inhibitors of yeasts which have been implicated in the contamination of commercial syrups.

The official syrups should be preserved in well-dried bottles, preferably those which have been sterilized. These

bottles should not hold more than is likely to be required during 4 to 6 weeks and should be filled completely, stoppered carefully and stored in a cool, dark place.

Syrups Prepared from Juices

Blackberry, pineapple and strawberry syrups may be prepared by following the directions for Raspberry Syrup BP. One volume of the concentrated raspberry juice is diluted with 11 volumes of syrup. Black Current Syrup BP is prepared in a similar manner but also can be prepared from black currants, with certain modifications. The pectin in the juice is destroyed with pectinase. The syrup is prepared by dissolving 700 g of sucrose in 560 mL of clarified juice and may be preserved with sodium metabisulfite. The addition of a dye is permitted, provided it complies with the pertinent government regulations. Cherry Syrup USP XXI is prepared from cherry juice by the addition of alcohol, sucrose and water (page 1393).

Syrups, either as a syrup or as a flavored syrup, are useful for preparing liquid oral dosage forms from not only the pure drug but also injections, capsules or tablets if the pure drug is not readily available. On one hand, if the drug and all the excipients in the preparation, eg, injectables or capsules, are water soluble, a solution will result if a syrup is prepared. On the other hand, if the preparation to be used contains water-insoluble ingredients, as is usually the case with tablets and some capsules, a suspension will be formed. Several of the above preparations have been described in the literature, not only in regard to their formulation but also in regard to stability and bioavailability. Some drugs which have been prepared from either the pure drug or an injectable form include midazolam, atropine, aminocaproic acid, terbutaline, procainamide, chloroquin, propranolol and citrated caffeine. If the appropriate salt of the drug is used, a solution will result. When tablets are used to prepare liquid formulations, a suspension usually is formed because there is usually a nonwater-soluble ingredient used in table preparations. Some formulations prepared from tablets are clonidine hydrochloride, cefuroxime axetil, famotidine, terbutaline sulfate, spironolactone, ranitidine, propranolol and rifampin. The resulting suspensions should have a uniform distribution of particles so that a consistent dose is obtained. If the materials are not distributed uniformly, more appropriate suspending formulations should be considered, which are described later in the chapter. If pharmaceutical preparations contain a liquid such as valproic acid or simethicone, to be incorporated into syrups, which is insoluble in water, an emulsion will form and a uniform product will not result.

Honeys

Honeys are thick liquid preparations somewhat allied to the syrups, differing in that honey, instead of syrup, is used as a base. They are unimportant as a class of preparations today but at one time, before sugar was available and honey was the most common sweetening agent, they were used widely. The BP lists one preparation for coughs containing honey. Squill Oxymel contains squill, water, acetic acid and honey and is prepared by a maceration process.

Honey and sugar pastes are used to a small extent and have been discussed in the pharmaceutical literature for topical application for the treatment of certain types of ulcers and abscesses. Thick and thin sugar pastes containing Caster sugar (very fine granular sugar), icing sugar (additive-free), polyethylene glycol 400 and hydrogen peroxide (in a final concentration of 0.15%) have been prepared and shown to be beneficial in the process of wound healing.

Mucilages

The official mucilages are thick, viscid, adhesive liquids, produced by dispersing gum in water, or by extracting the mucilaginous principles from vegetable substances with water. The mucilages all are prone to decomposition, showing appreciable decrease in viscosity on storage; they should never be made in quantities larger than can be used immediately, unless a preservative is added. Acacia Mucilage NF XII contains benzoic acid and Tragacanth Mucilage BPC (1973) contains alcohol and chloroform water. Chloroform in manufactured products for internal use is banned in some countries.

Acacia Mucilage may be prepared by placing 350 g of acacia in a graduated bottle, washing the drug with cold purified water, allowing it to drain and adding enough warm purified water, in which 2 g of benzoic acid has been dissolved, to make the product measure 1000 mL. The bottle then is stoppered, placed on its side, rotated occasionally and the product strained when the acacia has dissolved.

Tragacanth Mucilage BPC (1973) is prepared by mixing 12.5 g of tragacanth with 25 mL alcohol (90%) in a dry bottle and then quickly adding sufficient chloroform water to 1000 mL and shaking vigorously. The alcohol is used to disperse the gum to prevent agglomeration on addition of the water.

Mucilages are used primarily to aid in suspending insoluble subtances in liquids; their colloidal character and viscosity help prevent immediate sedimentation. Examples include sulfur in lotions, resin in mixtures and oils in emulsions. Both tragacanth and acacia either are partially or completely insoluble in alcohol. Tragacanth is precipitated from solution by alcohol, but acacia, on the other hand, is soluble in diluted alcoholic solutions. A 60% solution of acacia may be prepared with 20% alcohol and a 4% solution of acacia may be prepared even with 50% alcohol.

The viscosity of tragacanth mucilage is reduced by acid, alkali or sodium chloride, particularly if the mucilage is heated. It shows maximum viscosity at pH 5. Acacia is hydrolyzed by dilute mineral acids to arabinose, galactose, aldobionic and galacturonic acids. Its viscosity is low but is maintained over a wide pH range.

Recent research on mucilages includes the preparation of mucilage from plantain and the identification of its sugars, the preparation and suspending properties of cocoa gum, the preparation of glycerin ointments using flaxseed mucilage and the consideration of various gums and mucilages obtained from several Indian plants for pharmaceutical purposes.

Several synthetic mucilage-like substances such as *polyvinyl alcohol, methylcellulose, carboxymethylcellulose* and related substances, as described in Chapter 80, are used at the appropriate concentration as mucilage substitutes, emulsifying and suspending agents. Methylcellulose (page 1397) is used widely as a bulk laxative since it absorbs water and swells to a hydrogel in the intestine, in much the same manner as *psyllium* or *karaya gum*. Methylcellulose Oral Solution USP is a flavored solution of the agent. It may be prepared by adding slowly the methylcellulose to about one-third the amount of boiling water, with stirring, until it is thoroughly wetted. Cold water then should be added and the wetted material allowed to dissolve while stirring. The viscosity of the solution will depend upon the concentration and the specifications of the methylcellulose. The synthetic gums are nonglycogenetic and may be used in the preparation of diabetic syrups. Several formulas for such syrups, based on sodium carboxymethylcellulose, have been proposed.

Uniformly smooth mucilages sometimes are difficult to prepare due to the uneven wetting of the gums. In general, it is best to use fine gum particles and disperse them with good agitation in a little 95% alcohol or in cold water (except for methylcellulose). The appropriate amount of water then can be added with constant stirring. A review of the chemistry and properties of acacia and other gums has been prepared.[15]

Jellies

Jellies are a class of gels in which the structural coherent matrix contains a high portion of liquid, usually water. They are similar to mucilages, in that they may be prepared from

similar gums, but they differ from the latter in having a jelly-like consistency. A whole gum of the best quality, rather than a powdered gum, is desirable in order to obtain a clear preparation of uniform consistency. Tragacanth is the gum used in the preparation of Ephedrine Sulfate Jelly NF XII. While the specific thickening agent in the USP jellies is not indicated, reference usually is made in the monograph to a water-soluble, sterile, viscous base. These preparations also may be formulated with water from acacia, chondrus, gelatin, carboxymethylcellulose, hydroxyethylcellulose and similar substances.

Jellies are used as lubricants for surgical gloves, catheters and rectal thermometers. Lidocaine Hydrochloride Jelly USP is used as a topical anesthetic. Therapeutic vaginal jellies are available and certain jelly-like preparations are used for contraceptive purposes, which often contain surface-active agents to enhance the spermatocidal properties of the jelly. Aromatics, such as methyl salicylate and eucalyptol, often are added to give the preparation a desirable odor.

Jellies are prone to microbial contamination and therefore contain preservatives, eg, methyl *p*-hydroxybenzoate is used as a preservative in a base for medicated jellies. This base contains sodium alginate, glycerin, calcium gluconate and water. The calcium ions cause a cross-linking with sodium alginate to form a gel of firmer consistency. A discussion of gels is provided later in the chapter.

Nonaqueous Solutions

It is difficult to evaluate fairly the importance of nonaqueous solvents in pharmaceutical processes. That they are important in the manufacture of pharmaceuticals is an understatement. However, pharmaceutical preparations, and, in particular, those intended for internal use, rarely contain more than minor quantities of the organic solvents that are common to the manufacturing or analytical operation. For example, industry uses large quantities of chloroform in some operations but the solvent is of only minor importance with respect to the final product. One mL of chloroform dissolves in about 200 mL of water and the solution so formed finds some use as a vehicle (see the section on *Aromatic Waters*). Chloroform has been an ingredient in a number of cough syrups in the past but it has been banned in the US by the FDA in manufactured products intended for internal use. Solvents such as acetone, benzene and petroleum ether must not be ingredients in preparations intended for internal use.

Products of commerce for internal use may contain solvents such as ethanol, glycerin, propylene glycol, certain oils and liquid paraffin. Preparations intended for external use may contain solvents in addition to those just mentioned, namely isopropyl alcohol, polyethylene glycols, various ethers and certain esters. A good example of preparations of this type are the rubefacient rubbing alcohols. Rubbing Alcohol must be manufactured in accordance with the requirements of the Bureau of Alcohol, Tobacco and Firearms, US Treasury Dept, using Formula 23-H denatured alcohol. This mixture contains 8 parts by volume of acetone, 1.5 parts by volume of methyl isobutyl ketone and 100 parts by volume of ethanol. Besides the alcohol in the Rubbing Alcohol, the final product must contain water, sucrose octaacetate or denatonium benzoate and may contain color additives, perfume oils and a suitable stabilizer. The alcohol content, by volume, is not less than 68.5% and not more than 71.5%. The isopropyl alcohol content in Isopropyl Rubbing Alcohol can vary from 68.0% to 72.0% and the finished product may contain color additives, perfume oils and suitable stabilizers.

Although the lines between aqueous and nonaqueous preparations tend to blur in those cases where the solvent is water-soluble, it is possible to categorize a number of products as nonaqueous. This section is, therefore, devoted to groups of nonaqueous solutions; the alcoholic or hydroalcoholic solutions (eg, elixirs and spirits), ethereal solutions (eg, collodions), glycerin solutions (eg, glycerins), oleaginous solutions (eg, liniments, oleovitamins and toothache drops), inhalations and inhalants.

Although the above list is limited, a wide variety of solvents are used in various pharmaceutical preparations. Solvents such as glycerol formal, dimethylacetamide and glycerol dimethylketal have been suggested for some products produced by the industry. However, the toxicity of many of these solvents is not well-established and, for this reason, careful clinical studies should be carried out on the formulated product before it is released to the marketplace.

It is essential that the toxicity of solvents be tested appropriately and approved in order to avoid problems: for example, the tragic loss of life which occurred during 1937 when diethylene glycol was used in an elixir of sulfanilamide. The result of this tragedy was the 1938 Federal Food, Drug and Cosmetic Act, which required that products be tested for both safety and effectiveness.

Collodions

Collodions are liquid preparations containing pyroxylin (a nitrocellulose) in a mixture of ethyl ether and ethanol. They are applied to the skin by means of a soft brush or other suitable applicator and, when the ether and ethanol have evaporated, leave a film of pyroxylin on the surface. The official medicated collodion, Salicylic Acid Collodion USP, contains 10% *w/v* of salicylic acid in Flexible Collodion USP and is used as a keratolytic agent in the treatment of corns and warts. Collodion USP and Flexible Collodion USP are water-repellent protectives for minor cuts and scratches. Collodion is made flexible by the addition of castor oil and camphor. Collodion has been used to reduce or eliminate the side effects of fluorouracil treatment of solar keratoses. Vehicles other than flexible collodion, such as a polyacrylic base, have been used to incorporate salicylic acid for the treatment of warts with less irritation.

Elixirs

Elixirs are clear, pleasantly flavored, sweetened hydroalcoholic liquids intended for oral use. The main ingredients in elixirs are ethanol and water but glycerin, sorbitol, propylene glycol, flavoring agents, preservatives and syrups often are used in the preparation of the final product. Elixirs are more fluid than syrups, due to the use of less viscous ingredients such as alcohol and the minimal use of viscosity-improving agents such as sucrose. They are used as flavors and vehicles such as Aromatic Elixir USP (page 1394) for drug substances and, when such substances are incorporated into the specified solvents, they are classified as medicated elixirs, eg, Dexamethasone Elixir USP and Phenobarbital Elixir USP. Occasionally, certain adverse effects, eg, mucosal erosions, may be eliminated or reduced if the active drug, eg, potassium chloride, is administered in elixir rather than in a solid dosage form.

The distinction between some of the medicated syrups and elixirs is not always clear. For example, Ephedrine Sulfate Syrup USP contains between 20 and 40 mL of alcohol in 1000 mL of product. Ephedrine Elixir BP contains a suitable flavored vehicle and 12% alcohol. Definitions are, sometimes, inconsistent and, in some instances, not too important with respect to the naming of the articles of commerce. To be designated as an elixir, however, the solution must contain alcohol.

The alcoholic content will vary greatly, from elixirs containing only a small quantity to those that contain a considerable portion as a necessary aid to solubility. For example, Aro-

matic Elixir USP contains 21 to 23% of alcohol; Compound Benzaldehyde Elixir USP, on the other hand, contains 3 to 5%.

Elixirs also may contain glycerin and syrup. These may be added to increase the solubility of the medicinal agent for sweetening purposes or to decrease the pharmacological effects of the alcohol. Some elixirs contain propylene glycol. Claims have been made for this solvent as a satisfactory substitute for both glycerin and alcohol. Sumner,[16] in his paper on terpin hydrate preparations, summarized the advantages and disadvantages of this solvent and suggested several formulations with therapeutic characteristics superior to those of the elixir described in NF XIII.

One of the four formulations described in Sumner's paper is given below:

Terpin Hydrate	6.0 g
Orange Oil	0.1 mL
Benzaldehyde	0.005 mL
Sorbitol Solution USP	10.0 mL
Propylene Glycol	40.0 mL
Alcohol	43.0 mL
Purified Water, a sufficient quantity to make	100.0 mL

Dissolve the terpin hydrate in the propylene glycol and sorbitol solution which have been heated to 50°. Add the oil and the benzaldehyde to the alcohol and mix with the terpin hydrate solution at 25°. Add sufficient purified water to make the product measure 100 mL.

