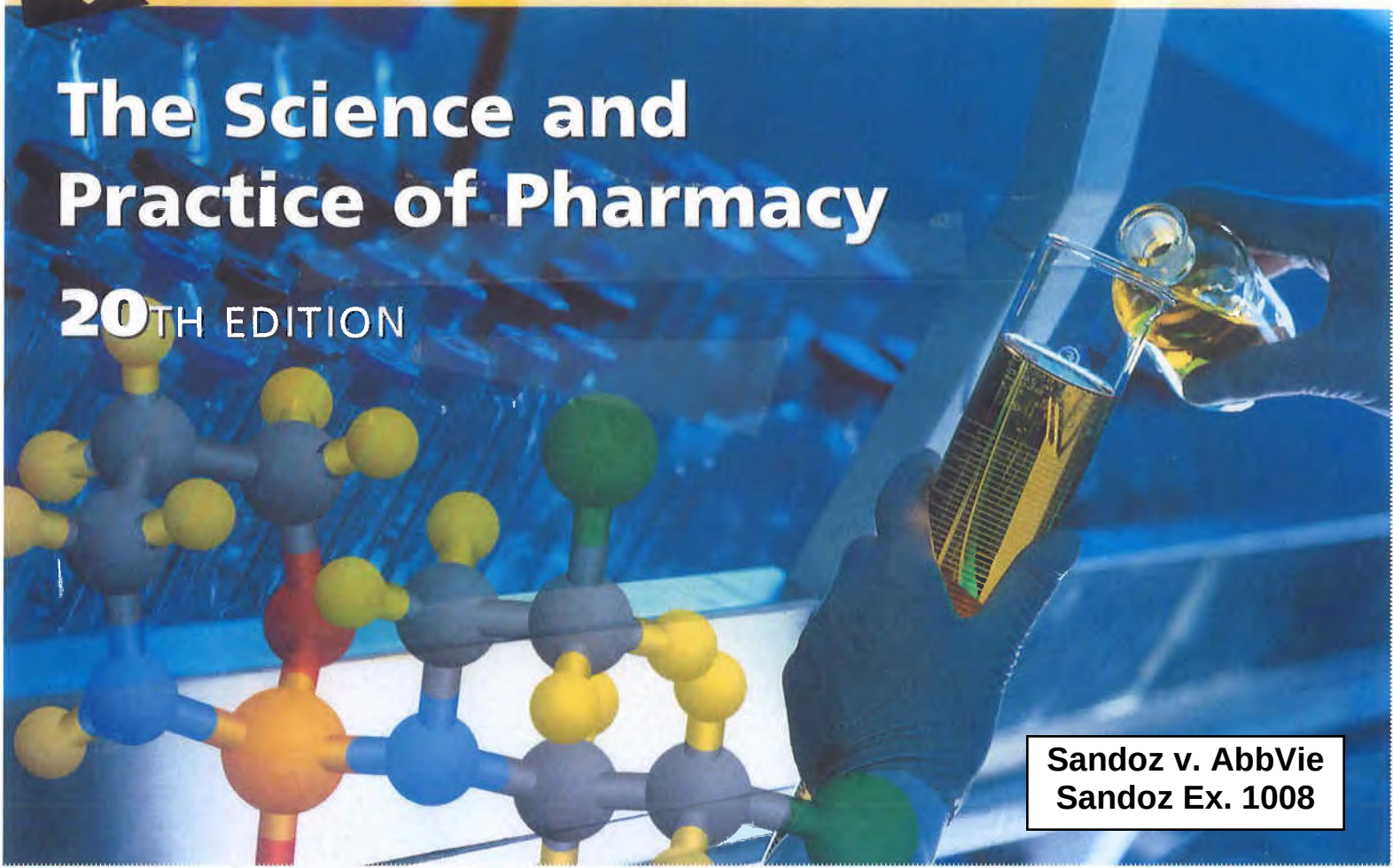
REMINGTON

The Science and Practice of Pharmacy

20TH EDITION



20 TH EDITION

Remington: The Science and Practice of Pharmacy

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CHAPTER 18

Tonicity, Osmoticity, Osmolality, and Osmolarity

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BASIC DEFINITIONS

If a solution is placed in contact with a membrane that is permeable to molecules of the solvent, but not to molecules of the solute, the movement of solvent through the membrane is called *osmosis.* Such a membrane often is called *semi-permeable.* As the several types of membranes of the body vary in their permeability, it is well to note that they are *selectively* permeable. Most normal living-cell membranes maintain various solute concentration gradients. A selectively permeable membrane may be defined either as one that does not permit free, unhampered diffusion of all the solutes present, or as one that maintains at least one solute concentration gradient across itself. Osmosis, then, is the diffusion of water through a membrane that maintains at least one solute concentration gradient across itself.

Assume that Solution A is on one side of the membrane, and Solution B of the same solute but of a higher concentration is on the other side; the solvent will tend to pass into the more concentrated solution until equilibrium has been established. The pressure required to prevent this movement is the osmotic pressure. It is defined as the excess pressure, or pressure greater than that above the pure solvent, that must be applied to Solution B to prevent passage of solvent through a perfect semipermeable membrane from A to B. The concentration of a solution with respect to effect on osmotic pressure is related to the number of particles (unionized molecules, ions, macromolecules, aggregates) of solute(s) in solution and thus is affected by the degree of ionization or aggregation of the solute. See Chapter 16 for review of colligative properties of solutions.

Body fluids, including blood and lacrimal fluid, normally have an osmotic pressure that often is described as corresponding to that of a 0.9% solution of sodium chloride. The body also attempts to keep the osmotic pressure of the contents of the gastrointestinal (GI) tract at about this level, but there the normal range is much wider than that of most body fluids. The 0.9% sodium chloride solution is said to be *iso-osmotic* with physiological fluids. In medicine, the term *isotonic,* meaning equal tone, is commonly used interchangeably with iso-osmotic. However, terms such as isotonic and tonicity should be used *only* with reference to a physiological fluid. Iso-osmotic actually is a physical term that compares the osmotic pressure (or another colligative property, such as freezing-point depression) of two liquids, neither of which may be a physiological fluid, or which may be a physiological fluid only under certain circumstances. For example, a solution of boric acid that is iso-osmotic with both blood and lacrimal fluid is isotonic only with the lacrimal fluid. This solution causes hemolysis of red blood cells because molecules of boric acid pass freely through the erythrocyte membrane regardless of concentration. Thus, isotonicity infers a sense of physiological compatibility where isoosmoticity need not. As another example, a *chemically defined elemental diet* or enteral nutritional fluid can be iso-osmotic with the contents of the GI tract, but would not be considered a physiological fluid, or suitable for parenteral use.

A solution is isotonic with a living cell if there is no net gain or loss of water by the cell, or other change in the cell, when it is in contact with that solution. Physiological solutions with an osmotic pressure lower than that of body fluids, or of 0.9% sodium chloride solution, are referred to commonly as being *hypotonic.* Physiological solutions having a greater osmotic pressure are termed *hypertonic.*

Such qualitative terms are of limited value, and it has become necessary to state osmotic properties in quantitative terms. To do so, a term must be used that will represent all the particles that may be present in a given system. The term used is *osmol:* the weight, in grams, of a solute, existing in a solution as molecules (and/or ions, macromolecules, aggregates, etc), which is osmotically equivalent to a mole of an ideally behaving nonelectrolyte. Thus, the osmol weight of a nonelectrolyte, in a dilute solution, generally is equal to its gram molecular weight. A *milliosmol,* abbreviated mOsm, is the weight stated in milligrams.

If one extrapolates this concept of relating an osmol and a mole of a nonelectrolyte as being equivalent, then one also may define an osmol in the following ways. It is the amount of solute that will provide 1 Avogadro's number (6.02×10^{23}) of particles in solution and it is the amount of solute that, on dissolution in 1 kg of water, will result in an osmotic pressure increase of 17,000 torr at 0° or 19,300 torr at 37°. One mOsmol is 1/1000 of an osmol. For example, 1 mol of anhydrous dextrose is equal to 180 g. One osmol of this nonelectrolyte is also 180 grams. One mOsmol would be 180 mg. Thus, 180 mg of this solute dissolved in 1 kg of water will produce an increase in osmotic pressure of 19.3 torr at body temperature.

For a solution of an electrolyte such as sodium chloride, one molecule of sodium chloride represents one sodium and one chloride ion. Hence, 1 mol will represent 2 osmol of sodium chloride theoretically. Accordingly, 1 osmol NaCl = 58.5 g/2 or 29.25 g. This quantity represents the sum total of 6.02×10^{23} ions as the total number of particles. Ideal solutions infer very dilute solutions or infinite dilution.

However, as the concentration is increased, other factors enter. With strong electrolytes, interionic attraction causes a decrease in their effect on colligative properties. In addition, and in opposition, for all solutes, including nonelectrolytes, solvation and possibly other factors operate to intensify their colligative effect. Therefore, it is very difficult and often impossible to predict accurately the osmoticity of a solution. It may be possible to do so for a dilute solution of a single pure and well-characterized solute, but not for most parenteral and enteral medicinal and/or nutritional fluids; experimental determination likely is required.

THERAPEUTIC CONSIDERATIONS

It generally is accepted that osmotic effects have a major place in the maintenance of homeostasis (the state of equilibrium in the living body with respect to various functions and to the chemical composition of the fluids and tissues, eg, temperature, heart rate, blood pressure, water content, or blood sugar). To a great extent these effects occur within or between cells and tissues where they cannot be measured. One of the most troublesome problems in clinical medicine is the maintenance of adequate body fluids and proper balance between extracellular and intracellular fluid volumes in seriously ill patients. It should be kept in mind, however, that fluid and electrolyte abnormalities are not diseases, but are the manifestations of disease.

The physiological mechanisms that control water intake and output appear to respond primarily to serum osmoticity. Renal regulation of output is influenced by variation in rate of release of pituitary antidiuretic hormone (ADH) and other factors in response to changes in serum osmoticity. Osmotic changes also serve as a stimulus to moderate thirst. This mechanism is sufficiently sensitive to limit variations in osmoticity in the normal individual to less than about 1%. Body fluid continually oscillates within this narrow range. An increase of plasma osmoticity of 1% will stimulate ADH release, result in reduction of urine flow, and, at the same time, stimulate thirst that results in increased water intake. Both the increased renal reabsorption of water (without solute) stimulated by circulating ADH and the increased water intake tend to lower serum osmoticity.

The transfer of water through the cell membrane occurs so rapidly that any lack of osmotic equilibrium between the two fluid compartments in any given tissue usually is corrected within a few seconds and, at most, within a minute or so. However, this rapid transfer of water does not mean that complete equilibration occurs between the extracellular and intracellular compartments throughout the entire body within this same short period of time. The reason is that fluid usually enters the body through the gut and then must be transported by the circulatory system to all tissues before complete equilibration can occur. In the normal person it may require 30 to 60 min to achieve reasonably good equilibration throughout the body after drinking water. Osmoticity is the property that largely determines the physiological acceptability of a variety of solutions used for therapeutic and nutritional purposes.

Pharmaceutical and therapeutic consideration of osmotic effects has been, to a great extent, directed toward the side effects of ophthalmic and parenteral medicinals due to abnormal osmoticity, and either to formulating to avoid the side effects or to finding methods of administration to minimize them. More recently this consideration has been extended to total (central) parenteral nutrition, to enteral hyperalimentation ("tube" feeding), and to concentrated-fluid infant formulas.[1] Also, in recent years, the importance of osmometry of serum and urine in the diagnosis of many pathological conditions has been recognized.

There are a number of examples of the direct therapeutic effect of osmotic action, such as the *intravenous* (IV) use of mannitol as a diuretic that is filtered at the glomeruli and thus increases the osmotic pressure of tubular urine. Water must then be reabsorbed against a higher osmotic gradient than otherwise, so reabsorption is slower and diuresis is observed. The same fundamental principle applies to the IV administration of 30% urea used to affect intracranial pressure in the control of cerebral edema. Peritoneal dialysis fluids tend to be somewhat hyperosmotic to withdraw water and nitrogenous metabolites. Two to five percent sodium chloride solutions or dispersions in an oleaginous base (Muro, *Bausch & Lomb*) and a 40% glucose ointment are used topically for corneal edema. Ophthalgan (*Wyeth-Ayerst*) is ophthalmic glycerin employed for its osmotic effect to clear edematous cornea to facilitate an ophthalmoscopic or gonioscopic examination. Glycerin solutions in 50% concentration Osmoglyn (*Alcon*) and isosorbide solution Ismotic (*Alcon*) are oral osmotic agents for reducing intraocular pressure.

The osmotic principle also applies to plasma extenders such as polyvinylpyrrolidone and to saline laxatives such as magnesium sulfate, magnesium citrate solution, magnesium hydroxide (via gastric neutralization), sodium sulfate, sodium phosphate, and sodium biphosphate oral solution and enema (*Fleet*).

An interesting osmotic laxative that is a nonelectrolyte is a lactulose solution. Lactulose is a nonabsorbable disaccharide that is colon-specific, wherein colonic bacteria degrade some of the disaccharide to lactic and other simple organic acids. These, in toto, lead to an osmotic effect and laxation. An extension of this therapy is illustrated by Cephulac (*Marion Merrell Dow*) solution, which uses the acidification of the colon via lactulose degradation to serve as a trap for ammonia migrating from the blood to the colon. The conversion of ammonia of blood to the ammonium ion in the colon ultimately is coupled with the osmotic effect and laxation, thus expelling undesirable levels of blood ammonia. This product is employed to prevent and treat frontal systemic encephalopathy.

Osmotic laxation is observed with the oral or rectal use of glycerin and sorbitol. Epsom salt has been used in baths and compresses to reduce edema associated with sprains. Another approach is the indirect application of the osmotic effect in therapy via osmotic pump drug delivery systems.[2]

OSMOLALITY AND OSMOLARITY

It is necessary to use several additional terms to define expressions of concentration in reflecting the osmoticity of solutions. The terms include *osmolality,* the expression of osmolal concentration, and *osmolarity,* the expression of osmolar concentration.

OSMOLALITY—A solution has an osmolal concentration of one when it contains 1 osmol of solute/kg of water. A solution has an osmolality of n when it contains n osmol/kg of water. Osmolal solutions, like their counterpart molal solutions, reflect a weight-to-weight relationship between the solute and the solvent. Because an osmol of any nonelectrolyte is equivalent to 1 mol of that compound, then a 1 osmolal solution is synonymous to a 1 molal solution for a typical nonelectrolyte.

With a typical electrolyte like sodium chloride, 1 osmol is approximately 0.5 mol of sodium chloride. Thus, it follows that a 1 osmolal solution of sodium chloride essentially is equivalent to a 0.5 molal solution. Recall that a 1 osmolal solution of dextrose or sodium chloride each will contain the same particle concentration. In the dextrose solution there will be 6.02×10^{23} molecules/kg of water and in the sodium chloride solution one will have 6.02×10^{23} total ions/kg of water, one-half of which are Na^+ ions and the other half Cl^- ions.

As in molal solutions, osmolal solutions usually are employed where quantitative precision is required, as in the measurement of physical and chemical properties of solutions (ie, colligative properties). The advantage of the *w/w* relationship is that the concentration of the system is not influenced by temperature.

OSMOLARITY—The relationship observed between molality and osmolality is shared similarly between molarity and osmolarity. A solution has an osmolar concentration of 1 when it contains 1 osmol of solute per liter of solution. Likewise, a solution has an osmolarity of n when it contains n osmols/L of solution. Osmolar solutions, unlike osmolal solution, reflect a weight in volume relationship between the solute and final solution. A 1 molar and 1 osmolar solution would be identical for nonelectrolytes. For sodium chloride a 1 osmolar solution would contain 1 osmol of sodium chloride per liter which approximates a 0.5 molar solution. The advantage of employing osmolar concentrations over osmolal concentrations is the abil-

ity to relate a specific number of osmols or milliosmols to a volume, such as a liter or milliliter. Thus, the osmolar concept is simpler and more practical. Volumes of solution, rather than weights of solution, are more practical in the delivery of liquid dosage forms.

Many health professionals do not have a clear understanding of the difference between osmolality and osmolarity. In fact, the terms have been used interchangeably. A 1 osmolar solution of a solute always will be more concentrated than a 1 osmolal solution. With dilute solutions the difference may be acceptably small. For example, a 0.9% *w/v* solution of sodium chloride in water contains 9 g of sodium chloride/L of solution, equivalent to 0.308 osmolar; or 9 g of sodium chloride/996.5 g of water, equivalent to 0.309 osmolal, less than a 1% error. For concentrated solutions the percent difference between osmolarity and osmolality is much greater and may be highly significant; 3.5% for 5% *w/v* dextrose solution and 25% for 25% *w/v* dextrose solution. One should be alerted to the sizable errors that may occur with concentrated solutions or fluids, such as those employed in total parenteral nutrition, enteral hyperalimentation, and oral nutritional fluids for infants.

Reference has been made to the terms hypertonic and hypotonic. Analogous terms are hyperosmotic and hypo-osmotic. Assuming normal serum osmolality to be 285 mOsmol/kg, as serum osmolality increases due to water deficit, the following signs and symptoms usually are found to accumulate progressively at approximately these values: 294 to 298—thirst (if the patient is alert and communicative); 299 to 313—dry mucous membranes; 314 to 329—weakness, doughy skin; above 330—disorientation, postural hypotension, severe weakness, fainting, CNS changes, stupor, and coma. As serum osmolality decreases due to water excess the following may occur: 275 to 261—headache; 262 to 251—drowsiness, weakness; 250 to 233—disorientation, cramps; below 233—seizures, stupor, and coma.

As indicated previously, the mechanisms of the body actively combat such major changes by limiting the variation in osmolality for normal individuals to less than about 1% (approximately in the range 282 to 288 mOsmol/kg, based on the above assumption).

The value given for normal serum osmolality above was described as an assumption because of the variety of values found in the literature. Serum osmolality often is stated loosely to be about 300 mOsmol/L. Various references report 280 to 295 mOsmol/L, 275 to 300 mOsmol/L, 290 mOsmol/L, 306 mOsmol/L, and 275 to 295 mOsmol/kg.

In recent years, much attention has been directed at determining osmoticity of total parenteral nutrition solutions, enteral formulas, and parenteral and enteral medications.[3–5] Hyperosmoticity of parenteral and enteral formulas and medications serves as an indicator for potential risks, including thrombophlebitits, pain at injection site, diarrhea, and abdominal cramping. However, the terms osmolality and osmolarity often have been used interchangeably and caused much confusion for practitioners. Often, when the term osmolarity is used, one cannot discern whether this simply is incorrect terminology, or if osmolarity actually has been calculated from osmolality.

Another current practice that can cause confusion is the use of the terms *normal* or *physiological* for isotonic sodium chloride solution (0.9%). The solution surely is iso-osmotic. However, as to being physiological, the concentration of ions are each of 154 mEq/L whereas serum contains about 140 mEq of sodium and about 103 mEq of chloride.

The range of mOsmol values found for serum raises the question as to what really is meant by the terms hypotonic and hypertonic for medicinal and nutritional fluids. One can find the statement that fluids with an osmolality of 50 mOsmol or more above normal are hypertonic; and, if they are 50 mOsmol or more below normal, they are hypotonic. One also can find the statement that peripheral infusions should not have an osmolarity exceeding 700 to 800 mOsmol/L.[6] Examples of osmol concentrations of solutions used in peripheral infusions are (D5W) 5% dextrose solution, 252 mOsmol/L; (D10W) 10% dextrose solution, 505 mOsmol/L; and Lactated Ringer's 5% Dextrose, 525 mOsmol/L. When a fluid is hypertonic, undesirable effects often can be decreased by using relatively slow rates of infusion, and/or relatively short periods of infusion. For example, 25% dextrose solution (D25W)—4.25% Amino Acids is a representative of a highly osmotic hyperalimentation solution. It has been stated that when osmolal loading is needed, a maximum safe tolerance for a normally hydrated subject would be an approximate increase of 25 mOsmol/kg of water over 4 hours.[7]

COMPUTATION OF OSMOLARITY

Several methods are used to obtain numerical values of osmolarity. The osmolar concentration, sometimes referred to as the *theoretical osmolarity,* is calculated from the *w/v* concentration using the following equation:

$$\frac{\text{g}}{\text{L}} \times \frac{\text{mols}}{\text{g}} \times \frac{\text{osmol}}{\text{mol}} \times \frac{1000\ \text{mOsmol}}{\text{osmol}} = \frac{\text{mOsmol}}{\text{L}} \qquad (1)$$

The number of osmol/mol is equal to 1 for nonelectrolytes and is equal to the number of ions per molecule for strong electrolytes.

This calculation omits consideration of factors such as solvation and interionic forces. By this method of calculation, 0.9% sodium chloride has an osmolar concentration of 308 mOsmol/L and a concentration of 154 mOsmol/L in either sodium or chloride ion.

Two other methods compute osmolarity from values of osmolality. The determination of osmolality will be discussed later. One method has a strong theoretical basis of physical-chemical principles[8] using values of the partial molal volume(s) of the solute(s). A 0.9% sodium chloride solution, found experimentally to have an osmolality of 286 mOsmol/kg, was calculated to have an osmolarity of 280 mOsmol/L, rather different from the value of 308 mOsmol/L calculated as above. The method, using partial molal volumes, is relatively rigorous, but many systems appear to be too complex and/or too poorly defined to be dealt with by this method.

The other method is based on calculating the weight of water from the solution density and concentration

$$\frac{\text{g water}}{\text{mL solution}} = \frac{\text{g solution}}{\text{mL solution}} - \frac{\text{g solute}}{\text{mL solution}}$$

then

$$\text{osmolarity}\left(\frac{\text{mOsmol}}{\text{L solution}}\right) = \text{osmolality}\left(\frac{\text{mOsmol}}{1000\ \text{g water}}\right) \times \frac{\text{g water}}{\text{mL solution}}$$

The experimental value for the osmolality of 0.9% sodium chloride solution was 292.7 mOsmol/kg; the value computed for osmolarity was 291.4 mOsmol/L. This method uses easily obtained values of density of the solution and of its solute content and can be used with all systems. For example, the osmolality of a nutritional product was determined by the freezing-point depression method to be 625 mOsmol/kg;[10] its osmolarity was calculated as $625 \times 0.839 = 524$ mOsmol/L.

Monographs in the USP for solutions provide IV replenishment of fluid, nutrients, or electrolytes, and for osmotic diuretics such as Mannitol Injection, require the osmolar concentration be stated on the label in osmol/L; however, when the contents are less than 100 mL, or when the label states the article is not for direct injection but is to be diluted before use,

the label alternatively may state the total osmolar concentration in mOsmol/mL.

An example of the use of the first method described above is the computation of the approximate osmolar concentration (*theoretical osmolarity*) of a Lactated Ringer's 5% Dextrose Solution (*Abbott*), which is labeled to contain, per liter, dextrose (hydrous) 50 g, sodium chloride 6 g, potassium chloride 300 mg, calcium chloride 200 mg, and sodium lactate 3.1 g. Also stated is that the total osmolar concentration of the solution is approximately 524 mOsmol/L in part contributed by 130 mEq of Na^+, 109 mEq of Cl^-, 4 mEq of K^+, 3 mEq of Ca^{2+}, and 28 mEq of lactate ion.

The derivation of the osmolar concentrations from the stated composition of the solution may be verified by calculations using Equation 1.

Dextrose

$$\frac{50\text{ g}}{\text{L}} \times \frac{1\text{ mol}}{198\text{ g}} \times \frac{1\text{ osmol}}{\text{mol}} \times \frac{1000\text{ mOsmol}}{\text{Osmol}} = 252\text{ mOsmol/L}$$

Sodium Chloride

$$\frac{6\text{g}}{\text{L}} \times \frac{1\text{ mol}}{58.4\text{ g}} \times \frac{2\text{ osmol}}{\text{mol}} \times \frac{1000\text{ mOsmol}}{\text{osmol}}$$

$$= 205\ \frac{\text{mOsmol}}{\text{L}} \begin{cases} (102.7\text{ mOsmol } Na^+) \\ (102.7\text{ mOsmol } Cl^-) \end{cases}$$

Potassium Chloride

$$\frac{0.3\text{ g}}{\text{L}} \times \frac{1\text{ mol}}{74.6\text{ g}} \times \frac{2\text{ osmol}}{\text{mol}} \times \frac{1000\text{ mOsmol}}{\text{osmol}}$$

$$= \frac{8.04\text{ mOsmol}}{\text{L}} \begin{cases} (4.02\text{ mOsmol } K^+) \\ (4.02\text{ mOsmol } Cl^-) \end{cases}$$

Calcium Chloride

$$\frac{0.2\text{ g}}{\text{L}} \times \frac{1\text{ mol}}{111\text{ g}} \times \frac{3\text{ osmol}}{\text{mol}} \times \frac{1000\text{ mOsmol}}{\text{osmol}}$$

$$= \frac{5.41\text{ mOsmol}}{\text{L}} \begin{cases} (1.80\text{ mOsmol } Ca^{2+}) \\ (3.61\text{ mOsmol } Cl^-) \end{cases}$$

Sodium Lactate

$$\frac{3.1\text{ g}}{\text{L}} \times \frac{1\text{ mol}}{112\text{ g}} \times \frac{2\text{ osmol}}{\text{mol}} \times \frac{1000\text{ mOsmol}}{\text{osmol}}$$

$$= \frac{55.4\text{ mOsmol}}{\text{L}} \begin{cases} (27.7\text{ mOsmol } Na^+) \\ (27.7\text{ mOsmol lactate}) \end{cases}$$

The total osmolar concentration of the five solutes in the solution is 526, in good agreement with the labeled total osmolar concentration of approximately 524 mOsmol/L.

The mOsmol of sodium in 1 L of the solution is the sum of the mOsmol of the ion from sodium chloride and sodium lactate: 102 + 27.6 = 129.6 mOsmol. Chloride ions come from the sodium chloride, potassium chloride, and calcium chloride, the total osmolar concentration being 102 + 4.02 + 3.61 = 109.6 mOsmol. The mOsmol values of potassium, calcium, and lactate are calculated to be 4.02, 1.80, and 27.6, respectively.

The osmolarity of a mixture of complex composition, such as an enteral hyperalimentation fluid, cannot be calculated with any acceptable degree of certainty; therefore, the *osmolality* of such preparations should be determined experimentally.

OSMOMETRY AND THE CLINICAL LABORATORY

Serum and urine osmometry may assist in the diagnosis of certain fluid and electrolyte problems. However, osmometry values have little meaning unless the clinical situation is known. Osmometry is used in renal dialysis as a check on the electrolyte composition of the fluid. In the clinical laboratory, as stated above, the term *osmolality* is used generally, but usually is reported as mOsmol/L. It may seem unnecessary to mention that osmolality depends not only on the number of solute particles, but also on the quantity of water in which they are dissolved. However, it may help one to understand the statement that the normal range of urine osmolality is 50 to 1400 mOsmol/L, and for a random specimen is 500 to 800 mOsmol/L.

Serum Osmoticity

Sodium is by far the principal solute involved in serum osmoticity. Therefore, abnormal serum osmoticity is most likely to be associated with conditions that cause abnormal sodium concentration and/or abnormal water volume.

Thus, hyperosmotic serum is likely to be caused by an increase in serum sodium and/or loss of water. It may be associated with diabetes insipidus, hypercalcemia, diuresis during severe hyperglycemia, or with early recovery from renal shutdown. Alcohol ingestion is said to be the most common cause of the hyperosmotic state and of coexisting coma and the hyperosmotic state. An example of hyperosmoticity is a comatose diabetic with a serum osmoticity of 365 mOsmol/L.

In a somewhat analogous fashion, hypo-osmotic serum is likely to be due to decrease in serum sodium and/or excess of water. It may be associated with the postoperative state (especially with excessive water replacement therapy), treatment with diuretic drugs and low-salt diet (as with patients with heart failure, cirrhosis, etc), adrenal disease (eg, Addison's disease, adrenogenital syndrome), or SIADH (syndrome of inappropriate ADH secretion). There are many diseases that cause ADH to be released inappropriately (ie, in spite of serum osmoticity and volume having been normal initially). These include oat-cell carcinoma of the lung, bronchogenic carcinoma, congestive heart failure, inflammatory pulmonary lesions, porphyria, severe hypothyroidism, or cerebral disease (such as tumor, trauma, infection, and vascular abnormalities). It also may be found with some patients with excessive diuretic use. Serum and urine osmoticity are measured when SIADH is suspected. In SIADH there is hypo-osmoticity of the blood in association with a relative hyperosmoticity of urine. The usual cause is a malfunction of the normal osmotic response of osmoreceptors, an excess of exogenous vasopressin, or a production of a vasopressin-like hormone that is not under the regular control of serum osmoticity. The diagnosis is made by simultaneous measurement of urine and serum osmolality. The serum osmolality will be lower than normal and much lower than the urine osmolality, indicating inappropriate secretion of a concentrated urine in the presence of a dilute serum.

Cardiac, renal, and hepatic disease characteristically reduce the sodium/osmolality ratio, this being partially attributed to the effects of increased blood sugar, urea, or unknown metabolic products. Patients in shock may develop disproportionately elevated measured osmolality compared to calculated osmolality, which points toward the presence of circulating metabolic products.

There are several approximate methods for estimating serum osmolality from clinical laboratory values for sodium ion. They may be of considerable value in an emergency situation.

1. Serum osmolality may be estimated from

$$\text{mOsmol} = (1.86 \times \text{sodium}) + \frac{\text{blood sugar}}{18} + \frac{\text{BUN}}{2.8} + 5$$

(Na in mEq/L, blood sugar and BUN in mg/100 mL).

2. A quick approximation is

$$\text{mOsmol} = 2\ \text{Na} + \frac{\text{BS}}{20} + \frac{\text{BUN}}{3}$$

3. The osmolality is usually, *but not always,* very close to two times the sodium reading plus 10.

Urine Osmoticity

The two main functions of the kidney are glomerular filtration and tubular reabsorption. Clinically, tubular function is measured best by tests that determine the ability of the tubules to concentrate and dilute the urine. Tests of urinary dilution are not as sensitive in the detection of disease, as are tests of urinary concentration. As concentration of urine occurs in the renal medulla (interstitial fluids, loops of Henle, capillaries of the medulla, and collecting tubules), the disease processes that disturb the function or structure of the medulla produce early impairment of the concentrating power of the kidney. Such diseases include acute tubular necrosis, obstructive uropathy, pyelonephritis, papillary necrosis, medullary cysts, hypokalemic and hypercalcemic nephropathy and sickle cell disease.

Measurement of urine osmolality is an accurate test for the diluting and concentrating ability of the kidneys. In the absence of ADH, the daily urinary output is likely to be 6 to 8 liters or more. The normal urine osmolality depends on the clinical setting; normally, with maximum ADH stimulation, it can be as much as 1200 mOsmol/kg, and with maximum ADH suppression as little as 50 mOsmol/kg. Simultaneous determination of serum and urine osmolality often is valuable in assessing the distal tubular response to circulating ADH. For example, if the patient's serum is hyperosmolal, or in the upper limits of normal ranges, and the patient's urine osmolality measured at the same time is much lower, a decreased responsiveness of the distal tubules to circulating ADH is suggested.

Measurement of urine osmolality during water restriction is an accurate, sensitive test of decreased renal function. For example, under the conditions of one test, normal osmolality would be greater than 800 mOsmol/kg. With severe impairment the value would be less than 400 mOsmol/kg. Knowledge of urine osmolality may point to a problem even though other tests are normal (eg, the Fishberg concentration test, blood urea nitrogen, PSP excretion, creatinine clearance, or IV pyelogram). Knowledge of its value may be useful especially in diabetes mellitus, essential hypertension, and silent pyelonephritis. The urine/serum osmolality ratio should be calculated and should be equal to or greater than 3.

UNDESIRABLE EFFECTS OF ABNORMAL OSMOTICITY

OPHTHALMIC MEDICATION—It is generally accepted that ophthalmic preparations intended for instillation into the cul-de-sac of the eye should, if possible, be approximately isotonic to avoid irritation (see Chapter 43). It also has been stated that the abnormal tonicity of contact lens solutions can cause the lens to adhere to the eye and/or cause burning or dryness and photophobia.

PARENTERAL MEDICATION—Osmoticity is of great importance in parenteral injections, its effects depending on such factors as the degree of deviation from tonicity, the concentration, the location of the injection, the volume injected, the speed of the injection, and the rapidity of dilution and diffusion, etc. When formulating parenterals, solutions otherwise hypotonic usually have their tonicity adjusted by the addition of dextrose or sodium chloride. Hypertonic parenteral drug solutions cannot be adjusted. Hypotonic and hypertonic solutions usually are administered slowly in small volumes, or into a large vein such as the subclavian, where dilution and distribution occur rapidly. Solutions that differ from the serum in tonicity generally cause tissue irritation, pain on injection, and electrolyte shifts, the effect depending on the degree of deviation from tonicity:

Excessive infusion of *hypotonic* fluids may cause swelling of red blood cells, hemolysis, and water invasion of the body's cells in general. When this is beyond the body's tolerance for water, water intoxication results, with convulsions and edema, such as pulmonary edema.

Excessive infusion of *isotonic* fluids can cause an increase in extracellular fluid volume, which can result in circulatory overload.

Excessive infusion of *hypertonic* fluids leads to a wide variety of complications. For example, the sequence of events when the body is presented with a large IV load of hypertonic fluid, rich in dextrose, is as follows: hyperglycemia, glycosuria and intracellular dehydration, osmotic diuresis, loss of water and electrolytes, dehydration, and coma.

One cause of osmotic diuresis is the infusion of dextrose at a rate faster than the ability of the patient to metabolize it (as greater than perhaps 400 to 500 mg/kg per hour for an adult on total parenteral nutrition). A heavy load of unmetabolizable dextrose increases the osmoticity of blood and acts as a diuretic; the increased solute load requires more fluid for excretion, 10 to 20 mL of water being required to excrete each gram of dextrose. Solutions such as those for total parenteral nutrition should be administered by means of a metered constant-infusion apparatus over a lengthy period (usually more than 24 hr) to avoid sudden hyperosmotic dextrose loads. Such solutions may cause osmotic diuresis; if this occurs, water balance is likely to become negative because of the increased urinary volume, and electrolyte depletion may occur because of excretion of sodium and potassium secondary to the osmotic diuresis. If such diuresis is marked, body weight falls abruptly and signs of dehydration appear. Urine should be monitored for signs of osmotic diuresis, such as glycosuria and increased urine volume.

If the IV injection rate of hypertonic solution is too rapid, there may be catastrophic effects on the circulatory and respiratory systems. Blood pressure may fall to dangerous levels, cardiac irregularities or arrest may ensue, respiration may become shallow and irregular, and there may be heart failure and pulmonary edema. Probably the precipitating factor is a bolus of concentrated solute suddenly reaching the myocardium and the chemoreceptors in the aortic arch and carotid sinus.[7]

Abrupt changes in serum osmoticity can lead to cerebral hemorrhage. It has been shown experimentally that rapid infusions of therapeutic doses of hypertonic saline with osmotic loads produce a sudden rise in cerebrospinal fluid (CSF) pressure and venous pressure (VP) followed by a precipitous fall in CSF pressure. This particularly may be conducive to intracranial hemorrhage, as the rapid infusion produces an increase in plasma volume and venous pressure at the same time the CSF pressure is falling. During the CSF pressure rise, there is a drop in hemoglobin and hematocrit, reflecting a marked increase in blood volume.

Hyperosmotic medications, such as sodium bicarbonate (osmolarity of 1560 at 1 mEq/mL), which are administered intravenously, should be diluted prior to use and should be injected slowly to allow dilution by the circulating blood. Rapid *push* injections may cause a significant increase in blood osmoticity.[8]

As to other possibilities, there may be crenation of red blood cells and general cellular dehydration. Hypertonic dextrose or saline infused through a peripheral vein with small blood volume may traumatize the vein and cause thrombophlebitis. Infiltration can cause trauma and necrosis of tissues. Safety, therefore, demands that all IV injections, especially highly osmotic solutions, be performed slowly, usually being given preferably over a period not less than that required for a complete circulation of the blood, for example, 1 min. The exact danger point varies with the state of the patient, the concen-

tration of the solution, the nature of the solute, and the rate of administration.

Hyperosmotic solutions also should not be discontinued suddenly. In dogs, marked increase in levels of intracranial pressure occur when hyperglycemia produced by dextrose infusions is reversed suddenly by stopping the infusion and administering saline. It also has been shown that the CSF pressure in humans rises during treatment of diabetic ketoacidosis in association with a fall in the plasma concentration of dextrose and a fall in plasma osmolality. These observations may be explained by the different rates of decline in dextrose content of the brain and of plasma. The concentration of dextrose in the brain may fall more slowly than in the plasma, causing a shift of fluid from the extracellular fluid space to the intracellular compartment of the CNS, resulting in increased intracranial pressure.

Clinical Applications

Although there are many issues with abnormal osmoticity, most pharmacists are concerned with preventable adverse effects such as thrombophlebitis and pain at the injection site. The understanding of these potential risks from hyperosmotic parenteral medications has fine-tuned IV administration techniques. The site of administration—peripheral versus central venous catheter—plays a significant role in determining the final concentration of parenteral medications infused IV. Attention should be directed toward establishing the optimal osmolarity of IV administered parenteral medications via the peripheral venous route that will result in the least adverse effects.

Since the introduction of parenteral nutrition support, hyperosmoticity of these nutrition solutions remains a concern. The commonly accepted osmolarity of less than 900 mOsmol/L has been quoted for safe peripheral administration of parenteral nutrition solutions.[11,12] All attempts should be made to prepare solutions with osmoticity close to that of serum osmoticity or no greater than 900 mOsmol/L. This can be achieved by carefully selecting the diluent for dilution and determining the final concentration of the parenteral medication. Dextrose 5% in Water for Injection and Sodium Chloride 0.9% have been used routinely as diluents. When comparing the two diluents, parenteral medications diluted with Dextrose 5% in Water for Injection have a lower osmolarity than do solutions diluted with Sodium Chloride 0.9% at the same final concentration.

Several studies have been conducted to determine optimal final concentration of commonly used parenteral medications.[3–5] The published final concentrations for most parenteral medications are recommended for peripheral as well as central venous catheter IV administration for patients with no special needs, such as fluid restriction. In the event that fluid restriction is required or the recommended final concentration is not achievable, the parenteral medication should be administered via a central venous catheter, where immediate dilution and distribution is achieved rapidly. This will minimize potential for the phlebitis and pain at the injection site.

Osmoticity issues associated with parenteral medications are also applicable to *total parenteral nutrition* (TPN) solutions, especially via peripheral venous administration. Peripheral parenteral nutrition support remains an integral part of therapeutic options for hospitalized patients. The peripheral route of administration often is preferred for patients who require short-term therapy or supplemental nutrition support.

In clinical practice, however, many institutions use the macronutrient dextrose as the sole determinant for the safety of peripheral parenteral nutrition administration. For example, the approximate osmolarity of dextrose is 50 mOsmol/% of dextrose. Thus, a 10% dextrose solution equals 500 mOsmol/L. It is assumed that with *normal* protein and micronutrient requirements, the final osmolarity is estimated to be approximately 900 mOsmol/L. Therefore, guidelines for most institutions recommend any parenteral nutrition solution with a dextrose concentration less than or equal to 10% is safe for peripheral administration, irrespective of other components. Conversely, a parenteral nutrition solution with a final dextrose concentration greater than 10% should not be administered peripherally and should be considered for central venous catheter administration. Although this method appears to be practical and provides quick decision-making ability, it ignores the contributions of the other components, restricts its validity to adult parenteral nutrition solutions with *normal* protein and micronutrient requirements, and does not address neonatal and pediatric parenteral nutrition solutions. Because of the different fluid and nutrient requirements of neonates and pediatric patients, the final concentration of dextrose and amino acids are generally greater to provide the calories and protein requirements in a smaller volume of liquid. For example, protein requirements of neonates are much higher compared with adult requirements, 3 g/kg/day versus 1 g/k/day. Thus, the final percentage of amino acid in neonatal parenteral nutrition solution is generally higher. Coupled with an approximate osmolarity of amino acid equal to 100 mOsmol/%, amino acids may contribute equally to the final osmolarity of a parenteral nutrition solution. Therefore, components other than dextrose cannot be ignored.

Currently, most institutions use automated compounding systems to prepare parenteral nutrition solutions. These systems often are computerized and include programs that will calculate the osmolarity of the final parenteral nutrition solution. This has helped clinicians determine the safety of parenteral nutrition solutions with various macro- and micronutrient combinations, thereby accounting for all components of parenteral nutrition solutions.

OSMOTICITY AND ENTERAL HYPERALIMENTATION

Some aspects of nutrition are discussed briefly here because of the potential major side effects due to abnormal osmoticity of nutritional fluids, and because there exists increasing dialogue on nutrition among pharmacists, dietitians, nurses, and physicians. The professional organization ASPEN (The American Society for Parenteral and Enteral Nutrition), for example, has a membership open to all of the above health practitioners. Pharmacists should be able to discuss these matters with other health professionals in terms of nutrition as well as medicine.

Osmoticity has been of special importance in the IV infusion of large volumes of highly concentrated nutritional solutions. Their hyperosmoticity has been a major factor in the requirement that they be injected centrally into a large volume of rapidly moving blood, instead of using peripheral infusion. Use of such solutions and knowledge of their value have led, more recently, to the use of similar formulations administered, not parenterally, but by instillation into some part of the GI tract, orally, by nasogastric tube, via feeding gastrostomy, or by needle-catheter jejunostomy. This method has given excellent total nutrition, for a period of time, to many patients and obviously avoids some of the problems associated with injections.

Enteral nutritional formulas can be modular, allowing individual supplementation of protein, carbohydrate, or fat. Other formulas are called *defined formula diets* and contain protein, carbohydrate, fat, minerals, and vitamins. These nutritionally complete formulations can be monomeric (or oligomeric), based on aminoacids, short peptides, and simple carbohydrates, or can be polymeric, based on complex protein and carbohydrates.

These diets are necessarily relatively high in osmoticity because their smaller molecules result in more particles per gram than in normal foods. An example is a fluid consisting of

L-amino acids, dextrose oligosaccharides, vitamins (including fat-soluble vitamins), fat as a highly purified safflower oil or soybean oil, electrolytes, trace minerals, and water. As it contains fat, that component is not in solution and therefore should have no direct effect on osmoticity. However, the potential for interactions can cause some significant changes in total particle concentration and indirectly affect the osmoticity.[13]

Although it is easily digested, dextrose contributes more particles than most other carbohydrate sources such as starch, and is more likely to cause osmotic diarrhea, especially with bolus feeding. Osmoticity is improved (decreased) by replacing dextrose with dextrose oligosaccharides (carbohydrates that yield on hydrolysis 2 to 10 monosaccharides). Flavoring also increases the osmoticity of a product, different flavors causing varying increases.

Commercial diets are packaged as fluids or as powders for reconstitution. Reconstitution is usually with water. These products are categorized on caloric density, (calories/mL), protein content, or osmolality (mOsm/kg of H_2O). Parenteral nutritional products, on the other hand, are labeled in terms of osmolarity (mOsm/L).

The enteric route for hyperalimentation frequently is overlooked in many diseases or post-trauma states, if the patient is not readily responsive to traditional oral feedings. Poor appetite, chronic nausea, general apathy, and a degree of somnolence or sedation are common concomitants of serious disease. This frequently prevents adequate oral alimentation and results in progressive energy and nutrient deficits. Often, supplementary feedings of a highly nutritious formula are taken poorly or refused entirely. However, the digestive and absorptive capabilities of the GI tract are frequently intact and, when challenged with appropriate nutrient fluids, can be used effectively. By using an intact GI tract for proper alimentation, the major problems of sepsis and metabolic derangement that relate to IV hyperalimentation largely are obviated, and adequate nutritional support is simplified greatly. Because of this increased safety and ease of administration, the enteric route for hyperalimentation should be used whenever possible.[14]

When certain foods are ingested in large amounts or as concentrated fluids, their osmotic characteristics can cause an upset in the normal water balance within the body. For a given weight of solute the osmolality of the solution is inversely proportional to the size of the particles. Nutritional components can be listed in an approximate order of decreasing osmotic effect per gram, as[15]

1. Electrolytes such as sodium chloride
2. Relatively small organic molecules such as dextrose (glucose) and amino acids
3. Dextrose oligosaccharides
4. Starches
5. Proteins
6. Fats (as fats are not water soluble, they have no osmotic effect)

Thus, in foods, high proportions of electrolytes, amino acids, and simple sugars have the greatest effect on osmolality and, as a result, on tolerance. The approximate osmolality of a few common foods and beverages is

	mOsmol/kg
Whole milk	295
Tomato juice	595
Orange juice	935
Ice cream	1150

When nutrition of high osmoticity is ingested, large amounts of water will transfer to the stomach and intestines from the fluid surrounding those organs in an attempt to lower the osmoticity. The higher the osmoticity, the larger the amount of water required; a large amount of water in the GI tract can cause distention, cramps, nausea, vomiting, hypermotility, and shock. The food may move through the tract too rapidly for the water to be reabsorbed, and result in diarrhea; severe diarrhea can cause dehydration. The hyperosmotic enteral effects have been observed by the administration of undiluted hypertonic oral medication.[16–17] Table I from this work lists average osmolality values of some commercially available drug solutions and suspensions. Thus, there is some analogy to the effect of hyperosmotic IV infusions.

Hyperosmotic feedings may result in mucosal damage in the GI tract. Rats given hyperosmotic feeding showed transient decrease in disaccharidase activity, and an increase in alkaline phosphatase activity. They also showed morphological alterations in the microvilli of the small intestines. After a period of severe gastroenteritis, the bowel may be unusually susceptible to highly osmotic formulas, and their use may increase the frequency of diarrhea. Infant formulas that are hyperosmotic may affect preterm infants adversely during the early neonatal period, and they may produce or predispose neonates to necrotizing enterocolitis when the formulas delivered to the jejunum through a nasogastric tube. The body attempts to keep the osmoticity of the contents of the stomach and intestines at approximately the same level as that of the fluid surrounding them. As a fluid of lower osmoticity requires the transfer of less water to dilute it, it should be tolerated better than one of higher osmoticity.