The elixir contains 300 mg of terpin hydrate/5 mL, a minimal quantity of alcohol and flavoring agents which adequately mask the taste of propylene glycol.

Although alcohol is an excellent solvent for some drugs, it does accentuate the saline taste of bromides and similar salts. It often is desirable, therefore, to substitute some other solvent that is more effective in masking such tastes for part of the alcohol in the formula. In general, if taste is a consideration, the formulator is more prone to use a syrup rather than a hydroalcoholic vehicle.

Because only relatively small quantities of ingredients have to be dissolved, elixirs are more readily prepared and manufactured than syrups, which frequently contain considerable amounts of sugar. An elixir may contain both water- and alcohol-soluble ingredients. If such is the case, the following procedure is indicated:

Dissolve the water-soluble ingredients in part of the water. Add and solubilize the sucrose in the aqueous solution. Prepare an alcoholic solution containing the other ingredients. Add the aqueous phase to the alcoholic solution, filter and make to volume with water.

Sucrose increases viscosity and decreases the solubilizing properties of water and so must be added after primary solution has been effected. A high alcoholic content is maintained during preparation by adding the aqueous phase to the alcoholic solution. Elixirs always should be brilliantly clear. They may be strained or filtered and, if necessary, subjected to the clarifying action of purified talc or siliceous earth.

One of the former official elixirs, Iso-Alcoholic Elixir NF XV (RPS-18 page 1328), actually is a combination of two solutions, one containing 8 to 10% alcohol and the other containing 73 to 78%. It is used as a vehicle for various medicaments that require solvents of different alcoholic strengths. For example, the alcoholic strength of the elixir to be used with a single liquid galenical, which is a liquid preparation of vegetable origin, is approximately the same as that of the galenical. When preparations with different alcoholic strengths are em- ployed in the same prescription, the elixir to be used is the one that produces the best solution. This is usually the average of the alcoholic strengths of the several preparations. For nonextractive substances, the lowest alcoholic strength of elixir that will produce a clear solution should be selected.

The formula for High-Alcoholic Elixir is

Compound Orange Spirit	4 mL
Saccharine	3 g
Glycerin	200 mL
Alcohol, a sufficient quantity, to make	1000 mL

This elixir, and many other liquid preparations intended for internal use eg, the diabetic syrups thickened with sodium carboxymethylcellulose or similar substances, contain saccharin as a sweetening agent. In the past, scientists have studied the toxic effects of this sweetening agent and found bladder tumors in rats. However, it is now generally accepted that this does not apply to humans when saccharin is used as a sweetener. Research on another sweetening agent, cyclamate,[17] showed that it could produce cancer in animals and, as a result, this substance was removed from a wide variety of products.

Cyclamates and saccharin have been banned in some countries as ingredients in manufactured products. Much research has been done to find a safe synthetic substitute for sucrose. As a result, aspartame (methyl *N*(-L-α-aspartyl)-L-phenylalaninate), which is about 200 times sweeter than sucrose, is being used now in many commercial preparations as the sweetening agent. It is sparingly soluble in water and is most stable at a pH of 4.3.

Incompatibilities—Since elixirs contain alcohol, incompatibilities of this solvent are an important consideration during formulation. Alcohol precipitates tragacanth, acacia and agar from aqueous solutions. Similarly, it will precipitate many inorganic salts from similar solutions. The implication here is that such substances should be absent from the aqueous phase or present in such concentrations that there is no danger of precipitation on standing.

If an aqueous solution is added to an elixir, a partial precipitation of alcohol-soluble ingredients may occur. This is due to the reduced alcoholic content of the final preparation. Usually, however, the alcoholic content of the mixture is not sufficiently decreased to cause separation. As vehicles for tinctures and fluidextracts, the elixirs generally cause a separation of extractive matter from these products due to a reduction of the alcoholic content.

Many of the incompatibilities between elixirs, and the substances combined with them, are due to the chemical characteristics of the elixir *per se*, or of the ingredients in the final preparation. Thus, certain elixirs are acid in reaction while others may be alkaline and will, therefore, behave accordingly.

Glycerins

Glycerins or glycerites are solutions or mixtures of medicinal substances in not less than 50% by weight of glycerin. Most of the glycerins are extremely viscous and some are of a jelly-like consistency. Few of them are used extensively. Glycerin is a valuable pharmaceutical solvent forming permanent and concentrated solutions not otherwise obtainable.

Glycerin is used as the sole solvent for the preparation of Antipyrine and Benzocaine Otic Solution USP. As noted under *Otic Solutions*, glycerin alone is used to aid in the removal of cerumen. Externol, a commercial product, contains 5% carbamide peroxide (urea hydrogen peroxide) in glycerin, has shown superior qualities in dispersing ear wax. A glycerin base was chosen as the optimum solvent for an otic preparation in a study involving the stability and antimicrobial activity of kanamycin sulfate otic drops.

Glycerins are hygroscopic and should be stored in tightly closed containers.

Inhalations and Inhalants

Inhalations

These preparations are so used or designed that the drug is carried into the respiratory tree of the patient. The vapor or mist reaches the affected area and gives prompt relief from the symptoms of bronchial and nasal congestion. The USP defines Inhalations in the following way:

Inhalations are drugs or solutions or suspensions of one or more drug substances administered by the nasal or oral respiratory route for either a local or systemic effect. Solutions of drug substances in sterile water for

inhalation or in sodium chloride inhalation solution may be nebulized by the use of inert gases. Nebulizers are suitable for the administration of inhalation solutions only if they give droplets sufficiently fine and uniform in size so that the mist reaches the bronchioles. Nebulized solutions may be breathed directly from the nebulizer, or the nebulizer may be attached to a plastic face mask, tent or intermittent positive pressure breathing (IPPB) machine.

Another group of products, also known as metered dose inhalers (MDIs) are propellant-driven drug suspensions or solution in liquified-gas propellant with or without a cosolvent and are intended for delivering metered doses of the drug to the respiratory tract. An MDI contains multiple doses, often exceeding several hundred. The most common single-dose volumes delivered are from 25 to 100 μL (also expressed as mg) per actuation.

Examples of MDIs containing drug solutions and suspension in this pharmacopeia are Epinephrine Inhalation Aerosol and Isoproterenol Hydrochloride and Phenylephrine Bitartrate Inhalation Aerosol, respectively.

Powders also may be administered by mechanical devices that require manually produced pressure or a deep inhalation by the patient, eg, Cromolyn Sodium for Inhalation.

As stated in the USP, particle size is of major importance in the administration of this type of preparation. The various mechanical devices that are used in conjunction with inhalations are described in some detail in Chapter 107. It has been reported that the optimum particle size for penetration into the pulmonary cavity is of the order of 0.5 to 7 μm. Fine mists are produced by pressurized aerosols and hence possess basic advantages over the older nebulizers; in addition, metered aerosols deliver more uniform doses. See Chapter 95. A number of inhalations are described in the USP XXI, eg, Epinephrine Inhalation Solution is a solution of Epinephrine in Purified Water prepared with the aid of Hydrochloric Acid, and Isoproterenol Inhalation Solution is a solution of Isoproeterenol Hydrochloride in Purified Water and may contain Sodium Chloride.

The term *inhalations*, defined by the BP, has a different meaning. These are solutions or suspensions of one or more active ingredients which may contain an inert, suspended diffusing agent. They are intended to release volatile constituents for inhalation, either when placed on a pad or when added to hot, but not boiling, water. Benzoin Inhalation BP contains benzoin, storax and alcohol. The vapors from a preparation containing 1 teaspoonful of the tincture and 1 qt of boiling water may be inhaled. The device known as a *vaporizer* may be used with a number of commercially available preparations of this type (see Chapter 107).

Inhalants

The USP defines inhalants as follows:

A special class of inhalations termed "inhalants" consists of drugs or combinations of drugs that, by virtue of their high vapor pressure, can be carried by an air current into the nasal passage where they exert their effect. The container from which the inhalant is administered is known as an inhaler.

Propylhexedrine Inhalant USP and Tuaminoheptane Inhalant USP consist of cylindrical rolls of suitable fibrous material im pregnated with propylhexedrine or tuaminoheptane (as car bonate), usually aromatized, and contained in a suitable inhaler. Propylhexedrine is the active ingredient in the widely used Benzedrex Inhaler. Both of these drugs are vasoconstrictors used to relieve nasal congestion. Inhalers which come in contact with the mouth or nasal passages become contaminated by bacteria, thus, they should be restricted to personal use.

Another inhalant is Amyl Nitrite USP which is very flammable and should not be used where it may be ignited. It is packaged in sealed glass vials in a protective gauze. Upon breaking the vial, the gauze absorbs the drug which is then inhaled for the treatment of anginal pain. See page 953.

Liniments

Liniments are solutions or mixtures of various substances in oil, alcoholic solutions of soap or emulsions and may contain suitable antimicrobial preservatives. They are intended for external application and should be so labeled. They are rubbed onto the affected area and, because of this, were once called *embrocations*.

Liniments usually are applied with friction and rubbing of the skin, the oil or soap base providing for ease of application and massage. Alcoholic liniments are used generally for their rubefacient, counterirritant, mildly astringent and penetrating effects. Such liniments penetrate the skin more readily than do those with an oil base. The oily liniments, therefore, are milder in their action but are more useful when massage is required. Depending on their ingredients, such liniments may function solely as protective coatings. Liniments should not be applied to skin that is bruised or broken.

Many of the marketed "white" liniments are based on the formulation below or variations thereof.

White Liniment BP

Oleic Acid	85 mL
Turpentine Oil	250 mL
Dilute Ammonia Solution	45 mL
Ammonium Chloride	12.5 mL
Purified Water	625 mL

Mix the oleic acid with the turpentine oil. Dilute the dilute ammonia solution with 45 mL of the water, previously warmed, add to the oily solution and shake to form an emulsion. Separately dissolve the ammonium chloride in the remainder of the water, add to the emulsion and mix.

Other liniments contain antipruritics, astringents, emollients or analgesics and are classified on the basis of their active ingredient. An example is:

Compound Calamine Application PC
(Compound Calamine Liniment)

Calamine	100 g
Zinc Oxide	50 g
Wool Fat	25 g
Zinc Stearate	25 g
Yellow Soft Paraffin	250 g
Liquid Paraffin	550 g

The powders are triturated to a smooth paste with some of the liquid paraffin (Liquid Petrolatum). The wool fat, zinc stearate and yellow soft paraffin (Petrolatum) are melted, mixed with some of the liquid paraffin, the mixture incorporated with the triturated powders and the rest of the liquid paraffin added with mixing.

Dermatologists prescribe products of this type but only those containing the rubefacients are advertised extensively and used by consumers for treating minor muscular aches and pains. It is essential that these applications be marked clearly for external use only.

Because of the confusion of camphorated oil (camphor liniment) with castor oil, which has resulted in ingestion and, perhaps, to poisoning, camphorated oil has been banned from the market. Camphorated Oil presently is classified as a new drug by the FDA for which a new drug application is required.

Oleovitamins

Oleovitamins are fish-liver oils diluted with edible vegetable oil or solutions of the indicated vitamins or vitamin concentrates (usually vitamin A and D) in fish-liver oil. The definition is broad enough to include a wide variety of marketed products.

Oleovitamin A and D is official; vitamin D may be present as ergocalciferol or cholecalciferol obtained by the activation of ergosterol or 7-dehydrocholesterol or may be obtained from natural sources. Synthetic vitamin A, or a concentrate, may be used to prepare oleovitamin A. The starting material for the concentrate is a fish-liver oil, the active ingredient being isolated by molecular distillation or by a saponification and extraction procedure. The latter procedure is described in detail in the monograph for Concentrated Vitamin A Solution PC.

These vitamins are unstable in the presence of rancid oils and, therefore, these preparations and, in particular, Oleovita-

min A, should be stored in small, tight containers, preferably under vacuum or under an atmosphere of an inert gas, protected from light.

Spirits

Spirits, sometimes known as essences, are alcoholic or hydroalcoholic solutions of volatile substances. Like the aromatic waters, the active ingredient in the spirit may be a solid, liquid or gas. The genealogical tree for this class of preparations begins with the distinguished pair of products, Brandy (*Spiritus Vini Vitis*) and Whisky (*Spiritis Frumenti*), and ends with a wide variety of products that comply with the definition given above. Physicians have debated the therapeutic value of the former products and these are no longer official in the compendia.

Some of these spirits are used internally for their medicinal value, a few medicinally by inhalation and a large number as flavoring agents. The latter group provides a convenient and ready means of obtaining the volatile oil in the proper quantity. For example, a spirit or spirit-like preparation may be used in the formulation of aromatic waters or other pharmaceuticals that require a distinctive flavor.

The BP's definition of Spirits is very broad. Some examples are Aromatic Ammonia Spirits BP, which has a different formula from the USP XXI, is used as a flavoring agent, Soap Spirits BP is used instead of a shampoo for scalp disorders and Surgical Spirits BP is used for its astringent action on unbroken skin.

Spirits should be stored in tight, light-resistant containers and in a cool place. This tends to prevent evaporation and volatilization of either the alcohol or the active principle and to limit oxidative changes. Spirits usually contain a high alcohol content and consequently should be kept away from an open flame.

Preparation—There are four classic methods of preparation:

Simple Solution—This is the method by which the majority of spirits are prepared. Aromatic Ammonia Spirit USP is official and a formula and procedure is given in USP XXI, which illustrates this method of preparation.

Aromatic Ammonia Spirit USP XXI

Ammonium Carbonate, in translucent pieces	34 g
Strong Ammonium Solution	36 mL
Lemon Oil	10 mL
Lavender Oil	1 mL
Nutmeg Oil	1 mL
Alcohol	700 mL
Purified Water, a sufficient quantity to make	1000 mL

Dissolve the ammonium carbonate in the strong ammonia solution and 195 mL of purified water by gentle agitation and allow the solution to stand for 12 hours. Dissolve the oils in the alcohol, contained in a graduated bottle or cylinder, and gradually add the ammonium carbonate solution and enough purified water to make the product measure 1000 mL. Set the mixture aside in a cool place for 24 hours, occasionally agitating it, then filter, using a covered funnel.