As to tolerance, there is a great variation from one individual to another in sensitivity to the osmoticity of foods. The majority of patients receiving nutritional formulas, either orally or by tube, are able to tolerate feedings with a wide range of osmoticities when the formulas are administered slowly and when adequate additional fluids are given. However, certain patients are more likely to develop symptoms of intolerance when receiving fluids of high osmoticity. These include debilitated patients, patients with GI disorders, pre- and postoperative patients, gastrostomy-and jejunostomy-fed patients, and patients whose GI tracts have not been challenged for an extended period of time. Thus, osmoticity always should be considered in the selection of the formula for each individual patient.

With all products, additional fluid intake may be indicated for individuals with certain clinical conditions. Frequent feedings of small volume or a continual instillation (pumped) may be of benefit initially in establishing tolerance to a formula. For other than iso-osmotic formulas, feedings of reduced concentration (osmolality less than 400 mOsmol/kg) also may be helpful initially if tolerance problems arise in sensitive individuals. Concentration and size of feeding then can be increased gradually to normal as tolerance is established.

A common disturbance of intake encountered in elderly individuals relates to excess solid intake rather than to reduced water intake. For example, an elderly victim of a cerebral vascular accident who is being fed by nasogastric tube may be given a formula whose solute load requires a greatly increased water intake. Thus, tube feeding containing 120 g of protein and 10 g of salt will result in the excretion of more than 1000 mOsmol of solute. This requires the obligatory excretion of a volume of urine between 1200 and 1500 mL when the kidneys are capable of normal concentration ability. As elderly individuals often have significant impairment in renal function, water loss as urine may exceed 2000 to 2500 mL per day. Such an individual would require 3 to 4 liters of water per day simply to meet the increased demand created by this high solute intake. Failure of the physician to provide such a patient with the increased water intake needed will result in a progressive water deficit that rapidly may become critical. The importance of knowing the complete composition of the tube feeding formulas used for incapacitated patients cannot be overemphasized.

OSMOLALITY DETERMINATION

The need for experimental determination of osmolality has been established. In regard to this there are four properties of

solutions that depend only on the number of *particles* in the solution. They are *osmotic-pressure elevation, boiling-point elevation, vapor-pressure depression,* and *freezing-point depression.* These are called *colligative properties* and if one of them is known, the others can be calculated from its value. Osmotic-pressure elevation is the most difficult to measure satisfactorily. The boiling-point elevation may be determined, but the values are rather sensitive to changes in barometric pressure. Also, for an aqueous solution the molal boiling point elevation is considerably less than the freezing-point depression. Thus, it is less accurate than the freezing-point method. Determinations of vapor-pressure lowering are quite easy, rapid, and convenient. A vapor pressure osmometer with a precision of < 2 mOsmol/kg is reported by Dickerson *et al.*[16] Another commonly used method is that of freezing-point depression, which can be determined quite readily with a fair degree of accuracy (see *Freezing-Point Depression* in Chapter 16). It should be noted that the data in Appendix A can be converted readily to vapor-pressure lowering if desired.

The results of investigations by Lund *et al*[18] indicate that the freezing point of normal, healthy human blood is −0.52°. Inasmuch as water is the medium in which the various constituents of blood are either suspended or dissolved in this method, it is assumed that *any aqueous solution* freezing at −0.52° is *isotonic with blood.* Now it is rare that a simple aqueous solution of the therapeutic agent to be injected parenterally has a freezing point of −0.52°, and to obtain this freezing point it is necessary either to add some other therapeutically inactive solute if the solution is hypotonic (freezing point above −0.52°) or to dilute the solution if it is hypertonic (freezing point below −0.52°). The usual practice is to add either sodium chloride or dextrose to adjust hypotonic parenteral solutions to isotonicity. Certain solutes, including ammonium chloride, boric acid, urea, glycerin, and propylene glycol, cause hemolysis even when they are present in a concentration that is iso-osmotic, and such solutions obviously are not isotonic. See Appendix A.

In a similar manner solutions intended for ophthalmic use may be adjusted to have a freezing point identical to that of lacrimal fluid, namely −0.52°. Ophthalmic solutions with higher freezing points usually are made isotonic by the addition of boric acid or sodium chloride.

In laboratories where the necessary equipment is available, the method usually followed for adjusting hypotonic solutions is to determine the freezing-point depression produced by the ingredients of a given prescription or formula, and then to add a quantity of a suitable inert solute calculated to lower the freezing point to −0.52°, whether the solution is for parenteral injection or ophthalmic application. A final determination of the freezing-point depression may be made to verify the accuracy of the calculation. If the solution is hypertonic, it must be diluted if an isotonic solution is to be prepared, but it must be remembered that some solutions cannot be diluted without impairing their therapeutic activity. For example, solutions to be used for treating varicose veins require a high concentration of the active ingredient (solute) to make the solution effective. Dilution to isotonic concentration is not indicated in such cases.

FREEZING-POINT CALCULATIONS

As explained in the preceding section, freezing-point data often may be employed in solving problems of isotonicity adjustment. Obviously, the utility of such data is limited to those solutions where the solute does not penetrate the membrane of the tissue (eg, red blood cells) with which it is in contact. In such cases, Appendix A, which gives the freezing-point depression of solutions of different concentrations of various substances, provides information essential for solving the problem.

For most substances listed in the table, the concentration of an isotonic solution (one that has a freezing point of −0.52°) is given. If this is not listed in the table, it may be determined with sufficient accuracy by simple proportion using, as the basis for calculation, the figure that most nearly produces an isotonic solution. Actually the depression of the freezing point of a solution of an electrolyte is not absolutely proportional to the concentration but varies according to dilution; for example, a solution containing 1 g of procaine hydrochloride in 100 mL has a freezing-point depression of 0.12°, whereas a solution containing 3 g of the same salt in 100 mL has a freezing-point depression of 0.33°, *not* 0.36° (3 × 0.12°). Because the adjustment to isotonicity need not be absolutely exact, approximations may be made. Nevertheless, adjustments to isotonicity should be as exact as practicable.

EFFECT OF SOLVENTS—Besides water, certain other solvents frequently are employed in nose drops, ear drops, and other preparations to be used in various parts of the body. Liquids such as glycerin, propylene glycol, or alcohol may compose part of the solvent. In solving isotonicity adjustment problems for such solutions, it should be kept in mind that these solvent components contribute to the freezing-point depression but they may or may not have an effect on the *tone* of the tissue to which they are applied; thus, an *iso-osmotic* solution may not be *isotonic.* In such cases, it is apparent that the utility of the methods described above—or for that matter, of any other method of evaluating *tonicity*—is questionable.

TONICITY TESTING BY OBSERVING ERYTHROCYTE CHANGES

Observation of the behavior of human erythrocytes when suspended in a solution is the ultimate and direct procedure for determining whether the solution is isotonic, hypotonic, or hypertonic. If hemolysis or marked change in the appearance of the erythrocytes occurs, the solution is not isotonic with the cells. If the cells retain their normal characteristics, the solution is isotonic.

Hemolysis may occur when the osmotic pressure of the fluid in the erythrocytes is greater than that of the solution in which the cells are suspended, but the specific chemical reactivity of the solute in the solution often is far more important in producing hemolysis than is the osmotic effect. There is no certain evidence that any single mechanism of action causes hemolysis. The process appears to involve such factors as pH, lipid solubility, molecular and ionic sizes of solute particles, and possibly inhibition of cholinesterase in cell membranes and denaturing action on plasma membrane protein.

Some investigators test the tonicity of injectable solutions by observing variations of red blood cell volume produced by these solutions. This method appears to be more sensitive to small differences in tonicity than those based on observation of a hemolytic effect. Much useful information concerning the effect of various solutes on erythrocytes has been obtained by this procedure.

METHODS OF ADJUSTING TONICITY

There are several methods for adjusting the tonicity of an aqueous solution, provided, of course, that the solution is hypotonic when the drug and additives are dissolved. The most prominent of these methods are the freezing-point depression method, the sodium chloride equivalent method, and the isotonic solution V-value method. The first two of these methods can be used with a three-step problem-solving process based on sodium chloride.

1. Identify a reference solution and the associated tonicity parameter.
2. Determine the contribution of the drug(s) and additive(s) to the total tonicity.

L-amino acids, dextrose oligosaccharides, vitamins (including fat-soluble vitamins), fat as a highly purified safflower oil or soybean oil, electrolytes, trace minerals, and water. As it contains fat, that component is not in solution and therefore should have no direct effect on osmoticity. However, the potential for interactions can cause some significant changes in total particle concentration and indirectly affect the osmoticity.[13]

Although it is easily digested, dextrose contributes more particles than most other carbohydrate sources such as starch, and is more likely to cause osmotic diarrhea, especially with bolus feeding. Osmoticity is improved (decreased) by replacing dextrose with dextrose oligosaccharides (carbohydrates that yield on hydrolysis 2 to 10 monosaccharides). Flavoring also increases the osmoticity of a product, different flavors causing varying increases.

Commercial diets are packaged as fluids or as powders for reconstitution. Reconstitution is usually with water. These products are categorized on caloric density, (calories/mL), protein content, or osmolality (mOsm/kg of H_2O). Parenteral nutritional products, on the other hand, are labeled in terms of osmolarity (mOsm/L).

The enteric route for hyperalimentation frequently is overlooked in many diseases or post-trauma states, if the patient is not readily responsive to traditional oral feedings. Poor appetite, chronic nausea, general apathy, and a degree of somnolence or sedation are common concomitants of serious disease. This frequently prevents adequate oral alimentation and results in progressive energy and nutrient deficits. Often, supplementary feedings of a highly nutritious formula are taken poorly or refused entirely. However, the digestive and absorptive capabilities of the GI tract are frequently intact and, when challenged with appropriate nutrient fluids, can be used effectively. By using an intact GI tract for proper alimentation, the major problems of sepsis and metabolic derangement that relate to IV hyperalimentation largely are obviated, and adequate nutritional support is simplified greatly. Because of this increased safety and ease of administration, the enteric route for hyperalimentation should be used whenever possible.[14]

When certain foods are ingested in large amounts or as concentrated fluids, their osmotic characteristics can cause an upset in the normal water balance within the body. For a given weight of solute the osmolality of the solution is inversely proportional to the size of the particles. Nutritional components can be listed in an approximate order of decreasing osmotic effect per gram, as[15]

1. Electrolytes such as sodium chloride
2. Relatively small organic molecules such as dextrose (glucose) and amino acids
3. Dextrose oligosaccharides
4. Starches
5. Proteins
6. Fats (as fats are not water soluble, they have no osmotic effect)

Thus, in foods, high proportions of electrolytes, amino acids, and simple sugars have the greatest effect on osmolality and, as a result, on tolerance. The approximate osmolality of a few common foods and beverages is

	mOsmol/kg
Whole milk	295
Tomato juice	595
Orange juice	935
Ice cream	1150

When nutrition of high osmoticity is ingested, large amounts of water will transfer to the stomach and intestines from the fluid surrounding those organs in an attempt to lower the osmoticity. The higher the osmoticity, the larger the amount of water required; a large amount of water in the GI tract can cause distention, cramps, nausea, vomiting, hypermotility, and shock. The food may move through the tract too rapidly for the water to be reabsorbed, and result in diarrhea; severe diarrhea can cause dehydration. The hyperosmotic enteral effects have been observed by the administration of undiluted hypertonic oral medication.[16-17] Table I from this work lists average osmolality values of some commercially available drug solutions and suspensions. Thus, there is some analogy to the effect of hyperosmotic IV infusions.

Hyperosmotic feedings may result in mucosal damage in the GI tract. Rats given hyperosmotic feeding showed transient decrease in disaccharidase activity, and an increase in alkaline phosphatase activity. They also showed morphological alterations in the microvilli of the small intestines. After a period of severe gastroenteritis, the bowel may be unusually susceptible to highly osmotic formulas, and their use may increase the frequency of diarrhea. Infant formulas that are hyperosmotic may affect preterm infants adversely during the early neonatal period, and they may produce or predispose neonates to necrotizing enterocolitis when the formulas delivered to the jejunum through a nasogastric tube. The body attempts to keep the osmoticity of the contents of the stomach and intestines at approximately the same level as that of the fluid surrounding them. As a fluid of lower osmoticity requires the transfer of less water to dilute it, it should be tolerated better than one of higher osmoticity.

As to tolerance, there is a great variation from one individual to another in sensitivity to the osmoticity of foods. The majority of patients receiving nutritional formulas, either orally or by tube, are able to tolerate feedings with a wide range of osmoticities when the formulas are administered slowly and when adequate additional fluids are given. However, certain patients are more likely to develop symptoms of intolerance when receiving fluids of high osmoticity. These include debilitated patients, patients with GI disorders, pre- and postoperative patients, gastrostomy-and jejunostomy-fed patients, and patients whose GI tracts have not been challenged for an extended period of time. Thus, osmoticity always should be considered in the selection of the formula for each individual patient.

With all products, additional fluid intake may be indicated for individuals with certain clinical conditions. Frequent feedings of small volume or a continual instillation (pumped) may be of benefit initially in establishing tolerance to a formula. For other than iso-osmotic formulas, feedings of reduced concentration (osmolality less than 400 mOsmol/kg) also may be helpful initially if tolerance problems arise in sensitive individuals. Concentration and size of feeding then can be increased gradually to normal as tolerance is established.

A common disturbance of intake encountered in elderly individuals relates to excess solid intake rather than to reduced water intake. For example, an elderly victim of a cerebral vascular accident who is being fed by nasogastric tube may be given a formula whose solute load requires a greatly increased water intake. Thus, tube feeding containing 120 g of protein and 10 g of salt will result in the excretion of more than 1000 mOsmol of solute. This requires the obligatory excretion of a volume of urine between 1200 and 1500 mL when the kidneys are capable of normal concentration ability. As elderly individuals often have significant impairment in renal function, water loss as urine may exceed 2000 to 2500 mL per day. Such an individual would require 3 to 4 liters of water per day simply to meet the increased demand created by this high solute intake. Failure of the physician to provide such a patient with the increased water intake needed will result in a progressive water deficit that rapidly may become critical. The importance of knowing the complete composition of the tube feeding formulas used for incapacitated patients cannot be overemphasized.

OSMOLALITY DETERMINATION

The need for experimental determination of osmolality has been established. In regard to this there are four properties of

solutions that depend only on the number of *particles* in the solution. They are *osmotic-pressure elevation, boiling-point elevation, vapor-pressure depression,* and *freezing-point depression.* These are called *colligative properties* and if one of them is known, the others can be calculated from its value. Osmotic-pressure elevation is the most difficult to measure satisfactorily. The boiling-point elevation may be determined, but the values are rather sensitive to changes in barometric pressure. Also, for an aqueous solution the molal boiling point elevation is considerably less than the freezing-point depression. Thus, it is less accurate than the freezing-point method. Determinations of vapor-pressure lowering are quite easy, rapid, and convenient. A vapor pressure osmometer with a precision of < 2 mOsmol/kg is reported by Dickerson *et al.*[16] Another commonly used method is that of freezing-point depression, which can be determined quite readily with a fair degree of accuracy (see *Freezing-Point Depression* in Chapter 16). It should be noted that the data in Appendix A can be converted readily to vapor-pressure lowering if desired.

The results of investigations by Lund *et al*[18] indicate that the freezing point of normal, healthy human blood is −0.52°. Inasmuch as water is the medium in which the various constituents of blood are either suspended or dissolved in this method, it is assumed that *any aqueous solution* freezing at −0.52° is *isotonic with blood.* Now it is rare that a simple aqueous solution of the therapeutic agent to be injected parenterally has a freezing point of −0.52°, and to obtain this freezing point it is necessary either to add some other therapeutically inactive solute if the solution is hypotonic (freezing point above −0.52°) or to dilute the solution if it is hypertonic (freezing point below −0.52°). The usual practice is to add either sodium chloride or dextrose to adjust hypotonic parenteral solutions to isotonicity. Certain solutes, including ammonium chloride, boric acid, urea, glycerin, and propylene glycol, cause hemolysis even when they are present in a concentration that is iso-osmotic, and such solutions obviously are not isotonic. See Appendix A.

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1. Identify a reference solution and the associated tonicity parameter.
2. Determine the contribution of the drug(s) and additive(s) to the total tonicity.

3. Determine the amount of sodium chloride needed by subtracting the contribution of the actual solution from the reference solution.

The result of the third step also indicates whether the actual solution is hypotonic, isotonic, or hypertonic. If the actual solution contributes less to the total tonicity than the reference solution, then the actual solution is hypotonic. If, however, the actual solution contributes a greater amount to tonicity than the reference solution, the actual solution is hypertonic and can be adjusted to isotonicity only by dilution. This may not be possible on therapeutic grounds.

The amount of sodium chloride resulting in the third step also can be converted into an amount of other materials, such as dextrose, to render the actual solution isotonic.

FREEZING-POINT-DEPRESSION METHOD—The freezing-point method makes use of a *D value* (found in Appendix A) which has the units of degree centigrade/(*x*% drug). For example, in Appendix A, dexamethasone sodium phosphate has *D* values of 0.050°/(0.5% drug), 0.180°/(2.0% drug), 0.52°/(6.75% drug), etc. It is apparent that the *D* value is nearly proportional to concentration. If a *D* value is needed for a concentration of drug not listed in Appendix A, a *D* value can be calculated from the appendix by direct proportion, using a *D* value closest to the concentration of drug in the actual solution.

The reference solution for the freezing-point-depression method is 0.9% sodium chloride, which has a freezing-point depression of $\Delta T_f = 0.52°$. Using the three steps described above, the dexamethasone sodium phosphate solution in Example 1 can be rendered isotonic as follows:

Example 1

Dexamethasone Sodium Phosphate	0.1%
Purified Water qs	30 mL
Mft Isotonic Solution	

Step 1—Reference solution: 0.9% sodium chloride.

$$\Delta T_f = 0.52°$$

$$D = 0.050°/0.5\% \text{ (dexamethasone sod phosphate)}$$

Step 2—Contribution of drug.

$$\frac{0.050°}{0.5\% \text{ drug}} \times 0.1\% \text{ drug} = 0.010°$$

Step 3—Reference solution – Actual solution.

$$0.52° - 0.01° = 0.51°$$

Sodium chloride needed.

$$\frac{0.9\% \text{ NaCl}}{0.52°} \times 0.51° = 0.883\% \text{ NaCl}$$

$$\frac{0.883 \text{ g NaCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.265 \text{ g NaCl}$$

The above solution could be made isotonic with any appropriate material other than sodium chloride by using the *D* value for that material. For example, to make the solution isotonic with dextrose with a *D* value, *D* = 0.091°/1%;

$$\frac{1\% \text{ Dextrose}}{0.091°} \times 0.51° = 5.60\% \text{ Dextrose}$$

$$\frac{5.60 \text{ g Dextrose}}{100 \text{ mL}} \times 30 \text{ mL} = 1.68 \text{ g Dextrose}$$

Example 2

Naphazoline HCl (N.HCl)	0.02%
Zinc Sulfate	0.25%
Purified Water qs	30 mL
Mft Isotonic solution	

Step 1—Reference solution: 0.9% sodium chloride.

$$\Delta T_f = 0.52°$$

$$D = 0.14°/1\% \text{ (naphazoline HCl)}$$

$$D = 0.086°/1\% \text{ (zinc sulfate)}$$

Step 2—Contribution of drugs.

$$\frac{0.14°}{1\% \text{ N.HCl}} \times 0.02\% \text{ N.HCl} = 0.003°$$

$$\frac{0.086°}{1\% \text{ } ZnSO_4} \times 0.25\% \text{ } ZnSO_4 = 0.022°$$

$$0.003° + 0.022° = 0.025°$$

Step 3—Reference solution–actual solution.

$$0.52° - 0.025° = 0.495°$$

Sodium chloride needed.

$$\frac{0.9\% \text{ NaCl}}{0.52°} \times 0.495° = 0.857\% \text{ NaCl}$$

$$\frac{0.857 \text{ g NaCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.257 \text{ g NaCl}$$

The above solution could be made isotonic with any appropriate material other than sodium chloride by using the *D* value for that material. For example, to make the solution isotonic with dextrose with a *D* value, *D* = 0.091°/1%;

$$\frac{1\% \text{ Dextrose}}{0.091°} \times 0.495° = 5.44\% \text{ Dextrose}$$

$$\frac{5.44 \text{ g Dextrose}}{100 \text{ mL}} \times 30 \text{ mL} = 1.63 \text{ g Dextrose}$$

SODIUM CHLORIDE EQUIVALENT METHOD—A sodium chloride equivalent, *E value,* is defined as the weight of sodium chloride that will produce the same osmotic effect as 1 g of the drug. For example, in Appendix A, dexamethasone sodium phosphate has an *E* value of 0. 18 g NaCl/g drug at 0.5% drug concentration, 0.17 g NaCl/g drug at 1% drug concentration and a value of 0.16 g NaCl/g drug at 2% drug. This slight variation in the sodium chloride equivalent with concentration is due to changes in interionic attraction at different concentration of drug; the *E* value is not directly proportional to concentration as was the freezing-point-depression.

The reference solution for the sodium chloride equivalent method is 0.9% sodium chloride as it was for the freezing-point-depression method.

The dexamethasone sodium phosphate solution in Example 1 can be rendered isotonic using the sodium chloride equivalent method as follows:

Example 1

Dexamethasone Sodium Phosphate	0.1%
Purified Water qs	30 mL
Mft Isotonic Solution	

Step 1—Reference solution: 0.9% sodium chloride.

$$\frac{0.9 \text{ g NaCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.270 \text{ g NaCl}$$

$$E = 0.18 \text{ g NaCl/g drug}$$

Step 2—Contribution of drug.

$$\frac{0.18 \text{ g NaCl}}{1 \text{ g drug}} \times \frac{0.1 \text{ g drug}}{100 \text{ mL}} \times 30 \text{ mL} = 0.0054 \text{ g NaCl}$$

Step 3—Reference solution – Actual solution.

$$0.270 \text{ g NaCl} - 0.0054 \text{ g NaCl} = 0.265 \text{ g NaCl}$$

The above solution can be made isotonic with a material other than sodium chloride, such as dextrose, by using the E value of that material. For example, to make the solution isotonic with dextrose, $E = 0.16$ g NaCl/g dextrose, the amount of sodium chloride needed in Step 3, can be converted to dextrose as follows:

$$\frac{1 \text{ g Dextrose}}{0.16 \text{ g NaCl}} \times 0.265 \text{ g NaCl} = 1.66 \text{ g Dextrose}$$

Example 2

Naphazoline HCl (N.HCl)	0.02%
Zinc Sulfate	0.25%
Purified Water qs	30 mL
Mft Isotonic Solution	

Step 1—Reference solution: 0.9% sodium chloride.

$$\frac{0.9 \text{ g NaCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.270 \text{ g NaCl}$$

$$E = 0.27 \text{ g NaCl/g N.HCl}$$

$$E = 0.15 \text{ g NaCl/g } ZnSO_4$$

Step 2—Contribution of drugs.

$$\frac{0.27 \text{ g NaCl}}{1 \text{ g N.HCl}} \times \frac{0.02 \text{ g N.HCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.002 \text{ g NaCl}$$

$$\frac{0.15 \text{ g NaCl}}{1 \text{ g } ZnSO_4} \times \frac{0.25 \text{ g } ZnSO_4}{100 \text{ mL}} \times 30 \text{ mL} = 0.011 \text{ g NaCl}$$

$$0.002 \text{ g NaCl} + 0.011 \text{ g NaCl} = 0.013 \text{ g NaCl}$$

Step 3—Reference solution–actual solution.

$$0.270 \text{ g NaCl} - 0.013 \text{ g NaCl} = 0.257 \text{ g NaCl}$$

The above solution can be made isotonic with a material other than sodium chloride, such as dextrose, by using the E value of that material. For example, to make the solution isotonic with dextrose, $E = 0.16$ g NaCl/g dextrose, the amount of sodium chloride needed in Step 3 can be converted to dextrose as follows:

$$\frac{1 \text{ g Dextrose}}{0.16 \text{ g NaCl}} \times 0.257 \text{ g NaCl} = 1.61 \text{ g Dextrose}$$

ISOTONIC SOLUTION *V* VALUES—The *V value* of a drug is the volume of water to be added to a specified weight of drug (0.3 g or 1.0 g, depending on the table used) to prepare an isotonic solution. Appendix B gives such values for some commonly used drugs. The reason for providing data for 0.3 g of drug is for convenience in preparing 30 mL (approximately 1 fluidounce) of solution, a commonly prescribed volume. The basic principle underlying the use of V values is to prepare an isotonic solution of the prescribed drug and then dilute this solution to final volume with a suitable isotonic vehicle.

The two solutions in the previous examples can be prepared as follows using the V-value method:

Example 1

Dexamethasone Sodium Phosphate	0.1%
Purified Water qs	30 mL
Mft Isotonic Solution	

Step 1—The V value for dexamethasone sodium phosphate can be calculated from the sodium chloride equivalent, E, as outlined in the footnote in Appendix B.

$$\frac{100 \text{ mL Soln}}{0.9 \text{ g NaCl}} \times \frac{0.17 \text{ g NaCl}}{1 \text{ g drug}} \times 0.3 \text{ g drug} = 5.67 \text{ mL Soln}$$

for a dilute solution:

$$5.67 \text{ mL Soln} \cong 5.67 \text{ mL } H_2O \therefore V = (5.67 \text{ mL } H_2O)/(0.3 \text{ g } drug)$$

Step 2—Amount of drug needed.

$$\frac{0.1 \text{ g drug}}{100 \text{ mL}} \times 30 \text{ mL} = 0.030 \text{ g drug}$$

Volume of water needed to prepare an isotonic solution.

$$\frac{5.67 \text{ mL } H_2O}{0.3 \text{ g drug}} \times 0.030 \text{ g drug} = 0.57 \text{ mL } H_2O$$

Step 3—To prepare the solution, dissolve 0.030 g of drug in 0.57 mL water, and qs to volume with a suitable isotonic vehicle such as 0.9% sodium chloride solution, 5.51% dextrose, or an isotonic phosphate buffer.

Example 2

Naphazoline HCl (N.HCl)	0.02%
Zinc Sulfate	0.25%
Purified Water qs	30 mL
Mft Isotonic Solution	

Step 1—The V value for naphazoline HCl can be calculated from the sodium chloride equivalent, E, as outlined in the footnote in Appendix B; the V value for zinc sulfate is taken directly from Appendix B.

$$\frac{100 \text{ mL Soln}}{0.9 \text{ g NaCl}} \times \frac{0.27 \text{ g NaCl}}{1 \text{ g N.HCl}} \times 0.3 \text{ g N.HCl} = 9.00 \text{ mL Soln}$$

for a dilute solution:

$$9.00 \text{ mL Soln} \cong 9.00 \text{ mL } H_2O \therefore V = (9.00 \text{ mL } H_2O)/(0.3 \text{ g N.HCl})$$

$$V = 5.00 \text{ mL } H_2O/0.3 \text{ g } ZnSO_4$$

Step 2—Amount of drugs needed.

$$\frac{0.02 \text{ g N.HCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.006 \text{ g N.HCl}$$

$$\frac{0.25 \text{ g } ZnSO_4}{100 \text{ mL}} \times 30 \text{ mL} = 0.075 \text{ g } ZnSO_4$$

Volume of water needed to prepare an isotonic solution.

$$\frac{9.00 \text{ mL } H_2O}{0.3 \text{ g N.HCl}} \times 0.006 \text{ g drug} = 0.18 \text{ mL } H_2O$$

$$\frac{5.00 \text{ mL } H_2O}{0.3 \text{ g } ZnSO_4} \times 0.075 \text{ g } ZnSO_4 = 1.25 \text{ mL } H_2O$$

Step 3—To prepare the solution, dissolve 0.006 g of naphazoline HCl and 0.075 g zinc sulfate in 1.43 mL water, and qs to volume with a suitable isotonic vehicle such as 0.9% sodium chloride solution, 5.51% dextrose, or an isotonic phosphate buffer.

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Appendix A—Sodium Chloride Equivalents, Freezing-Point Depressions, and Hemolytic Effects of Certain Medicinals in Aqueous Solution

	0.5%		1%		2%		3%		5%		Iso-osmotic Concentration[a]				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Acetrizoate methylglucamine	0.09		0.08		0.08		0.08		0.08	12.12	0.07			0	7.1
Acetrizoate sodium	0.10	0.027	0.10	0.055	0.10	0.109	0.10	0.163	0.10	0.273	9.64	0.09	0.52	0	6.9[†]
Acetylcysteine	0.20	0.055	0.20	0.113	0.20	0.227	0.20	0.341			4.58	0.20	0.52	100*	2.0
Adrenaline HCl											4.24			68	4.5
Alphaprodine HCl	0.19	0.053	0.19	0.105	0.18	0.212	0.18	0.315			4.98	0.18	0.52	100	5.3
Alum (potassium)			0.18				0.15		0.15		6.35		0.14	24*	3.4
Amantadine HCl	0.31	0.090	0.31	0.180	0.31	0.354					2.95	0.31	0.52	91	5.7
Aminoacetic acid	0.42	0.119	0.41	0.235	0.41	0.470					2.20	0.41	0.52	0*	6.2
Aminohippuric acid	0.13	0.035	0.13	0.075											
Aminophylline				0.098[c]											
Ammonium carbonate	0.70	0.202	0.70	0.405							1.29	0.70	0.52	97	7.7
Ammonium chloride			1.12								0.8	1.12	0.52	93	5.0
Ammonium lactate	0.33	0.093	0.33	0.185	0.33	0.370					2.76	0.33	0.52	98	5.9
Ammonium nitrate	0.69	0.200	0.69	0.400							1.30	0.69	0.52	91	5.3
Ammonium phosphate, dibasic	0.58	0.165	0.55	0.315							1.76	0.51	0.52	0	7.9
Ammonium sulfate	0.55	0.158	0.55	0.315							1.68	0.54	0.52	0	5.3
Amobarbital sodium			0.25	0.143[c]			0.25				3.6	0.25	0.52	0	9.3
d-Amphetamine HCl											2.64			98	5.7
Amphetamine phosphate			0.34	0.20			0.27	0.47			3.47	0.26	0.52	0	4.5
Amphetamine sulfate			0.22	0.129[c]			0.21	0.36			4.23	0.21	0.52	0	5.9
Amprotropine phosphate											5.90			0	4.2
Amylcaine HCl			0.22				0.19				4.98	0.18		100	5.6
Anileridine HCl	0.19	0.052	0.19	0.104	0.19	0.212	0.18	0.316	0.18	0.509	5.13	0.18	0.52	12	2.6
Antazoline phosphate											6.05			90	4.0
Antimony potassium tartrate			0.18				0.13		0.10						
Antipyrine			0.17	0.10			0.14	0.24	0.14	0.40	6.81	0.13	0.52	100	6.1
Apomorphine HCl			0.14	0.080[c]											
Arginine glutamate	0.17	0.048	0.17	0.097	0.17	0.195	0.17	0.292	0.17	0.487	5.37	0.17	0.52	0	6.9
Ascorbic acid				0.105[c]							5.05	0.52[b]	100*	2.2	
Atropine methylbromide			0.14				0.13		0.13		7.03	0.13			
Atropine methylnitrate											6.52			0	5.2
Atropine sulfate			0.13	0.075			0.11	0.19	0.11	0.32	8.85	0.10	0.52	0	5.0
Bacitracin			0.05	0.03			0.04	0.07	0.04	0.12					
Barbital sodium			0.30	0.171[c]			0.29	0.50			3.12	0.29	0.52	0	9.8
Benzalkonium chloride			0.16				0.14		0.13						
Benztropine mesylate	0.26	0.073	0.21	0.115	0.15	0.170	0.12	0.203	0.09	0.242					
Benzyl alcohol			0.17	0.09[c]			0.15								
Bethanechol chloride	0.50	0.140	0.39	0.225	0.32	0.368	0.30	0.512			3.05	0.30		0	6.0
Bismuth potassium tartrate			0.09				0.06		0.05						
Bismuth sodium tartrate			0.13				0.12		0.11		8.91	0.10		0	6.1
Boric acid	0.50	0.288[c]									1.9	0.47	0.52	100	4.6
Brompheniramine maleate	0.10	0.026	0.09	0.050	0.08	0.084									
Bupivacaine HCl	0.17	0.048	0.17	0.096	0.17	0.193	0.17	0.290	0.17	0.484	5.38	0.17	0.52	83	6.8
Butabarbital sodium	0.27	0.078	0.27	0.155	0.27	0.313	0.27	0.470			3.33	0.27	0.52	0	6.8
Butacaine sulfate			0.20	0.12			0.13	0.23	0.10	0.29					
Caffeine and sodium benzoate			0.26	0.15			0.23	0.40			3.92	0.23	0.52	0	7.0

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Iso-osmotic Concentration[a]				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Caffeine and sodium salicylate			0.12	0.12			0.17	0.295	0.16	0.46	5.77	0.16	0.52	0	6.8
Calcium aminosalicylate											4.80			0	6.0
Calcium chloride			0.51	0.298[c]							1.70	0.53	0.52	0	5.6
Calcium chloride (6 H_2O)			0.35	0.20							2.5	0.36	0.52	0	5.7
Calcium chloride, anhydrous			0.68	0.39							1.3	0.69	0.52	0	5.6
Calcium disodium edetate	0.21	0.061	0.21	0.120	0.21	0.240	0.20	0.357			4.50	0.20	0.52	0	6.1
Calcium gluconate			0.16	0.091[c]			0.14	0.24							
Calcium lactate			0.23	0.13			0.12	0.36			4.5	0.20	0.52	0	6.7
Calcium lactobionate	0.08	0.022	0.08	0.043	0.08	0.085	0.07	0.126	0.07	0.197					
Calcium levulinate			0.27	0.16			0.25	0.43			3.58			0	7.2
Calcium pantothenate											5.50			0	7.4
Camphor			0.12[d]												
Capreomycin sulfate	0.04	0.011	0.04	0.020	0.04	0.042	0.04	0.063	0.04	0.106					
Carbachol				0.205[c]							2.82			0	5.9
Carbenicillin sodium	0.20	0.059	0.20	0.118	0.20	0.236	0.20	0.355			4.40	0.20	0.52	0	6.6
Carboxymethylcellulose sodium	0.03	0.007	0.03	0.017	0.145										
Cephaloridine	0.09	0.023	0.07	0.041	0.06	0.074	0.06	0.106	0.05						
Chloramine-T											4.10			100*	9.1
Chloramphenicol				0.06[d]											
Chloramphenicol sodium succinate	0.14	0.038	0.14	0.078	0.14	0.154	0.13	0.230	0.13	0.382	6.83	0.13	0.52	partial	6.1
Chlordiazepoxide HCl	0.24	0.068	0.22	0.125	0.19	0.220	0.18	0.315	0.17	0.487	5.50	0.16	0.52	66	2.7
Chlorobutanol (hydrated)			0.24	0.14											
Chloroprocaine HCl	0.20	0.054	0.20	0.108	0.18	0.210									
Chloroquine phosphate	0.14	0.039	0.14	0.082	0.14	0.162	0.14	0.242	0.13	0.379	7.15	0.13	0.52	0	4.3
Chloroquine sulfate	0.10	0.028	0.09	0.050	0.08	0.090	0.07	0.127	0.07	0.195					
Chlorpheniramine maleate	0.17	0.048	0.15	0.085	0.14	0.165	0.13	0.220	0.09	0.265					
Chlortetracycline HCl	0.10	0.030	0.10	0.061	0.10	0.121									
Chlortetracycline sulfate			0.13	0.08			0.10	0.17							
Citric acid			0.18	0.10			0.17	0.295	0.16	0.46	5.52	0.16	0.52	100*	1.8
Clindamycin phosphate	0.08	0.022	0.08	0.046	0.08	0.095	0.08	0.144	0.08	0.242	10.73	0.08	0.52	58*	6.8
Cocaine HCl			0.16	0.090[c]			0.15	0.26	0.14	0.40	6.33	0.14	0.52	47	4.4
Codeine phosphate			0.14	0.080[c]			0.13	0.23	0.13	0.38	7.29	0.12	0.52	0	4.4
Colistimethate sodium	0.15	0.045	0.15	0.085	0.15	0.170	0.15	0.253	0.14	0.411	6.73	0.13	0.52	0	7.6
Cupric sulfate			0.18	0.100[c]			0.15		0.14		6.85	0.13		trace*	3.9
Cyclizine HCl	0.20	0.060													
Cyclophosphamide	0.10	0.031	0.10	0.061	0.10	0.125									
Cytarabine	0.11	0.034	0.11	0.066	0.11	0.134	0.11	0.198	0.11	0.317	8.92	0.10	0.52	0	8.0
Deferoxamine mesylate	0.09	0.023	0.09	0.047	0.09	-0.093	0.09	0.142	0.09	0.241					
Demecarium bromide	0.14	0.038	0.12	0.069	0.10	0.108	0.08	0.139	0.07	0.192					
Dexamethasone sodium phosphate	0.18	0.050	0.17	0.095	0.16	0.180	0.15	0.260	0.14	0.410	6.75	0.13	0.52	0	8.9
Dextroamphetamine HCl	0.34	0.097	0.34	0.196	0.34	0.392					2.64	0.34	0.52		
Dextroamphetamine phosphate			0.25	0.14			0.25	0.44			3.62	0.25	0.52	0	4.7
Dextroamphetamine sulfate	0.24	0.069	0.23	0.134	0.22	0.259	0.22	0.380			4.16	0.22	0.52	0	5.9
Dextrose			0.16	0.091[c]			0.16	0.28	0.16	0.46	5.51	0.16	0.52	0	5.9
Dextrose (anhydrous)			0.18	0.101[c]			0.18	0.31			5.05	0.18	0.52	0	6.0
Diatrizoate sodium	0.10	0.025	0.09	0.049	0.09	0.098	0.09	0.149	0.09	0.248	10.55	0.09	0.52	0	7.9
Dibucaine HCl				0.074[c]											
Dicloxacillin sodium (1 H_2O)	0.10	0.030	0.10	0.061	0.10	0.122	0.10	0.182							
Diethanolamine	0.31	0.089	0.31	0.177	0.31	0.358					2.90	0.31	0.52	100	11.3
Dihydrostreptomycin sulfate			0.06	0.03			0.05	0.09	0.05	0.14	19.4	0.05	0.52	0	6.1
Dimethpyrindene maleate	0.13	0.039	0.12	0.070	0.11	0.120									
Dimethyl sulfoxide	0.42	0.122	0.42	0.245	0.42	0.480					2.16	0.42	0.52	100	7.6
Diperodon HCl	0.15	0.045	0.14	0.079	0.13	0.141									
Diphenhydramine HCl				0.161[c]							5.70			88*	5.5
Diphenidol HCl	0.16	0.045	0.16	0.09	0.16	0.180									
Doxapram HCl	0.12	0.035	0.12	0.070	0.12	0.140	0.12	0.210							
Doxycycline hyclate	0.12	0.035	0.12	0.072	0.12	0.134	0.11	0.186	0.09	0.264					
Dyphylline	0.10	0.025	0.10	0.052	0.09	0.104	0.09	0.155	0.08	0.245					
Echothiophate iodide	0.16	0.045	0.16	0.090	0.16	0.179									
Edetate disodium	0.24	0.070	0.23	0.132	0.22	0.248	0.21	0.360			4.44	0.20	0.52	0	4.7
Edetate trisodium monohydrate	0.29	0.079	0.29	0.158	0.28	0.316	0.27	0.472			3.31	0.27	0.52	0	8.0
Emetine HCl				0.058[c]				0.17		0.29					
Ephedrine HCl			0.30	0.165[c]			0.28				3.2	0.28		96	5.9
Ephedrine sulfate			0.23	0.13			0.20	0.35			4.54	0.20	0.52	0	5.7
Epinephrine bitartrate			0.18	0.104			0.16	0.28	0.16	0.462	5.7	0.16	0.52	100*	3.4
Epinephrine hydrochloride			0.29	0.16[b]			0.26				3.47	0.26			

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Iso-osmotic Concentration[a]				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Ergonovine maleate				0.089[c]											
Erythromycin lactobionate	0.08	0.020	0.07	0.040	0.07	0.078	0.07	0.115	0.06	0.187					
Ethyl alcohol											1.39			100	6.0
Ethylenediamine				0.253[c]							2.08			100*	11.4
Ethylmorphine HCl			0.16	0.088[c]			0.15	0.26	0.15	0.43	6.18	0.15	0.52	38	4.7
Eucatropine HCl				0.11[d]											
Ferric ammonium citrate (green)											6.83			0	5.2
Floxuridine	0.14	0.040	0.13	0.076	0.13	0.147	0.12	0.213	0.12	0.335	8.47	0.12	0.52	3*	4.5
Fluorescein sodium			0.31	0.181[c]			0.27	0.47			3.34	0.27	0.52	0	8.7
Fluphenazine 2-HCl	0.14	0.041	0.14	0.082	0.12	0.145	0.09	0.155							
d-Fructose											5.05			0*	5.9
Furtrethonium iodide	0.24	0.070	0.24	0.133	0.22	0.250	0.21	0.360			4.44	0.20	0.52	0	5.4
Galactose											4.92			0	5.9
Gentamicin sulfate	0.05	0.015	0.05	0.030	0.05	0.060	0.05	0.093	0.05	0.153					
D-Glucuronic acid											5.02			48*	1.6
Glycerin			0.203[c]								2.6			100	5.9
Glycopyrrolate	0.15	0.042	0.15	0.084	0.15	0.166	0.14	0.242	0.13	0.381	7.22	0.12	0.52	92*	4.0
Gold sodium thiomalate	0.10	0.032	0.10	0.061	0.10	0.111	0.09	0.159	0.09	0.250					
Hetacillin potassium	0.17	0.048	0.17	0.095	0.17	0.190	0.17	0.284	0.17	0.474	5.50	0.17	0.52	0	6.3
Hexafluorenium bromide	0.12	0.033	0.11	0.065											
Hexamethonium tartrate	0.16	0.045	0.16	0.089	0.16	0.181	0.16	0.271	0.16	0.456	5.68	0.16	0.52		
Hexamethylene sodium acetaminosalicylate	0.18	0.049	0.18	0.099	0.17	0.199	0.17	0.297	0.16	0.485	5.48	0.16	0.52	0*	4.0
Hexobarbital sodium				0.15[c]											
Hexylcaine HCl											4.30			100	4.8
Histamine 2HCl	0.40	0.115	0.40	0.233	0.40	0.466					2.24	0.40	0.52	79*	3.7
Histamine phosphate				0.149[c]							4.10	0	4.6		
Histidine HCl											3.45			40	3.9
Holocaine HCl			0.20	0.12											
Homatropine hydrobromide			0.17	0.097[c]			0.16	0.28	0.16	0.46	5.67	0.16	0.52	92	5.0
Homatropine methylbromide			0.19	0.11			0.15	0.26	0.13	0.38					
4-Homosulfanilamide HCl											3.69			0	4.9
Hyaluronidase	0.01	0.004	0.01	0.007	0.01	0.013	0.01	0.020	0.01	0.033					
Hydromorphone HCl											6.39			64	5.6
Hydroxyamphetamine HBr				0.15[d]							3.71			92	5.0
8-Hydroxyquinoline sulfate											9.75			59*	2.5
Hydroxystilbamidine isethionate	0.20	0.060	0.16	0.090	0.12	0.137	0.10	0.170	0.07	0.216					
Hyoscyamine hydrobromide											6.53			68	5.9
Imipramine HCl	0.20	0.058	0.20	0.110	0.13	0.143									
Indigotindisulfonate sodium	0.30	0.085	0.30	0.172											
Intracaine HCl											4.97			85	5.0
Iodophthalein sodium				0.07[c]							9.58			100	9.4
Isometheptene mucate	0.18	0.048	0.18	0.095	0.18	0.196	0.18	0.302			4.95	0.18	0.52	0	6.2
Isoproterenol sulfate	0.14	0.039	0.14	0.078	0.14	0.156	0.14	0.234	0.14	0.389	6.65	0.14	0.52	trace	4.5
Kanamycin sulfate	0.08	0.021	0.07	0.041	0.07	0.083	0.07	0.125	0.07	0.210					
Lactic acid				0.239[c]							2.30			100*	2.1
Lactose			0.07	0.040[c]			0.08		0.09		9.75	0.09		0*	5.8
Levallorphan tartrate	0.13	0.036	0.13	0.073	0.13	0.143	0.12	0.210	0.12	0.329	9.40	0.10	0.52	59*	6.9
Levorphanol tartrate	0.12	0.033	0.12	0.067	0.12	0.136	0.12	0.203							
Lidocaine HCl				0.13[c]							4.42			85	4.3
Lircomycin HCl	0.16	0.045	0.16	0.090	0.15	0.170	0.14	0.247	0.14	0.400	6.60	0.14	0.52	0	4.5
Lobeline HCl				0.09[b]											
Lyapolate sodium	0.10	0.025	0.09	0.051	0.09	0.103	0.09	0.157	0.09	0.263	9.96	0.09	0.52	0	6.5[†]
Magnesium chloride				0.45							2.02	0.45		0	6.3
Magnesium sulfate			0.17	0.094[c]			0.15	0.26	0.15	0.43	6.3	0.14	0.52	0	6.2
Magnesium sulfate, anhydrous	0.34	0.093	0.32	0.184	0.30	0.345	0.29	0.495			3.18	0.28	0.52	0	7.0
Mannitol				0.098[c]						5.07			0*	6.2	
Maphenide HCl		0.27	0.075	0.27	0.153	0.27	0.303	0.26	0.448		3.55	0.25	0.52		
Menadiol sodium diphosphate											4.36			0	8.2
Menadione sodium bisulfite											5.07			0	5.3
Menthol					0.12[d]										
Meperidine HCl					0.125[c]						4.80			98	5.0
Mepivacaine HCl	0.21	0.060	0.21	0.116	0.20	0.230	0.20	0.342			4.60	0.20	0.52	45	4.5
Merbromin				0.08[b]											
Mercuric cyanide			0.15				0.14		0.13						
Mersalyl				0.06[b]											
Mesoridazine besylate	0.10	0.024	0.07	0.040	0.05	0.058	0.04	0.071	0.03	0.087					
Metaraminol bitartrate	0.20	0.060	0.20	0.112	0.19	0.210	0.18	0.308	0.17	0.505	5.17	0.17	0.52	59	3.8
Methacholine chloride				0.184[c]							3.21			0	4.5
Methadone HCl				0.101[c]							8.59			100*	5.0

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Iso-osmotic Concentration[a]				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Methamphetamine HCl				0.213[c]							2.75			97	5.9
Methdilazine HCl	0.12	0.035	0.10	0.056	0.08	0.080	0.06	0.093	0.04	0.112					
Methenamine			0.23				0.24				3.68	0.25		100	8.4
Methiodal sodium	0.24	0.068	0.24	0.136	0.24	0.274	0.24	0.410			3.81	0.24	0.52	0	5.9
Methitural sodium	0.26	0.074	0.25	0.142	0.24	0.275	0.23	0.407			3.85	0.23	0.52	78	9.8
Methocarbamol	0.10	0.030	0.10	0.060											
Methotrimeprazine HCl	0.12	0.034	0.10	0.060	0.07	0.077	0.06	0.094	0.04	0.125					
Methoxyphenamine HCl	0.26	0.075	0.26	0.150	0.26	0.300	0.26	0.450			3.47	0.26	0.52	96	5.4
p-Methylaminoethanolphenol tartrate	0.18	0.048	0.17	0.095	0.16	0.190	0.16	0.282	0.16	0.453	5.83	0.16	0.52	0	6.2
Methyldopate HCl	0.21	0.063	0.21	0.122	0.21	0.244	0.21	0.365			4.28	0.21	0.52	partial	3.0
Methylergonovine maleate	0.10	0.028	0.10	0.056											
N-Methylglucamine	0.20	0.057	0.20	0.111	0.18	0.214	0.18	0.315	0.18	0.517	5.02	0.18	0.52	4	11.3
Methylphenidate HCl	0.22	0.065	0.22	0.127	0.22	0.258	0.22	0.388			4.07	0.22	0.52	66	4.3
Methylprednisolone Na succinate	0.10	0.025	0.09	0.051	0.09	0.102	0.08	0.143	0.07	0.200					
Minocycline HCl	0.10	0.030	0.10	0.058	0.09	0.107	0.08	0.146							
Monoethanolamine	0.53	0.154	0.53	0.306							1.70	0.53	0.52	100	11.4
Morphine HCl			0.15	0.086[c]			0.14								
Morphine sulfate			0.14	0.079[c]			0.11	0.19	0.09	0.26					
Nalorphine HCl	0.24	0.070	0.21	0.121	0.18	0.210	0.17	0.288	0.15	0.434	6.36	0.14	0.52	63	4.1
Naloxone HCl	0.14	0.042	0.14	0.083	0.14	0.158	0.13	0.230	0.13	0.367	8.07	0.11	0.52	35	5.2
Naphazoline HCl			0.27	0.14[d]			0.24				3.99	0.22		100	5.3
Neoarsphenamine											2.32		17	7.8	
Neomycin sulfate			0.11	0.063[c]			0.09	0.16	0.08	0.232					
Neostigmine bromide			0.22	0.127[c]			0.19				4.98			0	4.6
Neostigmine methylsulfate			0.20	0.115[c]			0.18		0.17		5.22	0.17			
Nicotinamide			0.26	0.148[c]			0.21	0.36			4.49	0.20	0.52	100	7.0
Nicotinic acid			0.25	0.144[c]											
Nikethamide				0.100[c]							5.94			100	6.9
Novobiocin sodium	0.12	0.033	0.10	0.057	0.07	0.073									
Oleandomycin phosphate	0.08	0.017	0.08	0.038	0.08	0.084	0.08	0.129	0.08	0.255	10.82	0.08	0.52	0	5.0
Orphenadrine citrate	0.13	0.037	0.13	0.074	0.13	0.144	0.12	0.204	0.10	0.285					
Oxophenarsine HCl											.67			trace*	2.3
Oxymetazoline HCl	0.22	0.063	0.22	0.124	0.20	0.232	0.19	0.335			4.92	0.18	0.52	86	5.7
Oxyquinoline sulfate	0.24	0.068	0.21	0.113	0.16	0.182	0.14	0.236	0.11	0.315					
d-Pantothenyl alcohol	0.20	0.053	0.18	0.100	0.17	0.193	0.17	0.283	0.16	0.468	5.60	0.16	0.52	92	6.8
Papaverine HCl			0.10	0.061[c]											
Paraldehyde	0.25	0.071	0.25	0.142	0.25	0.288	0.25	0.430			3.65	0.25	0.52	97	5.3
Pargyline HCl	0.30	0.083	0.29	0.165	0.29	0.327	0.28	0.491			3.18	0.28	0.52	91	3.8
Penicillin G, potassium			0.18	0.102[c]			0.17	0.29	0.16	0.46	5.48	0.16	0.52	0	6.2
Penicillin G, procaine				0.06[d]											
Penicillin G, sodium			0.18	0.100[c]			0.16	0.28	0.16	0.46	5.90			18	5.2
Pentazocine lactate	0.15	0.042	0.15	0.085	0.15	0.169	0.15	0.253	0.15	0.420					
Pentobarbital sodium				0.145[c]							4.07			0	9.9
Pentolinium tartrate											5.95			55*	3.4
Phenacaine HCl				0.09[d]											
Pheniramine maleate				0.09[d]											
Phenobarbital sodium			0.24	0.135[c]			0.23	0.40			3.95	0.23	0.52	0	9.2
Phenol	0.35	0.20									2.8	0.32	0.52	0*	5.6
Phentolamine mesylate	0.18	0.052	0.17	0.096	0.16	0.173	0.14	0.244	0.13	0.364	8.23	0.11	0.52	83	3.5
Phenylephrine HCl			0.32	0.184[c]			0.30				3.0	0.30		0	4.5
Phenylephrine tartrate												5.90		58*	5.4
Phenylethyl alcohol	0.25	0.070	0.25	0.141	0.25	0.283									
Phenylpropanolamine HCl			0.38	0.219[c]							2.6	0.35		95	5.3
Physostigmine salicylate			0.16	0.090[c]											
Physostigmine sulfate				0.074[c]											
Pilocarpine HCl			0.24	0.138[c]			0.22	0.38			4.08	0.22	0.52	89	4.0
Pilocarpine nitrate			0.23	0.132[c]			0.20	0.35			4.84	0.20	0.52	88	3.9
Piperocaine HCl				0.12[d]							5.22			65	5.7
Polyethylene glycol 300	0.12	0.034	0.12	0.069	0.12	0.141	0.12	0.216	0.13	0.378	6.73	0.13	0.52	53	3.8
Polyethylene glycol 400	0.08	0.022	0.08	0.047	0.09	0.098	0.09	0.153	0.09	0.272	8.50	0.11	0.52	0	4.4
Polyethylene glycol 1500	0.06	0.015	0.06	0.036	0.07	0.078	0.07	0.120	0.07	0.215	10.00	0.09	0.52	4	4.1
Polyethylene glycol 1540	0.02	0.005	0.02	0.012	0.02	0.028	0.03	0.047	0.03	0.094					
Polyethylene glycol 4000	0.02	0.004	0.02	0.008	0.02	0.020	0.02	0.033	0.02	0.067					
Polymyxin B sulfate			0.09	0.052			0.06	0.10	0.04	0.12					
Polysorbate 80	0.02	0.005	0.02	0.010	0.02	0.020	0.02	0.032	0.02	0.055					
Polyvinyl alcohol (99% hydrol)	0.02	0.004	0.02	0.008	0.02	0.020	0.02	0.035	0.03	0.075					
Polyvinylpyrrolidone	0.01	0.003	0.01	0.006	0.01	0.010	0.01	0.017	0.01	0.035					
Potassium acetate	0.59	0.172	0.59	0.342							1.53	0.59	0.52	0	7.6
Potassium chlorate											1.88			0	6.9
Potassium chloride			0.76	0.439[c]							1.19	0.76	0.52	0	5.9

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Iso-osmotic Concentration[a]				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Potassium iodide			0.34	0.196[c]							2.59	0.34	0.52	0	7.0
Potassium nitrate			0.56	0.324[c]							1.62	0.56	0	5.9	
Potassium phosphate			0.46	0.27							2.08	0.43	0.52	0	8.4
Potassium phosphate, monobasic			0.44	0.25							2.18	0.41	0.52	0	4.4
Potassium sulfate			0.44								2.11	0.43		0	6.6
Pralidoxime chloride	0.32	0.092	0.32	0.183	0.32	0.364					2.87	0.32	0.52	0	4.6
Prilocaine HCl	0.22	0.062	0.22	0.125	0.22	0.250	0.22	0.375			4.18	0.22	0.52	45	4.6
Procainamide HCl			0.22	0.13			0.19	0.33	0.17	0.49					
Procaine HCl			0.21	0.122[c]			0.19	0.33	0.18		5.05	0.18	0.52	91	5.6
Prochlorperazine edisylate	0.08	0.020	0.06	0.033	0.05	0.048	0.03	0.056	0.02	0.065					
Promazine HCl	0.18	0.050	0.13	0.077	0.09	0.102	0.07	0.112	0.05	0.137					
Proparacaine HCl	0.16	0.044	0.15	0.086	0.15	0.169	0.14	0.247	0.13	0.380	7.46	0.12	0.52		
Propiomazine HCl	0.18	0.050	0.15	0.084	0.12	0.133	0.10	0.165	0.08	0.215					
Propoxycaine HCl											6.40			16	5.3
Propylene glycol											2.00			100	5.5
Pyrathiazine HCl	0.22	0.065	0.17	0.095	0.11	0.123	0.08	0.140	0.06	0.170					
Pyridostigmine bromide	0.22	0.062	0.22	0.125	0.22	0.250	0.22	0.377			4.13	0.22	0.52	0	7.2
Pyridoxine HCl											3.05			31*	3.2
Quinacrine methanesulfonate				0.06[c]											
Quinine bisulfate			0.09	0.05			0.09	0.16							
Quinine dihydrochloride			0.23	0.130[c]			0.19	0.33	0.18		5.07	0.18	0.52	trace*	2.5
Quinine hydrochloride			0.14	0.077[c]			0.11	0.19							
Quinine and urea HCl			0.23	0.13			0.21	0.36			4.5	0.20	0.52	64	2.9
Resorcinol		0.161[c]									3.30			96	5.0
Rolitetracycline	0.11	0.032	0.11	0.064	0.10	0.113	0.09	0.158	0.07	0.204					
Rose Bengal	0.08	0.020	0.07	0.040	0.07	0.083	0.07	0.124	0.07	0.198	14.9	0.06	0.52		
Rose Bengal B	0.08	0.022	0.08	0.044	0.08	0.087	0.08	0.131	0.08	0.218					
Scopolamine HBr			0.12	0.07			0.12	0.21	0.12	0.35	7.85	0.11	0.52	8	4.8
Scopolamine methylnitrate			0.16				0.14		0.13	6.95	0.13	0	6.0		
Secobarbital sodium			0.24	0.14			0.23	0.40			3.9	0.23	0.52	trace	9.8
Silver nitrate			0.33	0.190[c]							2.74	0.33	0.52	0*	5.0
Silver protein, mild			0.17	0.10			0.17	0.29	0.16	0.46	5.51	0.16	0.52	0	9.0
Silver protein, strong				0.06[d]											
Sodium acetate			0.46	0.267							2.0	0.45	0.52		
Sodium acetazolamide	0.24	0.068	0.23	0.135	0.23	0.271	0.23	0.406			3.85	0.23	0.52		
Sodium aminosalicylate				0.170[c]							3.27			0	7.3
Sodium ampicillin	0.16	0.045	0.16	0.090	0.16	0.181	0.16	0.072	0.16	0.451	5.78	0.16	0.52	0	8.5
Sodium ascorbate											3.00			0	6.9
Sodium benzoate			0.40	0.230[c]							2.25	0.40	0.52	0	7.5
Sodium bicarbonate			0.65	0.375							1.39	0.65	0.52	0	8.3
Sodium biphosphate (H_2O)			0.40	0.23							2.45	0.37	0.52	0	4.1
Sodium biphosphate(2 H_2O)			0.36								2.77	0.32		0	4.0
Sodium bismuth thioglycollate	0.20	0.055	0.19	0.107	0.18	0.208	0.18	0.303	0.17	0.493	5.29			0	8.3
Sodium bisulfite			0.61	0.35							1.5	0.61	0.52	0*	3.0
Sodium borate			0.42	0.241[c]							2.6	0.35	0.52	0	9.2
Sodium bromide											1.60			0	6.1
Sodium cacodylate			0.32				0.28				3.3	0.27		0	8.0
Sodium carbonate, monohydrated			0.60	0.346							1.56	0.58	0.52	100	11.1
Sodium cephalothin	0.18	0.050	0.17	0.095	0.16	0.179	0.15	0.259	0.14	0.400	6.80	0.13	0.52	partial	8.5
Sodium chloride			1.00	0.576[c]			1.00	1.73	1.00	2.88	0.9	1.00	0.52	0	6.7
Sodium citrate			0.31	0.178[c]			0.30	0.52			3.02	0.30		0	7.8
Sodium colistimethate	0.16	0.045	0.15	0.087	0.14	0.161	0.14	0.235	0.13	0.383	6.85	0.13	0.52	0	8.4
Sodium hypophosphite											1.60			0	7.3
Sodium iodide			0.39	0.222[c]							2.37	0.38	0.52	0	6.9
Sodium iodohippurate											5.92			0	7.3
Sodium lactate											1.72			0	6.5
Sodium lauryl sulfate	0.10	0.029	0.08	0.046	0.07	0.068	0.05	0.086							
Sodium mercaptomerin											5.30			0	8.4
Sodium metabisulfite			0.67	0.386[c]							1.38	0.65	0.52	5*	4.5
Sodium methicillin	0.18	0.050	0.18	0.099	0.17	0.192	0.16	0.281	0.15	0.445	6.00	0.15	0.52	0	5.8
Sodium nafcillin	0.14	0.039	0.14	0.078	0.14	0.158	0.13	0.219	0.10	0.285					
Sodium nitrate			0.68								1.36	0.66		0	6.0
Sodium nitrite			0.84	0.480[c]							1.08	0.83		0*	8.5
Sodium oxacillin	0.18	0.050	0.17	0.095	0.16	0.177	0.15	0.257	0.14	0.408	6.64	0.14	0.52	0	6.0
Sodium phenylbutazone	0.19	0.054	0.18	0.104	0.17	0.202	0.17	0.298	0.17	0.488	5.34	0.17	0.52		
Sodium phosphate			0.29	0.168			0.27	0.47			3.33	0.27	0.52	0	9.2
Sodium phosphate, dibasic (2 H_2O)			0.42	0.24							2.23	0.40	0.52	0	9.2
Sodium phosphate, dibasic (12 H_2O)			0.22				0.21				4.45	0.20		0	9.2

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Iso-osmotic Concentration[a]				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Sodium propionate			0.61	0.35							1.47	0.61	0.52	0	7.8
Sodium salicylate			0.36	0.210[c]							2.53	0.36	0.52	0	6.7
Sodium succinate	0.32	0.092	0.32	0.184	0.31	0.361					2.90	0.31	0.52	0	8.5
Sodium sulfate, anhydrous			0.58	0.34							1.61	0.56	0.52	0	6.2
Sodium sulfite, exsiccated			0.65	0.38							1.45			0	9.6
Sodium sulfobromophthalein	0.07	0.019	0.06	0.034	0.05	0.060	0.05	0.084	0.04	0.123					
Sodium tartrate	0.33	0.098	0.33	0.193	0.33	0.385					2.72	0.33	0.52	0	7.3
Sodium thiosulfate			0.31	0.181[c]							2.98	0.30	0.52	0	7.4
Sodium warfarin	0.18	0.049	0.17	0.095	0.16	0.181	0.15	0.264	0.15	0.430	6.10	0.15	0.52	0	8.1
Sorbitol (½ H_2O)											5.48			0	5.9
Sparteine sulfate	0.10	0.030	0.10	0.056	0.10	0.111	0.10	0.167	0.10	0.277	9.46	0.10	0.52	19*	3.5
Spectinomycin HCl	0.16	0.045	0.16	0.092	0.16	0.185	0.16	0.280	0.16	0.460	5.66	0.16	0.52	3	4.4
Streptomycin HCl			0.17	0.10[c]			0.16	0.16							
Streptomycin sulfate			0.07	0.036[c]			0.06	0.10	0.06	0.17					
Sucrose			0.08	0.047[c]			0.09	0.16	0.09	0.26	9.25	0.10	0.52	0	6.4
Sulfacetamide sodium			0.23	0.132[c]			0.23	0.40			3.85	0.23	0.52	0	8.7
Sulfadiazine sodium			0.24	0.14			0.24	0.38			4.24	0.21	0.52	0	9.5
Sulfamerazine sodium			0.23	0.13			0.21	0.36			4.53	0.20	0.52	0	9.8
Sulfapyridine sodium			0.23	0.13			0.21	0.36			4.55	0.20	0.52	5	10.4
Sulfathiazole sodium			0.22	0.13			0.20	0.35			4.82	0.19	0.52	0	9.9
Tartaric acid				0.143[c]							3.90			75*	1.7
Tetracaine HCl			0.18	0.109[c]			0.15	0.26	0.12	0.35					
Tetracycline HCl			0.14	0.081[c]		0.10									
Tetrahydrozoline HCl											4.10			60*	6.7
Theophylline				0.02[b]											
Theophylline sodium glycinate											2.94			0	8.9
Thiamine HCl				0.139[c]							4.24			87*	3.0
Thiethylperazine maleate	0.10	0.030	0.09	0.050	0.08	0.089	0.07	0.119	0.05	0.153					
Thiopental sodium				0.155[c]							3.50			74	10.3
Thiopropazate diHCl	0.20	0.053	0.16	0.090	0.12	0.137	0.10	0.170	0.08	0.222					
Thioridazine HCl	0.06	0.015	0.05	0.025	0.04	0.042	0.03	0.055	0.03	0.075					
Thiotepa	0.16	0.045	0.16	0.090	0.16	0.182	0.16	0.278	0.16	0.460	5.67	0.16	0.52	10*	8.2
Tridihexethyl chloride	0.16	0.047	0.16	0.096	0.16	0.191	0.16	0.280	0.16	0.463	5.62	0.16	0.52	97	5.4
Triethanolamine	0.20	0.058	0.21	0.121	0.22	0.252	0.22	0.383			4.05	0.22	0.52	100	10.7
Trifluoperazine 2HCl	0.18	0.052	0.18	0.100	0.13	0.144									
Triflupromazine HCl	0.10	0.031	0.09	0.051	0.05	0.061	0.04	0.073	0.03	0.092					
Trimeprazine tartrate	0.10	0.023	0.06	0.035	0.04	0.045	0.03	0.052	0.02	0.061					
Trimethadione	0.23	0.069	0.23	0.133	0.22	0.257	0.22	0.378			4.22	0.21	0.52	100	6.0
Trimethobenzamide HCl	0.12	0.033	0.10	0.062	0.10	0.108	0.09	0.153	0.08	0.232					
Tripelennamine HCl				0.13[d]							5.50			100	6.3
Tromethamine	0.26	0.074	0.26	0.150	0.26	0.300	0.26	0.450			3.45	0.26	0.52	0	10.2
Tropicamide	0.10	0.030	0.09	0.050											
Trypan blue	0.26	0.075	0.26	0.150											
Tryparsamide				0.11[c]											
Tubocurarine chloride				0.076[c]											
Urea			0.59	0.34							1.63	0.55	0.52	100	6.6
Urethan				0.18[b]							2.93			100	6.3
Uridine	0.12	0.035	0.12	0.069	0.12	0.138	0.12	0.208	0.12	0.333	8.18	0.11	0.52	0*	6.1
Valethamate bromide	0.16	0.044	0.15	0.085	0.15	0.168	0.14	0.238	0.11	0.324					
Vancomycin sulfate	0.06	0.015	0.05	0.028	0.04	0.049	0.04	0.066	0.04	0.098					
Viomycin sulfate			0.08	0.05			0.07	0.12	0.07	0.20					
Xylometazoline HCl	0.22	0.065	0.21	0.121	0.20	0.232	0.20	0.342			4.68	0.19	0.52	88	5.0
Zinc phenolsulfonate											5.40			0*	5.4
Zinc sulfate			0.15	0.086[c]			0.13	0.23	0.12	0.35	7.65	0.12	0.52		

[a]The unmarked values were taken from Hammarlund *et al*[19–22] and Sapp *et al.*[23]
[b]Adapted from Lund *et al.*[17]
[c]Adapted from *British Pharmaceutical Codex.*[24]
[d]Obtained from several sources.
[e]*E,* sodium chloride equivalents; *D,* freezing-point depression, °C; *H,* hemolysis, %, at the concentration that is iso-osmotic with 0.9% NaCl, based on freezing-point determination or equivalent test; pH, approximate pH of solution studied for hemolytic action; *, change in appearance of erythrocytes and/or solution[23–25]; †, pH determined after addition of blood.
Note: See also Budavari S, ed, *Merck Index,* 11th ed, Rahway, NJ: Merck, 1988: pp MISC 79–103.

Appendix B—Isotonic Solution *V*—Values[26, a,b]

Drug (0.3 g)	Water Needed for Isotonicity (mL)	Drug (0.3 g)	Water needed for isotonicity, mL	Drug (0.3 g)	Water needed for isotonicity, mL
Alcohol	21.7	Epinephrine hydrochloride	9.7	Silver nitrate	11.0
Ammonium chloride	37.3	Ethylmorphine hydrochloride	5.3	Silver protein, mild	5.7
Amobarbital sodium	8.3	Fluorescein sodium	10.3	Sodium acetate	15.3
Amphetamine phosphate	11.3	Glycerin	11.7	Sodium bicarbonate	21.7
Amphetamine sulfate	7.3	Holocaine hydrochloride	6.7	Sodium biphosphate,	15.3
Antipyrine	5.7	Homatropine hydrobromide	5.7	anhydrous	
Apomorphine hydrochloride	4.7	Homatropine methylbromide	6.3	Sodium biphosphate	13.3
Ascorbic acid	6.0	Hyoscyamine sulfate	4.7	Sodium bisulfite	20.3
Atropine methylbromide	4.7	Neomycin sulfate	3.7	Sodium borate	14.0
Atropine sulfate	4.3	Oxytetracycline hydrochloride	4.3	Sodium iodide	13.0
Bacitracin	1.7	Penicillin G, potassium	6.0	Sodium metabisulfite	22.3
Barbital sodium	10.0	Penicillin G, sodium	6.0	Sodium nitrate	22.7
Bismuth potassium tartrate	3.0	Pentobarbital sodium	8.3	Sodium phosphate	9.7
Boric acid	16.7	Phenobarbital sodium	8.0	Sodium propionate	20.3
Butacaine sulfate	6.7	Physostigmine salicylate	5.3	Sodium sulfite, exsiccated	21.7
Caffeine and sodium benzoate	8.7	Pilocarpine hydrochloride	8.0	Sodium thiosulfate	10.3
Calcium chloride	17.0	Pilocarpine nitrate	7.7	Streptomycin sulfate	2.3
Calcium chloride (6 H_2O)	11.7	Piperocaine hydrochloride	7.0	Sulfacetamide sodium	7.7
Chlorobutanol (hydrated)	8.0	Polymyxin B sulfate	3.0	Sulfadiazine sodium	8.0
Chlortetracycline sulfate	4.3	Potassium chloride	25.3	Sulfamerazine sodium	7.7
Cocaine hydrochloride	5.3	Potassium nitrate	18.7	Sulfapyridine sodium	7.7
Cupric sulfate	6.0	Potassium phosphate,	14.7	Sulfathiazole sodium	7.3
Dextrose, anhydrous	6.0	monobasic		Tetracaine hydrochloride	6.0
Dibucaine hydrochloride	4.3	Procainamide hydrochloride	7.3	Tetracycline hydrochloride	4.7
Dihydrostreptomycin sulfate	2.0	Procaine hydrochloride	7.0	Viomycin sulfate	2.7
Ephedrine hydrochloride	10.0	Scopolamine hydrobromide	4.0	Zinc chloride	20.3
Ephedrine sulfate	7.7	Scopolamine methylnitrate	5.3	Zinc sulfate	5.0
Epinephrine bitartrate	6.0	Secobarbital sodium	8.0		

[a] This table of *Isotonic Solution Values* shows volumes in mL of water to be added to 300 mg of the specified drug in sterile water to produce an isotonic solution. The addition of an isotonic vehicle (commonly referred to as diluting solution) to make 30 mL yields a 1% solution. Solutions prepared as directed above are iso-osmotic with 0.9% sodium chloride solution but may not be isotonic with blood (see Appendix A for hemolysis data).

[b] The *V* values for drugs that do not appear in Appendix B but are listed in Appendix A can be calculated from the sodium chloride equivalent for 1% drug. *Example*—Calculate the *V* value for anileridine HCl (Appendix A defines $E = 0.19$).

$$\frac{100 \text{ mL Soln}}{0.9 \text{ NaCl}} \times \frac{0.19 \text{ g naCl}}{1 \text{ g drug}} \times 0.3 \text{ g drug} = 6.33 \text{ mL Soln}$$

for dilute solution

$$6.33 \text{ mL soln} \cong 6.33 \text{ mL water} \therefore V = 6.33 \text{ mL water/0.3 g drug.}$$

CHAPTER **20**

Interfacial Phenomena

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Very often it is desirable or necessary in the development of pharmaceutical dosage forms to produce multiphasic dispersions by mixing together two or more ingredients that are not mutually miscible and capable of forming homogeneous solutions. Examples of such dispersions include

Suspensions (solid in liquid)
Emulsions (liquid in liquid)
Foams (vapor in liquids)

Because these systems are not homogeneous and thermodynamically stable, over time they will show some tendency to separate on standing to produce the minimum possible surface area of contact between phases. Thus, suspended particles agglomerate and sediment, emulsified droplets cream and coalesce, and the bubbles dispersed in foams collapse to produce unstable and nonuniform dosage forms. One way to prevent or slow down this natural tendency for further phase separation is to add materials that can accumulate at the interface to provide some type of energy barrier to aggregation and coalescence. Such materials are said to exhibit *surface activity* or to act as *surface-active agents.*

In this chapter the fundamental physical chemical properties of molecules situated at interfaces will be discussed so that the reader can gain a better understanding of how problems involving interfaces can be resolved in designing pharmaceutical dosage forms by the use of surface-active agents.

INTERFACIAL FORCES AND ENERGETICS

In the bulk portion of each phase, molecules are attracted to each other equally in all directions, such that no resultant forces are acting on any one molecule. The strength of these forces determines whether a substance exists as a vapor, liquid, or solid at a particular temperature and pressure.

At the boundary between phases, however, molecules are acted upon unequally because they are in contact with other molecules exhibiting different forces of attraction. For example, the primary intermolecular forces in water are due to hydrogen bonds, whereas those responsible for intermolecular bonding in hydrocarbon liquids, such as mineral oil, are due to London dispersion forces.

Thus, molecules situated at the interface experience interaction forces dissimilar to those experienced in each bulk phase. In liquid systems such unbalanced forces can be satisfied by spontaneous movement of molecules from the interface into the bulk phase. This leaves fewer molecules per unit area at the interface (greater intermolecular distance) and reduces the actual contact area between dissimilar molecules.

Any attempt to reverse this process by increasing the area of contact between phases—that is, bringing more molecules into the interface—causes the interface to resist expansion and behave as though it is under a tension everywhere in a tangential direction. The force of this tension per unit length of interface generally is called the *interfacial tension,* except when dealing with the air–liquid interface, where the terms *surface* and *surface tension* are used.

To illustrate the presence of a tension in the interface, consider an experiment where a circular metal frame, with a looped piece of thread loosely tied to it, is dipped into a liquid. When the frame is removed and exposed to the air, a film of liquid will be stretched entirely across the circular frame, as when one uses such a frame to blow soap bubbles. Under these conditions (Fig 20-1*A*), the thread will remain collapsed. If a heated needle is used to puncture and remove the liquid film from within the loop (Fig 20-1*B*), the loop will stretch spontaneously into a circular shape.

The result of this experiment demonstrates the spontaneous reduction of interfacial contact between air and the liquid remaining; indeed, it illustrates that a tension causing the loop to remain extended exists parallel to the interface. The circular shape of the loop indicates that the tension in the plane of the interface exists at right angles or normal to every part of the looped thread. The total force on the entire loop divided by the circumference of the circle, therefore, represents the tension per unit distance of surface, or the surface tension.

Just as work is required to extend a spring under tension, work should be required to reverse the process seen in Figure 20-1*A* and *B*, thus bringing more molecules to the interface. This may be seen quantitatively by considering an experiment where tension and work may be measured directly. Assume that we have a rectangular wire with one movable side (Fig 20-2). Assume further that by dipping this wire into a liquid, a film of liquid will form within the frame when it is removed and exposed to the air. As seen earlier in Figure 20-1, when it comes in contact with air, the liquid surface will tend to contract with a force, F, as molecules leave the surface for the bulk. To keep the movable side in equilibrium, an equal force must be applied to oppose this tension in the surface. The surface tension, γ, of the liquid may be defined as $F/2l$, where $2l$ is the distance of surface over which F is operating. The factor 2 arises out of considering two surfaces, top and bottom. Upon expansion of the surface by a very small distance, Δx, the work done (W) is

$$W = F\Delta x \quad (1)$$

and therefore,

$$W = \gamma 2l\Delta x \quad (2)$$

Since

$$\Delta A = 2l\Delta x \quad (3)$$

where ΔA is the change in area due to the expansion of the surface, it may be concluded that

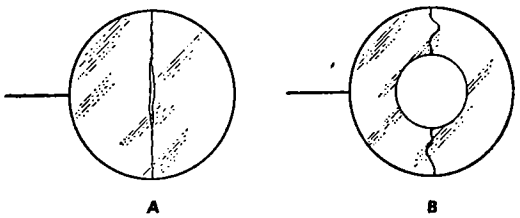

Figure 20-1. A circular wire frame with a loop of thread loosely tied to it: (*A*) a liquid film on the wire frame with a loop in it; (*B*) the film inside the loop is broken.[1]

$$W = \gamma \Delta A \qquad (4)$$

Thus, the work required to create a unit area of surface, known as the *surface free energy/unit area,* is equivalent to the surface tension of a liquid system—the greater the area of interfacial contact between phases, the greater the free-energy increase for the total system. Because a prime requisite for equilibrium is that the free energy of a system be at a minimum, it is not surprising to observe that phases in contact tend to reduce area of contact spontaneously.

Liquids, being mobile, may assume spherical shapes (smallest interfacial area for a given volume), as when ejected from an orifice into air or when dispersed into another immiscible liquid. If a large number of drops are formed, further reduction in area can occur by having the drops coalesce, as when a foam collapses or when the liquid phases making up an emulsion separate.

In the centigrade-gram-second (cgs) system, surface tension is expressed in units of dynes per centimeter (dyne/cm), while surface free energy is expressed in erg/cm^2. As an erg is a dyne-cm, both sets of units are equivalent. In the SI (international units) system, surface tension is expressed in mN/m and surface free energy in mJ/m^2.

Values for the surface tension of a variety of liquids are given in Table 20–1, and interfacial tension values for various liquids against water are given in Table 20-2. Other combinations of immiscible phases could be given, but most heterogeneous systems encountered in pharmacy usually contain water. Values for these tensions are expressed for a particular temperature. Because an increased temperature increases the thermal energy of molecules, the work required to bring molecules to the interface should be less, and thus the surface and interfacial tension will be reduced. For example, the surface tension of water is 76.5 dynes/cm at 0° and 63.5 dynes/cm at 75°.

As would be expected from the discussion so far, the relative values for surface tension should reflect the nature of intermolecular forces present, hence the relatively large values for mercury (metallic bonds) and water (hydrogen bonds), and the lower values for benzene, chloroform, carbon tetrachloride, and the *n*-alkanes.

Benzene, with π electrons, exhibits a higher surface tension than the alkanes of comparable molecular weight, but increasing the molecular weight of the alkanes (and hence intermolecular attraction) increases their surface tension closer to that of benzene. The lower values for the more nonpolar substances, perfluoroheptane and liquid nitrogen, demonstrate this point even more strongly.

Table 20-1. Surface Tension of Various Liquids at 20°

SUBSTANCE	SURFACE TENSION (dyne/cm)
Mercury	476
Water	72.8
Glycerin	63.4
Oleic acid	32.5
Benzene	28.9
Chloroform	27.1
Carbon tetrachloride	26.8
1-Octanol	26.5
Hexadecane	27.4
Dodecane	25.4
Decane	23.9
Octane	21.8
Heptane	19.7
Hexane	18.0
Perfluoroheptane	11.0
Nitrogen (at 75 K)	9.4

Values of interfacial tension should reflect the differences in chemical structure of the two phases involved—the greater the tendency to interact, the less the interfacial tension. The 20-dyne/cm difference between air–water tension and that at the octane–water interface reflects the small but significant interaction between octane molecules and water molecules at the interface. This is seen also in Table 20-2 by comparing the values for octane and octanol, oleic acid and the alkanes, or chloroform and carbon tetrachloride. In each case the presence of chemical groups capable of hydrogen bonding with water markedly reduces the interfacial tension, presumably by satisfying the unbalanced forces at the interface. These observations strongly suggest that molecules at an interface arrange themselves or orient so as to minimize differences between bulk phases.

That this phenomenon occurs even at the air–liquid interface is seen when one notes the relatively low surface-tension values of very different chemical structures such as the *n*-alkanes, octanol, oleic acid, benzene, and chloroform. Presumably, in each case the similar nonpolar groups are oriented toward the air with any polar groups oriented away toward the bulk phase. This tendency for molecules to orient at an interface is a basic factor in interfacial phenomena and will be discussed more fully in succeeding sections.

Solid substances such as metals, metal oxides, silicates, and salts, all containing polar groups exposed at their surface, may be classified as *high-energy solids,* whereas nonpolar solids such as carbon, sulfur, glyceryl tristearate, polyethylene, and polytetrafluoroethylene (Teflon) may be classified as *low-energy solids.* It is of interest to measure the surface free energy of solids; however, the lack of mobility of molecules at the surface

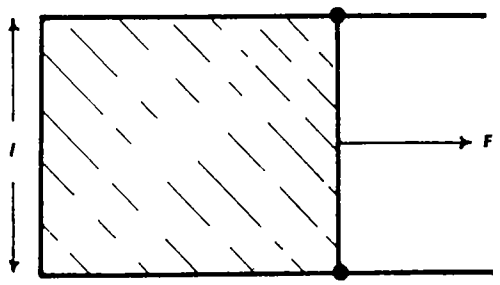

Figure 20-2. A movable wire frame containing a film of liquid being expanded with a force, *F*.

Table 20-2. Interfacial Tension of Various Liquids Against Water at 20°

SUBSTANCE	INTERFACIAL TENSION (dyne/cm)
Decane	52.3
Octane	51.7
Hexane	50.8
Carbon tetrachloride	45.0
Chloroform	32.8
Benzene	35.0
Mercury	428
Oleic acid	15.6
1-Octanol	8.51

of solids prevents the observation and direct measurement of a surface tension. It is possible to measure the work required to create new solid surface by cleaving a crystal and measuring the work involved. However, this work not only represents free energy due to exposed groups but also takes into account the mechanical energy associated with crystal fracture (ie, plastic and elastic deformation and strain energies due to crystal structure and imperfections in that structure).

Also contributing to the complexity of a solid surface is the heterogeneous behavior as a result of the exposure of different crystal faces, each having a different surface free energy/unit area. For example, adipic acid, $HOOC(CH_2)_4COOH$, crystallizes from water as thin hexagonal plates with three different faces, as shown in Figure 20-3. Each unit cell of such a crystal contains adipic acid molecules oriented such that the hexagonal planes (faces) contain exposed carboxyl groups, while the sides and edges (A and B faces) represent the side view of the carboxyl and alkyl groups and thus are quite nonpolar. Indeed, interactions involving these different faces reflect the differing surface free energies.[2]

Other complexities of solid surfaces include roughness and porosity.[3] Even in the absence of chemical contamination, such as that occurring during recystallization, surface energy changes in a solid can be induced by unit operations such as milling, resulting in an altered pattern of drug dissolution.[4,5] In view of all these potential complications that are difficult to quantify, surface free energy values for solids, when reported, should be regarded as average values, often dependent on the method used and not necessarily the same for other samples of the same substance.

Table 20-3 lists some average values of γ_{sv} for a variety of solids, ranging in polarity from Teflon to copper, obtained by various indirect techniques.

Table 20-3. Values of γ_{sv} for Solids of Varying Polarity

SOLID	γ_{SV} (dyne/cm)
Teflon	19.0
Paraffin	25.5
Polyethylene	37.6
Polymethyl methacrylate	45.4
Nylon	50.8
Indomethacin	61.8
Griseofulvin	62.2
Hydrocortisone	68.7
Sodium Chloride	155
Copper	1300

ADHESIONAL AND COHESIONAL FORCES

Of prime importance to those dealing with heterogeneous systems is the question of how two phases will behave when brought in contact with each other. It is well known, for instance, that some liquids, when placed in contact with other liquid or solid surfaces, will remain retracted in the form of a drop (known as a *lens*), while other liquids may exhibit a tendency to spread and cover the surface of this liquid or solid.

Based upon concepts developed to this point, it is apparent that the individual phases will exhibit a tendency to minimize the area of contact with other phases, thus leading to phase separation. On the other hand, the tendency for interaction between molecules at the new interface will offset this to some extent and give rise to the spontaneous spreading of one substance over the other.

In essence, therefore, phase affinity is increased as the forces of attraction between different phases (*adhesional forces*) become greater than the forces of attraction between molecules of the same phase (*cohesional forces*). If these adhesional forces become great enough, miscibility will occur and the interface will disappear. The present discussion is concerned only with systems of limited phase affinity, where an interface still exists.

A convenient approach used to express these forces quantitatively is work of adhesion and work of cohesion. The *work of adhesion*, W_a, is defined as the free energy/cm^2 required to separate two phases at their boundary and is equal but opposite in sign to the free energy/cm^2 released when the interface is formed. In an analogous manner the *work of cohesion* for a pure substance, W_c, is the work/cm^2 required to produce two new surfaces, as when separating different phases, but now both surfaces contain the same molecules. This is equal and opposite in sign to the free energy/cm^2 released when the same two pure liquid surfaces are brought together and eliminated.

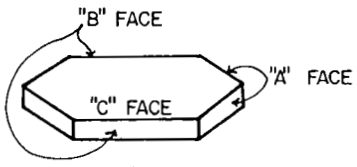

Figure 20-3. Adipic acid crystal showing various faces.[2]

By convention, when the work of adhesion between two substances, A and B, exceeds the work of cohesion for one substance (eg, B), spontaneous spreading of B over the surface of A should occur with a net loss of free energy equal to the difference between W_a and W_c. If W_c exceeds W_a, no spontaneous spreading of B over A can occur. The difference between W_a and W_c is known as the *spreading coefficient*, S. Only when S is positive will spreading occur.

The values for W_a and W_c (and hence S) may be expressed in terms of surface and interfacial tensions, when one considers that upon separation of two phases, A and B, γ_{AB} ergs of interfacial free energy/cm^2 (interfacial tension) are lost, but that γ_A and γ_B erg/cm^2 of energy (surface tensions of A and B) are gained; upon separation of bulk-phase molecules in an analogous manner, $2\gamma_A$ or $2\gamma_B$ erg/cm^2 will be gained. Thus,

$$W_a = \gamma_A + \gamma_B - \gamma_{AB} \tag{5}$$

and

$$W_c = 2\gamma_A \text{ or } 2\gamma_B \tag{6}$$

for B spreading on the surface of A. Therefore,

$$S_B = \gamma_A + \gamma_B - \gamma_{AB} - 2\gamma_B \tag{7}$$

or

$$S_B = \gamma_A - (\gamma_B + \gamma_{AB}) \tag{8}$$

Using Equation 8 and the values of surface and interfacial tension given in Tables 20-1 and 20-2, the spreading coefficient can be calculated for three representative substances—decane, benzene, and oleic acid—on water at 20°.

Decane: $S = 72.8 - (23.9 + 52.3) = -3.4$

Benzene: $S = 72.8 - (28.9 + 35.0) = 8.9$

Oleic Acid: $S = 72.8 - (32.5 + 15.6) = 24.7$

As expected, relatively nonpolar substances such as decane exhibit negative values of spreading coefficient, whereas the more-polar materials yield positive values—the greater the polarity of the molecule, the more positive the value of S.

The importance of the cohesive energy of the spreading liquid may be noted also by comparing the spreading coefficients for hexane on water and water on hexane.

$$S_{H/W} = 72.8 - (18.0 + 50.8) = 10.0$$

$$S_{W/H} = 18.0 - (72.8 + 50.8) = -105.6$$

Here, despite the fact that both liquids are the same, the high cohesion and air–liquid tension of water prevents spreading on the low-energy hexane surface, while the very low value for hexane allows spreading on the water surface. This also is seen when comparing the positive spreading coefficient of hexane to the negative value for decane on water.

To see whether spreading does or does not occur, a powder such as talc or charcoal can be sprinkled over the surface of water such that it floats; then, a drop of each liquid is placed on this surface. As predicted, decane will remain as an intact drop, while hexane, benzene, and oleic acid will spread out, as shown by the rapid movement of solid particles away from the point where the liquid drop was placed originally.

An apparent contradiction to these observations may be noted for hexane, benzene, and oleic acid when more of each substance is added: lenses now appear to form even though initial spreading occurred. Thus, in effect a substance does not appear to spread over itself.

It is now established that the spreading substance forms a monomolecular film that creates a new surface that has a lower surface free energy than pure water. This arises because of the apparent orientation of the molecules in such a film so that their most hydrophobic portion is oriented toward the spreading phase. It is the lack of affinity between this exposed portion of the spread molecules and the polar portion of the remaining molecules that prevents further spreading. This may be seen by calculating a final spreading coefficient where the new surface tension of water plus monomolecular film is used. For example, the presence of benzene reduces the surface tension of water to 62.2 dyne/cm so that the final spreading coefficient, is

$$S = 62.2 - (28.9 + 35.0) = -1.7$$

The lack of spreading exhibited by oleic acid should be reflected in an even more negative final spreading coefficient, as the very polar carboxyl groups should have very little affinity for the exposed alkyl chain of the oleic acid film. Spreading so as to form a second layer with polar groups exposed to the air also would seem very unlikely, thus leading to the formation of a lens.

WETTING PHENOMENA

In the experiment described above it was shown that talc or charcoal sprinkled onto the surface of water float despite the fact that their densities are much greater than that of water. In order for immersion of the solid to occur, the liquid must displace air and spread over the surface of the solid; when liquids cannot spread over a solid surface spontaneously, and, therefore, S, the spreading coefficient, is negative, we say that the solid is not wetted.

Table 20-4. Contact Angle on Paraffin and Nylon for Various Liquids of Differing Surface Tension

SUBSTANCE	SURFACE TENSION (dyne/cm)	CONTACT ANGLE (°) PARAFFIN	NYLON
Water	72.8	105	70
Glycerin	63.4	96	60
Formamide	58.2	91	50
Methylene iodide	50.8	66	41
α-Bromonaphthalene	44.6	47	16
tert-Butylnaphthalene	33.7	38	spreads
Benzene	28.9	24	spreads
Dodecane	25.4	17	spreads
Decane	23.9	7	spreads
Nonane	22.9	spreads	spreads

An important parameter reflecting the degree of wetting is the angle made by the liquid with the solid surface at the point of contact (Fig 20-4). By convention, when wetting is complete, the contact angle is 0°; in nonwetting situations it theoretically can increase to a value of 180°, where a spherical droplet makes contact with solid at only one point.

To express contact angle in terms of solid–liquid–air equilibria, one can balance forces parallel to the solid surface at the point of contact between all three phases (see Fig 20-4), as expressed in

$$\gamma_{SV} = \gamma_{SL} + \gamma_{LV} \cos \theta \qquad (9)$$

where γ_{SV}, γ_{SL}, and γ_{LV} represent the surface free energy/unit area of the solid–air, solid–liquid and liquid–air interfaces, respectively. Although difficult to use quantitatively because of uncertainties with γ_{SV} and γ_{SL} measurements, conceptually the equation, known as the Young equation, is useful because it shows that the loss of free energy due to elimination of the air–solid interface by wetting is offset by the increased solid–liquid and liquid–air area of contact as the drop spreads out.

The $\gamma_{LV} \cos \theta$ term arises as the horizontal vectorial component of the force acting along the surface of the drop, as represented by γ_{LV}. Factors tending to reduce γ_{LV} and γ_{SL}, therefore, will favor wetting, while the greater the value of γ_{SV}, the greater the chance for wetting to occur. This is seen in Table 20-4 for the wetting of a low-energy surface, paraffin (hydrocarbon), and a higher energy surface, nylon (polyhexamethylene adipamide). Here, the lower the surface tension of a liquid, the smaller the contact angle on a given solid, and the more polar the solid, the smaller the contact angle with the same liquid.

With Equation 9 in mind and looking at Figure 20-5, it is now possible to understand how the forces acting at the solid–liquid–air interface can cause a dense nonwetted solid to float if γ_{SL} and γ_{LV} are large enough relative to γ_{SV}.

The significance of reducing γ_{LV} was first developed empirically by Zisman[6] when he plotted cos θ versus the surface tension of a series of liquids and found that a linear relationship, dependent on the solid, often was obtained. When such

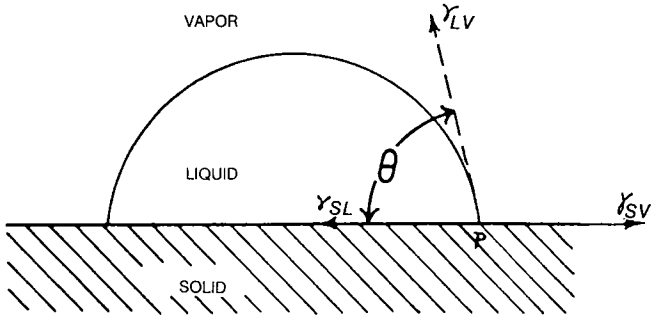

Figure 20-4. Forces acting on a nonwetting liquid drop exhibiting a contact angle of θ.[6]

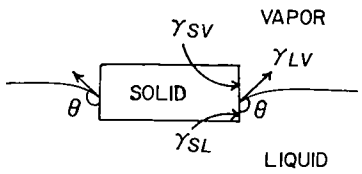

Figure 20-5. Forces acting on a nonwettable solid at the air+liquid+solid interface: contact angle θ greater than 90°.