The spirit is a respiratory stimulant and is administered by inhalation of the vapor as required. It is marketed in suitable tight, light-resistant containers but is also available in a single-dose glass vial wrapped in a soft cotton envelope. The vial is broken easily; the cotton acts as a sponge for the spirit.

Ammonium carbonate is a mixture of ammonium bicarbonate and ammonium carbamate (NH_2COONH_4). The carbamate reacts with water to form the carbonate. An ammonium carbonate solution is, therefore, a solution of ammonium bicarbonate and ammonium carbonate in water. However, it decomposes in water, the decomposition products being ammonia, carbon dioxide and water. The stability of the spirit is improved by the addition of strong ammonia solution. This represses the hydrolysis of ammonium carbonate and, in this way, decreases the loss of dissolved gases.

Solution with Maceration—In this procedure, the leaves of a drug are macerated in purified water to extract water-soluble matter. They are expressed and the moist, macerated leaves are added to a prescribed quantity of alcohol. The volatile oil is added to the filtered liquid. Peppermint Spirit USP is made by this process (RPS-18 page 798). Peppermint Spirit BP differs from the official product in that it is a solution of the volatile oil in ethanol 90% only. The concentration of volatile oil in the final product is about the same but the official preparation possesses a green color.

Chemical Reaction—No official spirits are prepared by this process. Ethyl nitrite is made by the action of sodium nitrite on a mixture of alcohol and sulfuric acid in the cold. This substance then is used to prepare Ethyl Nitrite Spirit (Sweet Spirit of Nitre), a product no longer official and which has been removed from the market.

Distillation—Brandy and Whisky are made by distillation. The latter is derived from the fermented mash of wholly or partially germinated malted cereal grains and the former from the fermented juice of ripe grapes.

Incompatibilities—Spirits are, for the most part, preparations of high alcoholic strength and do not lend themselves well to dilution with aqueous solutions or liquids of low alcoholic content. The addition of such a solution invariably causes separation of some of the material dissolved in the spirit, evidenced by a turbidity which, in time, may disappear as distinct layering occurs. Salts may be precipitated from their aqueous solutions by the addition of spirits due to their lesser solubility in alcoholic liquids.

Some spirits show incompatibilities characteristic of the ingredients they contain. For example, Aromatic Ammonia Spirit cannot be mixed with aqueous preparations containing alkaloids (eg, codeine phosphate). An acid-base reaction (ammonia-phosphate) occurs and, if the alcohol content of the final mixture is too low, codeine will precipitate.

Toothache Drops

Toothache drops are preparations used for temporary relief of toothache by application of a small pledget of cotton saturated with the product into the tooth cavity. Anesthetic compounds include clove oil, eugenol or benzocaine; other ingredients include camphor, creosote, menthol and alcohol. Clove oil, containing a high concentration of eugenol, which is the main constituent, has been considered safe and effective for toothache.

These preparations no longer are recognized officially. Furthermore, dentists do not recommend the use of toothache drops if the patient has ready access to adequate dental services. Some preparations may damage the gums and produce complications more severe than the original toothache. However, many areas do not have adequate dental services and the pharmacist will, of necessity, handle these preparations, and should warn the patient of possible hazards associated with their use.

Toothache Drops NF XI contains 25 g of chlorobutanol in sufficient clove oil to make the product measure 100 mL. Another formulation contains creosote, clove oil, benzocaine and alcohol in a flexible collodion base.

Emulsions

An emulsion is a two-phase system prepared by combining two immiscible liquids, one of which is dispersed uniformly throughout the other and consists of globules that have diameters equal to or greater than those of the largest colloidal particles. The liquid that is dispersed into small droplets is called the dispersed, internal or discontinuous phase. The other liquid is the dispersion medium, external phase or continuous phase.

Most emulsions incorporate an aqueous phase into a nonaqueous phase (or *vice versa*). However, it is possible to

prepare emulsions that are basically nonaqueous. For example, investigations of the emulsifying effects of anionic and cationic surfactants on the nonaqueous immiscible system, glycerin and olive oil, have shown that certain amines and three cationic agents produced stable emulsions. This broadening of the basic definition for the term *emulsion* is recognized in the USP.

While the USP definition, given below, is broad enough to encompass nonaqueous systems, emphasis is placed on those emulsions which contain water, as they are by far the most common in pharmacy.

The USP defines emulsions as follows:

Emulsions are two-phase systems in which one liquid is dispersed throughout another liquid in the form of small droplets. Where oil is the dispersed phase and an aqueous solution is the continuous phase, the system is designated as an oil-in-water (O/W) emulsion. Conversely, where water or an aqueous solution is the dispersed phase and oil or oleaginous material is the continuous phase, the system is designated as a water-in-oil (W/O) emulsion.

Applications

When it is necessary to administer oils by the oral route, patient acceptance is enhanced when the oil is prepared in emulsion form. Thus, mineral oil, a laxative, valproic acid an anticonvulsant, oil-soluble vitamins, vegetable oils and preparations for enteral feeding are formulated frequently in an O/W emulsion form to enhance their palatability.

The bioavailability of oils for absorption may be enhanced when the oil is in the form of small droplets. Furthermore, the absorption of some drugs, eg, griseofulvin, sulfonamides and vitamin A, may be enhanced when they are prepared in the form of an O/W emulsion. Emulsion formulations of drugs such as erythromycin and physostigmine salicylate have been considered, in order to improve their stability. Finally, the greatest use of emulsions is for topical preparations. Both O/W and W/O emulsions are used widely, depending upon the effect desired. Emulsion bases of the W/O type tend to be more occlusive and emollient than O/W emulsion bases, which tend to be removed more easily by water. Further information may be found in Chapter 90. The effects of viscosity, surface tension, solubility, particle size, complexation and excipients on the bioavailability of oral suspensions and emulsions have been discussed in detail by Rettig.[17]

Practically, emulsions possess a number of important advantages over other liquid forms. These may be summarized in the following way:

1. In an emulsion, the therapeutic properties and the spreading ability of the constituents are increased.
2. The unpleasant taste or odor of an oil can be masked partially or wholly, by emulsification. Secondary masking techniques are available to the formulator but these must be used with caution. If flavors and sweetening agents are added to the emulsion, only minimal amounts should be used in order to prevent the nausea or gastric distress that results on ingestion of larger quantities of these.
3. The absorption and penetration of medicaments are controlled more easily if they are incorporated into an emulsion.
4. Emulsion action is prolonged and the emollient effect is greater than that observed with comparable preparations.
5. Water is an inexpensive diluent and a good solvent for the many drugs and flavors that are incorporated into an emulsion.

While this section on emulsions focuses primarily on those for oral use and to a lesser degree those for topical application, it should be noted that there are a number of emulsions used parenterally which are described in specialized textbooks on this topic. For example, emulsions of the O/W type are used for intravenous feeding of lipid nutrients. These are used to provide a source of calories and essential fatty acids. These emulsions must meet exacting standards in regard to particle size, safety and stability. Examples of commercial products include Intralipid (*Cutter*) and Liposyn (*Abbott*). Other specialized uses of emulsions include radiopaque emulsions which are used as diagnostic agents for X-ray examination. Other types of emulsions employed parenterally include W/O emulsions of allerginic extracts which are given subcutaneously and radiopaque O/W sustained-release depot preparations given intramuscularly.

Ingredients

The selection of the oil phase for oral preparations depends upon the purpose of the product. For example, mineral oil is used as a laxative and corn oil is used for its nutrient properties. Vegetable oils can be used to dissolve or suspend pharmaceuticals such as oil-soluble vitamins. The selection of the oil phase for topical O/W or W/O preparations is discussed in Chapter 90.

Emulsions are thermodynamically unstable because of the large increase in surface energy due to the combination of interfacial tension and large surface area of the dispersed phase and the different densities of the two phases. As a result, emulsions tend to cream, ie, the less dense phase rises and the more dense phase falls in the container. Subsequently, the droplets can coalesce with a considerable reduction in surface free energy. Consequently, considerable research has been conducted on their preparation and stabilization. The theory of emulsification is described in Chapter 20. In order to prepare suitable emulsions and to have them remain stable for a suitable period of time, a number of excipients are used in their preparation. The most important are those called emulsifying agents, which may be divided into three classes.

1. **Natural Emulsifying Agents**—These substances may be derived from vegetable sources and include acacia, tragacanth, alginates, chrondrus and pectin. While the surface activity of these is low, they achieve their emulsifying power by increasing the viscosity of the aqueous phase, as indicated by White.[18] Examples of emulsifying agents derived from animal sources include gelatin, egg yolk, casein, wool fat, cholesterol and lecithin. Because of the widely different chemical constitution of these compounds, they have a variety of uses, depending upon the specific compound, in both oral and topical preparations. All naturally occurring agents show variations in their emulsifying properties from batch to batch.
2. **Finely Divided Solids**—The compounds most frequently used in pharmacy are the colloidal clays: bentonite (aluminum silicate) and veegum (magnesium aluminum silicate). These compounds are good emulsifiers and tend to be absorbed at the interface, effect an increase in viscosity, generally in the aqueous phase, and usually are used in conjunction with a surfactant to prepare O/W emulsions, but both O/W and W/O preparations can be prepared by adding the clay to the external phase first. They are used frequently for external purposes such as a lotion or cream.
3. **Synthetic Emulsifying Agents**—This group of emulsifying agents is most effective at lowering the interfacial tension between the oil and water phases because the molecule possess both hydrophilic and hydrophobic properties. This property is described by their hydrophilic-lipophilic balance (HLB) number which may vary from 40 for sodium dodecyl sulfate to 1 for oleic acid. Emulsifying agents, sometimes used singly, are preferably a combination of two emulsifying agents, which will give a weighted HLB of 8 to 16 which is satisfactory for O/W emulsions and an HLB 3 to 8 for W/O emulsions. These emulsifying agents are available in different ionic types: anionic, eg, sodium dodecyl sulfate; cationic, eg, benzalkonium chloride; nonionic, eg, polyethylene glycol 400 monostearate and ampholytic, eg, long-chain amino acid derivatives. Many of these agents are described in Chapter 80 and the mechanism of action is discussed in Chapter 20.

In addition to the emulsifying agents, viscosity agents are employed, namely the hydrophilic colloids such as naturally occurring gums, noted above, and partially synthetic polymers such as cellulose derivatives, eg, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose or a number of synthetic polymers that may be used, such as carbomer polymers. These materials are hydrophilic in nature and dissolve or disperse in water to give a viscous solution and function as emulsion stabilizers.

The aqueous phase of the emulsion favors the growth of microorganisms and, because of this, a preservative usually is added to the product. Some of the preservatives that have been used include chlorocresol, chlorobutanol, mercurial preparations, salicylic acid, the esters of *p*-hydroxybenzoic acid, benzoic acid, sodium benzoate or sorbic acid. The preservative should be selected with regard for the ultimate use of the preparation and possible incompatibilities between

the preservative and the ingredients in the emulsion, eg, binding between the surface-active agent and the preservative. Low pH values of 5 to 6 and low concentrations of water are characteristics also likely to inhibit microbiological growth in emulsions.

Most emulsions consist of a nonaqueous (or oil or lipid) phase and an aqueous (or water) phase, thus some of the preservative may pass into the oil phase and be removed from the aqueous phase. It is in the aqueous phase that microorganisms tend to grow. As a result, water-soluble preservatives are more effective since the concentration of the unbound preservative in the aqueous phase assumes a great deal of importance in inhibiting the microbial growth. Esters of *p*-hydroxybenzoic acid appear to be the most satisfactory preservatives for emulsions. Many mathematical models have been used to determine the availability of preservatives in emulsified systems. However, because of the number of factors which reduce the effectiveness of the preservative, a final microbiological evaluation of the emulsion must be performed.

While emphasis concerning preservation of emulsions deals with the aqueous phase, microorganisms can reside also in the lipid phase. Consequently, it has been recommended that pairs of preservatives be used to ensure adequate concentration in both phases. Esters of *p*-hydroxybenzoic acid can be used to ensure appropriate concentrations in both phases because of their difference in oil and water solubilities.

The oxidative decomposition of certain excipients in the oil phase in some pharmaceuticals is possible in emulsions, not only because of the usual amount of air dissolved in the liquid, and the possible incorporation of air during the preparation of the product, but also the large interfacial area between the oil and water phase. The selection of the appropriate antioxidant briefly described at the beginning of the chapter depends on such factors as stability, compatibility with the ingredients of the emulsion, toxicity, effectiveness in emulsions, odor, taste and distribution between the two phases. Additional information can be found in appropriate references and in textbooks listed in the *Bibliography*.

Other excipients for the proper formation of emulsions include flavoring agents and fragrances.

Preparation

After the purpose of the emulsions has been determined, ie., oral or topical use, and the type of emulsions, O/W or W/O, and appropriate ingredients selected and the theory of emulsification considered, described in Chapter 21, experimental formulations may be prepared. One method is suggested by Griffin.[19]

1. Group the ingredients on the basis of their solubilities in the aqueous and nonaqueous phases.
2. Determine the type of emulsion required and calculate an approximate HLB (hydrophile-lipophile balance) value.
3. Blend a low HLB emulsifier and a high HLB emulsifier to the calculated value. For experimental formulations, use a higher concentration of emulsifier (eg, 10 to 30% of the oil phase) than that required to produce a satisfactory product. Emulsifiers should, in general, be stable chemically, nontoxic and suitably low in color, odor and taste. The emulsifier is selected on the basis of these characteristics, the type of equipment being used to blend the ingredients and the stability characteristics of the final product. Emulsions should not coalesce at room temperature, when frozen and thawed repeatedly or at elevated temperatures of up to 50°. Mechanical energy input varies with the type of equipment used to prepare the emulsion. The more the energy input, the less the demand on the emulsifier. Both process and formulation variables can affect the stability of an emulsion.
4. Dissolve the oil-soluble ingredients and the emulsifiers in the oil. Heat, if necessary, to approximately 5 to 10° over the melting point of the highest melting ingredient or to a maximum temperature of 70 to 80°.
5. Dissolve the water-soluble ingredients (except acids and salts) in a sufficient quantity of water.
6. Heat the aqueous phase to a temperature which is 3 to 5° higher than that of the oil phase.
7. Add the aqueous phase to the oily phase with suitable agitation.
8. If acids or salts are employed, dissolve them in water and add the solution to the cold emulsion.
9. Examine the emulsion and make adjustments in the formulation if the product is unstable. It may be necessary to add more emulsifier, to change to an emulsifier with a slightly higher or lower HLB value or to use an emulsifier with different chemical characteristics.

The technique of emulsification of pharmaceutical preparations has been described by White.[18] The preparation of an emulsion requires work to reduce the internal phase into small droplets and disperse them throughout the external phase. This can be accomplished by a mortar and pestle or a high-speed emulsifier. The addition of emulsifying agents not only reduces this work but also stabilizes the final emulsion. Emulsions may be prepared by four principle methods.

Addition of Internal Phase to External Phase—This is usually the most satisfactory method for preparing emulsions since there is always an excess of the external phase present which promotes the type of emulsion desired. If the external phase is water and the interal phase is oil, the water-soluble substances are dissolved in the water and the oil- soluble substances mixed thoroughly in the oil. The oil mixture is added in portions to the aqueous preparation with agitation. Sometimes, in order to give a better shearing action during the preparation, all of the water is not mixed with the emulsifying agent until the primary emulsion with the oil is formed; subsequently, the remainder of the water is added. An example using gelatin Type A is given below.

Addition of the External Phase to the Internal Phase—Using an O/W emulsion as an example, the addition of the water (external phase) to the oil (internal phase) will promote the formation of a W/O emulsion due to the preponderance of the oil phase. After further addition of the water, phase inversion to an O/W emulsion should take place. This method especially is useful and successful when hydrophilic agents such as acacia, tragacanth or methylcellulose are first mixed with the oil, effecting dispersion without wetting. Water is added and, eventually, an O/W emulsion is formed. This "dry gum" technique is a rapid method for preparing small quantities of emulsion. The ratio 4 parts of oil, 2 parts of water and 1 part of gum provides maximum shearing action on the oil globules in the mortar. The emulsion then can be diluted and triturated with water to the appropriate concentrations. The preparation of Mineral Oil Emulsion described below is an example.

Mixing Both Phases after Warming Each—This method is used when waxes or other substances which require melting are used. The oil-soluble emulsifying agents, oils and waxes are melted and mixed thoroughly. The water-soluble ingredients dissolved in the water are warmed to a temperature slightly higher than the oil phase. The two phases then are mixed and stirred until cold. For convenience, but not necessity, the aqueous solution is added to the oil mixture. This method frequently is used in the preparation of ointments and creams. An example of an oral preparation containing an insoluble drug is given below.

Alternate Addition of the Two Phases to the Emulsifying Agent—A portion of the oil, if an O/W emulsion is being prepared, is added to all of the oil-soluble emulsifying agents with mixing, then an equal quantity of water containing all the water-soluble emulsifying agents is added with stirring until the emulsion is formed. Further portions of the oil and water are added alternately until the final product is formed. The high concentration of the emulsifying agent in the original emulsion makes the initial emulsification more likely and the high viscosity provides effective shearing action leading to small droplets in the emulsion. This method often is used successfully with soaps.

Examples of some emulsions are given below.

In NF XIII it was suggested that only O/W emulsions are suitable for oral use because these are water-miscible and thus their oiliness is masked. This compendium gave specific directions for the preparation of emulsions using gelatin as an emulsifying agent. These preparations are based on either Type A or Type B gelatin.

Type A gelatin is prepared by acid-treated precursors and is used at a pH of about 3.2. It is incompatible with anionic emulsifying agents such as the vegetable gums. The following formula was recommended.

Gelatin (Type A)	8 g
Tartaric Acid	0.6 g
Flavor as desired	
Alcohol	60 mL
Oil	500 mL
Purified Water, to make	1000 mL

Add the gelatin and the tartaric acid to about 300 mL of purified water, allow to stand for a few minutes, heat until the gelatin is dissolved, then raise the temperature to about 98° and maintain this temperature for about 20 min. Cool to 50°, add the flavor, the alcohol and sufficient purified water to make 500 mL. Add the oil, agitate the mixture thoroughly and

pass it through a homogenizer or a colloid mill until the oil is dispersed completely and uniformly.

This emulsion cannot be prepared by trituration or by the use of the usual stirring devices.

Type B gelatin is prepared from alkali-treated precursors and is used at a pH of about 8.0. It may be used with other anionic emulsifying agents but is incompatible with cationic types. If the emulsion contains 50% oil, 5 g of Type B gelatin, 2.5 g of sodium bicarbonate and sufficient tragacanth or agar should be incorporated into the aqueous phase to yield 1000 mL of product of the required viscosity.

An emulsion that may be prepared by the mortar and pestle method is the following Mineral Oil Emulsion USP.

Mineral Oil	500 mL
Acacia, in very fine powder	125 g
Syrup	100 mL
Vanillin	40 mg
Alcohol	60 mL
Purified Water, a sufficient quantity	1000 mL

The mineral oil and acacia are mixed in a dry Wedgwood mortar. Purified water (250 mL) is added and the mixture triturated vigorously until an emulsion is formed. A mixture of the syrup, 50 mL of purified water and the vanillin dissolved in alcohol is added in divided portions with trituration; sufficient purified water is then added to the proper volume, the mixture mixed well and homogenized.

An Oral Emulsion (O/W) Containing an Insoluble Drug[20]

Cottonseed Oil	460.0 g
Sulfadiazine	200.0 g
Sorbitan Monostearate	84.0 g
Polyoxyethylene 20 Sorbitan Monostearate	36.0 g
Sodium Benzoate	2.0 g
Sweetener	qs
Purified Water	1000.0 g
Flavor Oil	qs

The procedure as indicated by Rieger[20] is

1. Heat the first three ingredients to 50° and pass through colloid mill.
2. Add the next four ingredients at 50° to the first three ingredients at 65° and stir while cooling to 45°.
3. Add the flavor oil and continue to stir until room temperature is reached.

Properties

The type of emulsion O/W or W/O depends, to some extent, on the phase-volume ratio. The higher the fraction of one phase, the greater likelihood it will form the external phase. Thus, O/W emulsions are favored if water forms a greater fraction of the volume than the oil phase. However, it is possible for the internal phase of an emulsion to occupy up to 0.74 of the volume of the emulsion and still form a stable product. Emulsifiers with high HLB level values (8 to 16) tend to form an O/W emulsion, while those with low HLB values (3 to 8) tend to form a W/O emulsion.

The consistency of emulsions, as suggested by White,[18] can be increased by increasing the viscosity of the continuous phase, increasing the fractional volume of the internal phase, reducing the particle size of the internal phase, increasing the proportion of the emulsifying agent or adding hydrophobic emulsifying agents to the oil phase of the emulsion.

The physical stability of emulsions may be defined by a number of expressions. The first of these, which is called *creaming*, is the movement of the droplets either upward or downward, depending upon their density. This gives a product which is not homogenous and can lead to a nonuniform dose. Generally, creaming is not a serious problem because a moderate amount of shaking will redisperse the droplets uniformly. The rate of creaming may be decreased by considering the theory of creaming using Stokes law, Chapter 20. This equation relates the rate of creaming to the size of the droplets, the difference in densities and the viscosity of the external phase. Thus, the rate of creaming may be decreased by decreasing the size of the droplets and increasing the viscosity of the external phases, both of which have been discussed above. Minimizing the difference between densities is more difficult to achieve due to a number of practical difficulties.

When the droplets aggregate, they come together and act as a single unit, but do not fuse. As a result of the larger size, they tend to cream faster and further provoke physical instability. Aggregation is to some extent reversible and may be controlled by choosing a somewhat different surfactant system and controlling the electrical potential of the droplets. Coalescence of an emulsion is the fusion of the droplets, leading to a decrease in their numbers and eventually the complete separation of the two phases, yielding an unsatisfactory product which should be reformulated completely (see Chapter 21).

Multiple Emulsions—A recent innovation in emulsion technology is the development of multiple emulsions. The dispersed phase of these emulsions contains even smaller droplets which are miscible with the continuous phase. Thus, the multiple emulsion may be O/W/O where the aqueous phase is between two oil phases, or W/O/W where the internal and external aqueous phases are separated by an oil phase. In these systems both hydrophobic and hydrophilic emulsifiers are used and both have an effect on the yield and stability, as noted by Florence and Whitehill.[21]

It appears that O/W/O emulsions are formed better by lipophilic, nonionic surfactants using gum acacia-emulsified simple systems, while W/O/W multiple emulsions are formed better by nonionic surfactants in a two-stage emulsification procedure. A specific formulation for a W/O/W emulsion may be prepared by forming the primary (W/O) emulsion from isopropyl myristate (47.5%), sorbitan monooleate (2.5%) and distilled water to 100%. This primary emulsion (50%) is added to a polyoxyethylene sorbitan monooleate (2% *w/v*) solution in water as suggested by Florence and Whitehill.[21] Other formulations of multiple emulsions include carboxymethylcellulose sodium, microcrystalline cellulose, sorbitan monooleate and sorbitan trioleate.

While the technique of preparing these emulsions is more complicated, research indicates potential use of these emulsions for prolonged action, taste-masking, more effective dosage forms, improved stability, parenteral preparations, protection against the external environment and enzyme entrapment. These emulsions also may be used to separate two incompatible hydrophilic substances in the inner and outer aqueous phases by the middle oil phase.

Microemulsions—The coarse pharmaceutical macro emulsions appear white and tend to separate on standing. Microemulsions are translucent or transparent, do not separate and have a droplet diameter in the nanometer size range. The microemulsions are not always distinguishable from micellar solutions.

Both O/W and W/O types are possible and may be converted, one to the other, by adding more of the internal phase or by altering the type of emulsifier. As the internal phase is added, the emulsion will pass through a viscoelastic gel stage; with further addition, an emulsion of the opposite type will occur.

The most obvious benefit of microemulsions is their stability, thus providing dose uniformity. Usually, the emulsifier should be 20 to 30% of the weight of the oil used. The W/O systems are prepared by blending the oil and emulsifier with a little heat, if required, and then adding the water. The order of mixing for O/W systems is more flexible. One of the simplest methods is to blend the oil and the emulsifier and pour this into water with a little stirring. In no case can a microemulsion be formed unless there is a match between the oil and emulsifier.

If the emulsifier has been selected properly, microemulsification will occur almost spontaneously, leading to a satisfactory and stable preparation. The details of various preparations and the relationship between microemulsions and

micellar solutions have been reviewed by Prince *et al.*[22] Microemulsions containing hydrocortisone have been prepared.

Other authors suggest that the preparation of microemulsions is considerably more difficult than the preparation of coarse suspensions. Rosano *et al*[23] discusses the use of a primary surfactant adsorbed at the interface which influences the curvature of the dispersed phase. The amount of surfactant required may be estimated from the surface area of the droplets and the cross-sectional area of the surfactant molecule. The use of a cosurfactant to form a duplex film has been indicated. The authors also suggest that the order of mixing is important.

General methods are available for testing the instability of emulsions including bulk changes, centrifugal and ultracentrifugal studies, dielectric measurement, surface-area measurement and accelerated-motion studies. Low-shear rheological studies measuring viscoelasticity are suggested as the optimal method of stability testing.

Equipment

The preparation of emulsions requires a certain amount of energy to form the interface between the two phases, and additional work must be done to stir the system to overcome the resistance to flow. In addition, heat often is supplied to the system to melt waxy solids and/or reduce the viscosity of the oil phase. Consequently the preparation of emulsions on a large scale usually requires the expenditure of considerable amounts of energy for heating and mixing. Careful consideration of these processes has led to the development of low-energy emulsification by using an appropriate emulsification temperature and selective heating of the ingredients. This process, described by Lin,[24] involves the preparation of an emulsion concentrate subsequently diluted with the external phase at room temperature.

Because of the variety of oils used, emulsifier agents, phase-volume ratios and the desired physical properties of the product, a wide selection of equipment is available for preparing emulsions and an outline of the main classes of equipment is discussed below. Further information may be obtained from the *Bibliography*.

Special techniques and equipment in certain instances, will produce superior emulsions, including rapid cooling, reduction in particle size or ultrasonic devices. A wide selection of equipment for processing both emulsions and suspensions has been described by Eisberg.[25] A number of improvements have been made to make the various processes more effective and energy-efficient.

The mortar and pestle may be used to prepare small quantities of an emulsion, and it is one of the simplest and least expensive methods. It may be used for most of the different techniques of preparing emulsions. Generally, the final particle size is considerably larger than is achieved by the equipment described below. In addition, it is necessary for the ingredients to have a certain viscosity prior to trituration in order to achieve a satisfactory shear. Satisfactory emulsions of low-viscosity ingredients and small volumes may be prepared using the appropriate equipment described below.

Agitators—Ordinary agitation or shaking may be used to prepare the emulsion. This method frequently is employed by the pharmacist, particularly in the emulsification of easily dispersed, low-viscosity oils. Under certain conditions, intermittent shaking is considerably more effective than ordinary continuous shaking. Continuous shaking tends to break up not only the phase to be dispersed but also the dispersion medium and, in this way, impairs the ease of emulsification. Laboratory shaking devices may be used for small-scale production.

Mechanical Mixers—Emulsions may be prepared by using one of several mixers which are available. Propeller-type mixers which have a propeller attached to a shaft driven by an electric motor are convenient and portable and can be used for both stirring and emulsification. This type operates best in mixtures which have low viscosity, ie, mixtures with a viscosity of glycerin or less. They are also useful for preparing emulsions. A turbine mixer has a number of blades which may be straight or curved, with or without a pitch, mounted on a shaft. The turbine tends to give a greater shear than propellers. The shear can be increased by using diffuser rings which are perforated and surround the turbine so that the liquid from the turbine must pass through holes. The turbines can be used for both low-viscosity mixtures and medium-viscosity liquids, up to that of molasses. The degree of stirring and shear by propeller or turbine mixers depends upon several factors, such as the speed of rotation, pattern of liquid flow, position in the container and baffles in the container as discussed by Fox.[26]

Production-size mixers include high-powered propeller-shaft stirrers immersed in a tank or self-contained units with propeller and paddle systems. The latter usually are constructed so that the contents of the tank either may be heated or cooled during the production process. Baffles often are built into a tank and these increase the efficiency of mixing. Two mixers manufactured by the same company are shown in Figs 2 and 3.