Table 20-5. Critical Surface Tensions of Various Polymeric Solids

POLYMERIC SOLID	γ_c (dyne/cm AT 20°C)
Polymethacrylic ester of ϕ'-octanol	10.6
Polyhexafluoropropylene	16.2
Polytetrafluoroethylene	19
Polytrifluoroethylene	22
Poly(vinylidene fluoride)	25
Poly(vinyl fluoride)	28
Polyethylene	31
Polytrifluorochloroethylene	31
Polystyrene	33
Poly(vinyl alcohol)	37
Poly(methyl methacrylate)	39
Poly(vinyl chloride)	39
Poly(vinylidene chloride)	40
Poly(ethylene terephthalate)	43
Poly(hexamethylene adipamide)	46

plots are extrapolated to cos θ equal to 1, or 0° contact angle, a value of surface tension required to just cause complete wetting is obtained. Doing this for a number of solids, it was shown that this surface tension (known as the critical surface tension, γ_c) parallels expected solid surface energy γ_{SV}—the lower γ_c, the more nonpolar the surface.

Table 20-5 indicates some of these γ_c values for different surface groups, indicating such a trend. Thus, water with a surface tension of about 72 dyne/cm will not wet polyethylene (γ_c = 31 dyne/cm) but heptane, with a surface tension of about 20 dyne/cm, will. Likewise, Teflon (polytetrafluoroethylene) (γ_c = 19) is not wetted by heptane but is wetted by perfluoroheptane with a surface tension of 11 dyne/cm.

One complication associated with the wetting of high-energy surfaces is the lack of wetting after the initial formation of a monomolecular film caused by the spreading substance. As in the case of oleic acid spreading on the surface of water, the remaining liquid retracts because of the low-energy surface produced by the oriented film. This phenomenon, often called *autophobic behavior,* is an important factor in many systems of pharmaceutical interest because many solids expected to be wetted easily by water may be rendered hydrophobic if other molecules dissolved in the water can form these monomolecular films at the solid surface.

CAPILLARITY

Because water shows a strong tendency to spread out over a polar surface such as clean glass (contact angle equal to 0°), one would expect to observe a meniscus forming when water is contained in a glass vessel such as a pipet or buret. This behavior is accentuated dramatically if a fine-bore capillary tube is placed into the liquid (Fig 20-6). Not only will the wetting of the glass produce a more highly curved meniscus,

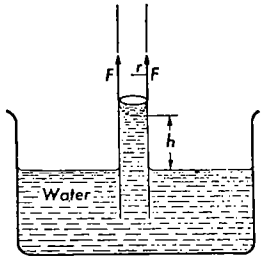

Figure 20-6. Capillary rise for a liquid exhibiting 0° contact angle.[1]

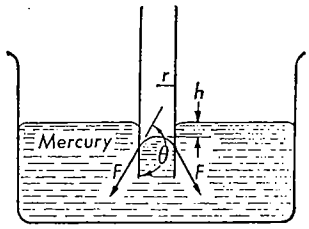

Figure 20-7. Capillary fall for a liquid exhibiting a contact angle, θ, that is greater than 90°.[1]

but the level of the liquid in the tube will be appreciably higher than the level of the water in the beaker.

The spontaneous movement of a liquid into a capillary or narrow tube due to surface forces is defined as *capillarity* and is responsible for a number of important processes involving the penetration of liquids into porous solids. In contrast to water in contact with glass, if the same capillary is placed into mercury (contact angle on glass: 130°), not only will the meniscus be inverted (Fig 20-7), but the level of the mercury in the capillary will be lower than in the beaker. In this case one does not expect mercury or other *nonwetting* liquids to penetrate pores easily unless external forces are applied.

To examine more closely the factors giving rise to the phenomenon of capillarity, consider the case of a liquid that rises to a height, h, above the bulk liquid in a capillary having a radius, r. As shown in Figure 20-6, if the contact angle of water on glass is 0, a force, F, will act upward and vertically along the circle of liquid–glass contact. Based upon the definition of surface tension, this force will be equal to the surface tension, γ, multiplied by the circumference of the circle, $2\pi r$. Thus,

$$F = \gamma 2\pi r \tag{10}$$

This force upward must support the column of water, and because the mass, m, of the column is equal to the density, d, multiplied by the volume of the column, $\pi r^2 h$, the force W opposing the movement upward will be

$$W = mg = \pi r^2 dgh \tag{11}$$

where g is the gravity constant.

Equating the two forces at equilibrium gives

$$\pi r^2 dgh = \gamma 2\pi r \tag{12}$$

so that

$$h = \frac{2\gamma}{rdg} \tag{13}$$

Thus, the greater the surface tension and the finer the capillary radius, the greater the rise of liquid in the capillary.

If the contact angle of liquid is not 0 (Fig 20-8), the same relationship may be developed, except the vertical component of F which opposes the weight of the column is $F \cos \theta$ and, therefore

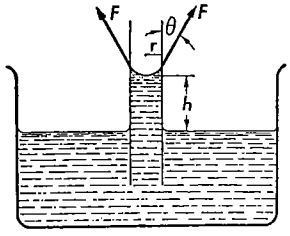

Figure 20-8. Capillary rise for a liquid exhibiting a contact angle, θ, that is greater than 0° but less than 90°.[1]

$$h = \frac{2\gamma \cos \theta}{rdg} \tag{14}$$

This indicates the very important fact that if θ is less than 90°, but greater than 0°, the value of h will decrease with increasing contact angle until at 90° ($\cos \theta = 0°$), $h = 0$. Above 90°, values of h will be negative, as indicated in Figure 20-7 for mercury. Thus, based on these equations it may be concluded that capillarity will occur spontaneously in a cylindrical pore even if the contact angle is greater than 0°, but it will not occur at all if the contact angle becomes 90° or more. In solids with irregularly shaped pores the relationships between parameters in Equation 14 will be the same, but they will be more difficult to quantitate because of nonuniform changes in pore radius throughout the porous structure.

PRESSURE DIFFERENCES ACROSS CURVED SURFACES

From the preceding discussion of capillarity another important concept follows. In order for the liquid in a capillary to rise spontaneously it must develop a higher pressure than the lower level of the liquid in the beaker. However, because the system is open to the atmosphere, both surfaces are in equilibrium with the atmospheric pressure. To be raised above the level of liquid in the beaker and produce a hydrostatic pressure equal to hgd, the pressure just below the liquid meniscus, in the capillary, P_1, must be less than that just below the flat liquid surface, P_0, by hgd, and therefore

$$P_0 - P_1 = hgd \tag{15}$$

Because, according to Equation 14,

$$h = \frac{2\gamma \cos \theta}{rgd}$$

then

$$P_0 - P_1 = \frac{2\gamma \cos \theta}{r} \tag{16}$$

For a contact angle of 0°, where the radius of the capillary is the radius of the hemisphere making up the meniscus,

$$P_0 - P_1 = \frac{2\gamma}{r} \tag{17}$$

The consequences of this relationship (known as the Laplace equation) are important for any curved surface when r becomes very small and γ is relatively significant. For example, a spherical droplet of air formed in a bulk liquid and having a radius r will have a greater pressure on the inner concave surface than on the convex side, as expressed in Equation 17. Direct measurement of the pressure difference, $(P_0 - P_1)$, for an air bubble of known radius allows the determination of the surface tension of either a pure liquid or a solution of surface active substance. Both static (constant radius) and dynamic (radius changing in a cyclic fashion as a function of time) measurements have been employed. The latter treatment, known as the pulsating bubble method, has been very useful in the study of some of the biophysical properties and associated disease states of pulmonary surfactant, a mixture of surface active materials lining the small airways of the mammalian lung.[7] One of the less appreciated advantages of this method for measuring surface tension is the need for only a very small sample size, typically on the order of 50 μL.

Another direct consequence of what Equation 17 expresses is the fact that very small droplets of liquid, having highly curved surfaces, will exhibit a higher vapor pressure, VP, than observed are over a flat surface of the same liquid at VP'.

Table 20-6. Ratio of Observed Vapor Pressure (P) to Expected Vapor Pressure (P') of Water at 25°C With Varying Droplet Size

P/P'	DROPLET SIZE (μm)
1.001	1
1.01	0.1
1.1	0.01
2.0	0.005
3.0	0.001
4.2	0.00065
5.2	0.00060

Equation 18, called the *Kelvin equation,* expresses the ratio of VP/VP' to droplet radius r, and surface tension γ:

$$\log \frac{P}{P'} = \frac{2\gamma M}{2.303RT\rho r} \tag{18}$$

where M is the molecular weight, R is the gas constant in erg/mol/degree, T is temperature, and ρ is the density in g/cm^3. Values for the ratio of vapor pressures are given in Table 20-6 for water droplets of varying size. Such ratios indicate why it is possible for very fine water droplets in clouds to remain uncondensed despite their close proximity to one another.

This same behavior may be seen when measuring the solubility of very fine solid particles, as both vapor pressure and solubility are measures of the escaping tendency of molecules from a surface. Indeed, the equilibrium solubility of extremely small particles has been shown to be greater than the usual value noted for coarser particles; the greater the surface energy and smaller the particles, the greater this effect.

ADSORPTION

Vapor Adsorption on Solid Surfaces

It was suggested earlier that a high surface or interfacial free energy may exist at a solid surface if the unbalanced forces at the surface and the area of exposed groups are quite great.

Substances such as metals, metal oxides, silicates, and salts—all containing exposed polar groups—may be classified as high-energy or hydrophilic solids; nonpolar solids such as carbon, sulfur, polyethylene, or Teflon (polytetrafluoroethylene) may be classified as low-energy or hydrophobic solids (see Table 20-3). Whereas liquids satisfy their unbalanced surface forces by changes in shape, pure solids (which exhibit negligible surface mobility) must rely on reaction with molecules either in the vapor state or in a solution that comes in contact with the solid surface to accomplish this.

Vapor adsorption is the simplest model demonstrating how solids reduce their surface free energy in this manner. Depending on the chemical nature of the adsorbent (solid) and the adsorbate (vapor), the strength of interaction between the two species may vary from strong specific chemical bonding to interactions produced by the weaker, more nonspecific London dispersion forces. Ordinarily, these latter forces are those responsible for the condensation of relatively nonpolar substances such as N_2, O_2, CO_2, or hydrocarbons.

When chemical reaction occurs, the process is called *chemisorption;* when dispersion forces predominate, the term *physisorption* is used. Physisorption occurs at temperatures approaching the liquefaction temperature of the vapor; for chemisorption, temperatures depend on the particular reaction involved. Water-vapor adsorption to various polar solids can occur at room temperature through

hydrogen-bonding, with binding energies intermediate to physisorption and chemisorption.

To study the adsorption of vapors onto solid surfaces, one must measure the amount of gas adsorbed/unit area or unit mass of solid, at different pressures of gas. Because such studies usually are conducted at constant temperature, plots of volume adsorbed versus pressure are known as *adsorption isotherms*. If the physical or chemical adsorption process is monomolecular, the adsorption isotherm should appear similar to those shown in Figure 20-9. Adsorption significantly increases with increasing pressure, followed by a leveling off, which is due either to a saturation of available specific chemical groups, as in chemisorption, or to the entire available surface being covered by physically adsorbed molecules. Adsorption reduction with increasing temperature occurs because the adsorption process is exothermic. In the case of physical adsorption at low temperatures after adsorption levels off, often a marked increase in adsorption occurs, presumably due to multilayered adsorption. In this case vapor molecules essentially condense upon themselves as the liquefaction pressure of the vapor is approached. Figure 20-10 illustrates one type of isotherm generally seen with multilayered physisorption.

To have a quantitative understanding of the adsorption process and to be able to compare different systems, two factors must be evaluated. It is important to know the capacity of the solid or the maximum amount of adsorption under a given set of conditions and the affinity of a given substance for the solid surface—how readily does it adsorb for a given amount of pressure? In effect, the second term is the equilibrium constant for the process. For many systems vapor-adsorption data may fit a very general, but somewhat empirical equation, the Freundlich equation:

$$V_a = kp^n \tag{19}$$

where V_a is the volume of gas adsorbed, p is the gas pressure, and k and n are constants reflecting adsorption affinity and capacity.

A significant theoretical improvement along these lines was the theory of *monomolecular adsorption* proposed by Langmuir. He postulated that for adsorption to occur a solid must contain uniform adsorption sites, each capable of holding a single gas molecule. Molecules colliding with the surface may bounce off elastically or they may remain in contact for a period of time. It is this contact over a period of time that Langmuir termed *adsorption*.

Two major assumptions were made in deriving the adsorption equation:

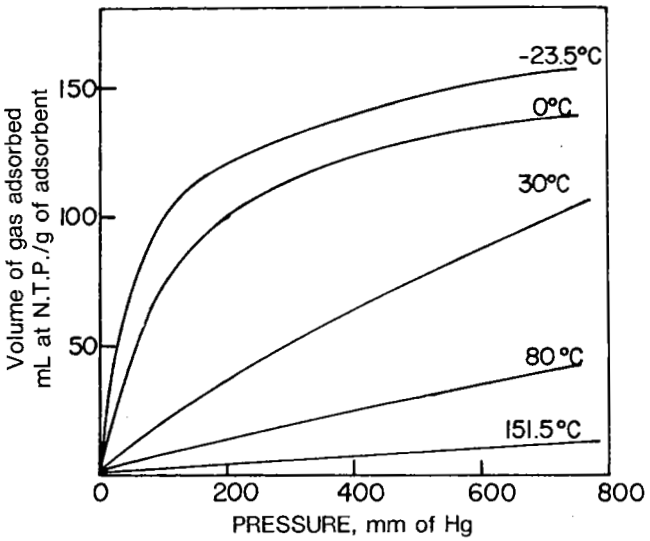

Figure 20-9. Adsorption isotherms for ammonia on charcoal.[8]

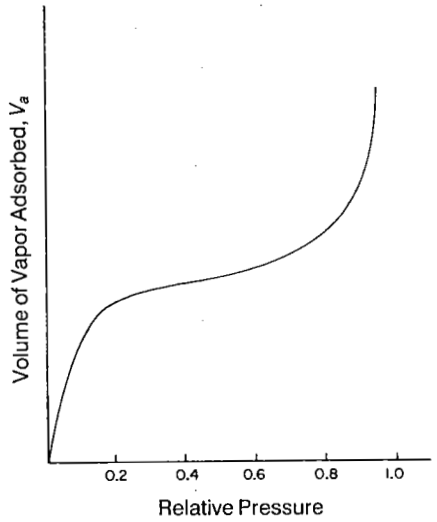

Figure 20-10. Typical plot for multilayer physical adsorption of a vapor on a solid surface.

1. Only those molecules striking an empty site can be adsorbed; hence, only monomolecular adsorption occurs.
2. The forces of interaction between adsorbed molecules are negligible and, therefore, the probability of a molecule adsorbing onto or desorbing from any site is independent of the surrounding sites.

With these assumptions and applying the kinetic theory of gases, it can be shown that

$$V_a = (V_m k'p)/(1 + k'p) \tag{20}$$

where V_m is the volume of gas covering all of the adsorption sites with a single layer of molecules and k' is a constant that reflects the affinity of the gas for the solid.

A test of fit to this equation can be made by expressing it in linear form.

$$\frac{p}{V_a} = \frac{1}{V_m k'} + \frac{p}{V_m} \tag{21}$$

The value of k' is, in effect, the equilibrium constant and may be used to compare affinities of different substances for the solid surface. The value of V_m is valuable because it indicates the maximum number of sites available for adsorption. In the case of physisorption the maximum number of sites is actually the total surface area of the solid; therefore, the value of V_m can be used to estimate surface area if the volume and area/molecule of vapor are known.

Since physisorption most often involves some multilayered adsorption, an equation based on the Langmuir equation, the B.E.T. equation, normally is used to determine V_m and solid surface areas. Equation 22 is the B.E.T. equation:

$$V_a = \frac{V_m cp}{(p_0 - p)[1 + (C - 1)(p/p_0)]} \tag{22}$$

where c is a constant and p_0 is the vapor pressure of the adsorbing substance.[9] Experimentally, the most widely used vapor for this purpose is nitrogen, which adsorbs nonspecifically on most solids near its boiling point at –195° and appears to occupy about 16 Å^2/molecule on a solid surface.

Adsorption from Solution

By far one of the most important aspects of interfacial phenomena encountered in pharmaceutical systems is the tendency for substances dissolved in a liquid to adsorb to various interfaces.

Adsorption from solution is generally more complex than that from the vapor state because of the influence of the solvent and any other solutes dissolved in the solvent. Although such adsorption generally is limited to one or two molecular layers at most, the presence of other molecules often makes the interpretation of adsorption mechanisms much more difficult than for chemisorption or physisorption of a vapor. Because monomolecular adsorption from solution is so widespread at all interfaces, we will first discuss the nature of monomolecular films and then return to a discussion of adsorption from solution.

Insoluble Monomolecular Films

It was suggested above that molecules exhibiting a tendency to spread out at an interface might be expected to orient so as to reduce the interfacial free energy produced by the presence of the interface. Direct evidence for molecular orientation has been obtained from studies dealing with the spreading on water of insoluble polar substances containing long hydrocarbon chains, such as fatty acids.

In the late 19th century Pockels and Rayleigh showed that a very small amount of olive or castor oil, when placed on the surface of water, spreads out, as discussed above. If the amount of material was less than could physically cover the entire surface, only a slight reduction in the surface tension of water was noted. However, if the surface was compressed between barriers, as shown in Figure 20-11, the surface tension was reduced considerably.

Devaux extended the use of this technique by dissolving small amounts of solid in volatile solvents and dropping the solution onto a water surface. After assisting the water-insoluble molecules to spread, the solvent evaporated, leaving a surface film containing a known amount of solute.

Compression and measurement of surface tension indicated that a maximum reduction of surface was reached when the number of molecules/unit area was reduced to a value corresponding to complete coverage of the surface. This suggested that a monomolecular film forms and that surface tension is reduced upon compression because contact between air and water is reduced by the presence of the film molecules. Beyond the point of closest packing, the film apparently collapses very much as a layer of corks floating on water would be disrupted when laterally compressed beyond the point of initial physical contact.

Using a refined quantitative technique based on these studies, Langmuir[11] spread films of pure fatty acids, alcohols, and esters on the surface of water. Comparing a series of saturated fatty acids, differing only in chain length, he found that the area/molecule at collapse was independent of chain length, corresponding to the cross-sectional area of a molecule oriented in a vertical position (see Fig 20-11). He further concluded that this molecular orientation involved association of the polar carboxyl group with the water phase and the nonpolar alkyl chain out toward the vapor phase.

In addition to the evidence for molecular orientation, Langmuir's work with surface films revealed that each substance exhibits film properties which reflect the interactions between

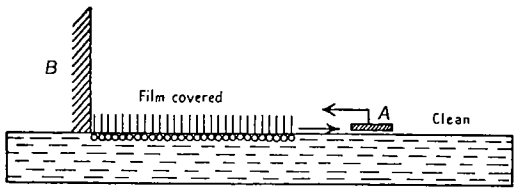

Figure 20-11. Insoluble monomolecular film compressed between a fixed barrier *B*, and a movable barrier *A*.[10]

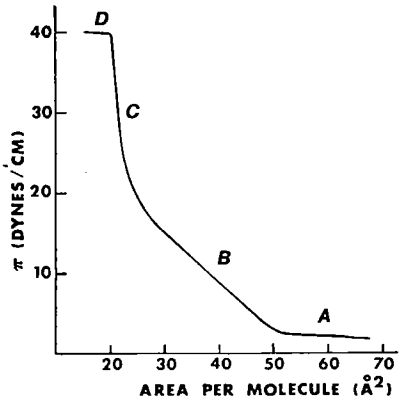

Figure 20-12. A surface pressure–area curve for an insoluble monomolecular film: Region *A*, gaseous film; Region *B*, liquid film; Region *C*, solid film; Region *D*, film collapse.

molecules in the surface film. This is seen best by plotting the difference in surface tension of the clean surface γ_0, and that of the surface covered with the film γ, versus the area/molecule A produced by film compression (total area/the number of molecules). The difference in surface tension is called the surface pressure, π, and thus

$$\pi = \gamma_0 - \gamma \qquad (23)$$

Figure 20-12 depicts such a plot for a typical fatty acid monomolecular film. At areas greater than 50Å^2/molecule the molecules are far apart and do not cover enough surface to reduce the surface tension of the clean surface to any extent and thus the lack of appreciable surface pressure. Because the molecules in the film are quite free to move laterally in the surface, they are said to be in a two-dimensional *gaseous* or *vapor* state.

As the intermolecular distance is reduced upon compression, the surface pressure rises because the air–water surface is being covered to a greater extent. The rate of change in π with A, however, will depend on the extent of interaction between film molecules—the greater the rate of change, the more "condensed" the state of the film.

In Figure 20-12, from 50 to 30 Å^2/molecule, the curve shows a steady increase in π, representative of a two-dimensional "liquid" film, where the molecules become more restricted in their freedom of movement because of interactions. Below 30 Å^2/molecule, the increase in π occurs over a narrow range of A, characteristic of closest packing and a two-dimensional "solid" film.

Any factor tending to increase polarity or bulkiness of the molecule—such as increased charge, number of polar groups, reduction in chain length, or the introduction of aromatic rings, side chains, and double bonds—should reduce molecular interactions. On the other hand, the longer the alkyl chain and the less bulky the polar group, the closer the molecules can approach and the stronger the extent of interaction in the film.

Soluble Films and Adsorption from Solution

If a fatty acid exhibits highly gaseous film behavior on an aqueous surface, a relatively small change in π with A over a considerable range of compression should be expected. Indeed, for short-chain compounds such as lauric acid (12 carbons) or decanoic acid, not only is the change in π small with decreasing A, but at a point just before the expected closest packing area, the surface pressure becomes constant without any collapse.

If lauric acid is converted to the laurate ion, or if a shorter chain acid such as octanoic acid is used, spreading on water and compression of the surface produces no increase in π. These

results illustrate that the more polar the molecule (hence, the more *gaseous* the film), the higher the area/molecule where a constant surface pressure occurs. This behavior may be explained by assuming that polar molecules form monomolecular films when spread on water but that, upon compression, they are caused to enter the aqueous bulk solution rather than to remain as an intact insoluble film. The constant surface pressure with increased compression arises because a constant number of molecules/unit area remain at the surface in equilibrium with dissolved molecules. The extent of such behavior will be greater for substances exhibiting weaker intermolecular interaction and greater water solubility.

Starting from the other direction, it can be shown that short-chain acids and alcohols (when dissolved in water) reduce the surface tension of water, thus producing a surface pressure, just as with insoluble films (see Equation 23). That dissolved molecules are accumulating at the interface in the form of a monomolecular film is suggested from the similarity in behavior to systems where lightly soluble molecules are spread on the surface. For example, compressing the surface of a solution containing "surface-active" molecules has no effect on the initial surface pressure, whereas increasing bulk-solution concentration tends to increase surface pressure, presumably by shifting the equilibrium between surface and bulk molecules.

At this point one may ask, why should water-soluble molecules leave an aqueous phase and accumulate or *adsorb* at an air–solution interface? Because any process will occur spontaneously if it results in a net loss in free energy, such must be the case for the process of adsorption. A number of factors will produce such a favorable change in free energy.

- The presence of the oriented monomolecular film reduces the surface free energy of the air–water interface.
- The hydrophobic group on the molecule is in a lower state of energy at the interface, where it no longer is as surrounded by water molecules, than when it is in the bulk-solution phase.
- Increased interaction between film molecules also will contribute to this process.

A further reduction in free energy occurs upon adsorption because of the gain in entropy associated with a change in water structure. Water molecules, in the presence of dissolved alkyl chains are more highly organized or *ice-like* than they are as a pure bulk phase; hence, the entropy of such structured water is lower than that of bulk water.

The process of adsorption requires that the ice-like structure *melt* as the chains go to the interface, and thus an increase in the entropy of water occurs. The adsorption of molecules dissolved in oil can occur but it is not influenced by water structure changes, and hence, only the first factors mentioned are important here.

It is very rare that significant adsorption can occur at the hydrocarbon–air interface as little loss in free energy comes about by bringing hydrocarbon chains with polar groups attached to this interface. On the other hand, at oil–water interfaces, the polar portions of the molecule can interact with water at the interface, leading to significant adsorption.

Thus, whereas water-soluble fatty acid salts are adsorbed from water to air–water and oil–water interfaces, their undissociated counterparts, the free fatty acids, which are water insoluble, form insoluble films at the air–water interface, are not adsorbed from oil solution to an oil–air interface, but show significant adsorption at the oil–water interface when dissolved in oil.

From this discussion it is possible also to conclude that adsorption from aqueous solution requires a lower solute concentration to obtain the same level of adsorption if the hydrophobic chain length is increased or if the polar portion of the molecule is less hydrophilic. On the other hand, adsorption from nonpolar solvents is favored when the solute is quite polar.

Because soluble or adsorbed films cannot be compressed, there is no simple, direct way to estimate the number of molecules/unit area coming to the surface under a given set of conditions. For relatively simple systems it is possible to estimate this value by application of the Gibbs equation, which relates surface concentration to the surface-tension change produced at different solute activities. The derivation of this equation is beyond the scope of this discussion, but it arises from a classical thermodynamic treatment of the change in free energy when molecules concentrate at the boundary between two phases. The equation may be expressed as

$$\Gamma = -\frac{a}{RT}\frac{d\gamma}{da} \tag{24}$$

where Γ is the moles of solute adsorbed/unit area, R is the gas constant, T is the absolute temperature and $d\gamma$ is the change in surface tension with a change in solute activity, da, at activity a.

For dilute solutions of nonelectrolytes, or for electrolytes when the Debye–Hückel equation for activity coefficient is applicable, the value of a may be replaced by solute concentration, c. Because the term dc/c is equal to $d \ln c$, the Gibbs equation is often written as

$$\Gamma = -\frac{1}{RT}\frac{d\gamma}{d \ln c} \tag{25}$$

In this way the slope of a plot of γ versus $\ln c$ multiplied by $1/RT$ should give Γ at a particular value of c.

Figure 20-13 depicts typical plots for a series of water-soluble surface-active agents differing only in the alkyl chain length. A greater reduction of surface tension occurs at lower concentrations for longer chain-length compounds. In addition, there are greater slopes with increasing concentration, indicating more adsorption (Equation 25), and an abrupt leveling of surface tension at higher concentrations. This latter behavior reflects the self-association of surface-active agent to form micelles which exhibit no further tendency to reduce surface tension. The topic of micelles will be discussed later in Chapter 21.

If one plots the values of surface concentration, Γ versus concentration c, for substances adsorbing to the vapor–liquid and liquid–liquid interfaces, using data such as those given in Figure 20-13, one generally obtains an adsorption isotherm shaped like those in Figure 20-9 for vapor adsorption. Indeed, it can be shown that the Langmuir equation (Equation 20) can be fitted to such data when written in the form

$$\Gamma = \frac{\Gamma_{max} k'c}{1 + k'c} \tag{26}$$

where Γ_{max} is the maximum surface concentration attained with increasing concentration and k' is related to k in Equation

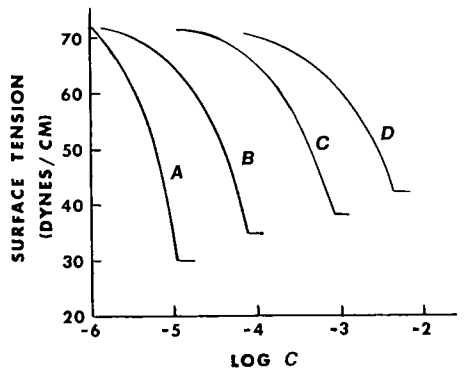

Figure 20-13. The effect of increasing chain length on the surface activity of a surfactant at the air–aqueous solution interface (each curve differs from the preceding or succeeding by two methylene groups with *A*, the longest chain, and *D*, the shortest).

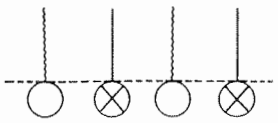

Figure 20-14. A mixed monomolecular film. ⊗, a long-chain ion; ○, a long-chain nonionic compound.

20. Combining Equations 24 and 26 leads to a widely used relationship between surface-tension change Π (see Equation 23), and solute concentration c, known as the Syszkowski equation.

$$\Pi = \Gamma_{max} RT \ln (1 + k'c) \tag{27}$$

Mixed Films

It would seem reasonable to expect that the properties of a surface film could be varied greatly if a mixture of surface-active agents were in the film. As an example, consider that a mixture of short- and long-chain fatty acids would be expected to show a degree of *condensation* varying from the gaseous state when the short-chain substance is used in high amount to a highly condensed state when the longer chain substance predominates. Thus, each component in such a case would operate independently by bringing a proportional amount of film behavior to the system.

More often, the ingredients of a surface film do not behave independently, but rather interact to produce a new surface film. An obvious example would be the combination of organic amines and acids which are charged oppositely and would be expected to interact strongly. In addition to such polar-group interactions, chain–chain interactions strongly favor mixed condensed films. An important example of such a case occurs when a long-chain alcohol is introduced along with an ionized long-chain substance. Together the molecules form a highly condensed film despite the presence of a high number of like charges. Presumably this occurs as seen in Figure 20-14, by arranging the molecules so that ionic groups alternate with alcohol groups; however, if chain–chain interactions are not strong, the ionic species often will be displaced by the more nonpolar unionized species and will "desorb" into the bulk solution.

On the other hand, sometimes the more soluble surface-active agent produces surface pressures in excess of the collapse pressure of the insoluble film and displaces it from the surface. This is an important concept because it is the underlying principle behind cell lysis by surface-active agents and some drugs, and behind the important process of detergency.

Adsorption from Solution on to Solid Surfaces

Adsorption to solid surfaces from solution may occur if the dissolved molecules and the solid surface have chemical groups capable of interacting. Nonspecific adsorption also will occur if the solute is surface active and if the surface area of the solid is high. This latter case would be the same as occurs at the vapor–liquid and liquid–liquid interfaces. As with adsorption to liquid interfaces, adsorption to solid surfaces from solution generally leads to a monomolecular layer, often described by the Langmuir equation in the form

$$x/M = [(x/M)mk^*c]/(1 + k^*c) \tag{28}$$

where x is the amount of adsorbed solute, M is the total weight of solid, x/M is the amount of solute adsorbed per unit weight of solid at concentration c, k^* is a constant, and $(x/M)m$ is the amount of solute per unit weight covering the surface with a complete monolayer. However, as Giles[12] has pointed out, the variety of combinations of solutes and solids, and hence the variety of possible mechanisms of adsorption, can lead to a number of more complex isotherms. In particular, adsorption of surfactants and polymers, of great importance in a number of pharmaceutical systems, still is not understood well on a fundamental level, and may in some situations even be multilayered.

Adsorption from solution may be measured by separating solid and solution and either estimating the amount of adsorbate adhering to the solid or the loss in concentration of adsorbate from solution. In view of the possibility of solvent adsorption, the latter approach really only gives an apparent adsorption. For example, if solvent adsorption is great enough, it is possible to end up with an increased concentration of solute after contact with the solid; here, the term *negative adsorption* is used.

Solvent not only influences adsorption by competing for the surface, but as discussed in connection with adsorption at liquid surfaces, the solvent will determine the escaping tendency of a solute; for example, the more polar the molecule, the less the adsorption that occurs from water. This is seen in Figure 20-15, where adsorption of various fatty acids from water onto charcoal increases with increasing alkyl chain length or nonpolarity. It is difficult to predict these effects, but, in general, the more chemically unlike the solute and solvent and the more alike the solid surface groups and solute, the greater the extent of adsorption. Another factor that must be kept in mind is that charged solid surfaces, such as polyelectrolytes, will strongly adsorb oppositely charged solutes. This is similar to the strong specific binding seen in gas chemisorption, and it is characterized by significant monolayer adsorption at very low concentrations of solute. See Figure 20-16 for an example of such adsorption.

Adsorption onto activated charcoal has been shown to be extremely useful in the emergency treatment of acute overdosage of a variety of drugs taken by the oral route.[15] Overall effectiveness of commercially available activated-charcoal suspensions as an antidote in oral poisonings appears to be directly related to the total charcoal surface area.[16] Drug adsorption to charcoal tends to follow both the Langmuir model as well as the Freundlich model. In addition, a drug that is un-

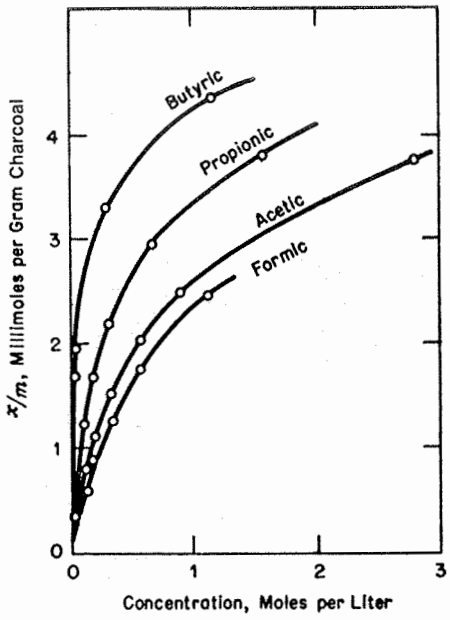

Figure 20-15. The relation between adsorption and molecular weight of fatty acids.[13]

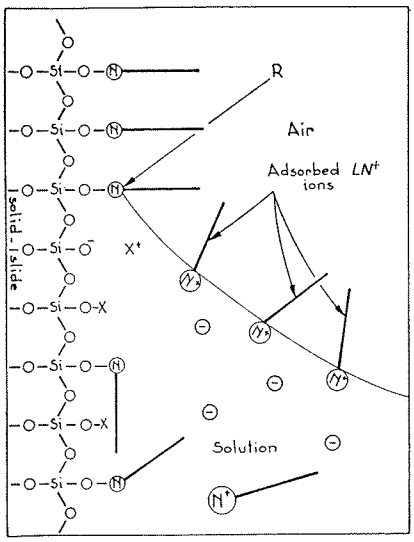

Figure 20-16. The adsorption of a cationic surfactant, LN^+, onto a negatively charged silica or glass surface, exposing a hydrophobic surface as the solid is exposed to air.[14]

ionized at gastric pH will adsorb to charcoal to a greater extent than will the ionized form of the drug, probably because of less repulsive interactions in the adsorbed state of neutral molecules. Great care must be exercised in the formulation of activated-charcoal suspensions because pharmaceutical adjuvants employed in suspensions have the potential to adsorb to the charcoal and block sites for drug adsorption.

SURFACE-ACTIVE AGENTS

Throughout the discussion so far, examples of surface-active agents (surfactants) have been restricted primarily to fatty acids and their salts. It has been shown that both a hydrophobic portion (alkyl chain) and a hydrophilic portion (carboxyl and carboxylate groups) are required for their surface activity, the relative degree of polarity determining the tendency to accumulate at interfaces. It now becomes important to look at some of the specific types of surfactants available and to see what structural features are required for different pharmaceutical applications.

The classification of surfactants is quite arbitrary, but one based on chemical structure appears best as a means of introducing the topic. It is generally convenient to categorize surfactants according to their polar portions because the nonpolar portion usually is made up of alkyl or aryl groups. The major polar groups found in most surfactants may be divided as follows: anionic, cationic, amphoteric, and nonionic. As shall be seen, the last group is the largest and most widely used for pharmaceutical systems, so that it will be emphasized in the discussion that follows.

Types

ANIONIC AGENTS—The most commonly used anionic surfactants are those containing carboxylate, sulfonate, and sulfate ions. Those containing carboxylate ions are known as soaps and generally are prepared by the saponification of natural fatty acid glycerides in alkaline solution. The most common cations associated with soaps are sodium, potassium, ammonium, and triethanolamine; the chain length of the fatty acids ranges from 12 to 18.

The extent of solubility in water is influenced greatly by the length of the alkyl chain and the presence of double bonds. For example, sodium stearate is quite insoluble in water at room temperature, whereas sodium oleate under the same conditions is quite water soluble.

Multivalent ions, such as calcium and magnesium, produce marked water insolubility, even at lower alkyl chain lengths; thus, soaps are not useful in hard water that is high in content of these ions. Soaps, being salts of weak acids, are subject also to hydrolysis and the formation of free acid plus hydroxide ion, particularly when in more concentrated solution.

To offset some of the disadvantages of soaps, a number of long alkyl chain sulfonates, as well as alkyl aryl sulfonates such as sodium dodecylbenzene sulfonate, may be used; the sulfonate ion is less subject to hydrolysis and precipitation in the presence of multivalent ions. A popular group of sulfonates, widely used in pharmaceutical systems, are the dialkyl sodium sulfosuccinates, particularly sodium bis-(2-ethylhexyl)sulfosuccinate, best known as Aerosol OT or docusate sodium. This compound is unique in that it is soluble both in oil and water, and hence forms micelles in both phases. It reduces surface and interfacial tension to low values and acts as an excellent wetting agent in many types of solid dosage forms (Table 20-7).

A number of alkyl sulfates are available as surfactants, but by far the most popular member of this group is sodium lauryl sulfate, which is used widely as an emulsifier and solubilizer in pharmaceutical systems. Unlike the sulfonates, sulfates are susceptible to pH-dependent hydrolysis leading to the formation of the long-chain alcohol.

CATIONIC AGENTS—A number of long-chain cations, such as amine salts and quaternary ammonium salts, often are used as surface-active agents when dissolved in water; however, their use in pharmaceutical preparations is limited to that of antimicrobial preservation rather than as surfactants. This arises because the cations adsorb so readily at cell membrane structures in a nonspecific manner, leading to cell lysis (eg, hemolysis), as do anionics to a lesser extent. It is in this way that they act to destroy bacteria and fungi.

Since anionic and nonionic agents are not as effective as preservatives, one must conclude that the positive charge of these compounds is important; however, the extent of surface activity has been shown to determine the amount of material needed for a given amount of preservation. Quaternary ammonium salts are preferable to free amine salts as they are not subject to effect by pH in any way; however, the presence of organic anions such as dyes and natural polyelectrolytes is an important source of incompatibility and such a combination should be avoided.

AMPHOTERIC AGENTS—The major groups of molecules falling into the amphoteric category are those containing carboxylate or phosphate groups as the anion, and amino or quaternary ammonium groups as the cation. The former group is represented by various polypeptides, proteins, and the alkyl betaines; the latter group consists of natural phospholipids such as the lecithins and cephalins. In general, long-chain

Table 20-7. Effect of Aerosol OT Concentration on the Surface Tension of Water and the Contact Angle of Water with Magnesium Stearate

CONCENTRATION ($m \times 10^6$)	γ_{s_L}	θ (°)
1.0	60.1	120
3.0	49.8	113
5.0	45.1	104
8.0	40.6	89
10.0	38.6	80
12.0	37.9	71
15.0	35.0	63
20.0	32.4	54
25.0	29.5	50

amphoterics, which exist in solution in zwitterionic form, are more surface active than are ionic surfactants having the same hydrophobic group, because in effect the oppositely charged ions are neutralized. However, when compared to nonionics, they appear somewhere between ionic and nonionic.

PROTEINS—Considering the rapidly growing importance of proteins as therapeutic agents, the unique surface characteristics of these biological macromolecules deserve some special attention. Therapeutic proteins have been shown to be extremely surface active, and they adsorb to clinically important surfaces such as glass bottles and syringes, sterile filters, and plastic IV bags and administration sets; the result is treatment failures. In general, proteins can adsorb to a whole variety of surfaces, both hydrophobic and hydrophilic. From the standpoint of the surface, protein adsorption appears to be maximized when the electrical charge of the surface is opposite that of the protein or when the surface is extremely hydrophobic. From the standpoint of the protein, the extent of adsorption depends on the molecular weight, the number of hydrophobic side chains, and the relative distribution of cationic and anionic side chains. The effect of ionic strength is usually to enhance adsorption by shielding adjacent proteins from repulsive electrical interactions. Adsorption is also maximized when the pH of the protein solution is equal to the pI (isoelectric point) of the molecule, again due to minimized electrical repulsion.

When different proteins compete for adsorption sites on a single surface, the effect of molecular weight becomes most striking. Early in the adsorption process the protein with the smaller molecular weight, which can diffuse to the surface more rapidly, initially occupies the interface. After some time, it is found that the larger molecular weight protein has displaced the smaller protein since the larger molecule has more possible interaction points with the surface and thus greater total energy of interaction.

The most important consequence of therapeutic protein adsorption is the loss of bioactivity, the reasons for which include loss of therapeutic agent by irreversible adsorption to the surface, possible structural changes in the protein induced by the interface, and surface-associated aggregation and precipitation of the protein. Each of these consequences is related to the structure adopted by the protein in the interfacial region. The native three-dimensional structure of a protein in solution is the result of a complex balance between attractive and repulsive forces. Surface can easily disrupt the balance of forces in proteins residing in the interfacial region and cause the molecule to undergo a change, unfolding from the native to the extended configuration. As it is unlikely that the extended configuration will refold back to the native state upon release from the interface, the protein is considered to be denatured. Like other polymers, the unfolding of the protein at the interface is thought to minimize the contact of apolar amino acid side chains with water.

In addition, electrical interactions, both within the protein and between the protein and the surface, strongly modulate the configuration assumed at the interface. Motion of the interface, such as comes about during shaking of a solution, appears to accelerate the surface-associated denaturation. Some proteins appear to be rather vulnerable to surface-induced structural alterations, whereas others are very resistant. Algorithms for predicting those proteins most vulnerable to the structure-damaging effects of interfaces are not yet available. Empirical observations suggest that those proteins easily denatured in solution by elevated temperatures may also be most sensitive to interfacial denaturation.

The best defense against untoward effects on the structure of proteins induced by surfaces appears to be prevention of adsorption. Research in the field of biomaterials has shown that surfaces that are highly hydrophilic are less likely to serve as sites for protein adsorption. Steric hindrance of adsorption by bonding hydrophilic polymers, such as polyethylene oxide, to a surface also appears to be successful in minimizing adsorption. Formulations of proteins intended for parenteral administration frequently contain synthetic surfactants to preserve bioactivity. The specific molecular mechanism of protection is not understood and can involve specific blocking of adsorption to the interface or enhanced removal from the interface before protein unfolding can occur. In support of the former mechanism is the observation that surfactants most successful at protecting proteins from interfacial denaturation contain long polyethylene oxide chains capable of blocking access of the protein to the surface.

PHOSPHOLIPIDS—All lecithins contain the L-α-glycerophosphoylcholine skeleton esterified to two long-chain fatty acids (often oleic, palmitic, stearic, and linoleic). Typically, for pharmaceutical use, lecithins are derived from egg yolk or soybean. Although possessing a polar zwitterionic *head* group, the twin hydrocarbon *tails* result in a surfactant with very low water solubility in the monomer state. With the exception of the skin, phospholipids make up a vast majority of the lipid component of cell membranes throughout the body. As a result, the biocompatibility of lecithin is high, accounting for the increasing popularity of use in formulations intended for oral, topical, and intravenous use. Egg yolk lecithins are used extensively as the main emulsifying agent in the fat emulsions intended for intravenous use.

The ability of the lecithins to form a tough but flexible film between the oil and water phases is responsible for the excellent physical stability shown the IV fat emulsions. In aqueous media, phospholipids are capable of assembling into concentric bilayer structures known as liposomes. The therapeutic advantage of such a lipid assembly for drug delivery depends upon the encapsulation of the active ingredient either within the interior aqueous environment or within the hydrophobic region of the bilayer. Deposition of the liposome within the body appears to be dependent upon a number of factors, including the composition of the phospholipids employed in the bilayer and the diameter of the liposome.

The unique surface properties of phospholipids are critical to the function of the pulmonary system. Pulmonary surfactant is a mixture of phospholipids and other associated molecules secreted by type II pneumocytes. In the absence of pulmonary surfactant (as in a neonate born prematurely), the high surface energy of the pulmonary alveoli and airways can be diminished only by physical collapse of these structures and resulting elimination of the air–water interface. As a consequence of airway collapse, the lung fails to act as an organ of gas exchange. Pulmonary surfactant maintains the morphology and function of the alveoli and airways by markedly decreasing surface energy through decreasing the surface tension of the air–water interface.

The most prevalent component of pulmonary surfactant, dipalmitoylphosphatidylcholine (DPPC), is uniquely responsible for forming the very rigid surface film necessary to reduce the surface tension of the interface to a value near 0. Such an extreme reduction in surface tension is most critical during the process of exhalation of the lung where the air–water interfacial area is decreasing. Although DPPC does form the rigid film, in the absence of additives it is unable to respread over an expanding interface typical of a lung during the inhalation phase. An anionic phospholipid, phosphatidylglycerol, in conjunction with a surfactant-associated protein, SP-C, appears to aid the respreading of DPPC and to maintain mechanical stability of the interface. A truly remarkable feature is that pulmonary surfactant is able to carry out the cycle of reducing surface tension to near 0 during exhalation and then reexpanding over the interface during inhalation at whatever rate is necessary by the respiratory pattern.

Commercially available pulmonary surfactant replacement preparations contain DPPC as the primary ingredient. Agents that aid in the respreading of DPPC may differ depending upon the source of the surface-active material.

NONIONIC AGENTS—The major class of compounds used in pharmaceutical systems are the nonionic surfactants, as their advantages with respect to compatibility, stability, and

potential toxicity are quite significant. It is convenient to divide these compounds into those that are relatively water insoluble and those that are quite water soluble. The major types of compounds making up this first group are the long-chain fatty acids and their water-insoluble derivatives. These include

- Fatty alcohols such as lauryl, cetyl (16 carbons), and stearyl alcohols.
- Glyceryl esters such as the naturally occurring mono-, di-, and triglycerides.
- Fatty acid esters of fatty alcohols and other alcohols such as propylene glycol, polyethylene glycol, sorbitan, sucrose, and cholesterol. Included also in this general class of nonionic water-insoluble compounds are the free steroidal alcohols such as cholesterol.

To increase the water solubility of these compounds and to form the second group of nonionic agents, polyoxyethylene groups are added through an ether linkage with one of their alcohol groups. The list of derivatives available is much too long to cover completely, but a few general categories will be given.

The most widely used compounds are the polyoxyethylene sorbitan fatty acid esters, found in pharmaceutical formulations that are to be used both internally and externally. Closely related compounds include polyoxyethylene glyceryl and steroidal esters, as well as the comparable polyoxypropylene esters. It is also possible to have a direct ether linkage with the hydrophobic group, as with a polyoxyethylene–stearyl ether or a polyoxyethylene–alkyl phenol. These ethers offer advantages because, unlike the esters, they are quite resistant to acidic or alkaline hydrolysis.