Small electric mixers may be used to prepare emulsions at the prescription counter. They will save time and energy and produce satisfactory emulsions when the emulsifying agent is acacia or agar.

The commercially available *Waring Blendor* disperses efficiently by means of the shearing action of rapidly rotating blades. It transfers large amounts of energy and incorporates air into the emulsion. If an emulsion first is produced by using a blender of this type, the formulator must remember that the emulsion characteristics obtained in the laboratory will not be duplicated necessarily by the production-size equipment.

Colloid Mills—The principle of operation of the colloid mill is the passage of the mixed phases of an emulsion formula between a stator and a high-speed rotor revolving at speeds of 2000 to 18,000 rpm. The clearance between the rotor and the stator is adjustable, usually from 0.001 in upward. The emulsion mixture, in passing between the rotor and stator, is subjected to a tremendous shearing action which effects a fine dispersion of uniform size as indicated by Griffin *et al.*[19] A colloid mill and various rotors are shown in Figs 4 and 5. The operating principle is the same for all, but each manufacturer incorporates specific features which result in changes in oper-

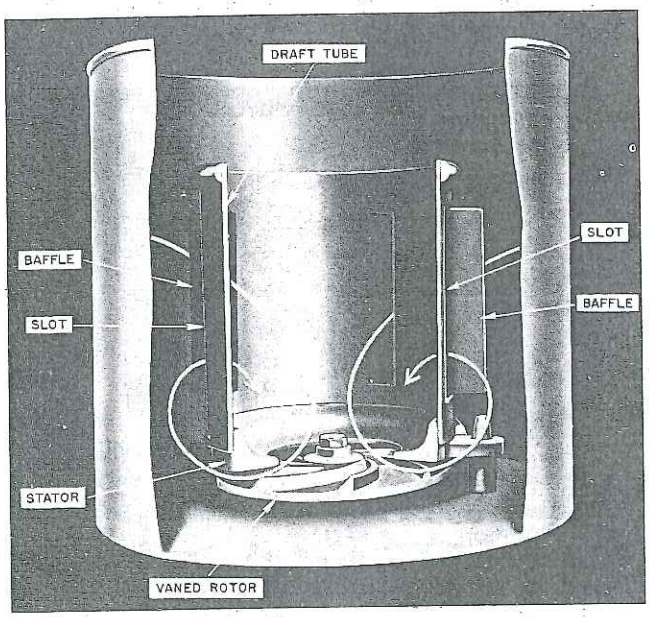


Fig 2. Standard slurry-type dispersall mixer with vaned-rotor "mixing" element and slotted draft-tube circulating element (courtesy, Abbe Eng).

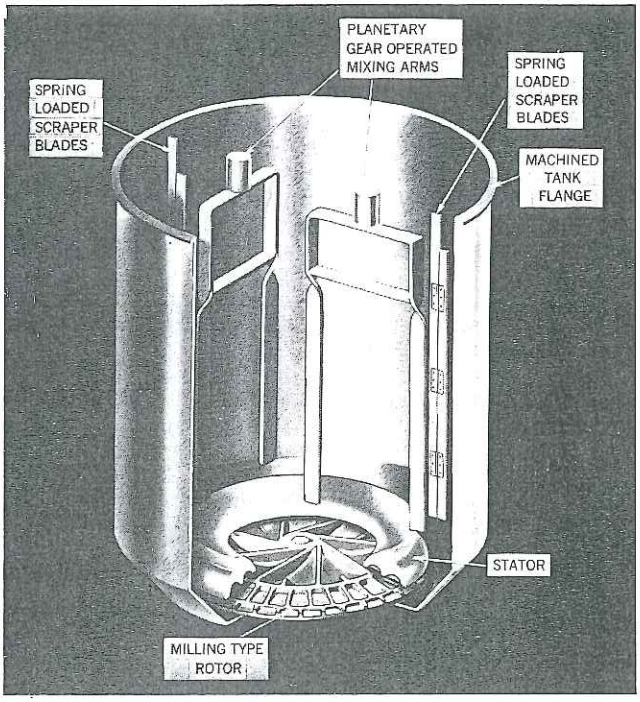


Fig 3. Standard paste-type dispersall mixer with "cupped-rotor" milling element and double-rotating mixing arm circulating element (courtesy, Abbe Eng).

ating efficiency. The shearing forces applied in the colloid mill usually result in a temperature increase within the emulsion. It may be necessary, therefore, to cool the equipment when the emulsion is being produced.

Colloid mills are used frequently for the comminution of solids and for the preparation of suspensions, especially suspensions containing solids which are not wetted by the dispersion medium.

Homogenizers—Impeller types of equipment frequently produce a satisfactory emulsion; however, for further reduction in particle size, homogenizers may be employed, as indicated by Scott.[27]

Homogenizers may be used in one of two ways:

1. The ingredients in the emulsion are mixed and then passed through the homogenizer to produce the final product.

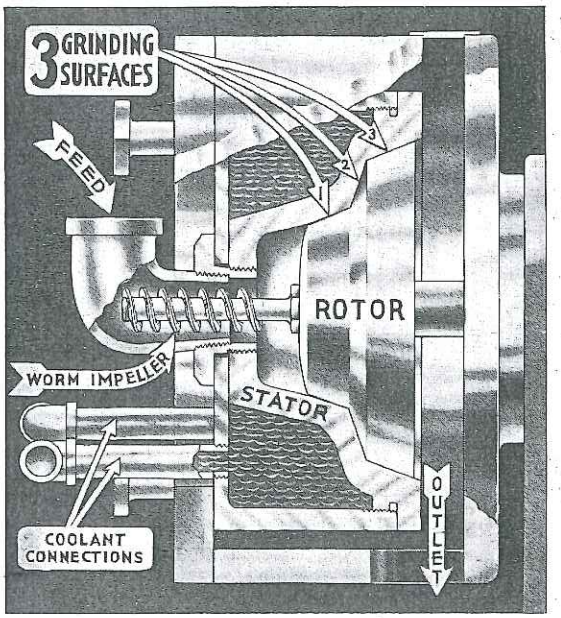


Fig 4. A colloid mill shown in cross section (courtesy, Tri-Homo).

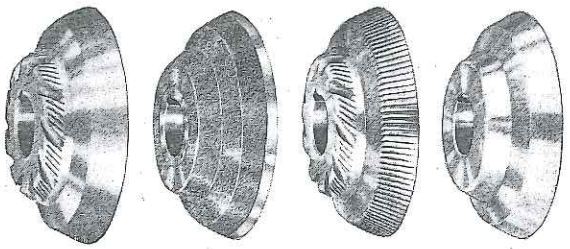


Fig 5. Types of rotors used in colloid mills. These may be smooth (for most emulsions), serrated (for ointments and very viscous products) or of vitrified stone (for the paints and pigment dispersions) (courtesy, Tri-Homo).

2. A coarse emulsion is prepared in some other way and then passed through a homogenizer for the purpose of decreasing the particle size and obtaining a greater degree of uniformity and stability.

The mixed phases or the coarse emulsion are subjected to homogenization and are passed between a finely ground valve and seat under high pressure. This, in effect, produces an atomization which is enhanced by the impact received by the atomized mixture as it strikes the surrounding metal surfaces. They operate at pressures of 1000 to 5000 psi and produce some of the finest dispersions obtainable in an emulsion.

Figure 6 shows the flow through the homogenizing valve, the heart of the high-pressure APV Gaulin homogenizer. The product enters the valve seat at high pressure, flows through the region between the valve and the seat at high velocity with a rapid pressure drop, causing cavitation; subsequently, the mixture hits the impact ring causing further disruption and then is discharged as a homogenized product. It is postulated that circulation and turbulence are responsible mainly for the homogenization that takes place. Different valve assemblies, two stage valve assemblies and equipment with a wide range of capacities are available.

Two-stage homogenizers are constructed so that the emulsion, after treatment in the first valve system, is conducted directly to another where it receives a second treatment. A single homogenization may produce an emulsion which, although its particle size is small, has a tendency to clump or form clusters. Emulsions of this type exhibit increased creaming tendencies. This is corrected by passing the emulsion through the first stage of homogenization at a high pressure (eg, 3000 to 5000 psi) and then through the second stage at a greatly reduced pressure (eg, 1000 psi). This breaks down any clusters formed in the first step.

The Macro Flow-Master *Kom-bi-nator* employs a number of different actions, each of which takes the ingredients a little further along in the process of subdividing droplets, until complete homogenization results. The machine is equipped with a pump which carries the liquid through the various stages of the process. In the first stage, the ingredients are forced between two specially designed rotors (gears) which shoot the liquid in opposite directions in a small chamber and, in this way, are mixed thoroughly. These rotors also set up a swirling action in the next chamber into which the liquid is forced and swirled back and forth in eddies and crosscurrents. The second stage is a pulsing or vibrating action at rapid frequency. The product then leaves this chamber, goes through a small valve opening and is dashed against the wall of

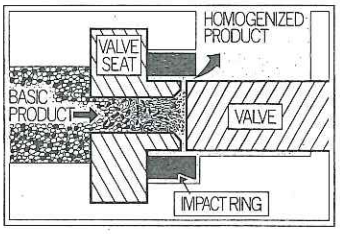


Fig 6. Operation of the homogenizer value assembly (Courtesy APV Gaulin).

the homogenizing chamber. Pressure is applied, but it is not as great as that used in other types of homogenizers. Pressure is controlled accurately by adjusting devices on the front of the machine, and temperature is controlled by passing coolants through the stators.

For small-scale extemporaneous preparation of emulsions, the inexpensive *hand-operated homogenizer* (available from *Central Scientific*) is particularly useful. It is probably the most efficient emulsifying apparatus available to the prescription pharmacist. The two phases, previously mixed in a bottle, are hand pumped through the apparatus. Recirculation of the emulsion through the apparatus will improve its quality.

A homogenizer does not incorporate air into the final product. Air may ruin an emulsion because the emulsifying agent is adsorbed preferentially at the air/water interface, followed by an irreversible precipitation termed *denaturization*. This is particularly prone to occur with protein emulsifying agents.

Homogenization may spoil an emulsion if the concentration of the emulsifying agent in the formulation is less than that required to take care of the increase in surface area produced by the process.

The temperature rise during homogenization is not very large. However, temperature does play an important role in the emulsification process. An increase in temperature will reduce the viscosity and, in certain instances, the interfacial tension between the oil and the water. There are, however, many instances, particularly in the manufacturing of cosmetic creams and ointments, where the ingredients will fail to emulsify properly if they are processed at too high a temperature. Emulsions of this type are processed first at an elevated temperature and then homogenized at a temperature not exceeding 40°.

Homogenizers have been used most frequently with liquid emulsions, but now they may be used with suspensions, as the metal surfaces are formed from wear-resistant alloys which will resist the wear of solid particles contained in suspensions.

Ultrasonic Devices—The preparation of emulsions by the use of ultrasonic vibrations also is possible. An oscillator of high frequency (100 to 500 kHz) is connected to two electrodes between which is placed a piezoelectric quartz plate. The quartz plate and electrodes are immersed in an oil bath and, when the oscillator is operating, high-frequency waves flow through the fluid. Emulsification is accomplished by simply immersing a tube containing the emulsion ingredients into this oil bath. Considerable research has been done on ultrasonic emulsification, particularly with regard to the mechanism of emulsion formation by this method. Limited data indicate that these devices will produce stable emulsions only with liquids of low viscosity. The method is not practical, however, for large-scale production of emulsions.

Commercial products may be prepared using ultrasonics based upon the device known as the Pohlman whistle. In this apparatus, the premixed liquids are forced through a thin orifice and are allowed to impinge upon the free end of a knife-edge bar which is made to vibrate. Ultrasonic waves are produced and areas of compression and rarefaction are formed. Shock waves are produced by the collapse of bubbles which produce a shear effect, thereby producing fine particle sizes as described by Scott.[27]

Suspensions

The physical chemist defines the word "suspension" as a two-phase system consisting of a finely divided solid dispersed in a solid, liquid or gas. The pharmacist accepts this definition and can show that a variety of dosage forms fall within the scope of the preceding statement. There is, however, a reluctance to be all-inclusive, and it is for this reason that the main emphasis is placed on solids dispersed in liquids. In addition, and because there is a need for more specific terminology, the pharmaceutical scientist differentiates between such preparations as suspensions, mixtures, magmas, gels and lotions. In a general sense, each of these preparations represents a suspension, but the state of subdivision of the insoluble solid varies from particles which settle gradually on standing to particles which are colloidal in nature. The lower limit of particle size is approximately 0.1 μm, and it is the preparations containing dispersed solids of this magnitude or greater that are defined pharmaceutically as suspensions.

Suspensions have a number of applications in pharmacy. They are used to supply drugs to the patient in liquid form. Many people have difficulty swallowing solid dosage forms, consequently a liquid preparation has an advantage for these people; in addition, the dose of a liquid form may be adjusted easily to meet the patient's requirements. Thus, if the drug is insoluble or poorly soluble, a suspension may be the most suitable dosage form. If a drug is unstable in an aqueous medium, a different form of the drug, such as an ester or insoluble salt, which does not dissolve in water, may be used in the preparation of a suspension.

In order to improve the stability of an antibiotic such as ampicillin, formulations are made in such a way that the dispersion medium, water, is added upon dispensing to form a satisfactory suspension. Generally, the taste of pharmaceuticals can be improved if they are supplied in suspension form, rather than solutions; thus, chloramphenicol palmitate is used instead of the more soluble form, chloramphenicol. Another way to decrease the solubility of the drug is to replace part of the water with another appropriate liquid such as alcohol or glycerin. Insoluble drugs may be formulated as suspensions for topical use such as calamine lotion.

Other preparations of suspensions, in addition to those noted above, include parenteral preparations, ophthalmic preparations or medicated applications discussed in Chapters 87, 89 and 90, respectively.

Certain authors also include liniments, and the newer sustained-release suspensions, in any discussion of this particular subject. The former preparations now usually are considered as solutions although a number of older liniments were, in fact, suspensions. The sustained-release suspensions represent a very specialized class of preparation and, as such, are discussed in more detail in Chapter 94. Some insoluble drugs also are administered in aerosol form; one example is dexamethasone phosphate suspended in a propellant mixture of fluorochlorocarbons. More detail on aerosols is available in Chapter 95.

Suspension formulation and control is based on the principles outlined in Chapters 20 and 22. Formulation involves more than suspending a solid in a liquid. A knowledge of the behavior of particles in liquids, of suspending agents and of flavors and colors is required to produce a satisfactory suspension.

Well-formulated suspensions should possess certain basic properties. The dispersed phase should settle slowly, if at all, and be redispersed readily on shaking. The particles should not cake on settling and the viscosity should be such that the preparation pours easily. As with all dosage forms, there should be no question as to the chemical stability of the suspension.

Ingredients

The main ingredients in a suspension are the drug and agents to wet the drug, influence flocculation, control viscosity, adjust pH, and the external medium, usually water. In addition, flavoring, sweetening and coloring agents and preservatives are employed.

A *wetting* agent, ie, a suitable surfactant with a HLB value between 7 and 9, is used; although surfactants with higher HLB values are recommended sometimes, eg, certain polysorbates and poloxamers. They are employed at a low concentration (0.05 to 0.5%) to allow the displacement of air from hydrophobic material and permit the liquid, usually water, to surround the particles and provide a proper dispersion. If it is desirable to flocculate the particles, then flocculating agents are employed. Usually low concentrations, less than 1%, of electrolytes such as sodium or potassium chloride are employed to induce flocculation. Water-soluble salts possessing divalent or trivalent ions may be considered if the particles are highly charged.

Viscosity agents such as natural gums, eg, acacia, xanthan and cellulose derivatives such as sodium carboxymethylcellulose and hydroxypropylmethylcellulose, may be used at low concentrations (<0.1%) to function as protective colloids, but at higher concentrations they can then function as viscosity-increasing agents and they decrease the rate of settling of deflocculated particles or provide stability in a flocculated suspension.

The choice of an appropriate viscosity agent depends upon the end-use of the product (external or internal), facilities for preparation and the duration of storage.

Extemporaneous preparations of suspensions for internal use showing good flow and suspending properties are provided by sodium carboxymethylcellulose 2.5%, tragacanth 1.25% and guar gum 0.5%. Avicel RC-591, a coprecipitate of microcrystalline cellulose and sodium carboxymethylcellulose stabilized with hydroxypropylmethylcellulose, has been used as a suspending vehicle for propranolol and orphenadrine hydrochloride dispersions prepared from tablets. It also may serve as a general-purpose suspending agent. Carbopol 934, 0.3% or greater, was a satisfactory suspending agent for sulfamethazine 10%, maintaining a permanent suspension for more than 6 months. Other agents include acacia, methylcellulose or other cellulose derivatives and sodium alginate or tragacanth.

Buffers may be considered if the drug has ionizable groups in order to maintain a low solubility of the drug. Buffers also may be considered to control the ionization of preservatives, ionic viscosity agents or to maintain the pH of the suspensions within a suitable range. The external phase is usually water for oral preparations; however, other polar liquids such as glycerin or alcohol may be considered in order to control solubility, stability and taste. The selection of the external phase is based upon taste, viscosity, density and stability. Nonpolar liquids such as aliphatic hydrocarbons and fatty esters may be considered if the preparation is used for external purposes.

Appropriate preservatives should be incorporated in order to minimize microbiological contamination as discussed previously. The suspension must be acceptable to the patient on the basis of its taste, color and cosmetic qualities (elegance), the latter two factors being of particular importance in preparations intended for external use.

Preparation

The preparation of suspensions involves several steps; the first is to obtain the particles in the proper size range which is in the lower micrometer size. Oral preparations should not feel gritty, topical preparations should feel smooth to the touch and injectables should not produce tissue irritation. Particle size and distribution also should be considered in terms of bioavailability, or alternately, to control the rate of release. Particles of an extremely small size, less than 1 μm will have a higher solubility than larger particles, which may cause problems in regard to dissolution and then the formation of larger particles.

Milling is the term given to the mechanical process of reducing the particle size, which may be accomplished by a number of different types of machines, as described by Parrot.[28] The hammer mill grinds the powders by the impact of rotating hammers and particles which subsequently fall through a screen in a range of 4 to 325 mesh are obtained. A ball mill contains a number of steel balls in a container which revolves, and the balls reduce the particle size to a 20 to 200 mesh by both attrition and impact. A fluid-energy mill produces particles 1 to 30 μm through violent turbulence in high-velocity air. Roller mills have two or more rollers which revolve at different speeds and the particles are reduced to a mesh of 20 to 200 by means of compression and a shearing action.

On a small scale, in a pharmacy, the particles should be wetted thoroughly with a small quantity of water-miscible solvent, such as glycerin or alcohol, which reduces the liquid/air interfacial tension. The suspending agent in the aqueous medium then is added. Alternately, the dry suspending agent can be triturated with the drug particles using a small quantity of glycerin or alcohol and then brought up to volume with the diluent water.

On a large scale, the drug particles are treated with a small portion of water which contains the wetting agent and allowed to stand for several hours in order to release entrapped air. At the same time, the suspending agent should be dissolved or dispersed in the main portion of the external phase and allowed to stand until complete hydration takes place. Subsequently, wetted drug particles should be added slowly to the main portion of the dissolved suspending agent. Other excipients such as electrolytes or buffers should be added in a careful manner to prevent variation in particle charge. The preservatives, flavoring agents and coloring agents are added. After all additions have been made, treatment with homogenizers or ultrasonic devices should be used to reduce the size of agglomerated particles, as described by Nash.[29]

Suspension equipment such as colloid mills or homogenizers normally are used in wet-milling finished suspensions to reduce particle agglomerates and to form a suitable preparation (Figs. 4, 5 and 6).

Quality

The quality of the suspension can be determined in a number of ways, such as photomicroscopy, to determine particle shape, size and flocculation. The Coulter counter can be used to determine the size distribution. Physical stability, ie, the degree of settling or flocculation, may be determined by using cylindrical graduates. Viscosity of the final product and the suspending agent dissolved in the liquid medium may be determined by moisture instruments such as the Brookfield viscometer. Specific-gravity measurements are useful for determining the degree of air entrapped. Of course both microbiological as well as aging tests should be performed to determine the efficiency of the preservative and the appropriateness of the formulation with respect to stability and time.

Suspensions from Tablets

Occasionally, it is necessary to prepare a liquid formulation of a drug in order to meet certain requirements of the patient such as inability to injest a solid dosage form or to prepare a product for a different route of administration or different strength. The pure drug should be used to prepare the dosage form rather than a tablet or a capsule because there is only one ingredient in the product; thus, no consideration has to be given to the excipients in the tablet or capsule. If it is necessary to prepare a liquid dosage form from tablets or capsules, a suspension is formed if either the drug or one of the excipients in the tablets or capsule is insoluble. The solubility of the drug may be determined from the literature; however, the excipients in the tablets or capsules are usually not known.

Insoluble excipients in these dosage forms may include certain disintegrants, lubricants, glidants, colors, diluents and coatings; consequently, although the drug may be soluble in water, many excipients are not. It is preferable to use the contents of capsules, or tablets which are not coated, or if coated, those tablets with a water-soluble coat. In any case,

the contents of the capsules or the tablets should be ground finely with a mortar and pestle and then wetted using a little alcohol or glycerin as mentioned above, or with the dispersion medium using the mortar and pestle.

Finally, it may be desirable to use a hand homogenizer to prepare a more suitable product. Some drugs which have been formulated in this manner include clonidine hydrochloride and simple syrup, cefuroxime axetil in an orange syrup vehicle, famotidine in cherry syrup, terbutaline in syrup, prednisone in a tuttifrutti formulation, metoprolol tartrate or spironolactone in a tragacanth-suspending vehicle or propranolol hydrochloride in a simple syrup. Many other examples may be found in current hospital and community pharmacy journals such as the *American Journal of Hospital Pharmacy, Canadian Journal of Hospital Pharmacy, U.S. Pharmacist Drug Development* and *Industrial Pharmacy*. Frequently, stability data and, occasionally, bioavailability and/or taste data are provided.

If the drug is soluble in water, a solution of the drug may be prepared by crushing the tablets in a mortar and pestle, triturating with water, filtering and bringing the solution up to appropriate volume with water or other suitable vehicle if the preparation is for topical application or with a flavored aqueous vehicle if it is for oral use.

If the active ingredient in the tablet or capsule is not stable in an aqueous system, a different method of preparing the suspension is required. The tablet may be crushed and placed in a powder paper and dispensed in the form of individual powders. Each paper contains the active drug in one tablet or an appropriate dose. The powder is placed in a glass of water or suitable liquid, stirred and administered immediately. See Chapter 91 for divided powders.

A general formula to prepare suspensions from crushed tablets is given in Martindale.[30]

Methylcellulose 20	0.75
Parabens	0.1
Purified Water	60.0
Propylene Glycol	2.0
Simple Syrup, to make	100.0

An extemporaneous suspension of cimetidine tablets which retained its potency at 40° over 14 days is:

Cimetidine 300-mg tablets	24 (7.2 g)
Glycerin	10 mL
Simple Syrup, to make	120 mL

The tablets are triturated to a fine powder using a mortar, the mixture is levigated with the glycerin, simple syrup added, mixed well, placed in a blender until smooth and then refrigerated as described by Tortorici.[31]

Satisfactory suspensions have been compounded from diazepam tablets and propranolol hydrochloride tablets, and they possess chemical stability for 60 days and 4 months, respectively, at room temperature or under refrigeration. Frequently, since the drug may be soluble, it is the excipients which are being suspended.

A comprehensive checklist of suspension formulations has been reported in the literature by Scheer.[32]

Gels

Pharmaceutical terminology is, at best, confusing and no two texts will classify gels, jellies magnas, milks and mixtures in the same way. The USP's definition for gels is given below.

> Gels (sometimes called Jellies) are semisolid systems consisting of either suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid. Where the gel mass consists of a network of small discrete particles, the gel is classified as a two-phase system (eg, *Aluminum Hydroxide Gel*). In a two-phase system, if the particle size of the dispersed phase is relatively large, the gel mass is sometimes referred to as a magma (eg, *Bentonite Magma*). Both gels and magmas may be thixotropic, forming semisolids on standing and becoming liquid on agitation. They should be shaken before use to ensure homogeneity and should be labeled to that effect. (See *Suspensions*.)
>
> Single-phase gels consist of organic macromolecules distributed uniformly throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Single-phase gels may be made from synthetic macromolecules (eg, *Carbomer*) or from natural gums (eg, *Tragacanth*). The latter preparations also are called mucilages. Although these gels are commonly aqueous, alcohols and oils may be used as the continuous phase. For example, mineral oil can be combined with a polyethylene resin to form an oleaginous ointment base.
>
> Gels can be used to administer drugs topically or into body cavities (eg, *Phenylephrine Hydrochloride Nasal Jelly*).

The definition in the BP tends to be more restrictive in the sense that the gels are homogenous and are intended to be applied to the skin or certain mucous membranes. Gels may contain auxiliary substances such as antimicrobial preservatives, antioxidants and stabilizers.

Schott[33] has described various aspects of gels. At appropriate concentrations of solute and solvent, gels consisting of two phases, eg, bentonite, are formed because of the attraction between positively charged edges and the negatively charged faces, producing a three-dimensional network penetrated by the liquid phase. In the case of a single-phase system, the gels are formed as a result of secondary valence forces between the polymer molecules due to entanglement of the chains. Permanent gels are formed when three-dimensional polymerization of multifunctional polymers occurs or when there is cross-linking of dissolved polymer molecules by primary valence bonds. These permanent gels are used as matrices for prolonged-release preparations (see Chapter 94) and are not discussed further in this chapter.

Two-phase gels containing bentonite may be used as a base for topical preparations such as plaster and ointment. Another two-phase gel, Aluminum Hydroxide Gel USP is used for its therapeutic properties.

The USP states that

> Aluminum Hydroxide Gel is a suspension, each 100 g of which contains the equivalent of not less than 5.5 g and not more than 6.7 g of aluminum hydroxide [$Al(OH)_3$], in the form of amorphous aluminum hydroxide in which there is a partial substitution of carbonate for hydroxide.

The gel itself usually is prepared by the interaction of a soluble aluminum salt, such as a chloride or sulfate, with ammonia solution, sodium carbonate or bicarbonate. The reactions which occur during the preparation are

$$3CO_3^{2-} + 3H_2O \rightarrow 3HCO_3^- + 3OH^-$$

$$[Al(H_2O)_6]^{3+} + 3OH^- \rightarrow [Al[H_2O)_3(OH)_3] + 3H_2O$$

$$2HCO_3^- \rightarrow CO_3^{2-} + H_2O + CO_2$$

The physical and chemical properties of the gel will be affected by the order of addition of reactants, pH of precipitation, temperature of precipitation, concentration of the reactants, the reactants used and the conditions of aging of the precipitated gel.

Aluminum Hydroxide Gel is soluble in acidic (or very strongly basic) media. The mechanism in acidic media is

$$\text{Aluminum Hydoxide Gel} + 3H_2O \rightarrow [Al(H_2O)_3(OH)_3]^0$$

$$[Al(H_2O)_3(OH)_3]^0 + H_3O^+ \rightarrow [Al(H_2O)_4(OH)_2]^+ + H_2O$$

$$[Al(H_2O)_4(OH)_2]^+ + H_3O^+ \rightarrow [Al(H_2O)_5(OH)^{2+} + H_2O$$

$$[Al(H_2O)_5(OH)]^{2+} + H_3O^+ \rightarrow [Al(H_2O)_6]^{3+} + H_2O$$

It is unlikely that the last reaction given proceeds to completion. Since the activity of the gel is controlled by its insolubility (solubility will decrease with an increase in the pH of the gastric media), there is no acid rebound. Further, since a certain quantity of insoluble gel always is available, the neutralizing capability of the gel extends over a considerable period of time.