Besides the classification of surfactants according to their polar portion, it is useful to have a method that categorizes them in a manner that reflects their interfacial activity and their ability to function as wetting agents, emulsifiers, and solubilizers. Variation in the relative polarity or nonpolarity of a surfactant significantly influences its interfacial behavior, so some measure of polarity or nonpolarity should be useful as a means of classification.

One such approach assigns a hydrophile–lipophile balance (HLB) number for each surfactant; although the method was developed by a commercial supplier of one group of surfactants, it has received widespread application.

The HLB value, as originally conceived for nonionic surfactants, is merely the percentage weight of the hydrophilic group divided by 5 in order to reduce the range of values. On a molar basis, therefore, a 100% hydrophilic molecule (polyethylene glycol) would have a value of 20. Thus, an increase in polyoxyethylene chain length increases polarity, and hence the HLB value; at constant polar chain length, an increase in alkyl chain length or number of fatty acid groups decreases polarity and the HLB value. One immediate advantage of this system is that to a first approximation one can compare any chemical type of surfactant to another type when both polar and nonpolar groups are different.

Values of HLB for nonionics are calculable on the basis of the proportion of polyoxyethylene chain present; however, to determine values for other types of surfactants, it is necessary to compare physical chemical properties reflecting polarity with those surfactants having known HLB values.

Relationships between HLB and phenomena such as water solubility, interfacial tension, and dielectric constant have been used. Those surfactants exhibiting values greater than 20 (eg, sodium lauryl sulfate) demonstrate hydrophilic behavior in excess of the polyoxyethylene groups alone. Refer to Chapter 22 for further information.

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CHAPTER 41

Parenteral Preparations

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The distinctive characteristics of parenteral (Gk, *para enteron,* beside the intestine) dosage forms of drugs are discussed in this chapter. These dosage forms differ from all other drug dosage forms because of the unique requirements imposed because they are injected directly into body tissue through the primary protective system of the human body, the skin, and mucous membranes. Therefore, they must be exceptionally pure and free from physical, chemical, and biological contaminants. These requirements place a heavy responsibility on the pharmaceutical industry to practice good manufacturing practices (GMPs) in the manufacture of parenteral dosage forms and upon pharmacists to practice good aseptic practices (GAPs) in dispensing them for administration to patients.

Many of the newer drugs, particularly those derived from the new developments in biotechnology, can only be given parenterally because they are inactivated in the gastrointestinal tract when given by mouth. Further, the potency and specificity of many of these drugs require strict control of their administration to the patient. A parenteral route of administration meets both of these critical requirements.

This chapter begins with a brief review of the historical events contributing to the development of this distinctive dosage form. Consideration is then given to some of the distinguishing characteristics of these dosage forms and how they are administered to patients. Most of the remainder of the chapter discusses the various factors required for the preparation of a pure, safe, and effective parenteral product.

HISTORY[1]

One of the most significant events in the beginnings of parenteral therapy was the first recorded injection of drugs into the veins of living animals, in about 1657, by the architect Sir Christopher Wren. From such a very crude beginning, the technique for intravenous injection and knowledge of the implications developed slowly during the next century and a half. In 1855 Dr Alexander Wood of Edinburgh described what was probably the first subcutaneous injection of drugs for therapeutic purposes using a true hypodermic syringe.

The latter half of the 19th century brought increasing concern for safety in the administration of parenteral solutions, largely because of the work of Robert Koch and Louis Pasteur. While Charles Chamberland was developing both hot-air and steam sterilization techniques and the first bacteria-retaining filter (made of unglazed porcelain), Stanislaus Limousin was developing a suitable container, the all-glass ampul. In the middle 1920s Dr Florence Seibert provided proof that the disturbing chills and fever that often followed the intravenous injection of drugs was caused by potent products of microbial growth, pyrogens, which could be eliminated from water by distillation and from glassware by heating at elevated temperatures.

Of the technical developments that have contributed to the high quality standards currently achievable in the preparation of parenteral dosage forms, the two that probably have contributed most are the development of high-efficiency particulate air (HEPA)-filtered laminar airflow and membrane microfiltration for solutions. The former made it possible to achieve ultraclean environmental conditions for processing, and the latter to achieve removal from solutions by filtration of both viable and non viable particles of microbial size and smaller. However, many other developments in recent years have produced an impressive advance in the technology associated with the safe and reliable preparation of parenteral dosage forms. The following list identifies a few of the events that have contributed to that development.

1926—Parenterals were accepted for inclusion in the fifth edition of the *National Formulary.*
1933—The practical application of freeze-drying to clinical materials was accomplished by a team of scientists at the University of Pennsylvania.
1938—The Food, Drug and Cosmetic Act was passed by Congress, establishing the Food and Drug Administration (FDA).
1944—The sterilant ethylene oxide was discovered.
1946—The Parenteral Drug Association was organized.
1961—The concept of laminar airflow was developed by WJ Whitfield.
1962—The FDA was authorized by Congress to establish current good manufacturing practice (cGMP or GMP) regulations.
1965—Total parenteral nutrition (TPN) was developed by SJ Dudrick.
1972—The Limulus Amebocyte Lysate test for pyrogens in parenteral products was developed by JF Cooper.
1974—The concept of validation of processes used in the manufacture of parenteral products was introduced by the FDA.
1977—The principles for clean-in-place (CIP) and steam-in-place (SIP) were introduced.
Early 1980s—Home health care emerged as an alternative for patients whose health status permitted release from a hospital to care in the home environment.
1982—Insulin, derived through the new discipline of biotechnology, ushered in the drug class of polypeptides with their inherent stability challenges for parenteral dosage-form development.
1987—Parametric release was accepted by the FDA for selected products terminally sterilized by a validated heat process.
The FDA published *Guideline on Sterile Products Produced by Aseptic Processing,* one of several nonregulatory publications to help industry know what the FDA considers to be acceptable.
Late 1980s—The development of computer capabilities has led to the automation of many process operations and to a revolution in documentation and recordkeeping.
1991—The FDA proposed requiring manufacturers to use a terminal sterilization process when preparing a sterile drug product unless such a process adversely affects the drug product.
Mid-1990s—The development of isolator technology to separate the product from the operator(s) to increase the sterility-assurance level of the processed product.
1995—The USP published an informational chapter, ⟨1206⟩ on the preparation of sterile products by pharmacists.

*Deceased

Late 1990s—Acceleration of international cooperation in establishing standards for the pharmaceutical industry.

ADMINISTRATION

Injections may be classified in six general categories:

1. Solutions ready for injection.
2. Dry, soluble products ready to be combined with a solvent just prior to use.
3. Suspensions ready for injection.
4. Dry, insoluble products ready to be combined with a vehicle just prior to use.
5. Emulsions.
6. Liquid concentrates ready for dilution prior to administration.

These injections may be administered by such routes as intravenous, subcutaneous, intradermal, intramuscular, intraarticular, and intrathecal. The nature of the product will determine the particular route of administration that may be employed. Conversely, the desired route of administration will place requirements on the formulation. For example, suspensions would not be administered directly into the bloodstream because of the danger of insoluble particles blocking capillaries. Solutions to be administered subcutaneously require strict attention to tonicity adjustment, otherwise irritation of the plentiful supply of nerve endings in this anatomical area would give rise to pronounced pain. Injections intended for intraocular, intraspinal, intracisternal, and intrathecal administration require the highest purity standards because of the sensitivity of tissues encountered to irritant and toxic substances.

When compared with other dosage forms, injections possess select advantages. If immediate physiological action is needed from a drug, it usually can be provided by the intravenous injection of an aqueous solution. Modification of the formulation or another route of injection can be used to slow the onset and prolong the action of the drug. The therapeutic response of a drug is controlled more readily by parenteral administration, since the irregularities of intestinal absorption are circumvented. Also, since the drug normally is administered by a professionally trained person, it confidently may be expected that the dose was actually and accurately administered. Drugs can be administered parenterally when they cannot be given orally because of the unconscious or uncooperative state of the patient or because of inactivation or lack of absorption in the intestinal tract. Among the disadvantages of this dosage form are the requirement of asepsis at administration, the risk of tissue toxicity from local irritation, the real or psychological pain factor, and the difficulty in correcting an error, should one be made. In the latter situation, unless a direct pharmacological antagonist is immediately available, correction of an error may be impossible. One other disadvantage is that daily or frequent administration poses difficulties, patients must either visit a professionally trained person or learn to inject themselves. However, the advent of home health care as an alternative to extended institutional care has mandated the development of programs for training lay persons to administer these dosage forms.

PARENTERAL COMBINATIONS

During the administration of large-volume injections (LVIs), such as 1000 mL of 0.9% sodium chloride solution, it is common practice for a physician to order the addition of a small-volume therapeutic injection (SVI), such as an antibiotic, to avoid the discomfort for the patient of a separate injection. While the pharmacist is the most qualified health professional to be responsible for preparing such combinations, as is clearly stated in the hospital accreditation manual of the Joint Commission on Accreditation of Healthcare Organizations,[2] interactions among the combined products can be troublesome even for the pharmacist. In fact, incompatibilities can occur and cause inactivation of one or more ingredients or other undesired reactions. Patient deaths have been reported from the precipitate formed by two incompatible ingredients. In some instances incompatibilities are visible as precipitation or color change, but in other instances there may be no visible effect.

The many potential combinations present a complex situation even for the pharmacist. To aid in making decisions concerning potential problems, a valuable compilation of relevant data has been assembled by Trissel[3] and is updated regularly. Further, the advent of computerized data storage and retrieval systems has provided a means to organize and gain rapid access to such information. Further information on this subject may be found in Chapter 42.

As studies have been undertaken and more information has been gained, it has been shown that knowledge of variable factors such as pH and the ionic character of the active constituents aids substantially in understanding and predicting potential incompatibilities. Kinetic studies of reaction rates may be used to describe or predict the extent of degradation. Ultimately, a thorough study should be undertaken of each therapeutic agent in combination with other drugs and IV fluids, not only of generic but also of commercial preparations, from the physical, chemical, and therapeutic aspects.

Ideally, no parenteral combination should be administered unless it has been studied thoroughly to determine its effect on the therapeutic value and the safety of the combination. However, such an ideal situation may not exist. Nevertheless, it is the responsibility of the pharmacist to be as familiar as possible with the physical, chemical, and therapeutic aspects of parenteral combinations and to exercise the best possible judgment as to whether or not the specific combination extemporaneously prescribed is suitable for use in a patient.

GENERAL CONSIDERATIONS

An inherent requirement for parenteral preparations is that they be of the very best quality and provide the maximum safety for the patient. Further, the constant adherance to high moral and professional ethics on the part of the responsible persons are the ingredients most vital to achieving the desired quality in the products prepared.

Types of Processes

The preparation of parenteral products may be categorized as small-scale dispensing, usually one unit at a time, or large-scale manufacturing, in which hundreds of thousands of units may constitute one lot of product. The former category illustrates the type of processing that is done in institutions such as hospital pharmacies. The latter category is typical of the processing done in the pharmaceutical industry, where the vast majority of parenteral products marketed today are made. Wherever they are made, parenteral products must be subjected to the same basic practices of good aseptic processing essential for the preparation of a safe and effective sterile product of very high quality, but the methods used must be modified appropriately for the scale of operation.

The small-scale preparation and dispensing of parenteral products usually uses sterile components in their preparation. Therefore, the overall process focuses on maintaining rather than achieving sterility in the process steps. Further, the final product normally has a shelf life measured in hours, as in a hospital setting. However, the extensive movement of patients out of the hospital to home care has modified dispensing of parenteral products, wherein multiple units are made for a given patient, and a shelf life of 30 days or more is required.

Such products are sometimes made in hospital pharmacies but increasingly in centers set up to provide this service. A discussion of such processing can be found in USP 24, ⟨1206⟩.

This chapter emphasizes the preparation of parenteral products from nonsterile components in the highly technologically advanced plants of the pharmaceutical industry, using cGMP principles. In the pursuit of cGMP, consideration should be given to

1. Ensuring that the personnel responsible for assigned duties are capable and qualified to perform them.
2. Ensuring that ingredients used in compounding the product have the required identity, quality, and purity.
3. Validating critical processes to be sure that the equipment used and the processes followed will ensure that the finished product will have the qualities expected.
4. Maintaining a production environment suitable for performing the critical processes required, addressing such matters as orderliness, cleanliness, asepsis, and avoidance of cross contamination.
5. Confirming through adequate quality-control procedures that the finished products have the required potency, purity, and quality.
6. Establishing through appropriate stability evaluation that the drug products will retain their intended potency, purity, and quality until the established expiration date.
7. Ensuring that processes always are carried out in accord with established, written procedures.
8. Providing adequate conditions and procedures for the prevention of mixups.
9. Establishing adequate procedures, with supporting documentation, for investigating and correcting failures or problems in production or quality control.
10. Providing adequate separation of quality-control responsibilities from those of production to ensure independent decision making.

The pursuit of cGMP is an ongoing effort that must flex with new technological developments and new understanding of existing principles. Because of the extreme importance of quality in health care of the public, the US Congress has given the responsibility of regulatory scrutiny over the manufacture and distribution of drug products to the FDA. Therefore, the operations of the pharmaceutical industry are subject to the oversight of the FDA and, with respect to manufacturing practices, to the application of the cGMPs.[4] These regulations are discussed more fully in Chapter 51.

In concert with the pursuit of cGMPs, the pharmaceutical industry has shown initiative and innovation in the extensive technological development and improvement in quality, safety, and effectiveness of parenteral dosage forms in recent years, eg, developments in sterilizing filtration, aseptic processing technology, and the control of particulate matter. These factors have been additive in providing the public with outstanding parenteral dosage forms of drugs at this time in history.

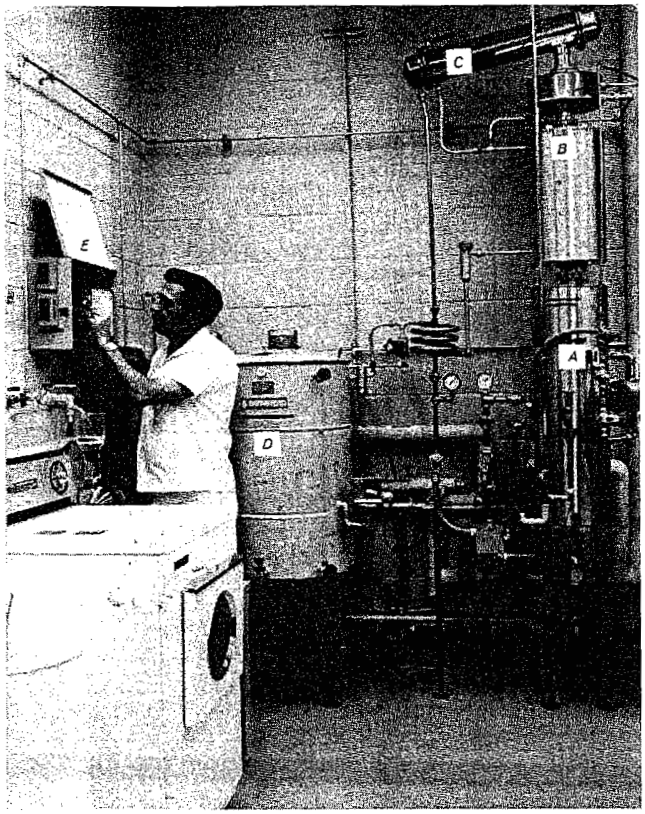

Figure 41-1. High-purity stilled and sealed water-storage system. *A,* evaporator; *B,* high-purity baffle unit; *C,* condenser; *D,* storage tank with ultraviolet lamp; *E,* control panel (courtesy, Ciba-Geigy).

GENERAL MANUFACTURING PROCESS

The preparation of a parenteral product may be considered to encompass four general areas

1. Procurement and accumulation in a warehouse area until released to manufacturing.
2. Processing the dosage form in appropriately designed and operated facilities.
3. Packaging and labeling in a quarantine area to ensure integrity and completion of the product.
4. Controlling the quality of the product throughout the process.

Procurement encompasses selecting and testing according to specifications of the raw-material ingredients and the containers and closures for the primary and secondary packages.

Processing includes cleaning containers and equipment to validated specifications, compounding the solution (or other dosage form), filtering the solution, sanitizing or sterilizing the containers and equipment, filling measured quantities of product into the sterile containers, and, finally, sealing them.

Packaging normally consists of the labeling and cartoning filled and sealed primary containers. The control of quality begins with the incoming supplies, being sure that specifications are met. Each step of the process involves checks and tests to be sure that the developing product is meeting the required specifications at the respective step. Finally, the quality control department must review the batch history and perform the release testing required to clear the product for shipment to users.

The following pages of this chapter present material organized in the approximate manner just discussed.

COMPONENTS

Establishing specifications to ensure the quality of each of the components of an injection is essential. These specifications will be coordinated with the requirements of the specific formulation and will not necessarily be identical for a particular component used in several different formulations. For example, particle-size control may be necessary for powders used in formulating a suspension but be relatively unimportant for preparing a solution.

The most stringent chemical-purity requirements normally will be encountered with aqueous solutions, particularly if the product is to be sterilized at an elevated temperature where reaction rates will be accelerated greatly. Modification of aque-

ous vehicles to include a glycol, for example, usually will reduce reaction rates. Dry preparations pose relatively few reaction problems but may require definitive physical specifications for ingredients that must have certain solution or dispersion characteristics when a vehicle is added.

Containers and closures are in prolonged, intimate contact with the product and may release substances into, or remove ingredients from, the product. Assessment and selection of containers and closures are necessary parts of product formulation, to ensure that the product retains its purity, potency, and quality during the intimate contact with the container throughout its shelf life. Administration devices that come in contact with the product should be assessed and selected with the same care as are containers and closures, even though the contact period is usually brief.

VEHICLES

Since most liquid injections are quite dilute, the component present in the highest proportion is the vehicle. A vehicle normally has no therapeutic activity and is nontoxic. However, it is of great importance in the formulation, since it presents to body tissues the form of the active constituent for absorption. Absorption normally occurs most rapidly and completely when a drug is presented as an aqueous solution. Modification of the vehicle with water-miscible liquids or substitution with water-immiscible liquids normally decreases the rate of absorption. Absorption from a suspension may be affected by such factors as the viscosity of the vehicle, its capacity for wetting the solid particles, the solubility equilibrium produced by the vehicle, and the distribution coefficient between the vehicle and aqueous body systems.

The vehicle of greatest importance for parenteral products is water. Water of suitable quality for compounding and rinsing product contact surfaces may be prepared either by distillation or by reverse osmosis, to meet USP specifications for Water for Injection (WFI). Only by these two methods is it possible to separate adequately various liquid, gas, and solid contaminating substances from water. These two methods for preparation of WFI are discussed in this chapter. It should be noted that there is no unit operation more important and none more costly to install and operate than the one for the preparation of WFI.

Preparation of Water for Injection (WFI)

The source water can be expected to be contaminated with natural suspended mineral and organic substances, dissolved mineral salts, colloidal silicates, and industrial or agricultural chemicals. The degree of contamination will vary with the source and will be markedly different, whether obtained from a well or from surface sources, such as a stream or lake. Hence, the source water usually must be pretreated by one or a combination of the following treatments: chemical softening, filtration, deionization, carbon adsorption, or reverse osmosis purification. Space does not permit discussion of these processes here; the interested reader is referred elsewhere for this information.[5,6]

In general, a conventional still consists of a boiler (evaporator) containing feed water (distilland); a source of heat to vaporize the water in the evaporator; a headspace above the level of distilland, with condensing surfaces for refluxing the vapor, thereby returning nonvolatile impurities to the distilland; a means for eliminating volatile impurities before the hot water vapor is condensed; and a condenser for removing the heat of vaporization, thereby converting the water vapor to a liquid distillate.

The specific construction features of a still and the process specifications will have a marked effect on the quality of distillate obtained from a still. Several factors must be considered in selecting a still to produce WFI.

1. The quality of the feed water will affect the quality of the distillate. Controlling the quality of the feed water is essential for meeting the required specifications for the distillate.
2. The size of the evaporator will affect the efficiency. It should be large enough to provide a low vapor velocity, thus reducing the entrainment of the distilland either as a film on vapor bubbles or as separate droplets.
3. The baffles (condensing surfaces) determine the effectiveness of refluxing. They should be designed for efficient removal of the entrainment at optimal vapor velocity, collecting and returning the heavier droplets contaminated with the distilland.
4. Redissolving volatile impurities in the distillate reduces its purity. Therefore, they should be separated efficiently from the hot water vapor and eliminated by aspirating them to the drain or venting them to the atmosphere.
5. Contamination of the vapor and distillate from the metal parts of the still can occur. Present standards for high-purity stills are that all parts contacted by the vapor or distillate should be constructed of metal coated with pure tin, 304 or 316 stainless-steel, or chemically resistant glass.

The design features of a still also influence its efficiency of operation, relative freedom from maintenance problems, or extent of automatic operation. Stills may be constructed of varying size, rated according to the volume of distillate that can be produced per hour of operation under optimum conditions. Only stills designed to produce high-purity water may be considered for use in the production of WFI. Conventional commercial stills designed for the production of high-purity water are available from several suppliers (see Fig 41-1) *(AMSCO, Barnstead, Corning, Vaponics)*.

COMPRESSION DISTILLATION—The vapor-compression still, primarily designed for the production of large volumes of high-purity distillate with low consumption of energy and water, is illustrated diagrammatically in Figure 41-2. To start, the feed water is heated from an external source in the evaporator to boiling. The vapor produced in the tubes is separated from the entrained distilland in the separator and conveyed to a compressor that compresses the vapor and raises its temperature to approximately 107°. It then flows to the steam chest where it condenses on the outer surfaces of the tubes containing the distilland; the vapor is thus condensed and drawn off as a distillate, while giving up its heat to bring the distilland in the tubes to the boiling point.

Vapor-compression stills are available in capacities from 50 to 2800 gal/hr *(Aqua-Chem, Barnstead, Meco)*.

MULTIPLE-EFFECT STILLS—The multiple-effect still also is designed to conserve energy and water usage. In principle, it is simply a series of single-effect stills running at

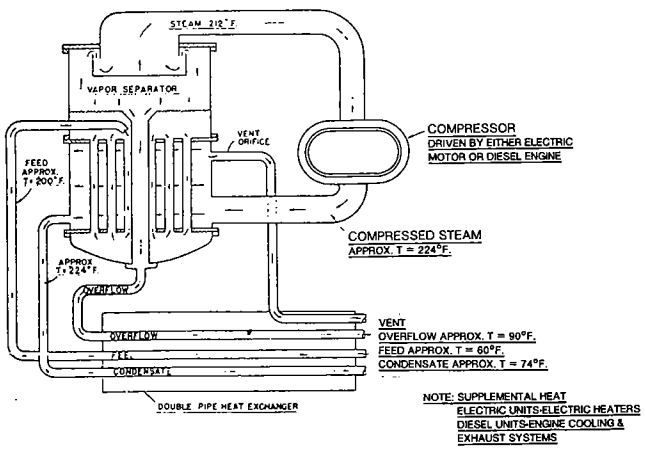

Figure 41-2. Vapor-compression still.

differing pressures. A series of up to seven effects may be used, with the first effect operated at the highest pressure and the last effect at atmospheric pressure. See a schematic drawing of a multiple-effect still in Figure 41-3. Steam from an external source is used in the first effect to generate steam under pressure from feed water; it is used as the power source to drive the second effect. The steam used to drive the second effect condenses as it gives up its heat of vaporization and forms a distillate. This process continues until the last effect, when the steam is at atmospheric pressure and must be condensed in a heat exchanger.

The capacity of a multiple-effect still can be increased by adding effects. The quantity of the distillate also will be affected by the inlet steam pressure; thus, a 600-gal/hr unit designed to operate at 115 psig steam pressure could be run at approximately 55 psig and would deliver about 400 gal/hr. These stills have no moving parts and operate quietly. They are available in capacities from about 50 to 7000 gal/hr *(AMSCO, Barnstead, Finn-Aqua, Kuhlman, Vaponics)*.

REVERSE OSMOSIS (RO)—As the name suggests, the natural process of selective permeation of molecules through a semipermeable membrane separating two aqueous solutions of different concentrations is reversed. Pressure, usually between 200 and 400 psig, is applied to overcome osmotic pressure and force pure water to permeate through the membrane. Membranes, usually composed of cellulose esters or polyamides, are selected to provide an efficient rejection of contaminant molecules in raw water. The molecules most difficult to remove are small inorganic ones such as sodium chloride. Passage through two membranes in series is sometimes used to increase the efficiency of removal of these small molecules and to decrease the risk of structural failure of a membrane to remove other contaminants, such as bacteria and pyrogens. For additional information, see *Reverse Osmosis* in Chapter 36 and *Water* in Chapters 39 and 55.

Reverse osmosis systems are available in a range of production sizes (*AMSCO, Aqua-Chem, Finn-Aqua, Meco, Millipore,* etc).

Whichever system is used for the preparation of WFI, validation is required to be sure that the system, consistently and reliably, will produce the chemical, physical, and microbiological quality of water required. Such validation should start with the determined characteristics of the source water and include the pretreatment, production, storage, and distribution systems. All of these systems together, including their proper operation and maintenance, determine the ultimate quality of the WFI. Because of space limitations here, more details concerning the design, operation, and validation of these highly important systems may be found in other literature sources.[5,6]

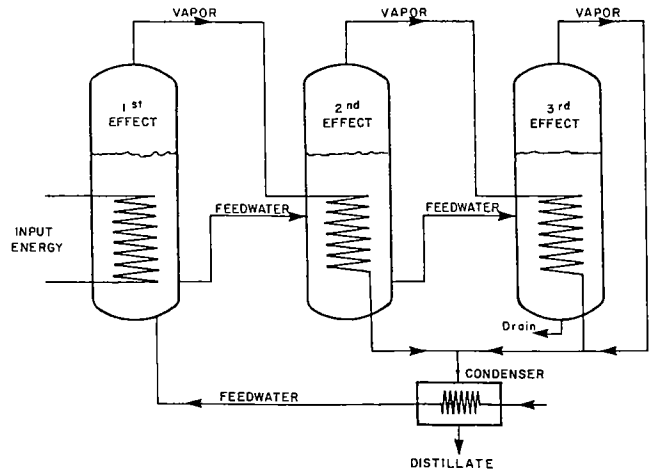

Figure 41-3. Multiple-effect still (courtesy, Dekker). (From Avis KE, Lieberman HA, Lachman L. *Pharmaceutical Dosage Forms: Parenteral Medications,* vol 2, 2nd ed. New York: Dekker, 1993.)

STORAGE AND DISTRIBUTION—The rate of production of WFI usually is not sufficient to meet processing demands; therefore, it is collected in a holding tank for subsequent use. In large operations the holding tanks may have a capacity of several thousand gallons and be a part of a continuously operating system. In such instances the USP requires that the WFI be held at a temperature too high for microbial growth. Normally, this temperature is a constant 80°.

The USP also permits the WFI to be stored at room temperature but for a maximum of 24 hr. Under such conditions the WFI usually is collected as a batch for a particular use with any unused water being discarded within 24 hr. Such a system requires frequent sanitization to minimize the risk of viable microorganisms being present. The stainless-steel storage tanks in such systems usually are connected to a welded stainless-steel distribution loop supplying the various use sites with a continuously circulating water supply. The tank is provided with a hydrophobic membrane vent filter capable of excluding bacteria and nonviable particulate matter. Such a vent filter is necessary to permit changes in pressure during filling and emptying. The construction material for the tank and connecting lines usually is electropolished 316L stainless steel with welded pipe. The tanks also may be lined with glass or a coating of pure tin. Such systems are very carefully designed and constructed and often constitute the most costly installation within the plant.

When the water cannot be used at 80°, heat exchangers must be installed to reduce the temperature at the point of use. Bacterial retentive filters should not be installed in such systems because of the risk of bacterial buildup on the filters and the consequent release of pyrogenic substances.

PURITY—While certain purity requirements have been alluded to above, the USP monographs provide the official standards of purity for WFI and Sterile Water for Injection (SWFI).

The chemical and physical standards for WFI recently have undergone significant changes, culminating in the simplified specifications in supplement 8 of USP 23. The only physical/chemical tests remaining are the new *total organic carbon* (TOC), with a limit of 500 ppb, and *conductivity,* with a limit of 1.3 μS/cm at 25 or 1.1 μS/cm at 20. The former is an instrumental method capable of detecting all organic carbon present, and the latter is a three-tiered instrumental test measuring the conductivity contributed by ionized particles (in microSiemens or micromhos) relative to pH. Since conductivity is integrally related to pH, the pH requirement of 5 to 7 in previous revisions has been eliminated. The TOC and conductivity specifications are now considered to be adequate minimal predictors of the chemical/physical purity of WFI. However, the *wet chemistry* tests still are used when WFI is packaged for commercial distribution and for SWFI.

Biological requirements continue to be, for WFI, not more than 10 colony-forming units (CFUs)/mL and 0.25 USP endotoxin units/mL. The SWFI requirements differ in that since it is a final product, it must pass the USP Sterility Test.

WFI and SWFI may not contain added substances. Bacteriostatic Water for Injection (BWFI) may contain one or more suitable antimicrobial agents in containers of 30 mL or less. This restriction is designed to prevent the administration of a large quantity of a bacteriostatic agent that probably would be toxic in the accumulated amount of a large volume of solution, even though the concentration was low.

The USP also provides monographs giving the specifications for Sterile Water for Inhalation and Sterile Water for Irrigation. The USP should be consulted for the minor differences between these specifications and those for SWFI.

Types of Vehicles

AQUEOUS VEHICLES—Certain aqueous vehicles are recognized officially because of their valid use in parenterals. Often they are used as isotonic vehicles to which a drug may be added at the time of administration. The additional osmotic effect of the drug may not be enough to produce any discomfort when administered. These vehicles include Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection.

WATER-MISCIBLE VEHICLES—A number of solvents that are miscible with water have been used as a portion of the vehicle in the formulation of parenterals. These solvents are used primarily to affect the solubility of certain drugs and to reduce hydrolysis. The most important solvents in this group are ethyl alcohol, liquid polyethylene glycol and propylene glycol. Ethyl alcohol is used particularly in the preparation of solutions of cardiac glycosides and the glycols in solutions of barbiturates, certain alkaloids and certain antibiotics. Such preparations usually are given intramuscularly. These solvents, as well as nonaqueous vehicles, have been reviewed by Spiegel and Noseworthy.[6]

NONAQUEOUS VEHICLES—The most important group of nonaqueous vehicles are the fixed oils. The USP provides specifications for such vehicles, indicating that the fixed oils must be of vegetable origin so that they will be metabolized, will be liquid at room temperature, and will not become rancid readily. The USP also specifies limits for the degree of unsaturation and free fatty acid content. The oils most commonly used are corn oil, cottonseed oil, peanut oil, and sesame oil. Fixed oils are used particularly as vehicles for certain hormone preparations. The label must state the name of the vehicle so that the user may beware in case of known sensitivity or other reactions to it.

SOLUTES

Care must be taken in selecting bulk active chemicals and excipients to ensure that their quality is suitable for parenteral administration. A low microbial level will enhance the effectiveness of either the aseptic or terminal sterilization process used for the drug product. Likewise, nonpyrogenic ingredients enhance the nonpyrogenicity of the finished injectable product. Chemical impurities should be virtually nonexistent in bulk substances for parenterals, because impurities are not likely to be removed by the processing of the product. Depending on the chemical involved, even trace residues may be harmful to the patient or cause stability problems in the product. Therefore, the compounder should use the best grade of chemicals obtainable and use its analytical profile to determine that each lot of chemical used in the formulation meets the required specifications.

Reputable chemical manufacturers accept the stringent quality requirements for parenteral products and, accordingly, apply good manufacturing practices to their chemical manufacturing. Examples of critical bulk manufacturing precautions include using dedicated equipment or properly validated cleaning to prevent cross-contamination and transfer of impurities, using WFI for rinsing equipment and for bulk manufacturing steps not followed by further purification, using closed systems wherever possible, and adhering to specified endotoxin and bioburden testing limits for the substance.

ADDED SUBSTANCES—The USP includes in this category all substances added to a preparation to improve or safeguard its quality. An added substance may

Effect solubility, as does sodium benzoate in Caffeine and Sodium Benzoate Injection.

Provide patient comfort, as do substances added to make a solution isotonic or near physiological pH.

Enhance the chemical stability of a solution, as do antioxidants, inert gases, chelating agents, and buffers.

Protect a preparation against the growth of microorganisms. The term *preservative* sometimes is applied only to those substances that prevent the growth of microorganisms in a preparation. However, such limited use is inappropriate, being better used for all substances that act to retard or prevent the chemical, physical, or biological degradation of a preparation.

While added substances may prevent a certain reaction from taking place, they may induce others. Not only may visible incompatibilities occur, but hydrolysis, complexation, oxidation, and other invisible reactions may decompose or otherwise inactivate the therapeutic agent or other added substances. Therefore, added substances must be selected with due consideration and investigation of their effect on the total formulation and the container-closure system.

ANTIMICROBIAL AGENTS—The USP states that antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to preparations contained in multiple-dose containers. They must be present in adequate concentration at the time of use to prevent the multiplication of microorganisms inadvertently introduced into the preparation while withdrawing a portion of the contents with a hypodermic needle and syringe. The USP provides a test for Antimicrobial Preservative Effectiveness to determine that an antimicrobial substance or combination adequately inhibits the growth of microorganisms in a parenteral product. Because antimicrobials may have inherent toxicity for the patient, the USP prescribes concentration limits for those that are used commonly in parenteral products, eg

Phenylmercuric nitrate and thimerosal 0.01%.
Benzethonium chloride and benzalkonium chloride 0.01%.
Phenol or cresol 0.5%.
Chlorobutanol 0.5%.

The above limit rarely is used for phenylmercuric nitrate, most frequently employed in a concentration of 0.002%. Methyl *p*-hydroxybenzoate 0.18% and propyl *p*-hydroxybenzoate 0.02% in combination, and benzyl alcohol 2% also are used frequently. In oleaginous preparations, no antibacterial agent commonly employed appears to be effective. However, it has been reported that hexylresorcinol 0.5% and phenylmercuric benzoate 0.1% are moderately bactericidal. A few therapeutic compounds have been shown to have antibacterial activity, thus obviating the need for added agents.

Antimicrobial agents must be studied with respect to compatibility with all other components of the formula. In addition, their activity must be evaluated in the total formula. It is not uncommon to find that a particular agent will be effective in one formulation but ineffective in another. This may be due to the effect of various components of the formula on the biological activity or availability of the compound; for example, the binding and inactivation of esters of *p*-hydroxybenzoic acid by macromolecules such as Polysorbate 80 or the reduction of phenylmercuric nitrate by sulfide residues in rubber closures. A physical reaction encountered is that bacteriostatic agents sometimes are removed from solution by rubber closures.

Single-dose containers and pharmacy bulk packs that do not contain antimicrobial agents are expected to be used promptly after opening or to be discarded. Large-volume, single-dose containers may not contain an added antimicrobial preservative. Therefore, special care must be exercised in storing such products after the containers have been opened to prepare an admixture, particularly those that can support the growth of microorganisms, such as total parenteral nutrition (TPN) solutions and emulsions. It should be noted that while refrigeration slows the growth of most microorganisms, it does not prevent their growth.

Buffers are used primarily to stabilize a solution against the chemical degradation that might occur if the pH changes appreciably. Buffer systems employed should normally have as low a buffering capacity as feasible so as not to disturb significantly the body's buffering systems when injected. In addition, the buffer range and effect on the activity of the product must

be evaluated carefully. The acid salts most frequently employed as buffers are citrates, acetates, and phosphates.

Antioxidants are required frequently to preserve products because of the ease with which many drugs are oxidized. Sodium bisulfite 0.1% is used most frequently. The use of sulfites has been reviewed by Schroeter.[7] Acetone sodium bisulfite, sodium formaldehyde sulfoxylate, and thiourea also are used sometimes. The sodium salt of ethylenediaminetetraacetic acid has been found to enhance the activity of antioxidants in some cases, apparently by chelating metallic ions that would otherwise catalyze the oxidation reaction.

Displacing the air (oxygen) in and above the solution by purging with an inert gas, such as nitrogen, also can be used as a means to control oxidation of a sensitive drug. Process control is required for assurance that every container is deaerated adequately and uniformly.

Tonicity agents are used in many parenteral and ophthalmic products to adjust the tonicity. However, not all preparations need to be isotonic. The agents most commonly used are electrolytes and mono- or disaccharides. This subject is considered much more extensively in Chapter 18.

A recent publication surveys excipients being used today in parenteral formulations in the United States.[8]

PYROGENS (ENDOTOXINS)

Pyrogens are products of metabolism of microorganisms. The most potent pyrogenic substances (endotoxins) are constituents of the cell wall of gram-negative bacteria. Gram-positive bacteria and fungi also produce pyrogens but of lower potency and of different chemical nature. Endotoxins are high-molecular-weight (about 20,000 daltons) lipopolysaccharides. Studies have shown that the lipid portion of the molecule is responsible for the biological activity. Since endotoxins are the most potent pyrogens and gram-negative bacteria are ubiquitous in the environment, this discussion focuses on endotoxins and the risk of their presence as contaminants in sterile products.

Pyrogens, when present in parenteral drug products and injected into patients, can cause fever, chills, pain in the back and legs, and malaise. While pyrogenic reactions are rarely fatal, they can cause serious discomfort and, in the seriously ill patient, shock-like symptoms that can be fatal. The intensity of the pyrogenic response and its degree of hazard will be affected by the medical condition of the patient, the potency of the pyrogen, the amount of the pyrogen, and the route of administration (intrathecal is most hazardous followed by intravenous, intramuscular, and subcutaneous). When bacterial (exogenous) pyrogens are introduced into the body, leukocytic phagocytosis is believed to occur, and endogenous pyrogen is produced. The endogenous pyrogen then produces the familiar physiological effects. Space does not permit further elaboration of these matters here; the reader is referred to the work by Pearson[9] if more information is needed.

CONTROL OF PYROGENS—Pyrogens are contaminants if present in parenteral drug products and should not be there. In general, it is impractical, if not impossible, to remove pyrogens once present without adversely affecting the drug product. Therefore, the emphasis should be on preventing the introduction or development of pyrogens in all aspects of the compounding and processing of the product.

Pyrogens may enter a preparation through any means that will introduce living or dead microorganisms. However, current technology generally permits the control of such contamination, and the presence of pyrogens in a finished product indicates processing under inadequately controlled conditions. It also should be noted that time for microbial growth to occur increases the risk for elevated levels of pyrogens. Therefore, compounding and manufacturing processes should be carried out as expeditiously as possible, preferably planning completion of the process, including sterilization, within one work day.

Pyrogens can be destroyed by heating at high temperatures. A typical procedure for depyrogenation of glassware and equipment is maintaining a dry heat temperature of 250° for 45 min. It has been reported that 650° for 1 min or 180° for 4 hr likewise will destroy pyrogens. The usual autoclaving cycle will not do so. Heating with strong alkali or oxidizing solutions will destroy pyrogens. It has been claimed that thorough washing with detergent will render glassware pyrogen-free if subsequently rinsed thoroughly with pyrogen-free water. Rubber stoppers cannot withstand pyrogen-destructive temperatures, so reliance must be placed on an effective sequence of washing, thorough rinsing with WFI, prompt sterilization, and protective storage to ensure adequate pyrogen control. Similarly, plastic containers and devices must be protected from pyrogenic contamination during manufacture and storage, since known ways of destroying pyrogens affect the plastic adversely. It has been reported that anion-exchange resins and positively charged membrane filters will remove pyrogens from water. Also, although reverse osmosis membranes will eliminate them, the most reliable method for their elimination from water is distillation.

A method that has been used for the removal of pyrogens from solutions is adsorption on adsorptive agents. However, since the adsorption phenomenon also may cause selective removal of chemical substances from the solution, this method has limited application. Other in-process methods for their destruction or elimination include selective extraction procedures and careful heating with dilute alkali, dilute acid, or mild oxidizing agents. In each instance, the method must be studied thoroughly to be sure it will not have an adverse effect on the constituents of the product. Although ultrafiltration now makes possible pyrogen separation on a molecular-weight basis and the process of tangential flow is making large-scale processing more practical, use of this technology is limited, except in biotechnological processing.

SOURCES OF PYROGENS—Through understanding the means by which pyrogens may contaminate parenteral products, their control becomes more achievable. Therefore, it is important to know that water is probably the greatest potential source of pyrogenic contamination, since water is essential for the growth of microorganisms. When microorganisms metabolize, pyrogens will be produced. Therefore, raw water can be expected to be pyrogenic and only when it is appropriately treated to render it free from pyrogens, such as WFI, should it be used for compounding the product or rinsing product contact surfaces such as tubing, mixing vessels, and rubber closures. Even when such rinsed equipment and supplies are left wet and improperly exposed to the environment, there is a high risk that they will become pyrogenic. Although proper distillation will provide pyrogen-free water, storage conditions must be such that microorganisms are not introduced and subsequent growth is prevented.

Other potential sources of contamination are containers and equipment. Pyrogenic materials adhere strongly to glass and other surfaces. Residues of solutions in used equipment often become bacterial cultures, with subsequent pyrogenic contamination. Since drying does not destroy pyrogens, they may remain in equipment for long periods. Adequate washing will reduce contamination and subsequent dry-heat treatment can render contaminated equipment suitable for use. However, all such processes must be validated to ensure their effectiveness.

Solutes may be a source of pyrogens. For example, the manufacturing of bulk chemicals may involve the use of pyrogenic water for process steps such as crystallization, precipitation, or washing. Bulk drug substances derived from fermentation will almost certainly be heavily pyrogenic. Therefore, all lots of solutes used to prepare parenteral products should be tested to ensure that they will not contribute unacceptable quantities of endotoxin to the finished product.

The manufacturing process must be carried out with great care and as rapidly as possible, to minimize the risk of microbial contamination. Preferably, no more product should be prepared than can be processed completely within one working day, including sterilization.

CONTAINERS AND CLOSURES

Containers are an integral part of the formulation of an injection. No container is totally insoluble or does not in some way affect the liquid it contains, particularly if the liquid is aqueous. Therefore, the selection of a container for a particular injection must be based on consideration of the composition of the container, as well as of the solution, and the treatment to which it will be subjected.

Table 41-1 provides a generalized comparison of the three compatibility properties—leaching, permeation, and adsorption—of container materials most likely to be involved in the formulation of aqueous parenterals. Further, the integrity of the container/closure system depends upon several characteristics, including container opening finish, closure modulus, durometer and compression set, and aluminum seal application force. These considerations have been reviewed by Morton.[10]

CONTAINER TYPES

Plastic

Thermoplastic polymers have been established as packaging materials for sterile preparations such as large-volume parenterals, ophthalmic solutions, and, increasingly, small-volume parenterals. For such use to be acceptable a thorough understanding of the characteristics, potential problems, and advantages for use must be developed. A historical review of these factors relative to pharmaceuticals has been prepared by Autian.[11] A discussion of polymers for IV solutions has been published by Lambert.[12] Autian stated that three principal problem areas exist in using these materials:

1. Permeation of vapors and other molecules in either direction through the wall of the plastic container.
2. Leaching of constituents from the plastic into the product.
3. Sorption (absorption and/or adsorption) of drug molecules or ions on the plastic material.

Permeation, the most extensive problem, may be troublesome by permitting volatile constituents, water, or specific drug molecules to migrate through the wall of the container to the outside and thereby be lost. This problem has been resolved, for example, by the use of an overwrap in the packaging of IV solutions in PVC bags to prevent the loss of water during storage. Reverse permeation also may occur in which oxygen or other molecules may penetrate to the inside of the container and cause oxidative or other degradation of susceptible constituents. Leaching may be a problem when certain constituents in the plastic formulation, such as plasticizers or antioxidants, migrate into the product. Thus, plastic polymer formulations should have as few additives as possible, an objective characteristically achievable for most plastics being used for parenteral packaging. *Sorption* is a problem on a selective basis, that is, sorption of a few drug molecules occurs on specific polymers. For example, sorption of insulin, vitamin A acetate, and warfarin sodium has been shown to occur on PVC bags and tubing when these drugs were present as additives in IV admixtures. A brief summary of some of these compatibility relationships is given in Table 41-1.

One of the principle advantages of using plastic packaging materials is that they are not breakable as is glass; also, there is a substantial weight reduction. The flexibility of the low-density polyethylene polymer, for ophthalmic preparations, makes it possible to squeeze the side wall of the container and discharge one or more drops without introducing contamination into the remainder of the product. The flexible bags of polyvinyl chloride or select polyolefins, currently in use for large-volume intravenous fluids, have the added advantage that no air interchange is required; the flexible wall simply collapses as the solution flows out of the bag.

Most plastic materials have the disadvantage that they are not as clear as glass and, therefore, inspection of the contents is impeded. In addition, many of these materials will soften or melt under the conditions of thermal sterilization. However, careful selection of the plastic used and control of the autoclave cycle has made thermal sterilization of some products possible, large-volume parenterals in particular. Ethylene oxide or radiation sterilization may be em-

Table 41-1. Comparative Compatibility Properties of Container Materials

	LEACHING		PERMEATION		ADSORPTION (SELECTIVE)
	EXTENT[a]	POTENTIAL LEACHABLES	EXTENT[a]	POTENTIAL AGENTS	EXTENT[a]
Glass					
Borosilicate	1	Alkaline earth and heavy metal oxides	0	N/A	2
Soda-lime	5	Alkaline earth and heavy metal oxides	0	N/A	2
Plastic polymers					
Polyethylene					
Low density	2	Plasticizers, antioxidants	5	Gases, water vapor, other molecules	2
High density	1	Antioxidants	3	Gases, water vapor, other molecules	2
PVC	4	HCl, especially plasticizers, antioxidants, other stabilizers	5	Gases, especially water vapor and other molecules	2
Polyolefins	2	Antioxidants	2	Gases, water vapor, other molecules	2
Polypropylene	2	Antioxidants, lubricants	4	Gases, water vapor	1
Rubber polymers					
Natural and related synthetic	5	Heavy metal salts, lubricants, reducing agents	3	Gases, water vapor	3
Butyl	3	Heavy metal salts, lubricants, reducing agents	1	Gases, water vapor	2
Silicone	2	Minimal	5	Gases, water vapor	1

[a] Approximate scale of 1 to 5, with 1 as the lowest.

ployed for the empty container with subsequent aseptic filling. However, careful evaluation of the residues from ethylene oxide or its degradation products and their potential toxic effect must be undertaken. Investigation is required concerning potential interactions and other problems that may be encountered when a parenteral product is packaged in plastic. For further details see Chapter 54.