Aluminum hydroxide gels also may contain peppermint oil, glycerin, sorbitol, sucrose, saccharin and various preservatives. Sorbitol improves the acid-consuming capac-

ity, apparently by inhibiting a secondary polymerization that takes place on aging. In addition, polyols such as mannitol, sorbitol and inositol have been shown to improve the stability of aluminum hydroxide and aluminum hydroxycarbonate gels.

Other two-phase gels of the USP include Aluminum Phosphate Gel and Aluminum Carbonate gels. Some of these products also occur in the dried form and are also called gels.

Single-Phase Gels—The single-phase gels are being used more frequently in pharmacy and cosmetics because of several properties: semisolid state, high degree of clarity, ease of application and ease of removal and use. The gels often provide a faster release of drug substance, independent of the water solubility of the drug, as compared to creams and ointments.

Some recent gel formulations include ophthalmic preparations of pilocarpine, carbachol and betamethasone valerate; topical preparations for burn therapy, anti-inflammatory treatment, musculoskeletal disorders and acne; peptic ulcer treatment with sucralfate gel and bronchoscopy using lidocaine. Cosmetic gels include shower gels, after shave gels and sunscreen gels. The USP lists a number of gels: Sodium Fluoride and Phosphoric Acid Gel for application to the teeth to reduce cavities, Betamethasone Benzoate Gel and Fluocinonide Gel, anti-inflammatory corticosteroids, Tolnaftate Gel, an antifungal agent and Tretinoin Gel for the treatment of acne. Gels may be used as lubricants for catheters, bases for patch testing, sodium chloride gels for electrocardiography.

Gels can be prepared from a number of pharmaceutical agents such as tragacanth 2 to 5%, sodium alginate 2 to 10%, gelatin 2 to 15%, methylcellulose 450 at 3 to 5%, sodium carboxymethylcellulose 2 to 5%, carbomer 0.3 to 5% or polyvinyl alcohols 10 to 20% as noted by Collett.[34] Other gelling agents include methylhydroxyethyl cellulose, polyoxyethylene-polyoxypropylene, hydroxyethylcellulose and gelatin. Gels prepared from nonpolar materials such as magnesium soap-hydrocarbon and hydrocarbons are being investigated. The percentages above indicate the concentration ranges of the gelling agent.

Some fluid gels at or below the lower of the above concentrations can be used as artificial saliva and artificial tears. The lower-percentage preparations, noted above, may be used as lubricants and the higher-percentage preparations as dermatological bases. Some of the gelling agents are available in different grades indicating the viscosity at a definite concentration. In general, high-viscosity grades result in gels at lower concentrations. An example of a gel containing a natural polymer, tragacanth, is:

Ephedrine Sulfate Jelly NF XII

Ephedrine Sulfate	10 g
Tragacanth	10 g
Methyl Salicylate	0.1 g
Eucalyptol	1.0 mL
Pine Needle Oil	0.1 mL
Glycerin	150 g
Purified Water	830 mL

Dissolve the ephedrine sulfate in the purified water and add the glycerin, tragacanth and then the remaining ingredients. Mix well and keep in a closed container for 1 week, stirring occasionally.

In order to prepare uniform gels, it is necessary to disperse the gelling agent in such a manner that it does not form clumps upon the addition of water. Some techniques include the addition of a small quantity of dispersing agent such as alcohol or glycerin and trituration. Another technique is to sprinkle the gelling agent into a vortex of stirred water. If there are a number of other powders in the preparation, the gelling agent first may be triturated with these powders, followed by the addition of water. Shaking the material in a bottle, mixing in a mortar with a pestle or using a mechanical stirrer also are employed. Specific information on the gelling agents is useful in preparing the gels, as described by Zatz and Kushla.[35]

Gels have been prepared in adhesive form in order to increase the contact time of the active ingredients, such as insulin with the oral and nasal mucosa, leading to a decrease in plasma glucose. This system also has been investigated as a vaginal dosage form for cervical cancer and a topical dosage form for aphthous stomatitis.

Preservatives should be incorporated into the gels, especially those prepared from natural sources. Appropriate preservatives, depending upon use and the gelling agent, include the parabens at about 0.2%, benzoic acid 0.2% (if the product is acidic) and chlorocresol 0.1%.

The preparation of a few gel bases is given below:

Sodium Alginate Gel Base

Sodium Alginate	2–10 g
Glycerin	2–10 g
Methyl Hydroxybenzoate	0.2 g
a soluble calcium salt (calcium or gluconate)	0.5 g
Purified Water, to make	100 mL

The sodium alginate is wetted in a mortar with glycerin, which aids the dispersion. The preservative is dissolved in about 80 mL of water with the aid of heat, allowed to cool and the calcium salt added, which will increase the viscosity of the preparation. This solution is stirred in a high speed stirrer and the sodium alginate-glycerin mixture added slowly while stirring, until the preparation is homogeneous. The preparation should be stored in a tightly sealed container in a wide mouth jar or tube.

Carbomer Jelly

Carbopol 934	2 g
Triethanolamine	1.65 mL
Parabens	0.2 g
Purified Water, to make	100 mL

The parabens are dissolved in 95 mL of water with the aid of heat and allowed to cool. The Carbopol 934, a commercial grade of carbomer, is added in small amounts to the solution using a high speed stirrer and, after a smooth dispersion is obtained, the preparation is allowed to stand permitting entrapped air to separate. Then the gelling agent, triethanolamine, is added, dropwise, stirring with a plastic spatula to avoid entrapping air and the remaining water incorporated. Other concentrations of carbomer can be used to prepare gels, creams or suspensions.

Gels may contract on standing and some of the solvent then is squeezed out. This process is called *syneresis* and will present a problem in the long-term stability of gels. The addition of relatively large quantities of salts may cause a salting-out of polymers, especially those of an ionic nature. The effect of increasing the temperature may cause rigid gels to melt. An example of an exception to this phenomenon is the gelification of methylcellulose which gels as the temperature rises above ≃50°. This phenomenon is called *thermal gelation*, as described by Schott.[33] In order to minimize water loss from single-phase gels, humectants such as propylene glycol, glycerin or sorbitol are added.

Lotions

Lotions are not defined specifically in the USP, but the BP provides a definition which is broad in nature and indicates that lotions are either liquid or semiliquid preparations which contain one or more active ingredients in an appropriate vehicle. Lotions may contain antimicrobial preservatives and other appropriate excipients such as stabilizers. Lotions are intended to be applied to the unbroken skin without friction. Lotions are usually suspensions of solids in an aqueous medium. A few lotions are, in fact, emulsions or solutions.

Even though lotions usually are applied without friction the insoluble matter should be divided very finely. Particles approaching colloidal dimensions are more soothing to inflamed areas and effective in contact with infected surfaces. A wide variety of ingredients may be added to the preparation to produce better dispersions or to accentuate its cooling, soothing, drying or protective properties. Bentonite is a good example of a suspending agent used in the preparation of lotions. Methylcellulose or sodium carboxymethylcellulose, eg, will localize and hold the active ingredient in contact with

the affected site and at the same time be rinsed off easily with water. A formulation containing glycerin will keep the skin moist for a considerable period of time. The drying and cooling effect may be accentuated by adding alcohol to the formula.

Dermatologists frequently prescribe lotions containing anesthetics, antipruritics, antiseptics, astringents, germicides, protectives or screening agents, to be used in treating or preventing various types of skin diseases and dermatitis. Antihistamines, benzocaine, calamine, resorcin, steroids, sulfur, zinc oxide, betamethasone derivatives, salicylic acid, safflower oil, minoxidil and zirconium oxide are ingredients common in unofficial lotions. In many instances the cosmetic aspects of the lotion are of great importance. Many lotions compare badly with cosmetic preparations of a similar nature. The manufacture of fine lotions to meet the specialized needs of the dermatologist provides the pharmacist with an excellent opportunity to demonstrate professional competence. Extensive studies on lotions, as described by Harb,[36] will assist the pharmacist to attain this goal.

Lotions may be prepared by triturating the ingredients to a smooth paste and then adding the remaining liquid phase with trituration. High-speed mixers or colloid mills produce better dispersions and, therefore, are used in the preparation of larger quantities of lotion. Calamine Lotion USP is the classic example of this type of preparation and consists of finely powdered, insoluble solids held in more or less permanent suspension by the presence of suspending agents and/or surface-active agents.

The formula and the method of preparation of Calamine Lotion USP is given

Calamine Lotion

Calamine	80 g
Zinc Oxide	80 g
Glycerin	20 mL
Bentonite Magma	250 mL
Calcium Hydroxide Topical Solution, a sufficient quantity, to make	1000 mL

Dilute the bentonite magma with an equal volume of calcium hydroxide topical solution. Mix the powder intimately with the glycerin and about 100 mL of the diluted magma, triturating until a smooth, uniform paste is formed. Gradually incorporate the remainder of the diluted magma. Finally add enough calcium hydroxide topical solution to make 1000 mL, and shake well.

If a more viscous consistency in the Lotion is desired, the quantity of bentonite magma may be increased to not more than 400 mL.

Many investigators have studied Calamine Lotion and this has led to the publication of many formulations, each possessing certain advantages over the others but none satisfying the collective needs of all dermatologists.

Formulations containing Avicel R (hydrated microcrystalline cellulose, *FMC*) and carboxymethylcellulose settle less than the official preparations.

Calamine Lotion

Calamine	8 g
Zinc Oxide	8 g
Glycerin	2 mL
Avicel R Gel	2 g
Carboxymethylcellulose	2 g
Calcium Hydroxide Solution, a sufficient quantity, to make	100 mL

Mix 45 g of Avicel R with 55 g of water with a suitable electric mixer. This gel is used in the preparation of the calamine lotion. Mix the calamine and the zinc oxide with the glycerin, the gel and the carboxymethylcellulose. Add sufficient calcium hydroxide solution to make the product measure 100 mL.

While most lotions are prepared by trituration, some lotions are formed by chemical interaction in the liquid. White Lotion is an example.

White Lotion

Zinc Sulfate	40 g
Sulfurated Potash	40 g
Purified Water, a sufficient quantity to make	1000 mL

Dissolve the zinc sulfate and the sulfurated potash separately, each in 450 mL of purified water and filter each solution. Add slowly the sulfurated potash solution to the zinc sulfate solution with constant stirring. Then add the required amount of purified water, and mix.

Sulfurated potash is a solid of variable composition but usually is described as $K_2S_3{\cdot}K_2S_2O_3$. The chemical reaction which occurs when sulfurated potash solution is added to the zinc sulfate is

$$ZnSO_4 \cdot 7H_2O + K_2S_3 \cdot K_2S_2O_3 \rightarrow ZnS + S_2 + K_2SO_4 + K_2S_2O_3 + 7H_2O$$

This lotion must be prepared fresh and does not contain a suspending agent. Bentonite Magma has been used in some formulations. Coffman and Huyck[37] include a detailed discussion of the chemistry and the problems involved in the preparation of a suitable product.

An example of a lotion that is an emulsion is Benzyl Benzoate Lotion USP. The formula and method of preparation are as follows:

Benzyl Benzoate	250 mL
Triethanolamine	5 g
Oleic Acid	20 g
Purified Water	750 mL
To make about	1000 mL

Mix the triethanolamine with the oleic acid, add the benzyl benzoate, and mix. Transfer the mixture to a suitable container of about 2000-mL capacity, add 250 mL of purified water, and shake the mixture thoroughly. Finally add the remaining purified water, and again shake thoroughly.

The triethanolamine forms a soap with the oleic acid and functions as the emulsifying agent to form a stable product. This type of emulsifying agent is almost neutral in water and gives a pH of about 8 and thus should not irritate the skin.[6] An example of the wide variety of formulations of benzyl benzoate is provided by Bhargava and Nicolai.[38]

Some lotions are clear solutions as exemplified by Aminobenzoic Acid Lotion BP.

Aminobenzoic Acid	50 g
Glycerol	200 mL
Ethanol 96%	600 mL
Purified Water freshly boiled and cooled, sufficient to produce	1000 mL

Dissolve the aminobenzoic acid in the ethanol 96%, add the glycerol and sufficient purified water to produce 1000 mL and mix. The ethanol is used to dissolve the aminobenzoic acid and provide a cooling effect. The glycerol (glycerin) is used for its emollient effect. Since lotions may be solutions, suspensions or emulsions, the method of preparation is similar to those types of formulations described above.

Several lotions are listed in the USP and contain, for example, antibiotics, steroids, scabicides and sunscreens.

A formula for hydrocortisone lotion is given in the PC.

Hydrocortisone Lotion

Hydrocortisone, in ultrafine powder	10.0 g
Chlorocresol	0.5 g
Self-emulsifying monostearin	40.0 g
Glycerol	63.0 g
Purified water, freshly boiled and cooled to make	1000.0 g

To prepare the base, the chlorocresol is dissolved in 850 mL of water with the aid of gentle heat, the self-emulsifying monostearin is added and the mixture heated to 60° with stirring until completely dispersed. The hydrocortisone is triturated with the glycerol and the trituration is then incorporated, with stirring, into the warm base, allowed to cool while stirring, then add the remainder of the water and mix.

Certain lotions tend to separate or stratify on long standing, and they require a label directing that they be shaken well before each use. All lotions should be labeled "For External Use Only."

Microorganisms may grow in certain lotions if no preservative is included. Care should be taken to avoid contaminating the lotion during preparation, even if a preservative is present.

Magmas and Milks

Magmas and milks are aqueous suspensions of insoluble, inorganic drugs and differ from gels mainly in that the suspended particles are larger. When prepared, they are thick and viscous and, because of this, there is no need to add a suspending agent.

Bentonite Magma USP is prepared by simple hydration. Two procedures are given for the preparation of this product, and these are described in Chapter 80. Dihydroxyaluminum Aminoacetate Magma is the other magma in the USP.