Glass

Glass is employed as the container material of choice for most SVIs. It is composed principally of silicon dioxide, with varying amounts of other oxides such as sodium, potassium, calcium, magnesium, aluminum, boron, and iron. The basic structural network of glass is formed by the silicon oxide tetrahedron. Boric oxide will enter into this structure, but most of the other oxides do not. The latter are only loosely bound, are present in the network interstices, and are relatively free to migrate. These migratory oxides may be leached into a solution in contact with the glass, particularly during the increased reactivity of thermal sterilization. The oxides thus dissolved may hydrolyze to raise the pH of the solution and catalyze or enter into reactions. Additionally, some glass compounds will be attacked by solutions and, in time, dislodge glass flakes into the solution. Such occurrences can be minimized by the proper selection of the glass composition.[13]

TYPES—The USP has aided in this selection by providing a classification of glass:

Type I, a borosilicate glass.
Type II, a soda-lime treated glass.
Type III, a soda-lime glass.
NP, a soda-lime glass not suitable for containers for parenterals.

Type I glass is composed principally of silicon dioxide and boric oxide, with low levels of the non-network-forming oxides. It is a chemically resistant glass (low leachability) also having a low thermal coefficient of expansion.

Types II and III glass compounds are composed of relatively high proportions of sodium oxide and calcium oxide. This makes the glass chemically less resistant. Both types melt at a lower temperature, are easier to mold into various shapes, and have a higher thermal coefficient of expansion than Type I. While there is no one standard formulation for glass among manufacturers of these USP type categories, Type II glass usually has a lower concentration of the migratory oxides than Type III. In addition, Type II has been treated under controlled temperature and humidity conditions with sulfur dioxide or other dealkalizers to neutralize the interior surface of the container. While it remains intact, this surface will increase substantially the chemical resistance of the glass. However, repeated exposures to sterilization and alkaline detergents will break down this dealkalized surface and expose the underlying soda-lime compound.

The glass types are determined from the results of two USP tests: the Powdered Glass Test and the Water Attack Test. The latter is used only for Type II glass and is performed on the whole container, because of the dealkalized surface; the former is performed on powdered glass, which exposes internal surfaces of the glass compound. The results are based upon the amount of alkali titrated by 0.02 *N* sulfuric acid after an autoclaving cycle with the glass sample in contact with a high-purity distilled water. Thus, the *Powdered Glass Test* challenges the leaching potential of the interior structure of the glass while the *Water Attack Test* challenges only the intact surface of the container.

Selecting the appropriate glass composition is a critical facet of determining the overall specifications for each parenteral formulation.

In general, Type I glass will be suitable for all products, although sulfur dioxide treatment sometimes is used for a further increase in resistance. Because cost must be considered, one of the other, less-expensive types may be acceptable. Type II glass may be suitable, for example, for a solution that is buffered, has a pH below 7, or is not reactive with the glass. Type III glass usually will be suitable principally for anhydrous liquids or dry substances. However, some manufacturer-to-manufacturer variation in glass composition should be anticipated within each glass type. Therefore, for highly chemically sensitive parenteral formulations it may be necessary to specify both USP Type and a specific manufacturer.

PHYSICAL CHARACTERISTICS—Some of the physical shapes of glass ampuls and vials are illustrated in Figure 41-4. Commercially available containers vary in size from 0.5 to 1000 mL. Sizes up to 100 mL may be obtained as ampuls and vials, and larger sizes as bottles. The latter are used mostly for intravenous and irrigating solutions. Smaller sizes also are available as cartridges. Ampuls and cartridges are drawn from glass tubing. The smaller vials may be made by molding or from tubing. Larger vials and bottles are made only by molding. Containers made by drawing tubing are generally optically clearer and have a thinner wall than molded containers (Fig 41-4). Molded containers are uniform in external dimensions, stronger, and heavier.

Easy-opening ampuls that permit the user to break off the tip at the neck constriction without the use of a file are weakened at the neck by scoring or applying a ceramic paint with a different coefficient of thermal expansion. An example of a modification of container design to meet a particular need is the double-chambered vial, under the name Univial *(Univial),* designed to contain a freeze-dried product in the lower, and solvent in the upper, chamber. Other examples are wide-mouth ampuls with flat or rounded bottoms to facilitate filling with dry materials or suspensions, and various modifications of the cartridge for use with disposable dosage units.

Glass containers must be strong enough to withstand the physical shocks of handling and shipping and the pressure differentials that develop, particularly during the autoclave sterilization cycle. They must be able to withstand the thermal shock resulting from large temperature changes during processing, for example, when the hot bottle and contents are exposed to room air at the end of the sterilization cycle. Therefore, a glass with a low coefficient of thermal expansion is necessary. The container also must be transparent to permit inspection of the contents.

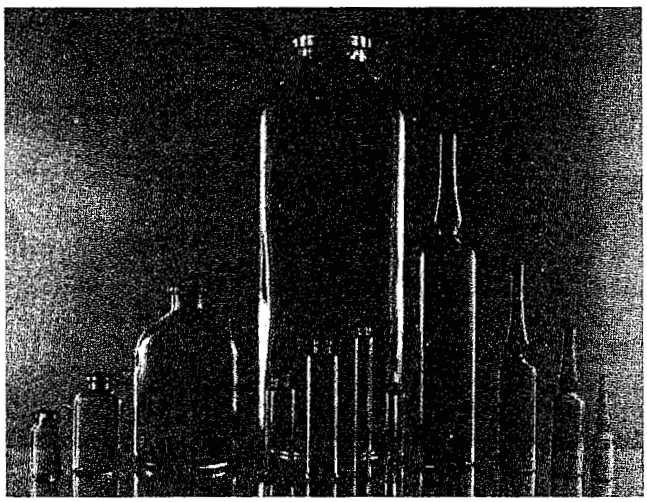

Figure 41-4. Various types of ampuls and multiple-dose vials for parenterals (courtesy, Kimble).

Preparations that are light-sensitive must be protected by placing them in amber glass containers or by enclosing flint glass containers in opaque cartons labeled to remain on the container during the period of use. It should be noted that the amber color of the glass is imparted by the incorporation of potentially leachable heavy metals, mostly iron and manganese, which may act as catalysts for oxidative degradation reactions. Silicone coatings sometimes are applied to containers to produce a hydrophobic surface, for example, as a means of reducing the friction of a rubber-tip of a syringe plunger.

The size of single-dose containers is limited to 1000 mL by the USP and multiple-dose containers to 30 mL, unless stated otherwise in a particular monograph. Multiple-dose vials are limited in size to reduce the number of punctures for withdrawing doses and the accompanying risk of contamination of the contents. As the name implies, single-dose containers are opened or penetrated with aseptic care, and the contents used at one time. These may range in size from 1000-mL bottles to 1-mL or less ampuls, vials, or syringes. The integrity of the container is destroyed when opened, so that the container cannot be closed and reused.

A multiple-dose container is designed so that more than one dose can be withdrawn at different times, the container maintaining a seal between uses. It should be evident that with full aseptic precautions, including sterile syringe and needle for withdrawing the dose and disinfection of the exposed surface of the closure, there is still a substantial risk of introducing contaminating microorganisms and viruses into the contents of the vial. Because of this risk, the USP requires that all multiple-dose vials must contain an antimicrobial agent or be inherently antimicrobial, as determined by the USP *Antimicrobial Preservatives-Effectiveness* tests. There are no comparable antiviral effectiveness tests, nor are antiviral agents available for such use. In spite of the advantageous flexibility of dosage provided by multiple-dose vials, single-dose, disposable container units provide the clear advantage of greater sterility assurance and patient safety.

RUBBER CLOSURES

To permit introduction of a needle from a hypodermic syringe into a multiple-dose vial and provide for resealing as soon as the needle is withdrawn, each vial is sealed with a rubber closure held in place by an aluminum cap. Figure 41-5 illustrates how this is done. This principle also is followed for single-dose containers of the cartridge type, except that there is only a single introduction of the needle to make possible the withdrawal or expulsion of the contents.

Rubber closures are composed of multiple ingredients that are plasticized and mixed together at an elevated temperature on milling machines. Subsequently, the plasticized mixture is placed in molds and vulcanized (cured) under high temperature and pressure. During vulcanization the polymer strands are cross-linked by the vulcanizing agent, assisted by the accelerator and activator, so that motion is restricted and the molded closure acquires the elastic, resilient character required for its use. Ingredients not involved in the cross-linking reactions remain dispersed within the compound and, along with the degree of curing, affect the properties of the finished closure. Examples of rubber-closure ingredients are given in Table 41-2.

Table 41-2. Examples of Ingredients Found in Rubber Closures

INGREDIENT	EXAMPLES
Elastomer	Natural rubber (latex)
	Butyl rubber
	Neoprene
Vulcanizing (curing) agent	Sulfur
	Peroxides
Accelerator	Zinc dibutyldithiocarbamate
Activator	Zinc oxide
	Stearic acid
Antioxidant	Dilauryl thiodipropionate
Plasticizer/lubricant	Paraffinic oil
	Silicone oil
Fillers	Carbon black
	Clay
	Barium sulfate
Pigments	Inorganic oxides
	Carbon black

The physical properties to be considered in the selection of a particular formulation include elasticity, hardness, tendency to fragment, and permeability to vapor transfer. The elasticity is critical in establishing a seal with the lip and neck of a vial or other opening and in resealing after withdrawal of a hypodermic needle from a vial closure. The hardness should provide firmness but not excessive resistance to the insertion of a needle through the closure, while minimal fragmentation of pieces of rubber should occur as the hollow shaft of the needle is pushed through the closure. While vapor transfer occurs to some degree with all rubber formulations, appropriate selection of ingredients makes it possible to control the degree of permeability. Physicochemical and toxicological tests for evaluating rubber closures are described in section ⟨381⟩ in the USP.

The ingredients dispersed throughout the rubber compound may be subject to leaching into the product contacting the closure. These ingredients, examples of which are given in Table 41-2, pose potential compatibility interactions with product ingredients if leached into the product solution, and these effects must be evaluated.[14,15] Further, some ingredients must be evaluated for potential toxicity. To reduce the problem of leachables, coatings have been applied to the product contact surfaces of closures, with various polymers, the most successful being Teflon. Recently, polymeric coatings have been developed that are claimed to have more integral binding with the rubber matrix, but details of their function are trade secrets.

The physical shape of some typical closures may be seen in Figure 41-5. Most of them have a lip and a protruding flange that extends into the neck of the vial or bottle. Many disk closures are being used now, particularly in the high-speed packaging of antibiotics. Slotted closures are used on freeze-dried products to permit the escape of water vapor, since they are inserted only partway into the neck of the vial until completion of the drying phase of the cycle. The plunger type is used to seal one end of a cartridge. At the time of use, the plunger expels the product by a needle inserted through the closure at the distal end of the cartridge. Intravenous solution closures often have permanent holes for adapters of administration sets; irrigating solution closures usually are designed for pouring.

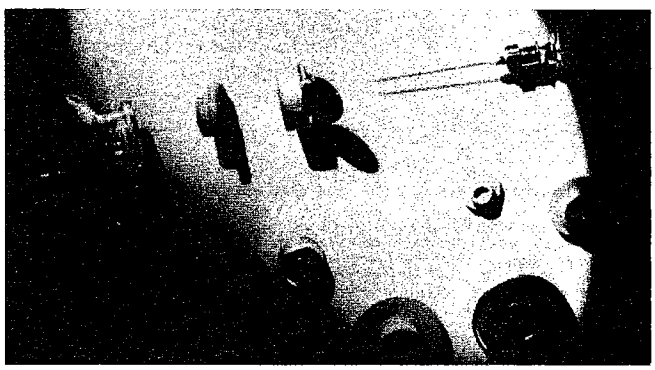

Figure 41-5. Extended view of sealing components for a multiple-dose vial (courtesy, West).

The production facility and its associated equipment must be designed, constructed, and operated properly for the manufacture of a sterile product to be achieved at the quality level required for safety and effectiveness. Further, the processes used must meet cGMP standards, both ethical and legal. In fact, the nearer these standards approach perfection, the better and safer should be the products.

FUNCTIONAL AREAS

To achieve the goal of a manufactured sterile product of exceptionally high quality, five functional production areas will be involved: warehousing or procurement, compounding, materials support, aseptic filling, and packaging and quarantine (see Fig 41-1). The extra requirements for the aseptic area are designed to provide an environment where, for example, a sterile fluid may be exposed to the environment for a brief period during subdivision from a bulk container to individual-dose containers without becoming contaminated. Contaminants such as dust, lint, and microorganisms normally are found floating in the air, lying on counters and other surfaces, on clothing and body surfaces of personnel, in the exhaled breath of personnel, and deposited on the floor. The design and control of an aseptic area is directed toward reducing the presence of these contaminants so that they are no longer a hazard to aseptic filling.

Although the aseptic area must be adjacent to support areas so that an efficient flow of components may be achieved, barriers must be provided to minimize ingress of contaminants to the critical aseptic area. Such barriers may consist of a variety of forms, including sealed walls, manual or automatic doors, airlock pass-throughs, ports of various types, or plastic curtains. Figure 41-6 shows an example of a floor plan for a clinical supply production facility (selected as an example of a small-scale, noncomplex facility), in which the two fill rooms and the staging area constitute the walled critical aseptic area, access to which is only by means of pass-through airlocks. Adjacent support areas (rooms) consist of glass preparation, equipment wash, capping, manufacturing (compounding), and various storage areas. Figure 41-7 shows an adjacent arrangement with the utilization of a through-the-wall port for passage of a filtrate into the critical aseptic filling room.

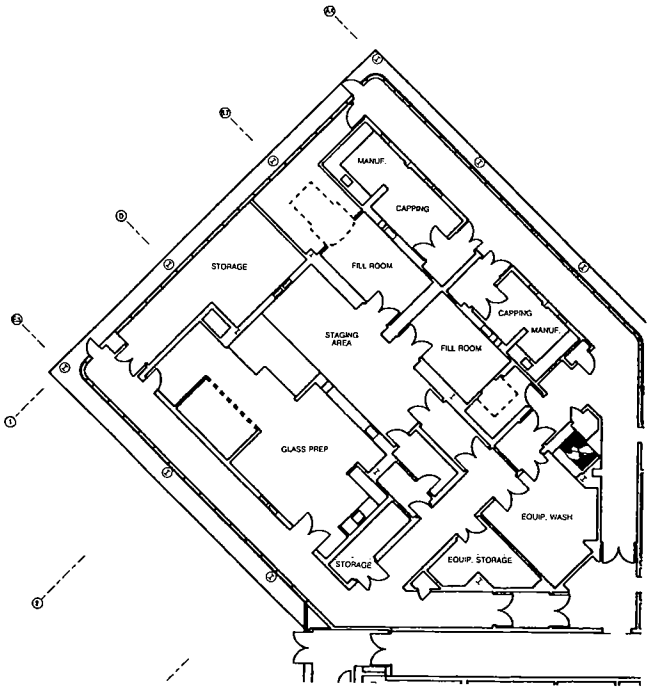

Figure 41-6. Floor plan of aseptic filling rooms and staging room with adjacent support areas (courtesy, Glaxo).

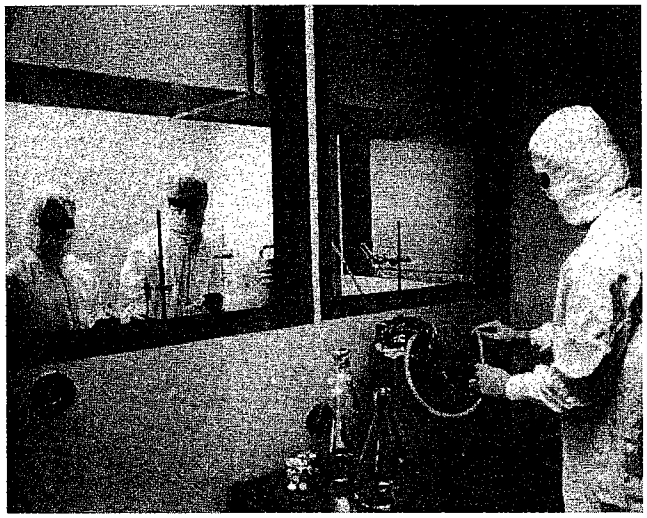

Figure 41-7. Product filtration from the aseptic staging room through a port into the aseptic filling room (courtesy, The University of Tennessee College of Pharmacy).

FLOW PLAN—In general, the components for a parenteral product flow (see Fig 41-1) either from the warehouse, after release, to the compounding area, as for ingredients of the formula, or to the materials support area, as for containers and equipment. After proper processing in these areas, the components flow into the security of the aseptic area for filling of the product in appropriate containers. From there the product passes into the quarantine and packaging area where it is held until all necessary tests have been performed. If the product is to be sterilized in its final container, its passage normally is interrupted after leaving the aseptic area for subjection to the sterilization process. After the results from all tests are known, the batch records have been reviewed, and the product has been found to comply with its release specifications, it passes to the finishing area for final release for shipment. There sometimes are variations from this flow plan to meet the specific needs of an individual product or to conform to existing facilities. Automated operations normally have much larger capacity and convey the components from one area to another with little or no handling by operators.

Clean Room Classified Areas

Because of the extremely high standards of cleanliness and purity that must be met by parenteral products, it has become standard practice to prescribe specifications for the environments in which these products are manufactured; ie, clean rooms. Clean room specifications are summarized in Federal Standard 209E[16], based on the maximum allowed number of airborne particles/ft^3, of 0.5 μm or larger size. The classifications used in pharmaceutical practice normally range from

Class 100,000 for materials support areas to Class 100 for aseptic areas. To achieve Class 100 conditions, HEPA filters are required for the incoming air, with the effluent air sweeping the downstream environment at a uniform velocity, normally 90 ft/min ± 20%, along parallel lines (laminar air flow). HEPA filters are defined as 99.97% or more efficient in removing from the air 0.3-μm particles generated by vaporized dioctylphthalate (DOP). More recently other agents, eg, the hydrocarbon Emory 3004, are being used because of concern about the toxicity of DOP.

AIR CLEANING—Since air is one of the greatest potential sources of contaminants in clean rooms, special attention must be given to air being drawn into clean rooms by the heating, ventilating, and air conditioning (HVAC) system. This may be done by a series of treatments that will vary somewhat from one installation to another.

In one such series air from the outside first is passed through a prefilter, usually of glass wool, cloth, or shredded plastic, to remove large particles. Then it may be treated by passage through an electrostatic precipitator (suppliers: *Am Air, Electro-Air*). Such a unit induces an electrical charge on particles in the air and removes them by attraction to oppositely charged plates. The air then passes through the most efficient cleaning device, a HEPA filter with an efficiency of at least 99.97% in removing particles of 0.3 μm and larger, based on the DOP (dioctylphthalate) test (suppliers: *Am Air, Cambridge, Flanders*).

For personnel comfort, air conditioning and humidity control should be incorporated into the system. The latter is also important for certain products such as those that must be lyophilized and for the processing of plastic medical devices. The clean, aseptic air is introduced into the Class 100 area and maintained under positive pressure, which prevents outside air from rushing into the aseptic area through cracks, temporarily open doors, or other openings.

LAMINAR-FLOW ENCLOSURES—The required environmental control of aseptic areas has been made possible by the use of laminar airflow, originating through a HEPA filter occupying one entire side of the confined space. Therefore, it bathes the total space with very clean air, sweeping away contaminants. The orientation for the direction of airflow can be horizontal (Fig 41-8) or vertical (see Fig 41-9), and may involve a limited area such as a workbench or an entire room. Figure 41-9 shows a vial-filling line protected with vertical laminar airflow from ceiling-hung HEPA filters, a Class 100 area. Plastic curtains are installed to maintain the laminarity of airflow to below the filling line and to circumscribe the critical filling portion of the line. The area outside the curtains can be maintained at a slightly lower level of cleanliness than that inside, perhaps Class 1000 or 10,000.

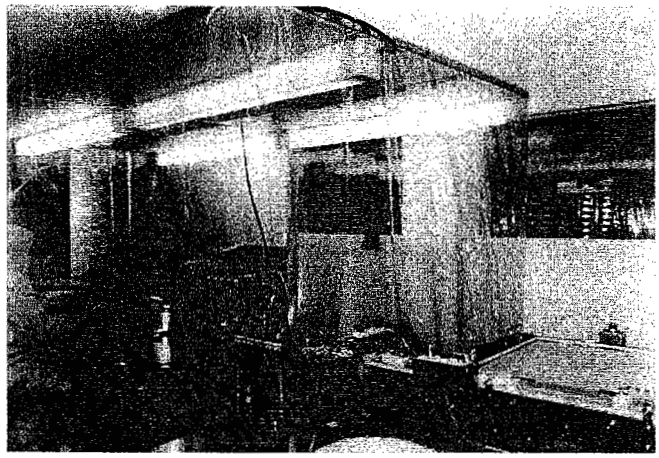

Figure 41-9. Vial filling line under vertical laminar airflow with critical area enclosed within plastic curtains (courtesy, Merck).

Today, it is accepted that critical areas of processing, wherein the product or product contact surfaces may be exposed to the environment, even for a brief period of time, should meet Class 100 clean room standards.

It must be borne in mind that any contamination introduced upstream by equipment, arms of the operator, or leaks in the filter will be blown downstream. In the instance of horizontal flow this may be to the critical working site, the face of the operator, or across the room. Should the contaminant be, for example, penicillin powder, a biohazard material, or viable microorganisms, the danger to the operator is apparent.

Further, great care must be exercised to prevent cross-contamination from one operation to another, especially with horizontal laminar air flow. For most large-scale operations, as shown in Figure 41-9, a vertical system is much more desirable, with the air flowing through perforations in the countertop or through return louvers at floor level, where it can be directed for decontamination. Laminar-flow environments provide well-controlled work areas only if proper precautions are observed. Any reverse air currents or movements exceeding the velocity of the HEPA-filtered airflow may introduce contamination, as may coughing, reaching, or other manipulations of operators. Therefore, laminar-flow work areas should be protected by being located within controlled environments. Personnel should be attired for aseptic processing, as described below. All movements and processes should be planned carefully to avoid the introduction of contamination upstream of the critical work area. Checks of the air stream should be performed initially and at regular intervals to be sure no leaks have developed through or around the HEPA filters. Workbenches and other types of laminar-flow enclosures are available from several commercial sources (suppliers: *Air Control, Atmos-Tech, Baker, Clean Air, Clestra, Envirco, Flanders, Laminaire, Liberty*).

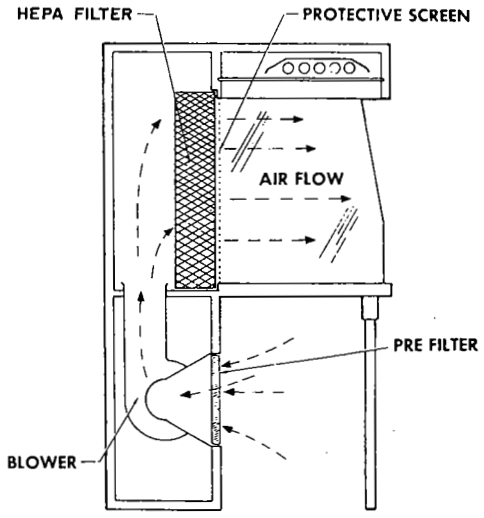

Figure 41-8. Horizontal laminar-flow workbench (courtesy, adaptation, Sandia).

MATERIALS SUPPORT AREA—The area is constructed to withstand moisture, steam, and detergents and is usually a Class 100,000 clean room. The ceiling, walls, and floor should be constructed of impervious materials so that moisture will run off and not be held. One of the finishes with a vinyl or expoxy sealing coat provides a continuous surface free from all holes or crevices. All such surfaces can be washed at regular intervals to keep them thoroughly clean. These areas should be exhausted adequately so that the heat and humidity will be removed for the comfort of personnel. Precautions must be taken to prevent the accumulation of dirt and the growth of

microorganisms because of the high humidity and heat. In this area preparation for the filling operation, such as cleaning and assembling equipment, is undertaken. Adequate sink and counter space must be provided. This area must be cleanable, and the microbial load must be monitored and controlled. Precautions also must be taken to prevent deposition of particles or other contaminants on clean containers and equipment until they have been properly boxed or wrapped preparatory to sterilization and depyrogenation.

COMPOUNDING AREA—In this area the formula is compounded. Although it is not essential that this area be aseptic, control of microorganisms and particulates should be more stringent than in the materials support area. For example, means may need to be provided to control dust generated from weighing and compounding operations. Cabinets and counters should, preferably, be constructed of stainless steel. They should fit snugly to walls and other furniture so that there are no catch areas where dirt can accumulate. The ceiling, walls, and floor should be similar to those for the materials support area.

ASEPTIC AREA—The aseptic area requires construction features designed for maximum microbial and particulate control. The ceiling, walls, and floor must be sealed so that they may be washed and sanitized with a disinfectant, as needed. All counters should be constructed of stainless steel and hung from the wall so that there are no legs to accumulate dirt where they rest on the floor. All light fixtures, utility service lines, and ventilation fixtures should be recessed in the walls or ceiling to eliminate ledges, joints, and other locations for the accumulation of dust and dirt. As much as possible, tanks containing the compounded product should remain outside the aseptic filling area, and the product fed into the area through hose lines. Figure 41-7 shows such an arrangement. Proper sanitization is required if the tanks must be moved in. Large mechanical equipment that is located in the aseptic area should be housed as completely as possible within a stainless steel cabinet to seal the operating parts and their dirt-producing tendencies from the aseptic environment. Further, all such equipment parts should be located below the filling line. Mechanical parts that will contact the parenteral product should be demountable so that they can be cleaned and sterilized.

Personnel entering the aseptic area should enter only through an airlock. They should be attired in sterile coveralls with sterile hats, masks, goggles, and foot covers. Movement within the room should be minimal and in-and-out movement rigidly be restricted during a filling procedure. The requirements for room preparation and the personnel may be relaxed somewhat if the product is to be sterilized terminally in a sealed container. Some are convinced, however, that it is better to have one standard procedure meeting the most rigid requirements.

ISOLATION (BARRIER) TECHNOLOGY—This technology is a relatively new approach to the control of aseptic processing. It is designed to isolate aseptic operations from personnel and the surrounding environment. Considerable experience has been gained in its use for sterility testing, with very positive results, including reports of essentially no false-positive test results.[17] In European circles favorable results also have been reported from use in hospital IV admixture programs. Because of such results, experimental efforts in adapting automated, large-scale, aseptic filling operations to isolators has gained momentum.[18]

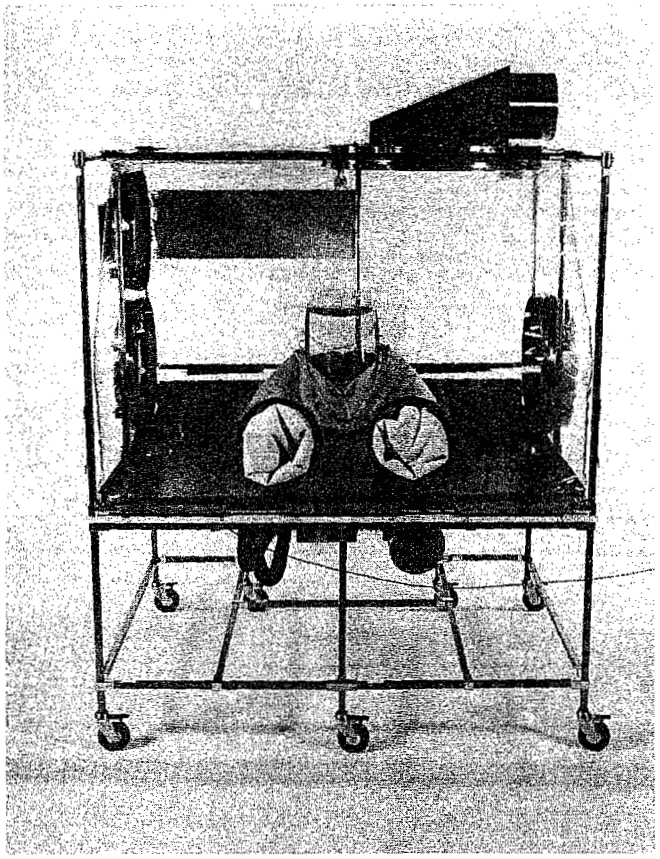

Figure 41-10. One configuration of an isolator (courtesy, Amsco).

Figure 41-10 illustrates a configuration of an isolator with transparent plastic sides and a halfsuit for operator access to the enclosure. Figure 41-11 illustrates the adaptation of a large-scale filling line to isolator technology. The operations are performed within windowed, sealed walls with operators working through glove ports. The sealed enclosures are presterilized, usually with peracetic acid, hydrogen peroxide vapor, or steam. Sterile supplies are introduced from sterilizable movable modules through uniquely engineered transfer ports or directly from attached sterilizers, including autoclaves and hot-air sterilizing tunnels. Results have been very promising, giving expectation of significantly enhanced control of the aseptic processing environment.[18]

MAINTENANCE OF CLEAN ROOMS

Maintaining the clean and sanitized conditions of clean rooms, particularly the aseptic areas, requires diligence and dedication of expertly trained custodians. Assuming the design of the facilities to be cleanable and sanitizable, a carefully planned schedule of cleaning should be developed, ranging from daily to monthly, depending on the location and its relation to the most critical Class 100 areas. Tools used should be nonlinting, designed for clean room use, held captive to the area and, preferably, sterilizable.

Liquid disinfectants (sanitizing agents) should be selected carefully because of data showing their reliable activity against inherent environmental microorganisms. They should be recognized as supplements to good housekeeping, never as substitutes. They should be rotated with sufficient frequency to avoid the development of resistant strains of microorganisms. Space does not permit a detailed discussion of these agents, but an excellent discussion can be found in the report of a PDA task force.[19]

It should be noted that ultraviolet (UV) light rays of 237.5 nm wavelength, as radiated by germicidal lamps, are an effective surface disinfectant. But, it must also be noted that they are only effective if they contact the target microorganisms at a sufficient intensity for a sufficient time. The limitations of their use must be recognized, including no effect in shadow

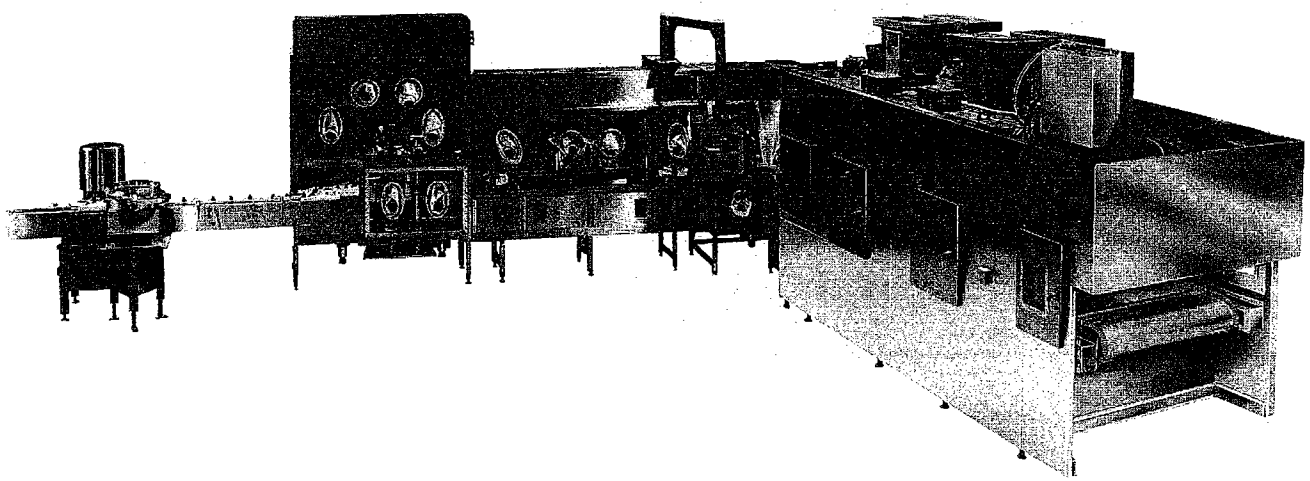

Figure 41-11. Large-scale production line showing, from right to left, container-sterilizing tunnel feeding into isolator enclosing filling and sealing, with access glove ports, and exiting to capper (courtesy, TL Systems).

areas, reduction of intensity by the square of the distance from the source, reduction by particulates in the ray path, and the toxic effect on epithelium of human eyes. It generally is stated that an irradiation intensity of 20 $\mu w/cm^2$ is required for effective antibacterial activity.

PERSONNEL

Personnel selected to work on the preparation of a parenteral product must be neat, orderly, and reliable. They should be in good health and free from dermatological conditions that might increase the microbial load. If they show symptoms of a head cold, allergies, or similar illness, they should not be permitted in the aseptic area until their recovery is complete. However, a healthy person with the best personal hygiene still will shed large numbers of viable and nonviable particles from body surfaces. This natural phenomenon creates continuing problems when personnel are present in clean rooms; effective training and proper gowning can reduce, but not eliminate, the problem of particle shedding from personnel.

Aseptic-area operators should be given thorough, formal training in the principles of aseptic processing and the techniques to be employed. Subsequently, the acquired knowledge and skills should be evaluated, to be sure training has been effective, before they are allowed to participate in the preparation of sterile products. Retraining should be performed on a regular schedule to enhance the maintenance of the required level of expertise. An effort should be made to imbue operators with an awareness of the vital role they play in determining the reliability and safety of the final product. This is especially true of supervisors, since they should be individuals who not only understand the unique requirements of aseptic procedures but who are able to obtain the full participation of other employees in fulfilling these exacting requirements.

The uniform worn is designed to confine the contaminants discharged from the body of the operator, thereby preventing their entry into the production environment. For use in the aseptic area, uniforms should be sterile. Fresh, sterile uniforms should be used after every break period or whenever the individual returns to the aseptic area. In some plants this is not required if the product is to be sterilized in its final container. The uniform usually consists of coveralls for both men and women, hoods to cover the hair completely, face masks, and Dacron or plastic boots (Fig 41-12). Sterile rubber or latex-free gloves are also required for aseptic operations, preceded by thorough scrubbing of the hands with a disinfectant soap. In addition, goggles may be required to complete the coverage of all skin areas.

Dacron or Tyvek uniforms are usually worn, are effective barriers to discharged body particles (viable and nonviable), are essentially lint-free, and are reasonably comfortable. Air showers are sometimes directed on personnel entering the processing area to blow loose lint from the uniforms.

Gowning rooms should be designed to enhance pregowning and gowning procedures by trained operators so that it is possible to ensure the continued sterility of the exterior surfaces of the sterile gowning components. Degowning should be performed in a separate exit room.

ENVIRONMENTAL CONTROL EVALUATION

As evidenced by the above discussion, manufacturers of sterile products use extensive means to control the environment so that these critical products can be prepared free from contamination. Nevertheless, tests should be performed to determine the level of control actually achieved. Normally, the tests consist of counting viable and nonviable particles suspended in the air or settled on surfaces in the workspace. A baseline count, determined by averaging multiple counts when the facility is operating under controlled conditions, is used to establish the optimal test results expected. During the subsequent monitoring program, the test results are followed carefully for high individual counts, a rising trend, or other abnormalities. If they exceed selected alert or action levels, a plan of action must be put into operation to determine if or what corrective measures are required.

The tests used generally measure either the particles in a volume of sampled air or the particles that are settling or are present on surfaces. A volume of air measured by an electronic particle counter will detect all particles instantly but not differentiate between viable and nonviable ones. However, because of the need to control the level of microorganisms in the environment in which sterile products are processed, it also is necessary to detect viable particles. These usually are fewer in number than nonviable ones and are only detectable as colony-forming units (CFUs) after a suitable incubation period at, for example, 30 to 35° for up to 48 hr. Thus, test results will not be known for 48 hr after the samples are taken.

Locations for sampling should be planned to reveal potential contamination levels that may be critical in the control of the environment. For example, the most critical process step is usually the filling of dispensing containers, a site obviously requiring monitoring. Other examples include the gowning

room, high-traffic sites in and out of the filling area, the penetration of conveyor lines through walls, and sites near the inlet and exit of the air system.

The sample should be large enough to obtain a meaningful particle count. At sites where the count is expected to be low, the size of the sample may need to be increased; for example, in Class 100 areas, Whyte and Niven,[20] suggest that the sample should be at least 30 ft^3 and, probably, much more. They also suggest that settling plates should be exposed in Class 100 areas for an entire fill (up to 7 to 8 hr) rather than the more common 1 hr. However, excessive dehydration of the medium must be avoided, particularly in the path of laminar-flow air.

To measure the total particle content in an air sample, electronic particle counters are available, operating on the principle of the measurement of light scattered from particles as they pass through the cell of the optical system (Suppliers: *Climet, HIAC Royco, Met One, Particle Measuring*). These instruments not only count particles but also provide a size distribution based on the magnitude of the light scattered from the particle.

Several air-sampling devices are used to obtain a count of microorganisms in a measured volume of air. A slit-to-agar (STA) sampler (suppliers: *Mattson-Garvin, New Brunswick, Vai*) draws by vacuum a measured volume of air through an engineered slit, causing the air to impact on the surface of a slowly rotating nutrient agar plate. Microorganisms adhere to the surface of the agar and grow into visible colonies that are counted as CFUs, since it is not known whether the colonies arise from a single microorganism or a cluster. A centrifugal sampler (supplier: *Biotest*) pulls air into the sampler by means of a rotating propeller and slings the air by centrifugal action against a peripheral nutrient agar strip. The advantages of this unit are that it can be disinfected easily and is portable, so that it can be hand-carried wherever needed. These two methods are used quite widely.

A widely used method for microbiological sampling consists of the exposure of nutrient agar culture plates to the settling of microorganisms from the air. This method is very simple and inexpensive to perform but will detect only those organisms that have settled on the plate; therefore, it does not measure the number of microorganisms in a measured volume of air. Nevertheless, if the conditions of exposure are repeated consistently, a comparison of CFUs at one sampling site from one time to another can be meaningful.[21]

The number of microorganisms on surfaces can be determined with nutrient agar plates having a convex surface *(Rodac Plates)*. With these it is possible to roll the raised agar surface over flat or irregular surfaces to be tested. Organisms will be picked up on the agar and will grow during subsequent incubation. This method also can be used to assess the number of microorganisms present on the surface of the uniforms of operators, either as an evaluation of gowning technique immediately after gowning or as a measure of the accumulation of microorganisms during processing. Whenever used, care must be taken to remove any agar residue left on the surface tested.

Further discussion of proposed viable particle test methods and the counts to be accepted will be found in Section ⟨1116⟩ "Microbial Evaluation and Classification of Clean Rooms and Other Controlled Environments" in USP 24.[22]

Results from the above tests, although not available until 2 days after sampling, are valuable to keep cleaning, production, and quality-control personnel apprised of the level of contamination in a given area and, by comparison with baseline counts, will indicate when more-extensive cleaning and sanitizing is needed. The results also may serve to detect environmental control defects such as failure in air-cleaning equipment or the presence of personnel who may be disseminating large numbers of bacteria without apparent physical ill effects.

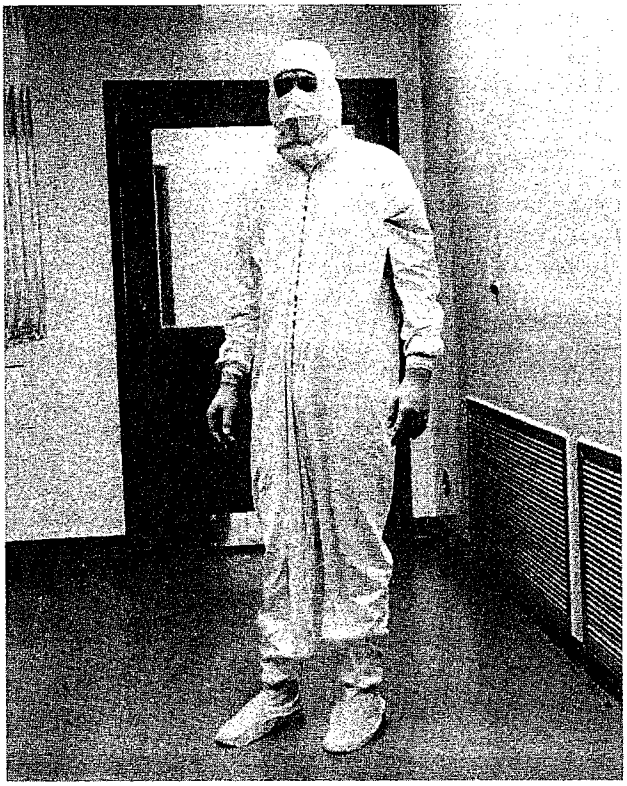

Figure 41-12. Appropriate uniform for operators entering an aseptic filling room (courtesy, Abbott).

MEDIA FILL (PROCESS SIMULATION TESTING)—An evaluation that is not strictly an environmental test, but which includes an evaluation of the environment along with the process, the operators, and the equipment, is the *media fill* or *process simulation test*. Sterile trypticase soy broth is filled into sterile containers under conditions simulating as closely as possible those characteristics of a filling process for a product. The entire lot, normally at least 3000 units, is then incubated at a suitable temperature, usually 20 to 25°, for at least 14 days and examined for the appearance of growth of microorganisms.[23] If growth occurs, contamination has entered the container(s) during the processing. To pass the test not more than 0.1% of the units may show growth. This evaluation also has been used as a measure of the proficiency of an individual or team of operators. This test is a very stringent evaluation of the efficiency of an aseptic filling process and, by many, is considered to be the most evaluative test available.

PRODUCTION PROCESS

The processes required for preparing sterile products constitute a series of events initiated with the procurement of approved raw materials (drugs, excipients, vehicles, etc) and primary packaging components (containers, closures, etc) and ending with the sterile product sealed in its dispensing package (see Fig 41-1). Each step in the process must be controlled very carefully so that the product will have its required quality. To ensure the latter, each process should be validated to be sure that it is accomplishing what it is intended to do. For example, an autoclave sterilization process must be validated by producing data showing that it effectively kills resistant forms of microorganisms; or, a cleaning process for rubber closures should provide evidence that it is cleaning closures to the required level of cleanliness. The validation of processes re-

quires extensive and intensive effort to be successful and is an integral part of cGMP requirements.

In the following sections the production procedures used in preparing sterile drug products are discussed.

CLEANING CONTAINERS AND EQUIPMENT

Containers and equipment coming in contact with parenteral preparations must be cleaned meticulously. It should be obvious that even new, unused containers and equipment will be contaminated with such debris as dust, fibers, chemical films, and other materials arising from such sources as the atmosphere, cartons, the manufacturing process, and human hands. Residues from previous use must be removed from used equipment before it will be suitable for reuse. Equipment should be reserved exclusively for use only with parenteral preparations and, where conditions dictate, only for one product in order to reduce the risk of contamination.

A variety of machines are available for cleaning new containers for parenteral products. These vary in complexity from a small, hand loaded, rotary rinser (Fig 41-13) to large automatic washers capable of processing several thousand containers an hour (Figs 41-14 and 41-15). The selection of the particular type will be determined largely by the physical type of containers, the type of contamination, and the number to be processed in a given period of time.

CHARACTERISTICS OF MACHINERY—Regardless of the type of cleaning machine selected, certain fundamental characteristics usually are required.

1. The liquid or air treatment must be introduced in such a manner that it will strike the bottom of the inside of the inverted container, spread in all directions, and smoothly flow down the walls and out the opening with a sweeping action. The pressure of the jet stream should be such that there is minimal splashing and turbulence inside. Splashing may prevent cleaning all areas, and turbulence may redeposit loosened debris. Therefore, direct introduction of the jet stream within the container with control of its flow is required.
2. The container must receive a concurrent outside rinse.
3. The cycle of treatment should provide a planned sequence alternating very hot and cool treatments. The final treatment should be an effective rinse with WFI.
4. All metal parts coming in contact with the containers and with the treatments should be constructed of stainless steel or some other noncorroding and noncontaminating material.

TREATMENT CYCLE—The cycle of treatments to be employed will vary with the condition of the containers to be cleaned. In general, loose debris can be removed by vigorous rinsing with water. Detergents rarely are used for new containers because of the risk of leaving detergent residues. However, a thermal-shock sequence in the cycle usually is employed to aid, by expansion and contraction, loosening of debris that may be adhering to the container wall. Sometimes only an air rinse is used for new containers, if only loose debris is present. In all instances the final rinse, whether air or WFI, must be ultraclean so that no particulate residues are left by the rinsing agent.

Figure 41-13. Rotary rinser (Cozzoli) in a clean environment provided by vertical laminar airflow within a curtained enclosure (courtesy, Ciba-Geigy).

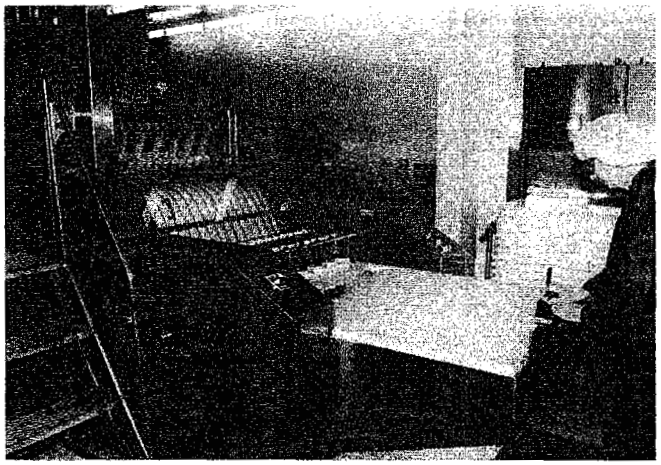

Figure 41-14. Loading end of large conveyor vial washer that subjects inverted vials to a series of cleaning steps before delivery from the far end of the washer. Note the vials in plastic blister packs at right of operator (courtesy, Merck).

Only new containers are used for parenterals. Improvements have been made in maintaining their cleanliness during shipment from the manufacturer through tight, low-shedding packaging, including plastic blister packs, as can be seen stacked on the right of Figure 41-14.

MACHINERY FOR CONTAINERS—The machinery available for cleaning containers embodies the above principles but varies in the mechanics by which it is accomplished. In one manual loading type, the jet tubes are arranged on arms like the spokes of a wheel, which rotate around a center post through which the treatments are introduced. An operator places the unclean containers on the jet tubes as they pass the loading point and removes the clean containers as they complete one rotation. Such a small-scale machine is pictured in Figure 41-14. A washer capable of cleaning hundreds of containers an hour, shown in Figure 41-14, uses a row of jet tubes across a conveyor belt. The belt moves the inverted containers past the programmed series of treatments and discharges the clean containers into a sterilizing oven (not shown), which ultimately discharges them through a wall into a clean room for filling.

Another type of machine is the rack-loading washer. Stainless-steel racks are designed to fit over the open ends of ampuls or vials as configured in trays of shipping cartons or blister packs. Inverting the trays permits the containers to slide into the racks so that they can be handled by the quantity in the tray, as shown in Figure 41-15. The clean containers may be transferred directly to the conveyor of a sterilizing tunnel (as shown), or they may be placed in stainless steel boxes for subsequent dry-heat sterilization and storage. A continuous automated line operation, capable of cleaning hundreds of containers an hour, is shown in Figure 41-16. The vials are fed into the rotary rinser in the foreground, transferred automatically to the covered sterilizing tunnel in the center, conveyed through the wall in the background, and discharged into the filling clean room.

HANDLING AFTER CLEANING—The wet, clean containers must be handled in such a way that contamination will

not be reintroduced. A wet surface will collect contaminants much more readily than will a dry surface. For this reason wet, rinsed containers must be protected, eg, by a laminar flow of clean air until covered, within a stainless steel box, or within a sterilizing tunnel. Although not clearly visible in each instance, the wet, clean containers in Figures 41-13 to 41-16 were so protected. In addition, microorganisms are more likely to grow in the presence of moisture. Therefore, wet, clean containers should be dry-heat sterilized as soon as possible after washing. Doubling the heating period generally is adequate also to destroy pyrogens; for example, increasing the dwell time at 250° from 1 to 2 hr, but the actual time-temperature conditions required must be validated.

Increases in process rates have necessitated the development of continuous, automated line processing with a minimum of individual handling, still maintaining adequate control of the cleaning and handling of the containers. In Figure 41-16, the clean, wet containers are protected by filtered, laminar-flow air from the rinser through the tunnel and until they are delivered to the filling line.

CLOSURES—The rough, elastic, and convoluted surface of rubber closures renders them difficult to clean. In addition, any residue of lubricant from molding or surface *bloom* of inorganic constituents must be removed. The normal procedure calls for gentle agitation in a hot solution of a mild water softener or detergent. The closures are removed from the solution and rinsed several times, or continuously for a prolonged period, with filtered WFI. The rinsing is to be done in a manner that will flush away loosened debris. The wet closures are carefully protected from pickup of environmental contamination, sterilized, usually by autoclaving, and stored in closed containers until ready for use. This cleaning and sterilizing process also must be validated with respect to rendering the closures free from pyrogens. Actually, it is the cleaning and final, thorough rinsing with WFI that must remove pyrogens, since autoclaving does not destroy pyrogens. If the closures were immersed during autoclaving, the solution is drained off before storage to reduce hydration of the rubber compound. If the closures must be dry for use, they may be subjected to vacuum drying at a temperature in the vicinity of 100°.

The equipment used for washing large numbers of closures is usually an agitator or horizontal basket-type automatic washing machine. Because of the risk of particulate generation from the abrading action of these machines, some procedures simply call for heating the closures in kettles in detergent solution, followed by prolonged flush rinsing. The final rinse always should be with low-particulate WFI.

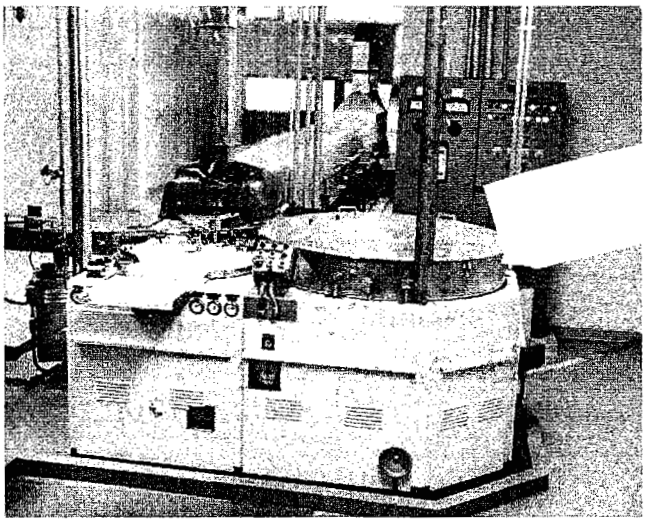

Figure 41-16. Continuous automatic line operation for vials from a rotary rinser through a sterilizing tunnel with vertical laminar-air-flow protection of clean vials (courtesy, Abbott).

EQUIPMENT—The details of certain prescribed techniques for cleaning and preparing equipment, as well as of containers and closures, have been presented elsewhere.[24] Here, a few points will be emphasized.

All equipment should be disassembled as much as possible to provide access to internal structures. Surfaces should be scrubbed thoroughly with a stiff brush, using an effective detergent and paying particular attention to joints, crevices, screw threads, and other structures where debris is apt to collect. Exposure to a stream of clean steam will aid in dislodging residues from the walls of stationary tanks, spigots, pipes, and similar structures. Thorough rinsing with distilled water should follow the cleaning steps.

Because of the inherent variation in manual cleaning, the difficult accessibility of large stationary tanks (as shown in Fig 41-17), and the need to validate the process, computer-controlled systems (usually automated) have been developed and are known as CIP.[25] Such an approach involves designing the system, normally of stainless steel, with smooth, rounded internal surfaces and without crevices. That is, for example, with welded rather than threaded connections. The cleaning is

Figure 41-15. Cleaning vials with rack-loading washer, permitting handling vials by a full rack. After multiple-washing treatments, the racks are placed directly on the conveyor belt of the hot-air sterilizing tunnel (courtesy, Merck).

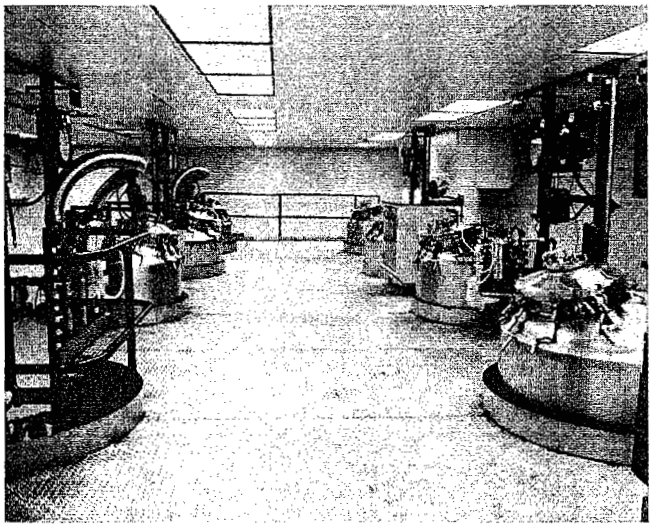

Figure 41-17. Large stainless steel tanks for product preparation showing mezzanine access level (courtesy, Abbott).

accomplished with the scrubbing action of high-pressure spray balls or nozzles delivering hot detergent solution from tanks captive to the system, followed by thorough rinsing with WFI. The system often is extended to allow sterilizing in place (SIP) to accomplish sanitizing or sterilizing as well.

Rubber tubing, rubber gaskets, and other rubber parts may be washed in a manner such as described for rubber closures. Thorough rinsing of tubing must be done by passing WFI through it. However, because of the relatively porous nature of rubber compounds and the difficulty in removing all traces of chemicals from previous use, it is considered by some inadvisable to reuse rubber or polymeric tubing. Rubber tubing must be left wet when preparing for sterilization by autoclaving.

PRODUCT PREPARATION

The basic principles employed in the compounding of the product are essentially the same as those used historically by pharmacists. However, large-scale production requires appropriate adjustments in the processes and their control.

A master formula would have been developed and be on file. Each batch formula sheet should be prepared from the master and confirmed for accuracy. All measurements of quantities should be made as accurately as possible and checked by a second qualified person. Frequently, today, the formula documents are generated by a computer and the measurements of quantities of ingredients computer controlled. Although most liquid preparations are dispensed by volume, they are prepared by weight, since weighings can be performed more accurately than volume measurements, and no consideration needs to be given to the temperature.

Care must be taken that equipment is not wet enough to dilute the product significantly or, in the case of anhydrous products, to cause a physical incompatibility. The order of mixing of ingredients may affect the product significantly, particularly those of large volume, where attaining homogeneity requires considerable mixing time. For example, the adjustment of pH by the addition of an acid, even though diluted, may cause excessive local reduction in the pH of the product so that adverse effects are produced before the acid can be dispersed throughout the entire volume of product.

Parenteral dispersions, including colloids, emulsions, and suspensions, provide particular problems. Parenteral emulsions have been reviewed by Singh and Ravin.[27] In addition to the problems of achieving and maintaining proper reduction in particle size under aseptic conditions, the dispersion must be kept in a uniform state of suspension throughout the preparative, transfer, and subdividing operations.

The formulation of a stable product is of paramount importance. Certain aspects of this are mentioned in the discussion of components of the product. Exhaustive coverage of the topic is not possible within the limits of this text, but further coverage is provided in Chapter 38. It should be mentioned here, however, that the thermal sterilization of parenteral products increases the possibility of chemical reactions. Such reactions may progress to completion during the period of elevated temperature in the autoclave or be initiated at this time but continue during subsequent storage. The assurance of attaining product stability requires a high order of pharmaceutical knowledge and responsibility.

FILTRATION

After a product has been compounded, it must be filtered if it is a solution. The primary objective of filtration is to clarify a solution. A high degree of clarification is termed *polishing* a solution. This term is used when particulate matter down to approximately 2 μm in size is removed. A further step, removing particulate matter down to 0.2 μm in size, would eliminate microorganisms and would accomplish *cold* sterilization. A solution with a high degree of clarity conveys the impression of high quality and purity, desirable characteristics for a parenteral solution.

Filters are thought to function by one or, usually, a combination of the following: (1) sieving or screening, (2) entrapment or impaction, and (3) electrostatic attraction. When a filter retains particles by sieving, they are retained on the surface of the filter. Entrapment occurs when a particle smaller than the dimensions of the passageway (pore) becomes lodged in a turn or impacted on the surface of the passageway. Electrostatic attraction causes particles opposite in charge to that of the surface of the filter pore to be held or adsorbed to the surface. It should be noted that increasing, prolonging, or varying the force behind the solution may tend to sweep particles initially held by entrapment or electrostatic charge through the pores and into the filtrate.

Membrane filters are used exclusively for parenteral solutions because of their particle-retention effectiveness, nonshedding property, nonreactivity, and disposable characteristics. However, it should be noted that nonreactivity does not apply in all cases. For example, polypeptide products may show considerable adsorption through some membrane filters, but those composed of polysulfone and polyvinylidine difluoride have been developed to be essentially nonadsorptive for these products. The most common membranes are composed of

Cellulose esters, Nylon, Polysulfone, Polycarbonate, Polyvinylidene difluoride, or Polytetrafluoroethylene (Teflon).

They are available as flat membranes or pleated into cylinders to increase surface area and, thus, flow rate (suppliers: *Cuno, Gelman, Meissner, Millipore, Pall, Sartorius Schleicher*). Each filter in its holder should be tested for integrity before and after use, particularly if it is being used to eliminate microorganisms. This integrity test usually is performed as the *bubble-point test,* a test to detect the largest pore or other opening through the membrane. The basic test is performed by gradually raising air pressure on the upstream side of a water-wet filter. The pressure at which bubbles first appear downstream is the bubble point. This pressure is characteristic for each pore size of a filter and is provided by the filter manufacturer. For example, a 0.2-μm cellulose ester filter will bubble at about 50 psig. If the filter is wetted with other liquids, such as a product, the bubble point will differ and must be determined experimentally. If the bubble point is lower than the rated pressure, the filter is defective, probably because of a puncture or tear, and should not be used. As the surface area of filters becomes large, diffusion of air through the water-filled pores tends to obscure the bubble point. Therefore, a diffusion, or pressure hold, test has been developed as an integrity test for filters with large surface areas. Particulars are obtainable from the filter manufacturer, including the most critical functional test for sterilizing grade filters, the bacterial retention test.

While membrane filters are disposable and thus discarded after use, the holders must be cleaned thoroughly between uses. Today, clean, sterile, pretested, disposable assemblies for small as well as large volumes of solutions are available commercially. Other characteristics of these filters, important for a full understanding of their use, are given in Chapter 40 and in a review article.[28]

FILLING

During the filling of containers with a product, the most stringent requirements must be exercised to prevent contamination, particularly if the product has been sterilized by filtration and will not be sterilized in the final container. Under the latter conditions the process usually is called an *aseptic fill* and is validated with media fills (see page 794). During the filling

operation, the product must be transferred from a bulk container and subdivided into dose containers. This operation exposes the sterile product to the environment, equipment, and manipulative technique of the operators until it can be sealed in the dose container. Therefore, this operation is carried out with a minimum exposure time, even though maximum protection is provided by filling under a blanket of HEPA-filtered laminar-flow air within the aseptic area.

Normally, the compounded product is in the form of either a liquid or a solid. A liquid is more readily subdivided uniformly and introduced into a container having a narrow mouth than is a solid. Mobile, nonsticking liquids are considerably easier to transfer and subdivide than viscous, sticky liquids, which require heavy-duty machinery for rapid production filling.

Although many devices are available for filling containers with liquids, certain characteristics are fundamental to them all. A means is provided for repetitively forcing a measured volume of the liquid through the orifice of a delivery tube that is introduced into the container. The size of the delivery tube will vary from that of about a 20-gauge hypodermic needle to a tube ½ in or more in diameter. The size required is determined by the physical characteristics of the liquid, the desired delivery speed, and the inside diameter of the neck of the container. The tube must enter the neck and deliver the liquid well into the neck to eliminate spillage, allowing sufficient clearance to permit air to leave the container as the liquid enters. The delivery tube should be as large in diameter as possible to reduce the resistance and decrease the velocity of flow of the liquid. For smaller volumes of liquids, the delivery usually is obtained from the stroke of the plunger of a syringe, forcing the liquid through a two-way valve providing for alternate filling of the syringe and delivery of mobile liquids. For heavy, viscous liquids, a sliding piston valve, the turn of an auger in the neck of a funnel, or the oscillation of a rubber diaphragm may be used. For large volumes the quantity delivered usually is measured in the container by the level of fill in the container, the force required to transfer the liquid being provided by gravity, a pressure pump, or a vacuum pump.

The narrow neck of an ampul limits the clearance possible between the delivery tube and the inside of the neck. Since a drop of liquid normally hangs at the tip of the delivery tube after a delivery, the neck of an ampul will be wet as the delivery tube is withdrawn, unless the drop is retracted. Therefore, filling machines should have a mechanism by which this drop can be drawn back into the lumen of the tube.

Since the liquid will be in intimate contact with the parts of the machine through which it flows, these must be constructed of nonreactive materials such as borosilicate glass or stainless steel. In addition, they should easily be demountable for cleaning and sterilization.

Because of the concern for particulate matter in injectable preparations, a final filter often is inserted in the system between the filler and the delivery tube, as shown in Figure 41-18. Most frequently this is a membrane filter, having a porosity of approximately 1 μm and treated to have a hydrophobic edge. This is necessary to reduce the risk of rupture of the membrane caused by filling pulsations. It should be noted that the insertion of the filter at this point should collect all particulate matter generated during the process. Only that which may be found in inadequately cleaned containers or picked up from exposure to the environment after passage through the final filter potentially remain as contaminants. However, the filter does cushion liquid flow and reduces the efficiency of drop retraction from the end of the delivery tube, sometimes making it difficult to control delivery volume as precisely as would be possible without the filter.

LIQUIDS—The filling of a small number of containers may be accomplished with a hypodermic syringe and needle, the liquid being drawn into the syringe and forced through the needle into the container. A device for providing greater speed of filling is the Cornwall Pipet *(Becton Dickinson)*. This has a two-way valve between the syringe and the needle and a means for setting the stroke of the syringe so that the same volume will be delivered each time. Clean, sterile, disposable assemblies (suppliers: *Burron, Pharmaseal*) operating on the same principle have particular usefulness in hospital pharmacy or experimental operations.

Mechanically operated instruments substitute a motor for the operator's hand in the previous devices described. Thereby, a much faster filling rate can be achieved. By careful engineering, the stroke of the syringe can be repeated precisely, and so, once a particular setting has been calibrated to the delivery, high delivery precision is possible. However, the speed of delivery, the expansion of the rubber tubing connecting the valve with the delivery tube, and the rapidity of action of the valves can affect the precision of delivery. A filling machine employing a piston is shown in Figure 41-18. Stainless steel syringes are required with viscous liquids because glass syringes are not strong enough to withstand the high pressures developed during delivery.

When high-speed filling rates are desired but accuracy and precision must be maintained, multiple filling units often are joined together in an electronically coordinated machine, such as shown in Figure 41-19. When the product is sensitive to metals, a peristaltic-pump filler may be used because the product comes in contact only with silicone rubber tubing. However, there is some sacrifice of filling accuracy.

Most high-speed fillers for large-volume solutions use the bottle as the measuring device, transferring the liquid either by vacuum or positive pressure from the bulk reservoir to the individual unit containers. Therefore, a high accuracy of fill is not achievable.

The USP requires that each container be filled with a sufficient volume in excess of the labeled volume to ensure withdrawal of the labeled volume and provides a table of suggested fill volumes.

SOLIDS—Sterile solids, such as antibiotics, are more difficult to subdivide evenly into containers than are liquids. The rate of flow of solid material is slow and often irregular. Even though a container with a larger-diameter opening is used to facilitate filling, it is difficult to introduce the solid particles, and the risk of spillage is ever-present. The accuracy of the quantity delivered cannot be controlled as well as with liquids. Because of these factors, the tolerances permitted for the content of such containers must be relatively large.

Some sterile solids are subdivided into containers by individual weighing. A scoop usually is provided to aid in approx-

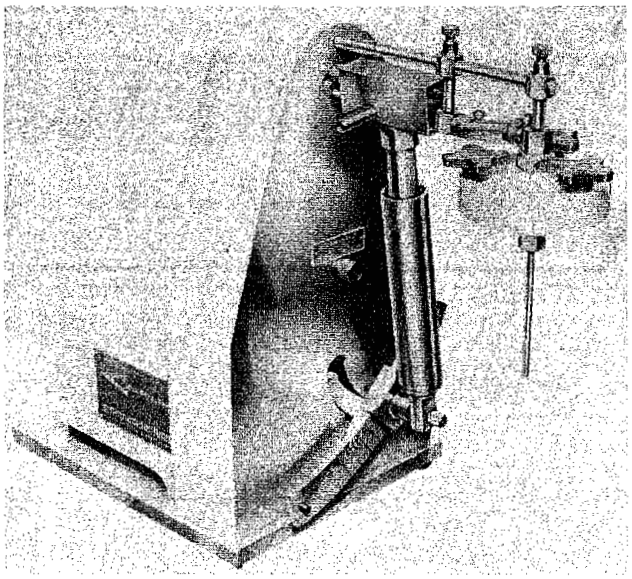

Figure 41-18. Filling machine employing a piston valve, a stainless steel syringe, and a final filter (courtesy, Cozzoli).

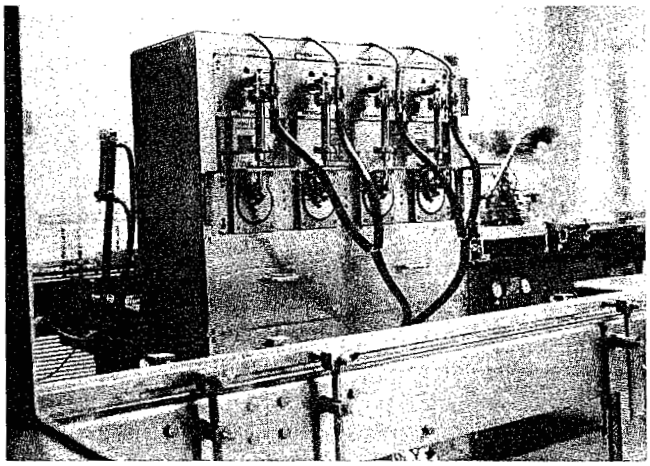

Figure 41-19. Four-pump liquid filler (rear view), with a conveyor line for vials protected by a vertical laminar airflow and plastic curtain; note the automatic stoppering machine on the right within the curtain (courtesy, Abbott)

imating the quantity required, but the quantity filled into the container finally is weighed on a balance. This is a slow process. When the solid is obtainable in a granular form so that it will flow more freely, other methods of filling may be employed. In general, these involve the measurement and delivery of a volume of the granular material that has been calibrated in terms of the weight desired. In the machine shown in Figure 41-20 an adjustable cavity in the rim of a wheel is filled by vacuum and the contents held by vacuum until the cavity is inverted over the container. The solid material then is discharged into the container by a puff of sterile air. Another machine employs an auger in the stem of a funnel at the bottom of a hopper. The granular material is placed in the hopper. By controlling the size of the auger and its rotation, a regulated volume of granular material can be delivered from the funnel stem into the container. Such a machine is shown in Figure 41-21.

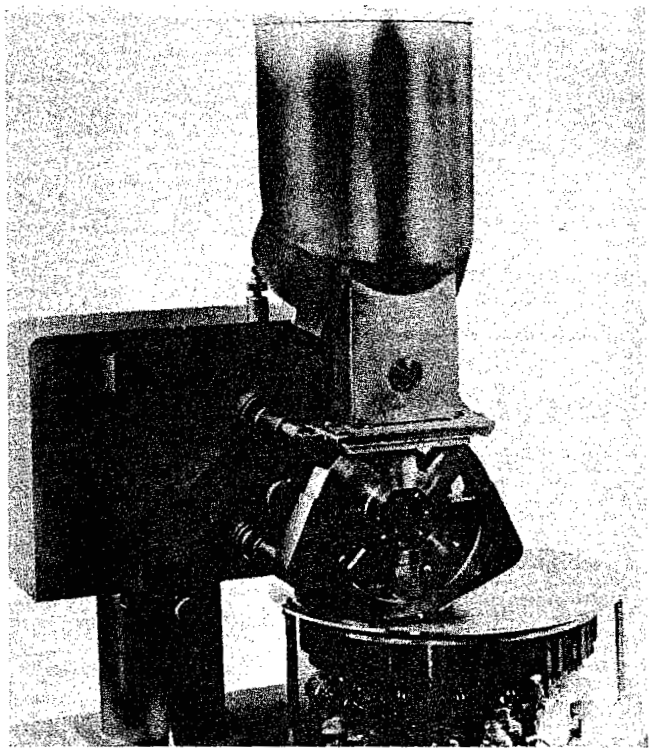

Figure 41-20. Accofil vacuum powder filler (courtesy, Perry).

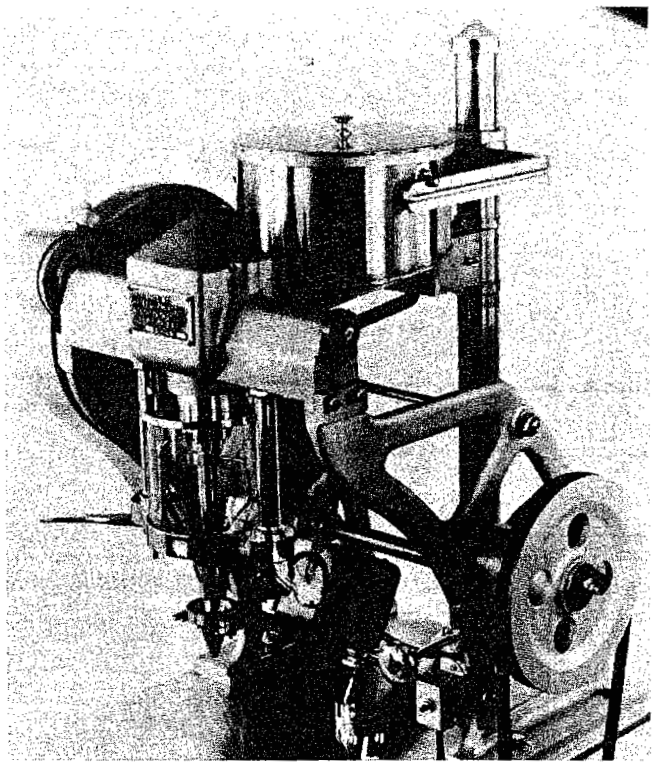

Figure 41-21. Auger-type powder filler (courtesy, Chase-Logeman).

SEALING

AMPULS—Filled containers should be sealed as soon as possible to prevent the contents from being contaminated by the environment. Ampuls are sealed by melting a portion of the glass neck. Two types of seals are employed normally: tip-seals (bead-seals) or pull-seals.

Tip-seals are made by melting enough glass at the tip of the neck of an ampul to form a bead and close the opening. These can be made rapidly in a high-temperature gas-oxygen flame. To produce a uniform bead, the ampul neck must be heated evenly on all sides, such as by burners on opposite sides of stationary ampuls or by rotating the ampul in a single flame. Care must be taken to adjust the flame temperature and the interval of heating properly to completely close the opening with a bead of glass. Excessive heating will result in the expansion of the gases within the ampul against the soft bead seal and cause a bubble to form. If it bursts, the ampul is no longer sealed; if it does not, the wall of the bubble will be thin and fragile. Insufficient heating will leave an open capillary through the center of the bead. An incompletely sealed ampul is called a *leaker*.

Pull-seals are made by heating the neck of the ampul below the tip, leaving enough of the tip for grasping with forceps or other mechanical devices. The ampul is rotated in the flame from a single burner. When the glass has softened, the tip is grasped firmly and pulled quickly away from the body of the ampul, which continues to rotate. The small capillary tube thus formed is twisted closed. Pull-sealing is slower, but the seals are more sure than tip-sealing. Figure 41-22 shows a machine combining the steps of filling and pull-sealing ampuls.

Powder ampuls or other types having a wide opening must be sealed by pull-sealing. Fracture of the neck of ampuls during sealing may occur if wetting of the necks occurred at the time

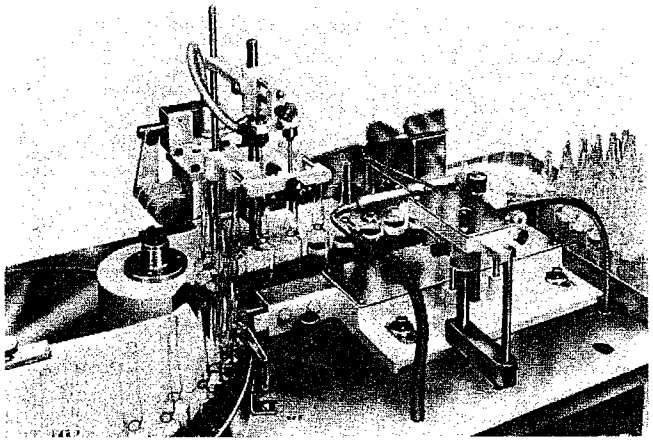

Figure 41-22. Automatic filling and pull-sealing of ampuls (courtesy, Cozzoli).

of filling. Also, wet necks increase the frequency of bubble formation and unsightly carbon deposits if the product is organic.

To prevent decomposition of a product, it is sometimes necessary to displace the air in the space above the product in the ampul with an inert gas. This is done by introducing a stream of the gas, such as nitrogen or carbon dioxide, during or after filling with the product. Immediately thereafter the ampul is sealed before the gas can diffuse to the outside. This process should be validated to ensure adequate displacement of air by the gas in each container.

VIALS AND BOTTLES—These are sealed by closing the opening with a rubber closure (stopper). This must be accomplished as rapidly as possible after filling and with reasoned care to prevent contamination of the contents. The large opening makes the introduction of contamination much easier than with ampuls. Therefore, during the critical exposure time the open containers should be protected from the ingress of contamination, preferably with a blanket of HEPA-filtered laminar airflow, as shown in Figures 41-9 and 41-19.

The closure must fit the mouth of the container snugly enough so that its elasticity will seal rigid to slight irregularities in the lip and neck of the container. However, it must not fit so snugly that it is difficult to introduce into the neck of the container. Closures preferably are inserted mechanically using an automated process, especially with high-speed processing. To reduce friction so that the closure may slide more easily through a chute and into the container opening, the closure surfaces often are halogenated or treated with silicone. When the closure is positioned at the insertion site, it is pushed mechanically into the container opening (Fig 41-23). When small lots are encountered, manual stoppering with forceps may be used, but such a process poses greater risk of introducing contamination than automated processes.

Rubber closures are held in place by means of aluminum caps. The caps cover the closure and are crimped under the lip of the vial or bottle to hold them in place (see Fig 41-5). The closure cannot be removed without destroying the aluminum cap; it is tamperproof. Therefore, an intact aluminum cap is proof that the closure has not been removed intentionally or unintentionally. Such confirmation is necessary to ensure the integrity of the contents as to sterility and other aspects of quality.

The aluminum caps are so designed that the outer layer of double-layered caps, or the center of single-layered caps, can be removed to expose the center of the rubber closure without disturbing the band that holds the closure in the container.

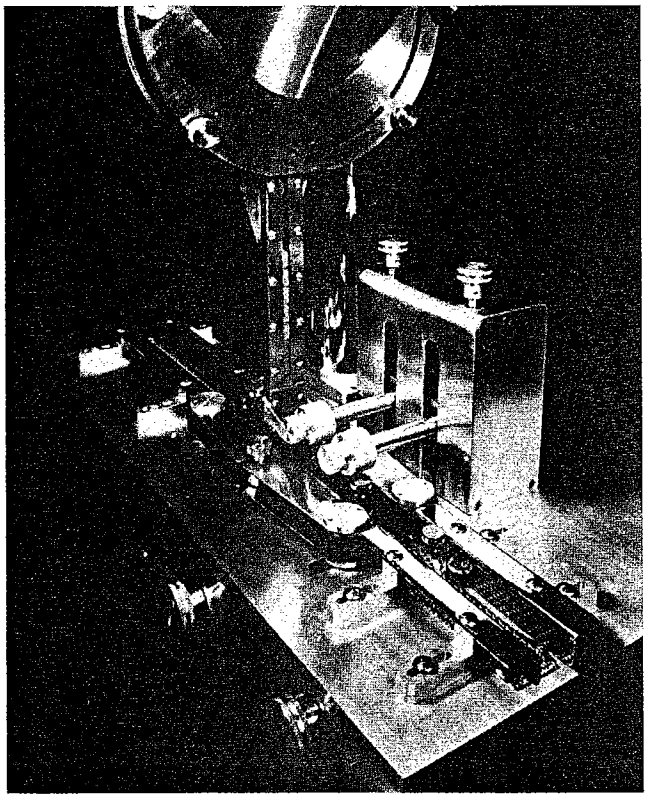

Figure 41-23. Mechanical device for inserting rubber closures in vials (courtesy, Perry).

Rubber closures for use with intravenous administration sets often have a permanent hole through the closure. In such cases, a thin rubber disk overlayed with a solid aluminum disk is placed between an inner and outer aluminum cap, thereby providing a seal of the hole through the closure.

Single-layered aluminum caps may be applied by means of a hand crimper known as the Fermpress (suppliers: *West, Wheaton*). Double- or triple-layered caps require greater force for crimping; therefore, heavy-duty mechanical crimpers (Fig 41-24) are required (suppliers: *Bosch, Cozzoli, Perry, West, Wheaton*).

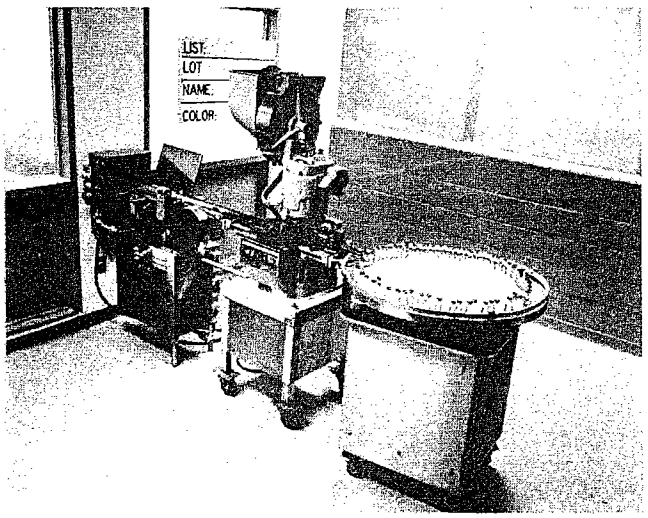

Figure 41-24. Applying aluminum caps to vials at the end of the process line (courtesy, Abbott).

STERILIZATION

Whenever possible, the parenteral product should be sterilized after being sealed in its final container (terminal sterilization) and within as short a time as possible after the filling and sealing have been completed. Since this usually involves a thermal process, due consideration must be given to the effect of the elevated temperature upon the stability of the product. Many products, both pharmaceutical and biological, will be affected adversely by the elevated temperatures required for thermal sterilization. Heat-labile products must, therefore, be sterilized by a nonthermal method, usually by filtration through bacteria-retaining filters. Subsequently, all operations must be carried out in an aseptic manner so that contamination will not be introduced into the filtrate. Colloids, oleaginous solutions, suspensions, and emulsions that are thermolabile may require a process in which each component is sterilized separately and the product is formulated and processed under aseptic conditions.

The performance of an aseptic process is challenging, but technical advances in aseptic processing, including improved automation, use of isolator systems, formulations to include antimicrobial effects, and combinations of limited sterilization with aseptic processing, have decreased the risk of contamination. Therefore, the successes realized should encourage continued efforts to improve the assurance of sterility achievable with aseptic processing. The importance of this is that for many drug solutions and essentially all biopharmaceutical products, aseptic processing is the only method that can be considered for preparing a sterile product.

Interaction between environmental conditions, the constituents in the closure, and the product may result in undesirable closure changes such as increased brittleness or stickiness, which may cause loss of container-closure seal integrity. Thus, shelf-life integrity is an important consideration in closure selection and evaluation.

The assessment of aseptic-processing performance is based on the contamination rate resulting from periodic process simulations using media-filling instead of product-filling of containers. A rate no greater than 0.1% has generally been considered as indicative of satisfactory performance in the industry. However, with current advances in aseptic processing capabilities, lower contamination rates may be achievable.[23]

Nonthermal methods of sterilization, such as irradiation, have been proposed for consideration. However, since there is limited understanding of the molecular transformations that may occur in drug molecules and excipients under exposure to the high-energy levels of the process, extensive research will be required to develop the knowledge needed for an adequate evaluation. The use of radiation for the sterilization of materials such as plastic medical devices is well established.

Dry-heat sterilization may be employed for a few dry solids that are not affected adversely by the high temperatures and for the relatively long heating period required. This method is applied most effectively to the sterilization of glassware and metalware. After sterilization, the equipment will be sterile, dry, and, if the sterilization period is long enough, pyrogen-free.

Saturated steam under pressure (autoclaving) is the most commonly used and the most effective method for the sterilization of aqueous liquids or substances that can be reached or penetrated by steam. A survival probability of 10^{-6} is readily achievable with terminal autoclaving of a thermally stable product. However, it needs to be noted that for terminal sterilization, the assurance of sterility is based upon an evaluation of the lethality of the process, ie, of the probable number of viable microorganisms remaining in product units. However, for aseptic processing, where the components used have been sterilized by a validated process and were based upon an evaluation of the probable number of product units that were contaminated during the process. This difference does not alter the outcome, only the basis for evaluating the assurance of sterility.

Figure 41-25 shows liter containers of solution being loaded into an autoclave for sterilization. Since the temperature employed in an autoclave is lower than that for dry-heat sterilization, equipment made of materials such as rubber and polypropylene may be sterilized if the time and temperature are controlled carefully. As mentioned previously, some injections will be affected adversely by the elevated temperature required for autoclaving. For some products, such as Dextrose Injection, a shortened cycle using an autoclave designed to permit a rapid temperature rise and rapid cooling with water spray will make it possible to use this method. It is ineffective in anhydrous conditions, such as within a sealed ampul containing a dry solid or an anhydrous oil. Other products that will not withstand autoclaving temperatures may withstand marginal thermal methods such as tyndallization or pasteurization, eg, 10 to 12 hr at 60°. These methods may be rendered more effective for some injections by the inclusion of a bacteriostatic agent in the product.

Articles to be sterilized must be properly wrapped or placed in suitable containers to permit penetration of sterilants and provide protection from contamination after sterilization. Sheets or bags made of special steam-penetrating paper or polymeric materials are available for this purpose. Further, containers or bags impervious to steam can be equipped with a microbe-excluding vent filter to permit adequate steam penetration and air exit. Multiple wrapping permits sequential removal of outer layers as articles are transferred from zones of lower to higher environmental quality. The openings of equipment subjected to dry-heat sterilization often are covered with silver-aluminum foil or with metal or glass covers. Wrapping materials commonly used for steam sterilization may be combustible or otherwise become degraded under dry-heat sterilization conditions.

The effectiveness of any sterilization technique must be proved (validated) before it is employed in practice. Since the goal of sterilization is to kill microorganisms, the ideal indicator to prove the effectiveness of the process is a resistant form of an appropriate microorganism, normally resistant spores (a biological indicator, or BI). Therefore, during validation of a sterilization process, BIs of known resistance and numbers are used in association with physical-parameter indicators, such as recording thermocouples. Once the lethality of the process is established in association with the physical measurements, the physical measurements can be used for subsequent monitoring of in-use processes without the BIs. Eliminating the use of BIs

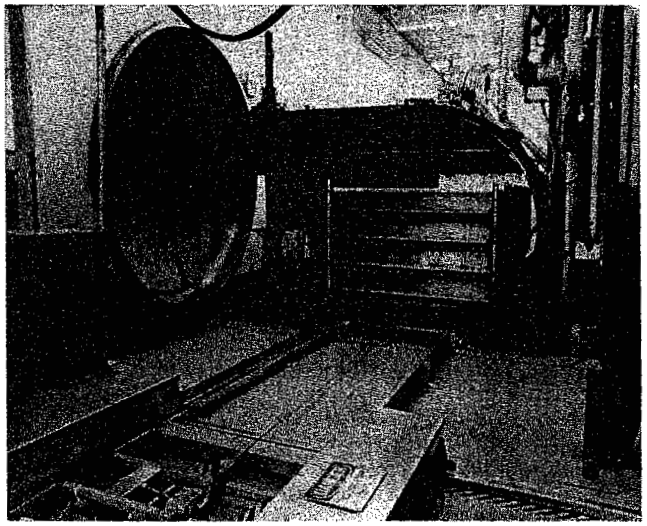

Figure 41-25. Large autoclave being loaded with liter bottles of parenteral solutions (courtesy, Abbott).

in direct association with human-use products is appropriate because of the ever-present risk of an undetected, inadvertent contamination of a product or the environment.

The number of spores and their resistance in BIs used for validation studies must be accurately known or determined. Additionally, the manner in which BIs are used in validation is critical and must be controlled carefully.[30]

In addition to the data printout from thermocouples, sometimes other physical indicators are used, such as color-change and melting indicators, to give visual indication that a package or truckload has been subjected to a sterilization process. Such evidence can become a part of the batch record to confirm that sterilization was accomplished.

Further details concerning methods of sterilization and their application can be found in Chapter 40. In addition, the USP provides suggestions concerning the sterilization of injections and related materials.

FREEZE-DRYING (LYOPHILIZATION)

Freeze-drying is a process of drying in which water is sublimed from the product after it is frozen.[29] The particular advantages of this process are that biologicals and pharmaceuticals that are relatively unstable in aqueous solution can be processed and filled into dosage containers in the liquid state, taking advantage of the relative ease of processing a liquid. They can be dried without elevated temperatures, thereby eliminating adverse thermal effects, and stored in the dry state, in which there are relatively few stability problems.

Further advantages are that these products are often more soluble and/or more rapidly soluble, dispersions are stabilized throughout their shelf life, and products subject to degradation by oxidation have enhanced stability because the process is carried out in a vacuum. However, the increased time and handling required for processing and the cost of the equipment limit the use of this process to those products which have significantly enhanced stability if stored in the dry state.

The fact that ice will sublime at pressures below 3 torr has been a long-established laboratory principle (see Chapter 20). The extensive program for freeze-drying human plasma during World War II provided the impetus for the rapid development of the process.

Freeze-drying essentially consists of

1. Freezing an aqueous product at a temperature below its eutectic temperature.
2. Evacuating the chamber, usually below 0.1 torr (100 μm Hg).
3. Subliming ice onto a cold, condensing surface at a temperature below that of the product, the condensing surface being within the chamber or in a connecting chamber.
4. Introducing heat to the product under controlled conditions, thereby providing energy for sublimation at a rate designed to keep the product temperature below its eutectic temperature.

Figure 41-26 shows a diagram of a small-scale lyophilization system and its functional components. The product may be frozen on the shelf in the chamber by circulating refrigerant (usually Freon, ammonia, or ethylene glycol) from the compressor through pipes within the shelf. After freezing is complete, which may require several hours, the chamber and condenser are evacuated by the vacuum pump, the condenser surface having been chilled previously by circulating refrigerant from the large compressor.

Heat then is introduced from the shelf to the product under graded control by electric resistance coils or by circulating hot water, silicone, or glycol. The process continues until the product is dry (usually 1% or less moisture), leaving a sponge-like matrix of the solids originally present in the product, the input of heat being controlled so as not to degrade the product.

For most pharmaceuticals and biologicals the liquid product is sterilized by filtration before being filled into the dosage container aseptically. The containers must remain open during the drying process to allow water vapor to escape; therefore, they must be protected from contamination during transfer from the filling area to the freeze-drying chamber, while in the freeze-drying chamber, and at the end of the drying process until sealed.

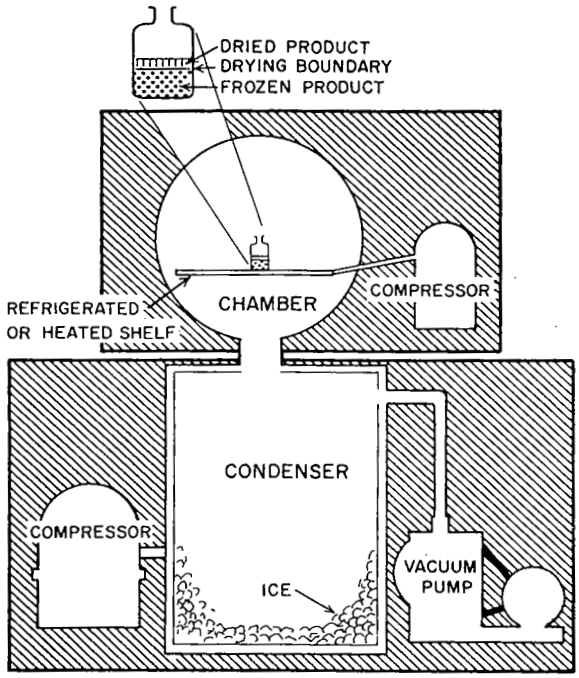

Figure 41-26. Essential components of a freeze-drying system.

Chambers of production size may be equipped with hydraulic or pneumatic internal-stoppering devices designed to push slotted rubber closures into the vials to be sealed while the chamber is still evacuated, the closures having been partially inserted immediately after filling, so that the slots were open to the outside. If internal stoppering is not available or containers such as ampuls are used, filtered dry air or nitrogen should be introduced into the chamber at the end of the process to establish atmospheric pressure.

FACTORS AFFECTING THE PROCESS RATE—The greater the depth of the product in the container, the longer will be the drying process. Therefore, a product to be frozen by placing the container on a refrigerated shelf (plug freezing) should be filled to a planned, limited depth. If large volumes of solution must be processed, the surface area relative to the depth may be increased by using such devices as freezing the container in a slanted position to increase the surface area.

The actual driving force for the process is the vapor pressure differential between the vapor at the surface where drying of the product is occurring (the drying boundary) and that at the surface of the ice on the condenser. The latter is determined by the temperature of the condenser as modified by the insulating effect of the accumulated ice. The former is determined by a number of factors, including

1. The rate of heat conduction through the container and the frozen material, both usually relatively poor thermal conductors, to the drying boundary while maintaining all of the product below its eutectic temperature.
2. The impeding effect of the increasing depth of dried, porous product above the drying boundary.
3. The temperature and heat capacity of the shelf itself.

This may be visualized by referring to Figure 41-26.

The passageways between the product surface and the condenser surface must be wide open and direct for effective operation. The condensing surfaces in large freeze-driers may be in the same chamber as the product or located in a separate

chamber connected by a duct to the drying chamber. Evacuation of the system is necessary to reduce the impeding effect that collisions with air molecules would have on the passage of water molecules. However, the residual pressure in the system must be greater than the vapor pressure of the ice on the condenser or the ice will be vaporized and pulled into the pump, an event detrimental to most pumps.

The amount of solids in the product, their precipitated particle size, and their thermal conductance will affect the rate of drying. The more solids present, the more impediment will be provided to the escape of the water vapor. The smaller the particle size, particularly the crystal size of the ice, the faster the drying generally will be. The poorer the thermal conducting properties of the solids in the product, the slower will be the rate of heat transfer through the frozen material to the drying boundary.

The rate of drying is slow, most often requiring 24 hr or longer for completion. The actual time required, the rate of heat input, and the product temperatures that may be used must be determined for each product and then reproduced carefully with successive processes.

FACTORS AFFECTING FORMULATION—The active constituent of many pharmaceutical products is present in such a small quantity that if freeze-dried alone its presence would be hard to detect visually. Therefore, excipients often are added to increase the amount of solids.

Some consider it ideal for the dried-product plug to occupy essentially the same volume as that of the original solution. To achieve this, the solids content of the original product must be between approximately 5 and 25%. Among the substances found most useful for this purpose, usually as a combination, are sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran.

Each of these substances contributes appearance characteristics of the plug, such as whether dull and spongy or sparkling and crystalline, firm or friable, expanded or shrunken, and uniform or striated. Therefore, the formulation of a product to be freeze-dried must include consideration not only of the nature and stability characteristics required during the liquid state, both freshly prepared and when reconstituted before use, but also the characteristics desired in the dried plug.

MODIFICATIONS IN THE PROCESS AND EQUIPMENT—In some instances a product may be frozen in a bulk container or in trays rather than in the final container and then handled as a bulk solid. Such a state requires a continuation of aseptic processing conditions as long as the product is exposed to the environment.