Milk of Magnesia USP is a suspension of magnesium hydroxide containing not less than 80 mg of $Mg(OH)_2$ per mL. The specifications for double strength or triple strength are that these products should contain not less than 160 mg or 240 mg of $Mg(OH)_2$ per mL, respectively. It has an unpleasant, alkaline taste which can be masked with 0.1% citric acid (to reduce alkalinity) and 0.05% of a volatile oil or a blend of volatile oils. Magnesium hydroxide is prepared by the hydration of magnesium oxide.

$$MgO + H_2O \rightarrow Mg(OH)_2$$

Milk of Bismuth USP contains bismuth hydroxide and bismuth subcarbonate in suspension in water. The Magma is prepared by reacting bismuth subnitrate with nitric acid and ammonium carbonate with ammonia solution and then mixing the resulting two solutions.

The following reactions occur during the preparation of the magma.

$$(NH_4)_2CO_3 \rightarrow 2NH_4^+ + CO_3^{2-}$$

$$NH_3 + H_2O \rightarrow NH_4^+ + OH^-$$

$$2BiO^+ + CO_3^{2-} \rightarrow (BiO)_2CO_3$$

$$BiO^+ + OH^- \rightarrow BiO(OH)$$

If the insoluble substance is precipitated fresh by mixing hot, dilute solutions, there is only slight sedimentation on standing. This characteristic of milks or magmas sometimes is enhanced by passing the product through a colloid mill.

For the most part, magmas and milks are intended for internal use, eg, Milk of Magnesia USP and Dihydroxy Aluminum Aminoacetate Magma USP, although Bentonite Magma is used primarily as a suspending agent for insoluble substances for local application and occasionally for internal use. All magmas require a "Shake Well" label. Freezing must be avoided.

Several antimicrobial preservatives have been tested in liquid antacid preparations for their stability and effectiveness, such as benzoic acid, chlorhexidine, methylparaben, propylparaben, sorbic acid, propylene glycol or ethanol. It was found that a combination of methylparaben and sorbic acid was superior to the parabens alone.

Mixtures

The USP does not recognize the term mixture; however, the BP defines the term as

> Mixtures are oral liquids containing one or more active ingredients, dissolved, suspended or dispersed in a suitable vehicle. Suspended solids may separate slowly on standing, but are easily redispersed on shaking.

The insoluble substance usually does not make the mixture very viscous, and the particles may be held in suspension by using suitable suspending or thickening agents. This class was introduced originally to secure uniformity in the formulas of certain well-known and largely used preparations. Frequently, the term *mixture* is applied loosely to aqueous preparations of every description. The term *shake mixture* is used often for liquid preparations which contain insoluble ingredients and, therefore, must be shaken before use. The term *suspension* is used to describe a number of similar preparations.

The following is a formula for a mixture in the BP, which is a solution for an extemporaneous preparation.

Ammonium Chloride Mixture

Ammonium Chloride	100 g
Aromatic Ammonia Solution	50 mL
Liquorice Liquid Extract	100 mL
Water for Preparations to	1000 mL

It should be prepared recently.

The following mixture is an example of a suspension and is used for the treatment of diarrhea. The pectin and the tragacanth in Kaolin Mixture with Pectin act as suspending agents. An alternate formula, based on Veegum (*Vanderbilt*) and sodium carboxymethylcellulose, has been proposed by Kalish.[39]

Kaolin Mixture with Pectin

Veegum	0.88 g
Sodium Carboxymethylcellulose	0.22 g
Purified Water	79.12 g
Kaolin	17.50 g
Pectin	0.44 g
Saccharin	0.09 g
Glycerin	1.75 g

Add the Veegum and the sodium carboxymethylcellulose to the water with continuous stirring. Add, with mixing, the kaolin. Mix the pectin, saccharin and glycerin and add to the suspension. A preservative and flavoring agent may be added to the product.

The insoluble material in mixtures must be in a very finely divided state and uniformly distributed throughout the preparation. This is accomplished with colloid mills, special methods of precipitation and suspending agents. There are three main reasons for having the insoluble substances in as fine a state of subdivision as possible.

1. The more nearly the colloidal state is approached by protectives, such as kaolin, magnesium trisilicate or magnesium phosphate, the more active they become as adsorbents and protectives when in contact with inflamed surfaces.
2. Finely divided particles are suspended more readily and settle out much more slowly than large particles, thus enabling the patient to obtain uniform doses of suspended substances. Homogeneous mixtures are desirable especially when administering medication to form an evenly distributed, protective coating on the gastrointestinal tract.
3. The palatability of many preparations is enhanced by the use of colloidal suspending agents.

Mixtures containing suspended material should have a "Shake Well" label affixed to the container in which they are dispensed.

Mixtures, including suspensions, are subject to contamination by microorganisms that remain viable and are a potential health hazard during the period of use of the products. Survival times of organisms depend on the preservative used. A kaolin pediatric mixture that contains benzoic acid kills organisms rapidly, whereas organisms survived for more than a week in a magnesium trisilicate mixture that contained no more than a trace of peppermint oil, as noted by Westwood.[40]

Official Suspensions

The USP places particular emphasis on the term suspension by providing specific definitions for a variety of oral, parenteral and ophthalmic preparations formulated in such a way that an insoluble substance is suspended in a liquid at some stage of the manufacturing or dispensing process. The USP definition begins as follows:

> Suspensions are liquid preparations which consist of solid particles dispersed throughout a liquid phase in which the particles are not soluble. Dosage forms officially categorized as Suspensions are designated as such if they are not included in other more specific categories of suspensions, such as Oral Suspensions, Topical Suspensions, etc. (see these other categories). Some suspensions are prepared and ready for use, while

others are prepared as solid mixtures intended for constitution just before use with an appropriate vehicle. Such products are designated "for Oral Suspension," etc.

This definition relates the term suspension to milks, magmas and lotions which have been described above.

While there are a number of monographs dealing with suspensions in the USP, neither the definition nor the monographs give specific directions for the preparation of the suspension, although pharmacopeias usually permit the addition of suitable flavoring agents, suspending agents, preservatives and certified color additives. One procedure for the preparation of the commonly used Trisulfapyrimidines Oral Suspension is given below.

Trisulfapyrimidines Oral Suspension

Veegum	1.00 g
Syrup USP	90.60 g
Sodium Citrate	0.78 g
Sulfadiazine	2.54 g
Sulfamerazine	2.54 g
Sulfamethazine	2.54 g

Add the Veegum, slowly and with continuous stirring, to the syrup. Incorporate the sodium citrate into the Veegum-syrup mixture. Premix the sulfa drugs, add to the syrup, stir and homogenize. Add sufficient 5% citric acid to adjust the pH of the product to 5.6. A preservative and a flavoring agent may be added to the product.

Methods of preparation for those formulations which contain several active ingredients and are produced in large quantities tend to be more complex than that given above and are described previously.

Many formulations for suspensions are given in the BP and the PC under *Mixtures*.

A properly prepared suspension has a number of desirable properties:

1. The suspended material should not settle rapidly.
2. Particles that do settle should not form a hard cake and easily should be resuspended uniformly on shaking.
3. The suspension should pour freely from the container.

Insoluble powders that do not disperse evenly throughout the suspending medium, when shaken, should be powdered finely and levigated with a small amount of an agent such as glycerin, alcohol or a portion of the dispersion of the suspending agent. The other ingredients are incorporated and the remainder of the dispersion of the suspending agent is incorporated gradually by trituration to produce the appropriate volume.

Suspensions intended for parenteral or ophthalmic use also are described in the USP. For a discussion of these suspensions, see Chapter 87 and 89.

Extracts

Extraction

Extraction, as the term is used pharmaceutically, involves the separation of medicinally active portions of plant or animal tissues from the inactive or inert components by using selective solvents in standard extraction procedures.

The products so obtained from plants are relatively impure liquids, semisolids or powders intended only for oral or external use. These include classes of preparations known as decoctions, infusions, fluidextracts, tinctures, pilular (semisolid) extracts and powdered extracts. Such preparations popularly have been called galenicals, after Galen, the 2nd century Greek physician. For additional information concerning extraction and extractives, see RPS 15, Chapter 86.

Extraction continues to be of considerable interest in order to obtain improved yields of drugs derived from plant and animal sources. For example, improved extraction of digitalis glycosides has been carried out using a pulsating, perforated, bottom column. Other techniques include ultrasonics, rotary-film evaporators, liquid and supercritical carbon dioxide, hydrodistillation, liquid chromatography, multiple-solvent extraction, countercurrent extraction and gravitation dynamics.

This discussion is concerned primarily with basic extraction procedures for crude drugs to obtain the therapeutically desirable portion and eliminate the inert material by treatment with a selective solvent, known as the menstruum. Extraction differs from solution in that the presence of insoluble matter is implied in the former process. The principal methods of extraction are maceration, percolation, digestion, infusion and decoction. The quality of the finished product can be enhanced by standardizing primary extracts and carrying out analytical assays during production on the raw materials, intermediate products and manufacturing procedures.

The processes of particular importance, insofar as the USP is concerned, are those of maceration and percolation, as described specifically for Belladonna Extract USP and Cascara Sagrada Extract USP. Most pharmacopeias refer to such processes for extraction of active principles from crude drugs. The USP provides general directions for both maceration and percolation under the heading of *Tinctures*.

Maceration—In this process the solid ingredients are placed in a stoppered container with 750 mL of the prescribed solvent and allowed to stand for a period of at least 3 days in a warm place with frequent agitation, until soluble matter is dissolved. The mixture is filtered and, after most of the liquid has drained, the residue on the filter is washed with sufficient quantity of the prescribed solvent or solvent mixture; the filtrates are combined to produce 1000 mL.

Percolation—The ground drug is mixed with the appropriate quantity of the prescribed solvent to make it evenly and uniformly damp. It is allowed to stand for 15 minutes, then transferred to a percolator (a narrow coned-shaped vessel, open at both ends). Sufficient prescribed solvent is added to saturate the drug. The top is placed on the percolator and, when the liquid is about to drip from the apparatus, the lower opening is closed. The drug is allowed to macerate for 24 hours or for the specified time. If no assay is directed, the percolation is allowed to proceed slowly or at the specified rate gradually adding sufficient solvent to produce 1000 mL of solution. If an assay is required, only 950 mL of percolate are collected and mixed and a portion assayed as directed. The rest of the percolate is diluted with the solvent to produce a solution that conforms to the required standard and then mixed.

Digestion—This is a form of maceration in which *gentle heat* is used during the process of extraction. It is used when moderately elevated temperature is not objectionable and the solvent efficiency of the menstruum is increased thereby.

Infusion—An infusion is a dilute solution of the readily soluble constituents of crude drugs. Fresh infusions are prepared by macerating the drugs for a short period of time with either cold or boiling water. US official compendia have not included infusions for some time. An example is Concentrated Compound Gentian Infusion BP 1973.

Decoction—This once-popular process extracts water-soluble and heat-stable constituents from crude drugs by boiling in water for 15 min, cooling, straining and passing sufficient cold water through the drug to produce the required volume.

Extractive Preparations

After a solution of the active constituents of a crude drug is obtained by maceration or percolation, it may be ready for use as a medicinal agent, as with certain tinctures or fluidextracts, or it may be processed further to produce a solid or semisolid extract.

For a discussion of *resins* and *oleoresins* obtained by solvent extraction of plant exudates see Chapter 26, under *Plant Exudates*.

Tinctures—Tinctures are defined in the USP as being alcoholic or hydroalcoholic solutions prepared from vegetable materials or from chemical substances, an example of the latter being Iodine Tincture. Traditionally, tinctures of potent vegetable drugs essentially represent the activity of 10 g of the drug in each 100 mL of tincture, the potency being

adjusted following assay. Most other tinctures of vegetable drugs represent the extractive from 20 g of the drug in 100 mL of tincture.

The USP specifically describes two general processes for preparing tinctures, one by percolation designated as Process P, and the other by maceration, as Process M. These utilize the methods described under *Extraction.*

Process P includes a modification so that tinctures that require assay for adjustment to specified potency thus may be tested before dilution to final volume. A tincture prepared by Process P as modified for assayed tinctures is Belladonna Tincture.

Examples of tinctures prepared by Process M are Compound Benzoin Tincture USP and Sweet Orange Peel Tincture USP XXI (the latter contains the extractive from 50 g of sweet orange peel in 100 mL of tincture).

Fluidextracts—The USP defines fluidextracts as being liquid preparations of vegetable drugs, containing alcohol as a solvent or as a preservative, or both, so made that, in general, each mL contains the therapeutic constituents of 1 g of the standard drug that it represents. While the USP states that pharmacopeial fluidextracts are made by percolation, the official compendia previously have described general procedures for three percolation methods used in making fluidextracts.

Process A is a percolation method that can be modified for fluidextracts that must be assayed.

Process E is an alternative for Process A in which percolation is conducted on a column of drug much greater in length than in diameter.

Process D is used for preparing fluidextracts with boiling water as the menstruum, alcohol being added as a preservative to the concentrated percolate; this is the procedure used for preparing Cascara Sagrada Fluidextract USP XXI.

The BP and PC use the designation *Liquid Extracts* for fluidextracts.

Extracts—Extracts are defined in the USP as 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.

Three forms of extracts were recognized in USP XXI: semiliquids or liquids of syrupy consistency, plastic masses (known as *pilular* or *solid extracts*) and dry powders (known as *powdered extracts*). Extracts, as concentrated forms of the drugs from which they are prepared, are used in a variety of solid or semisolid dosage forms. The USP states that pilular extracts and powdered extracts of any one drug are interchangeable medicinally, but each has its own pharmaceutical advantages. Pilular extracts, so-called because they are of a consistency to be used in pill masses and made into pills and are suited especially for use in ointments and suppositories. Powdered extracts are suited better for incorporation into a dry formulation, as in capsules, powders or tablets. Semiliquid extracts, or extracts of a syrupy consistency, may be used in the manufacture of some pharmaceutical preparations.

Most extracts are prepared by extracting the drug by percolation. The percolate is concentrated, generally by distillation under reduced pressure. The use of heat is avoided where possible because of potential injurious effect on active constituents. Powdered extracts which are made from drugs that contain inactive oily or fatty matter may have to be defatted or prepared from defatted drug. For diluents that may be used to adjust an extract to prescribed standards, see the USP XXI.

Pure Glycyrrhiza Extract USP XXI is an example of a pilular extract; Belladonna Extract USP and Hyoscyamus Extract PC are examples of powdered extracts (the former is prepared also as a pilular extract and the latter as a liquid extract).

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