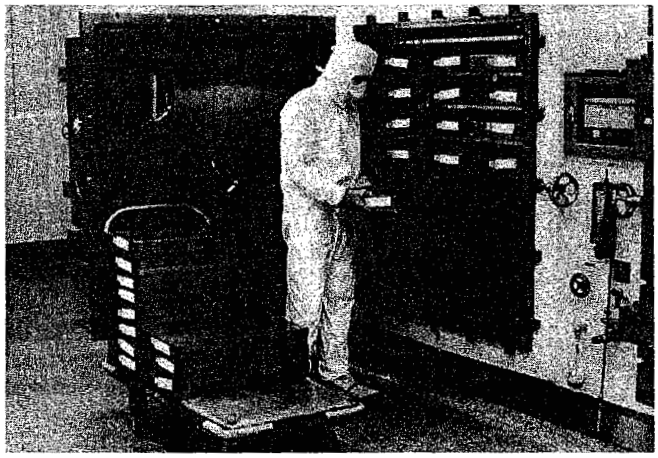

Figure 41-27. Aseptic loading of freeze-drier (courtesy, Upjohn).

When large quantities of material are processed it may be desirable to use ejection pumps in the equipment system. These draw the vapor into the pump and eject it to the outside, thereby eliminating the need for a condensing surface. Such pumps are expensive and usually practical only in large installations.

Available freeze-driers (suppliers: *BOC Edwards, FTS, Hull, Serail, Stokes, Usifroid, Virtic*) range in size from small laboratory units to large industrial models such as the one shown in Figure 41-27. Their selection requires consideration of such factors as

The tray area required
The volume of water to be removed
How the chamber will be sterilized
Whether internal stoppering is required
Whether separate freezers will be used for initial freezing of the product
The degree of automatic operation desired

Other factors involved in the selection and use of equipment are considered in the literature.[29]

Freeze-drying is being used now for research in the preservation of human tissue and is finding increasing application in the food industry. Most biopharmaceuticals require lyophilization to stabilize their protein content effectively. Therefore, many newer developments in the lyophilization process focus on the requirements of this new class of drug products.

QUALITY ASSURANCE AND CONTROL

The importance of undertaking every possible means to ensure the quality of the finished product cannot be overemphasized. Every component and step of the manufacturing process must be subjected to intense scrutiny to be confident that quality is attained in the finished product. The responsibility for achieving this quality is divided appropriately in concept and practice into Quality Assurance (QA) and Quality Control (QC). QA relates to the studies made and the plans developed for ensuring quality of a product prospectively, with a final confirmation of achievement. QC embodies the carrying out of these plans during production and includes all of the tests and evaluations performed to be sure that quality exists in a specific lot of product.

The principles for achieving quality are basically the same for the manufacture of any pharmaceutical. These are discussed in Chapter 51. During the discussion of the preparation of injections in this chapter, mention was made of numerous quality requirements for components and manufacturing processes. Here, only selected tests characteristically required before a finished parenteral product is released are discussed briefly, including sterility, pyrogen, and particulate tests.

STERILITY TEST

All lots of injections in their final containers must be tested for sterility. The USP prescribes the requirements for this test for official injections. The FDA uses these requirements as a guide for testing unofficial sterile products. The primary official test is performed by means of filtration, but direct transfer is used if membrane filtration is unsuitable. To give greater assurance that viable microorganisms will grow, if present, the USP requires that all lots of culture media be tested for their growth-promotion capabilities. However it must be recognized that the reliability of both test methods has the inherent limitations typical of microbial recovery tests. Therefore, it should be noted that this test is not intended as a thoroughly evaluative test for

a product subjected to a sterilization method of unknown effectiveness. It is intended primarily as a check test on the probability that a previously validated sterilization procedure has been repeated or to give assurance of its continued effectiveness. A discussion of sterility testing is given in Chapter 40.

In the event of a sterility-test failure, the immediate issue concerns whether the growth observed came from viable microorganisms in the product (true contamination) or from adventitious contamination during the testing (a false positive). The USP does permit a retest, but the position of the FDA is that retest results are only valid if persuasive evidence exists that the cause of the initial sterility-test failure resides in the laboratory. Therefore, a thorough investigation must be launched to support the justification for performing the retest and assessing the validity of the retest results relative to release of the lot of product.

It should be noted that a *lot* with respect to sterility testing is that group of product containers that has been subjected to the same sterilization procedure. For containers of a product that have been sterilized by autoclaving, for example, a lot would constitute those processed in a particular sterilizer cycle. For an aseptic filling operation, a lot would constitute all of those product containers filled during a period when there was no change in the filling assembly or equipment and which is no longer than one working day or shift.

PYROGEN TEST

The USP evaluates the presence of pyrogens in parenteral preparations by a qualitative fever response test in rabbits, the Pyrogen Test (Section ⟨151⟩), and by the Bacterial Endotoxins Test (Section ⟨85⟩). These two USP tests are described in Chapter 31. Rabbits are used as test animals in Section ⟨151⟩ because they show a physiological response to pyrogenic substances similar to that by man. While a minimum pyrogenic dose (MPD), the amount just sufficient to cause a positive USP Pyrogen Test response, sometimes may produce uncertain test results, a content equal to a few times the MPD will leave no uncertainty. Therefore, the test is valid and has continued in use since introduced by Seibert in 1923. It should be understood that not all injections may be subjected to the rabbit test, since the medicinal agent may have a physiological effect on the test animal such that any fever response would be masked.

The *Bacterial Endotoxins Test* (BET) is an *in vitro* test based on the formation of a gel or the development of color in the presence of bacterial endotoxins and the lysate of the amebocytes of the horseshoe crab *(Limulus polyphemus)*. The *Limulus Amebocyte Lysate* (LAL) test, as it also is called, is a biochemical test performed in a test tube and is simpler, more rapid, and of greater sensitivity than the rabbit test.[32] Although it detects only the endotoxic pyrogens of gram-negative bacteria, these are the most prominent environmental microbial contaminants likely to invade sterile products. The test also has been automated.[33]

The LAL test is a semiquantitative test. To provide standardization for the test, the USP has established a reference endotoxin against which lots of the lysate are standardized. Thus, the sensitivity of the lysate is given in terms of endotoxin units (EU). Most USP injections now have been given limits in terms of EUs (eg, Bacteriostatic Sodium Chloride Injection, 1.0 EU/mL), thus indicating an increasing priority for the BET in testing for the presence of endotoxin in parenteral products and in medical devices.

PARTICULATE EVALUATION

Particulate matter in parenteral solutions long has been recognized as unacceptable since the user could be expected to conclude that the presence of visible *dirt* would suggest that the product is of inferior quality. Today, it is recognized that the presence of particles in solution, particularly if injected intravenously, can be harmful. While data defining the extent of risk and the effects produced still are limited, it has been shown that particles of lint, rubber, insoluble chemicals, and other foreign matter can produce emboli in the vital organs of animals and man.[34] Further, it has been shown that the development of infusion phlebitis may be related to the presence of particulate matter in intravenous fluids.[35]

The particle size of particular concern has not been clearly delineated, but it has been suggested that since erythrocytes have a diameter of approximately 4.5 μm, particles of more than 5 μm should be the basis for evaluation. This is a considerably smaller particle than can be seen with the unaided eye; approximately 50 μm is the lower limit unless the Tyndall effect is used whereby particles as small as 10 μm can be seen by the light scattered from them.

The USP specifies that good manufacturing practice requires that each final container of an injection be subjected individually to a visual inspection and that containers in which visible particles can be seen should be discarded. This 100% inspection of a lot of product is designed to prevent the distribution and use of parenterals that contain particulate matter that may be harmful psychologically or organically to the participant. Therefore, all of the product units from a production line currently are being inspected individually by human inspectors under a good light, baffled against reflection into the eye and against a black-and-white background. This inspection is subject to the limitation of the size of particles that can be seen, the variation of visual acuity from inspector to inspector, their emotional state, eye strain, fatigue, and other personal factors that will affect what is seen. However, it does provide a means for eliminating the few units that normally contain visible particles. Automated inspection machines increasingly are being used today.

The assessment of the level of particulate matter below the visible size of about 50 μm has become an increasingly used QC indicator of process cleanliness in the manufacture of injections. The tests used, however, are destructive of container units. Therefore, they are performed on appropriately selected samples of products. Further, all of these methods require very stringent, ultraclean preparation techniques to ensure accuracy in the counting and sizing of particles only in the product, rather than those that may have been introduced inadvertently during the sample preparation or the testing procedure.

The USP has identified two test methods in ⟨788⟩, *Particulate Matter in Injections*. All LVIs for single-dose infusion and those SVIs for which the monograph specifies a limit (primarily those commonly added to infusion solutions) are subject to the specified limits given in Table 41-3. The first test to be used is the light obscuration test, which uses an electronic instrument designed to count and measure the size of particles by means of a shadow cast by the particle as it passes through a high-intensity light beam (suppliers: *Climet, HIAC/Royco*). If the injection formulation is not a clear, colorless solution (eg, an emulsion) or it exceeds the limits specified for the light obscuration test, it is to be subjected to the microscopic count test.

Table 41-3. Subvisible Particulate Matter Limits in USP Injections

Light obscuration particle count test		
	≥10 μm	≥25 μm
SVIs	6000	600/container
LVIs	25	3/mL
Microscopic particle count test		
	≥10 μm	≥25 μm
SVIs	3000	300/container
LVIs	12	2/mL

The latter method consists of filtering a measured sample of solution through a membrane filter under ultraclean conditions and then counting the particles on the surface of the filter, using a microscope and oblique light at 100× magnification. The time requirements for performing the latter test are very long. These standards are being met readily in the US today by the manufacturers of LVIs and the specified SVIs. Additional information may be found in the literature, particularly in an extensive review article.[36]

Whether or not these standards are realistic toxicologically has not been established; rather, the objective of the compendium is to establish specification limits that would encourage the preparation of clean parenteral solutions, particularly those to be given intravenously.

It also should be realized that administration sets and the techniques used for preparing and administering intravenous infusion fluids may introduce substantial amounts of particulate matter into an otherwise clean solution. Therefore, the pharmaceutical manufacturer, the administration set manufacturer, the pharmacist, the nurse, and the physician must share responsibility for making sure that the patient receives a clean intravenous injection.

LEAKER TEST

Ampuls that have been sealed by fusion must be subjected to a test to determine whether or not a passageway remains to the outside; if so, all or a part of the contents may leak to the outside and spoil the package, or microorganisms or other contaminants may enter. Changes in temperature during storage cause expansion and contraction of the ampul and contents, and will accentuate interchange if a passageway exists, even if microscopic in size.

This test usually is performed by producing a negative pressure within an incompletely sealed ampul while the ampul is submerged entirely in a deeply colored dye solution. Most often, approximately 1% methylene blue solution is employed. After carefully rinsing the dye solution from the outside, color from the dye will be visible within a leaker. Leakers, of course, are discarded.

Vials and bottles are not subjected to such a leaker test because the sealing material (rubber stopper) is not rigid. Therefore, results from such a test would be meaningless. However, assurance of container-closure sealing integrity should be an integral part of product development by developing specifications for the fit of the closure in the neck of the container, the physical characteristics of the closure, the need for lubrication of the closure, and the capping pressure.

SAFETY TEST

The National Institutes of Health requires of most biological products routine safety testing in animals. Under the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act, most pharmaceutical preparations are now required to be tested for safety. Because it is entirely possible for a parenteral product to pass the routine sterility test, pyrogen test, and chemical analyses, and still cause unfavorable reactions when injected, a safety test in animals is essential, particularly for biological products, to provide additional assurance that the product does not have unexpected toxic properties. Safety tests in animals are discussed in detail in the USP.

PACKAGING AND LABELING

A full discussion of the packaging of parenteral preparations is beyond the scope of this text. It is essential, of course, that the packaging should provide ample protection for the product against physical damage from shipping, handling, and storage as well as protecting light-sensitive materials from ultraviolet radiation. An extensive review of this subject has been published.[37]

PACKAGING—The USP includes certain requirements for the packaging and storage of injections, as follows:

1. The volume of injection in single-dose containers is defined as that which is specified for parenteral administration at one time and is limited to a volume of 1 L.
2. Parenterals intended for intraspinal, intracisternal, or peridural administration are packaged only in single-dose containers.
3. Unless an individual monograph specifies otherwise, no multiple-dose container shall contain a volume of injection more than sufficient to permit the withdrawal and administration of 30 mL.
4. Injections packaged for use as irrigation solutions or for hemofiltration or dialysis or for parenteral nutrition are exempt from the foregoing requirements relating to packaging. Containers for injections packaged for use as hemofiltration or irrigation solutions may be designed to empty rapidly and may contain a volume in excess of 1 L.
5. Injections intended for veterinary use are exempt from the packaging and storage requirements concerning the limitation to single-dose containers and to volume of multiple-dose containers.

LABELING—The labeling of an injection must provide the physician or other user with all of the information needed to ensure the safe and proper use of the product. Since all of this information cannot be placed on the immediate container and be legible, it may be provided on accompanying printed matter. General labeling requirements for drugs are discussed in Chapter 90.

A restatement of the labeling definitions and requirements of the USP for Injections is as follows:

The term *labeling* designates all labels and other written, printed, or graphic matter upon an immediate container or upon, or in, any package or wrapper in which it is enclosed, with the exception of the outer shipping container. The term *label* designates that part of the labeling upon the immediate container.

The label states the name of the preparation, the percentage content of drug of a liquid preparation, the amount of active ingredient of a dry preparation, the volume of liquid to be added to prepare an injection or suspension from a dry preparation, the route of administration, a statement of storage conditions, and an expiration date. Also, the label must indicate the name of the manufacturer or distributor and carry an identifying lot number. The lot number is capable of providing access to the complete manufacturing history of the specific package, including each single manufacturing step.

The container label is so arranged that a sufficient area of the container remains uncovered for its full length or circumference to permit inspection of the contents.

The label must state the name of the vehicle and the proportions of each constituent, if it is a mixture; the names and proportions of all substances added to increase stability or usefulness; and the expiration date where required by the individual monograph.

Preparations labeled for use as dialysis, hemofiltration, or irrigation solutions must meet the requirements for Injections other than those relating to volume and also must bear on the label statements that they are not intended for intravenous injection.

Injections intended for veterinary use are so labeled.

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CHAPTER 55

Pharmaceutical Necessities

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Changes have occurred recently in the practice of pharmacy. Organizations have emerged addressing the compounding aspects of the profession. The American Association of Compounding Pharmacists provides a regularly published journal for pharmacists engaged in compounding prescriptions. Companies such as Compounding Centers of America provide supplies and model formulations for the compounding pharmacist. These efforts have helped to reduce the number of community pharmacy compounding errors that were in the news headlines a scant 6 yr ago.

Also, pharmacy education has changed. Now the entry-level degree necessary for licensure is the PharmD degree. With this degree the focus on the clinical aspects of pharmacy has an even greater emphasis on the educational process. Much of this is at the expense of basic pharmaceutics and in some instances, because of course load, electives such as industrial pharmacy courses.

The pharmaceutical industry used to be able to hire graduates with pharmacy degrees for positions in production, quality control, and dosage-form development because of the breadth of understanding the graduate had of pharmaceutical processes. Unfortunately, gaining this understanding is becoming increasingly difficult unless a student pursues an advanced degree in industrial pharmacy or pharmaceutics. It is the personal experience of the author that young scientists today are lacking the basic understanding of what ingredients in a formulation are used for and how their functionality can be altered to result in a specific activity.

This chapter does not address the legal aspects of community compounding by a pharmacist, nor does it explain all the specifics of formulating a product for commercial manufacturing. The intent of this information is to inform both the community pharmacist and individuals interested in understanding the commercial formulations which ingredients are necessary for creating a drug product. These substances, known as excipients, are useful in both the community and commercial settings, although they might be used differently. The excipients described include antioxidants and preservatives, emulsifying and suspending agents, ointment bases, solvents, and miscellaneous ingredients. A more detailed review of these excipients and their commercial applicability to dosage-form development can be found in Chapters 36 through 54.

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

ALCOHOL—pages 1038 and 1507.

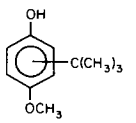
BENZALKONIUM CHLORIDE—page 1508.

BENZETHONIUM CHLORIDE—page 1508.

BENZYL ALCOHOL—page 1151.

BUTYLATED HYDROXYANISOLE

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



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

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

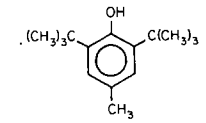
Description—White or slightly yellow, waxy solid having a faint, characteristic odor.

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

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

BUTYLATED HYDROXYTOLUENE

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



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

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

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

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

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

CHLOROBUTANOL

2-Propanol, 1,1,1-trichloro-2-methyl-, Chlorbutol; Chlorbutanol; Acetone Chloroform; Chloretone

$(CCl_3)C(CH_3)_2OH$

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

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

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

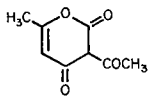
Solubility—1 g in 125 mL water, 1 mL alcohol or about 10 mL glycerin; freely soluble in chloroform, ether, or volatile oils.

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

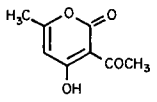
Uses—Topically, as a solution in clove oil as a *dental analgesic.* It has *local anesthetic* potency to a mild degree and has been employed as an anesthetic dusting powder (1 to 5%) or ointment (10%). It has antibacterial and germicidal properties. It is used chiefly as a *preservative* in solutions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

DEHYDROACETIC ACID

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



(keto form)



(enol form)

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

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

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

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

Uses—Preservative.

ETHYLENEDIAMINE

1,2-Ethanediamine

$H_2NCH_2CH_2NH_2$

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

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

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

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

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

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

ETHYL VANILLIN—page 1021.

GLYCERIN—pages 1039 and 1346.

HYPOPHOSPHOROUS ACID—page 1044.

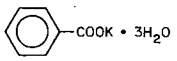
PHENOL—page 1045.

PHENYLETHYL ALCOHOL—page 1024.

PHENYLMERCURIC NITRATE—see RPS-19 page 1270.

POTASSIUM BENZOATE

Benzoic Acid, Potassium Salt



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

Description—Crystalline powder.

Solubility—Soluble in water or alcohol.

Uses—Preservative.

POTASSIUM METABISULFITE

Dipotassium Pyrosulfite

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

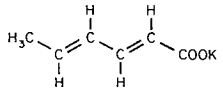
Description—White crystals or crystalline powder with an odor of SO_2. Oxidizes in air to the sulfate. May ignite on powdering in a mortar if too much heat develops.

Solubility—Freely soluble in water; insoluble in alcohol.

Uses—Antioxidant.

POTASSIUM SORBATE

2,4-Hexadienoic Acid, *(E,E)*-, Potassium Salt; 2,4-Hexadienoic Acid, Potassium Salt; Potassium 2,4-Hexadienoate



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

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

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

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

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

SASSAFRAS OIL—page 1027.

SODIUM BENZOATE—see RPS-19 page 1271.

SODIUM BISULFITE

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

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

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

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

Uses—An *antioxidant* and *stabilizing agent.* Epinephrine hydrochloride solutions may be stabilized by the addition of small quantities of the salt. It also is used to help solubilize kidney stones. It is useful for removing permanganate stains and for solubilizing certain dyes and other chemicals.

SODIUM METABISULFITE

Disulfurous acid, disodium salt

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

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

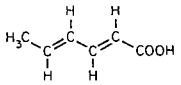
Description—White crystals or white to yellowish crystalline powder with an odor of sulfur dioxide; on exposure to air and moisture, it is slowly oxidized to sulfate.

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

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

SORBIC ACID

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



(6)

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

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

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

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

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

THIMEROSAL—see RPS-19 page 1271.

COLORING, FLAVORING, AND DILUTING AGENTS

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

Coloring Agents

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

NATURAL COLORING PRINCIPLES

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

Mineral colors frequently are termed *pigments* and are used to color lotions, cosmetics, and other preparations, usually for external application. Examples are *Red Ferric Oxide* (page 1049) and *Yellow Ferric Oxide* (page 1049), titanium dioxide (page 1217), and carbon black.

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

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

SYNTHETIC COLORING PRINCIPLES

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

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

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

STABILITY—Most dyes are relatively unstable chemicals because of their unsaturated structures. They are subject to fading because of light, metals, heat, microorganisms, oxidizing and reducing agents, plus strong acids and bases. In tablets, fading may appear as spotting and specking.

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

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

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

The word *permitted* is used in a restricted sense. It does not carry with it the right to use colors for purposes of deception,

even though they are *permitted* colors, for all food laws have clauses prohibiting the coloring of foods and beverages in a manner so as to conceal inferiority or to give a false appearance of value.

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

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

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

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

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

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

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

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

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

FLAVOR

The word flavor refers to a mixed sensation of taste, touch, smell, sight, and sound, all of which combine to produce an infinite number of gradations in the perception of a substance. The four primary tastes—*sweet, bitter, sour,* and *saline*—appear to result partly from physicochemical and partly from psychological action. Taste buds (Fig 55-1), located mainly on the tongue, contain very sensitive nerve endings that react, in the presence of moisture, with the flavors in the mouth, and as a result of physicochemical activity, electrical impulses are produced and transmitted via the seventh, ninth, and tenth cranial nerves to the areas of the brain that are devoted to the perception of taste. Some of the taste buds are specialized in their function, giving rise to areas on the tongue that are sensitive to only one type of taste. The brain, however, usually perceives taste as a composite sensation, and accordingly, the components of any flavor are not readily discernible. Children have more taste buds than adults and hence are more sensitive to tastes.

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

Persons suffering from a head cold find their food much less palatable than usual because their sense of smell is impaired, and if the nostrils are held closed, raw onions taste sweet and it is much easier to ingest castor oil and other nauseating medicines. The volatility of a substance is an important factor

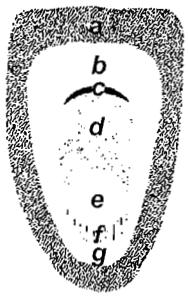


Figure 55-1. Upper surface of the tongue. *a,* Taste receptors for all tastes; *b,* sweet, salty, and sour; *c,* salty and sour; *d,* sour only; *e,* no taste sensation; *f,* sweet and sour; *g,* bitter, sweet, and sour. (Adapted from Crocker EC. *Flavor.* New York: McGraw-Hill, 1945, p 22.)

that is influenced by the warmth and moisture of the mouth, since the more volatile a compound, the more pronounced its odor. The sense of smell detects very minute amounts of material and is usually much more sensitive in detecting the presence of volatile chemicals, but the tongue is able to detect infinitesimal amounts of some vapors if it is protruded from the mouth so that solution of the gases in the saliva may take place. In this manner traces of sulfur dioxide can be detected in the air, since it dissolves in the saliva and creates a sour taste.

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

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

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

People are more sensitive to odor than to taste. There are about 10,000 to 30,000 identifiable scents, of which the average person can identify about 4000. Women are more sensitive to odors than men. Additional insights can be obtained by reading Beauchamp GK, *et al: Tasting and Smelling,* (New York: Academic, 1997) and Cagan RH, *et al: Neural Mechanisms in Taste* (Boca Raton, FL: CRC Press, 1989).

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

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

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

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

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

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

SELECTION OF FLAVORS

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

FLAVORING METHODOLOGY

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

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

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

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

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

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

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

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

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

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

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

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

SELECTION OF VEHICLES

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

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

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

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

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

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

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

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

A listing of substances, most of them official, used as flavors, flavored vehicles, or sweeteners, is given in Table 55-1. Additional information on flavoring ingredients may be obtained in Burdock GA, *Fenaroli's Handbook of Flavor Ingredients,* Cleveland: CRC, 1994.

ACACIA SYRUP—page 1027.

ANISE OIL

ANISEED OIL; STAR ANISE OIL

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

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

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

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

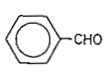
Solubility—Soluble in 3 volumes of 90% alcohol.

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

AROMATIC ELIXIR—page 1028.

BENZALDEHYDE

ARTIFICIAL ESSENTIAL ALMOND OIL



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

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

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

Table 55-1. Flavoring Agents

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

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

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

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

CARDAMOM SEED

Cardamom Fruit; Cardamom; Ceylon or Malabar Cardamom

The dried ripe seed of *Elettaria cardamomum* (Linné) Maton (Fam. *Zingiberaceae*). It should be removed recently from the capsule.

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

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

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

CHERRY SYRUP—page 1027.

CINNAMON

Saigon Cinnamon; True Cinnamon; Saigon Cassia

The dried bark of *Cinnamomum loureirii* Nees (Fam. *Lauraceae*). It contains, in each 100 g, not less than 2.5 mL of volatile oil.

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

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

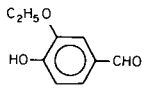
COCOA SYRUP—page 1027.

CORIANDER—page 1026.

DENATONIUM BENZOATE—page 1043.

ETHYL VANILLIN

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



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

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

Description—Fine, white or slightly yellowish crystals; odor and taste similar to those of vanillin; affected by light; solutions are acid to litmus; melts about 77°.

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

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

EUCALYPTUS OIL

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

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

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

Solubility—Soluble in 5 volumes of 70% alcohol.

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

FENNEL OIL

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

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

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

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

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

Uses—A flavoring agent

It formerly was employed in a dose of 0.1 mL as a *carminative*.

GLYCYRRHIZA

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

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

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

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

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

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

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

GLYCYRRHIZA ELIXIR—page 1028.

GLYCYRRHIZA SYRUP—page 1028.

HONEY—page 1049.

HYDRIODIC ACID SYRUP—page 1028.

ISO-ALCOHOLIC ELIXIR—page 1049.

LAVENDER OIL

Lavender Flowers Oil

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

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

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

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

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

LEMON OIL

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

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

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

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

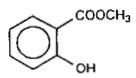
Description—Pale yellow to deep yellow or greenish yellow liquid, with the characteristic odor and taste of the outer part of fresh lemon peel; specific gravity 0.849 to 0.855.

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

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

METHYL SALICYLATE

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



Methyl salicylate [119-36-8] $C_6H_4(OH)COOCH_3$ (152.15); produced synthetically or obtained by maceration and subsequent distillation with steam from the leaves of *Gaultheria procumbens* Linné (Fam *Ericaceae*) or from the bark of *Betula lenta* Linné (Fam *Betulaceae*).

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

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

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

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

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

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

MONOSODIUM GLUTAMATE

Glutamic acid, monosodium salt, monohydrate

[142-47-2] $C_5H_8NNaO_4H_2O$ (187.13)

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

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

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

Uses—Flavoring agent and perfume.

NUTMEG OIL

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

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

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

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

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

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

ORANGE OIL

Sweet Orange Oil

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

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

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

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

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

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

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

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

ORANGE FLOWER WATER—page 1027.

SWEET ORANGE PEEL TINCTURE

Preparation—From sweet orange peel, which is the outer rind of the nonartificially colored, fresh, ripe fruit of *Citrus sinensis* (Linné) Osbeck (Fam *Rutaceae*), by Process M (page 750). Macerate 500 g of the sweet orange peel *Note—Exclude the inner, white portion of the rind)* in 900 mL of alcohol, and complete the preparation with alcohol to make the product measure 1000 mL. Use talc as the filtering medium.

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

Alcohol Content—62 to 72%.

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

COMPOUND ORANGE SPIRIT

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

Orange Oil	200 mL
Lemon Oil	50 mL
Coriander Oil	20 mL
Anise Oil	5 mL
Alcohol, a sufficient quantity, to make	1000 mL

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

Alcohol Content—65 to 75%.

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

ORANGE SYRUP

Syrup of Orange Peel

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

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

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

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

Alcohol Content—2 to 5%.

Uses—A pleasant, acidic vehicle.

PEPPERMINT

American Mint; Lamb Mint; Brandy Mint

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

Uses—The source of green color for *Peppermint Spirit* (see RPs-19 page 902). The odor of fresh peppermint is due to the presence of about 2% of a volatile oil, much of which is lost on drying the leaves in air. It is cultivated widely both in the US and France. It formerly was used as a carminative.

Peppermint Oil—The volatile oil distilled with steam from the fresh overground parts of the flowering plant *Mentha piperita* Linné (Fam *Labiatae*), rectified by distillation and neither partially nor wholly dementholized. It yields not less than 5% of esters, calculated as menthyl acetate $C_{12}H_{22}O_2$, and not less than 50% of total menthol $C_{10}H_{20}O$, free and as esters. *Constituents:* This is one of the most important of the group of volatile oils. The chief constituent is *Menthol* (page 1209), which occurs in the levorotatory form; its ester, *menthyl acetate,* is present in a much smaller amount. Other compounds that are present include the ketone *menthone, piperitone, α-pinene, l-limonene, phellandrene, cadinene, menthyl isovalerate, isovaleric aldehyde, acetaldehyde, menthofuran, cineol,* an unidentified *lactone* $C_{10}H_{16}O_2$, and probably *amyl acetate.*

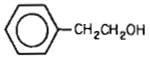
Description and Solubility—Colorless or pale yellow liquid, with a strong, penetrating odor of peppermint and a pungent taste, followed by a sensation of cold when air is drawn into the mouth; specific gravity 0.896 to 0.908; 1 volume dissolves in 3 volumes of 70% alcohol. *Uses:* A *flavoring agent,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

PEPPERMINT SPIRIT—see RPS-19 page 902.

PEPPERMINT WATER—page 1027.

PHENYLETHYL ALCOHOL

Benzeneethanol; 2-Phenylethanol



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

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

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

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

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

ROSE OIL

Otto of Rose; Attar of Rose

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

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

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

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

STRONGER ROSE WATER

Triple Rose Water

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

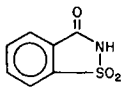
Note—When diluted with an equal volume of purified water, it may be supplied when *Rose Water* is required.

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

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

SACCHARIN

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



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

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

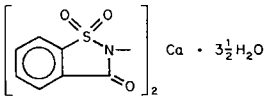
Description—White crystals or a white crystalline powder; odorless or with a faint aromatic odor; in dilute solution it is intensely sweet; solutions are acid to litmus; melts between 226° and 230°.

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

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

SACCHARIN CALCIUM

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



1,2-Benzisothiazolin-3-one 1,1-dioxide calcium salt hydrate (2:7) [6381-91-5] $C_{14}H_8CaN_2O_6S_2 \cdot 3½\ H_2O$ (467.48); *anhydrous* [6485-34-3] (404.43).

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

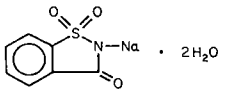
Description—White crystals or a white, crystalline powder; odorless or with a faint aromatic odor; and an intensely sweet taste even in dilute solutions; in dilute solution it is about 300 times as sweet as sucrose.

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

Uses—See *Saccharin.*

SACCHARIN SODIUM

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



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

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

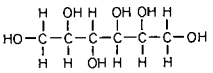
Description—White crystals or a white crystalline powder; odorless or with a faint aromatic odor, and an intensely sweet taste even in dilute solutions; in dilute solution it is about 300 times as sweet as sucrose; in powdered form it usually contains about 1/3 the theoretical amount of water of hydration because of efflorescence.

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

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

SORBITOL

Sionin; Sorbit; D-Sorbitol; D-Glucitol; Sorbo



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

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

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

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

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

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

SPEARMINT

Spearmint Leaves; Spearmint Herb; Mint

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

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

Uses—A flavoring agent.

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

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

SUCROSE

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

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

For the structural formula, see page 411.

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

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

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

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

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

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

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

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

CONFECTIONER'S SUGAR

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

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

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

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

SYRUP—page 1028.

TOLU BALSAM

Tolu

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

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

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

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

Uses—A *vehicle, flavoring agent,* and stimulating *expectorant* as a syrup. It is also an ingredient of *Compound Benzoin Tincture* (page 1203).

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

Tolu Balsam Tincture [Tolu Tincture]—*Preparation:* With tolu balsam (200 g), prepare a tincture by Process M (page 750), using alcohol as the menstruum. *Alcohol Content:* 77 to 83%. *Uses:* A balsamic preparation employed as an addition to expectorant mixtures; also used in the preparation of *Tolu Balsam Syrup*.

VANILLA

Vanilla Bean

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

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

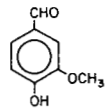
Uses—A flavor.

Note—Do not use if it has become brittle.

Vanilla Tincture [Extract of Vanilla]—*Preparation:* Add water (200 mL) to comminuted vanilla (cut into small pieces, 100 g) in a suitable covered container, and macerate during 12 hr, preferably in a warm place. Add alcohol (200 mL) to the mixture of vanilla and water, mix well, and macerate about 3 days. Transfer the mixture to a percolator containing sucrose (in coarse granules, 200 g), and drain; then pack the drug firmly, and percolate slowly, using diluted alcohol (qs) as the menstruum. If the percolator is packed with an evenly distributed mixture of the comminuted vanilla, sucrose, and clean, dry sand, the increased surface area permits more efficient percolation. This tincture is unusual in that it is the only official one in which sucrose is specified as an ingredient. *Alcohol Content:* 38 to 42%. *Uses:* A *flavoring agent.* See *Flavors,* page 1018.

VANILLIN

Benzaldehyde, 4-hydroxy-3-methoxy-,



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

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

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

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

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

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

WATER—page 1027.

WATER PURIFIED—page 1027.

WILD CHERRY SYRUP—page 1028.

OTHER FLAVORING AGENTS

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

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

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

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

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

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

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

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

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

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

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

Lemon Tincture USP XVIII [Lemon Peel Tincture]—*Preparation:* From lemon peel, which is the outer yellow rind of the fresh, ripe fruit of *Citrus limon* (Linné) Burmann filius (Fam *Rutaceae*), by *Process M* (page 750), 500 g of the peel being macerated in 900 mL alcohol, and the preparation being completed with alcohol to make the product measure 1000 mL. Use talc as the filtering medium. The white portion of the rind must not be used, as the proportion of oil, which is found only in the yellow rind, is reduced, and the bitter principle, hesperidin, introduced. *Alcohol Content:* 62 to 72%. *Uses:* A flavor, its fineness of flavor being ensured as it comes from the fresh fruit, and being an alcoholic solution it is more stable than the oil.

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

Orange Oil, Bitter—The volatile oil obtained by expression from the fresh peel of the fruit of *Citrus aurantium* Linné (Fam *Rutaceae*); contains primarily *d*-limonene. Pale yellow liquid with a characteristic aromatic odor of the Seville orange; if it has a terebinthinate odor, it should not be dispensed; refractive index 1.4725 to 1.4755 at 20°. It differs little from *Orange Oil* (page 1023) except for the botanical source. Miscible with anhydrous alcohol and with about 4 volumes alcohol. *Uses:* A *flavor.*

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

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

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

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

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

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

Sassafras Oil—The volatile oil distilled with steam from *Sassafras. Uses:* A *flavor* by confectioners, particularly in hard candies. Either the oil or safrol is used as a *preservative* in mucilage and library paste, being far superior to methyl salicylate for this purpose. Since the oil is

antiseptic, it sometimes is employed in conjunction with other agents for local application in diseases of the nose and throat; safrol also is used in this way.

Wild Cherry [Wild Black Cherry Bark]—The carefully dried stem bark of *Prunus serotina* Ehrhart (Fam *Rosaceae*), free of borke and preferably having been collected in autumn. *Constituents:* A glucoside of d-*mandelonitrile* ($C_6H_5 \cdot CHOH \cdot CN$) known as prunasin (page 414), the enzyme *emulsin,* tannin, a bitter principle, starch, resin, etc. In the BP and the English literature this drug has been termed *Virginian Prune*—a literal but incorrect translation of the older botanical name, *Prunus virginiana. Uses:* A *flavoring agent,* especially in cough preparations. It is an ingredient in *Wild Cherry Syrup.* As with bitter almond, contact with water, in the presence of emulsin, results in the production of benzaldehyde and HCN. All preparations of wild cherry should be made without heat, to avoid destruction of the enzyme that is responsible for the production of the free active principles.

DILUTING AGENTS

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

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

AQUEOUS DILUTING AGENTS

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

ORANGE FLOWER WATER

Stronger Orange Flower Water; Triple Orange Flower Water

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

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

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

PEPPERMINT WATER

A clear, saturated solution of peppermint oil in purified water, prepared by one of the processes described under *Aromatic Waters* (page 724).

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

TOLU BALSAM SYRUP—page 1025.

WATER

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

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

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

PURIFIED WATER

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

Caution—Do not use this in preparations intended for parenteral administration. For such purposes, use Water for Injection, Bacteriostatic Water for Injection, or Sterile Water for Injection, page 1029.

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

DISTILLATION PROCESS

Water	1000 vol
To make	750 vol

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

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

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

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

SYRUPS USED AS DILUTING AGENTS

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

ACACIA SYRUP

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

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

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

CHERRY SYRUP

Syrupus Cerasi

Cherry Juice	475 mL
Sucrose	800 g
Alcohol	20 mL
Purified Water, a sufficient quantity to make	1000 mL

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

Alcohol Content—1 to 2%.

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

COCOA SYRUP

Cacao Syrup; Chocolate-flavored Syrup; Chocolate Syrup

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

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

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

Uses—A pleasantly *flavored vehicle.*

SYRUP

Simple Syrup

Sucrose	850 g
Purified Water, a sufficient quantity, to make	1000 mL

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

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

Specific Gravity—Not less than 1.30.

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

OTHER SYRUPS USED AS DILUTING AGENTS

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

Hydriodic Acid Syrup—Contains, in each 100 mL, 1.3 to 1.5 g HI (127.91). *Preparation:* Mix diluted hydriodic acid (140 mL) with purified water (550 mL), and dissolve dextrose (450 g) in this mixture by agitation. Add purified water (qs) to make the product measure 1000 mL, and filter. *Caution: It must not be dispensed if it contains free iodine, as evidenced by a red coloration. Description:* Transparent, colorless, or not more than pale straw-colored, syrupy liquid; odorless, with a sweet, acidulous taste; specific gravity about 1.18; hydriodic acid is decomposed easily in simple aqueous solution (unless protected by hypophosphorous acid), free iodine being liberated, and if taken internally, when in this condition, it is irritating to the alimentary tract. The dextrose used in this syrup should be of the highest grade obtainable.

Incompatibilities—The reactions of the *acids* (page 725) as well as those of the water-soluble iodide salts. Oxidizing agents liberate iodine; alkaloids may be precipitated. *Uses:* Traditionally as a *vehicle for expectorant* drugs. Its therapeutic properties are those of the iodides. *Dose: Usual,* 5 mL.

Wild Cherry Syrup USP XVIII—*Preparation:* Pack wild cherry (in coarse powder, 150 g), previously moistened with water (100 mL), in a cylindrical percolator, and add water (qs) to leave a layer of it above the powder. Macerate for 1 hr, then proceed with rapid percolation, using added water, until 400 mL of percolate is collected. Filter the percolate, if necessary, add sucrose (675 g) and dissolve it by agitation, then add glycerin (150 mL), alcohol (20 mL), and water (qs) to make the product measure 1000 mL. Strain if necessary. *It may be made also in the following manner:* The sucrose may be dissolved by placing it in a second percolator as directed for preparing *Syrup,* and allowing the percolate from the wild cherry to flow through it and into a graduated vessel containing the glycerin and alcohol, until the total volume measures 1000 mL. *Note:* Heat is avoided, lest the enzyme emulsin be inactivated. If this should happen, the preparation would contain no free HCN, upon which its action as a sedative for coughs mainly depends. For a discussion of the chemistry involved, see *Wild Cherry* (page 1027). *Alcohol Content:* 1 to 2%. *Uses:* Chiefly as a *flavored vehicle* for cough syrups.

MUCILAGES USED AS DILUTING AGENTS

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

The following mucilage used for this purpose is described under *Emulsifying and Suspending Agents,* page 1030.

ACACIA MUCILAGE—page 1030.

HYDROALCOHOLIC DILUTING AGENTS

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

AROMATIC ELIXIR

Simple Elixir

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

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

Alcohol Content—21 to 23%.

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

OTHER HYDROALCOHOLIC DILUTING AGENTS

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

FLAVORED ALCOHOLIC SOLUTIONS

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

LEMON TINCTURE—page 1026.

ORANGE SPIRIT, COMPOUND—page 1023.

ORANGE PEEL, SWEET, TINCTURE—page 1023.

DILUTING AGENTS FOR INJECTIONS

Injections are liquid preparations, usually solutions or suspensions of drugs, intended to be injected through the skin into the body. Diluting agents used for these preparations may be aqueous or nonaqueous and must meet the requirements for sterility and also of the pyrogen test. Aqueous diluting agents include such preparations as *Sterile Water for Injection* and various sterile, aqueous solutions of electrolytes and/or dextrose. Nonaqueous diluting agents are generally fatty oils of vegetable origin, fatty esters, and polyols such as propylene glycol and polyethylene glycol. These agents are used to dissolve or dilute oil-soluble substances and to suspend water-soluble substances when it is desired to decrease the rate of absorption and, hence, prolong the duration of action of the drug substances. Preparations of this type are given intramuscularly. See *Parenteral Preparations,* page 780.

CORN OIL

Maize Oil

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

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

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

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

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

COTTONSEED OIL

Cotton Seed Oil; Cotton Oil

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

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

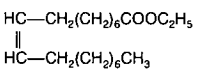
Description—Pale yellow, oily liquid with a bland taste; odorless or nearly so; particles of solid fat may separate below 10°; solidifies at about 0 to −5°; specific gravity 0.915 to 0.921.

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

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

ETHYL OLEATE

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



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

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

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

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

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

PEANUT OIL

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

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

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

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

Uses—A *solvent* in preparing oil solutions for injection (page 807). It also is used for making liniments, ointments, plasters, and soaps, as a substitute for olive oil.

SESAME OIL

Teel Oil; Benne Oil; Gingili Oil

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

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

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

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

WATER FOR INJECTION

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

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

Description—Clear, colorless, odorless liquid.

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

BACTERIOSTATIC WATER FOR INJECTION

Sterile water for injection containing one or more suitable antimicrobial agents

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

Uses—*Sterile vehicle* for parenteral preparations.

STERILE WATER FOR INJECTION

Water for Parenterals

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

Description—Clear, colorless, odorless liquid.

Uses—For the preparation of *all aqueous parenteral solutions,* including those used in animal assays. See page 783 for a detailed discussion.

STERILE WATER FOR IRRIGATION

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

Description—Clear, colorless, odorless liquid.

Uses—An *irrigating solution.*

An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid that is immiscible with the first liquid. Emulsions are formed and stabilized with the help of emulsifying agents, which are surfactants and/or viscosity-producing agents. A suspension is defined as a preparation containing finely divided insoluble material suspended in a liquid medium. The presence of a suspending agent is required to overcome agglomeration of the dispersed particles and to increase the viscosity of the medium so that the particles settle more slowly. Emulsifying and suspending agents are used extensively in the formulation of elegant pharmaceutical preparations for oral, parenteral, and external use. For the theoretical and practical aspects of emulsions the interested reader is referred to pages 323 and 738. More detailed information on the use of suspending agents is given on pages 318 and 737.

ACACIA

Gum Arabic

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

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

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

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

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

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

Uses—Extensively as a *suspending agent* for insoluble substances in water, in the preparation of emulsions (pages 323 and 737) and for making pills and troches (page 891).

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

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

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

AGAR

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

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

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

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

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

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

Uses—A relatively ineffective bulk-producing laxative used in a variety of proprietary cathartics. In mineral oil emulsions it acts as a stabilizer. It also is used in culture media for bacteriological work and in the manufacture of ice cream, confectionaries, etc.

ALGINIC ACID

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

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

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

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

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

SODIUM ALGINATE

Alginic acid, sodium salt; Algin; Kelgin; Manucol; Norgine

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

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

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

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

BENTONITE

Wilhinite; Soap Clay; Mineral Soap

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

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

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

The US Geological Survey has defined bentonite as *a transported stratified clay formed by the alteration of volcanic ash shortly after*

deposition. Chemically, it is $Al_2O_3 \cdot 4SiO_2 \cdot H_2O$ plus other minerals as impurities. It consists of colloidal crystalline plates, of less than microscopic dimensions in thickness, and of colloidal dimensions in breadth. This fact accounts for the extreme swelling that occurs when it is placed in water, since the water penetrates between an infinite number of plates. A good specimen swells 12 to 14 times its volume.

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

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

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

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

CARBOMER

Carboxypolymethylene

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

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

Solubility—neutralized with alkali hydroxides or amines); dissolves in water, alcohol, or glycerin.

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

CARRAGEENAN

Carrageenan [9000-07-1].

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

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

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

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

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

CARBOXYMETHYLCELLULOSE SODIUM

Carbose D; Carboxymethocel S; CMC; Cellulose Gum

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

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

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

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

POWDERED CELLULOSE

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

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

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

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

CETYL ALCOHOL—page 1035.

CHOLESTEROL

Cholest-5-en-3-ol, (3β)-, Cholesterin

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

For the structural formula, see page 418.

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

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

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

Uses—To enhance incorporation and emulsification of medicinal products in oils or fats. It is a pharmaceutical necessity for *Hydrophilic Petrolatum,* in which it enhances water-absorbing capacity. See Chapter 21.

DOCUSATE SODIUM—page 1233.

GELATIN

White Gelatin

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

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

Regarding the special gelatin for use in the preparation of emulsions, see *Emulsions* (page 737).

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

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

Uses—In pharmacy, to coat pills and form capsules, and as a vehicle for suppositories. It also is recommended as an emulsifying agent. See under *Emulsions* in Chapters 20 and 39, also *Suppositories* (page 851), and *Absorbable Gelatin Sponge* (page 1261). It also has been used as an adjuvant protein food in malnutrition.

GLYCERYL MONOSTEARATE—page 1036.

HYDROXYETHYL CELLULOSE

Cellulose, 2-hydroxyethyl ether; Cellosize; Natrosol

Cellulose hydroxyethyl ether 9004-62-0.

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

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

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

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

HYDROXYPROPYL CELLULOSE

Cellulose, 2-hydroxypropyl ether; Klucel

Cellulose hydroxypropyl ether [9004-64-2].

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

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

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

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

HYDROXYPROPYL METHYLCELLULOSE

Cellulose, 2-hydroxypropyl methyl ether

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

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

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

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

Uses—A protective colloid that is useful as a dispersing and thickening agent, and in ophthalmic solutions to provide the demulcent action and viscous properties essential for contact-lens use and in *artificial-tear* formulations. See *Hydroxypropyl Methylcellulose Ophthalmic Solution* (page 1204).

LANOLIN, ANHYDROUS—page 1035.

METHYLCELLULOSE

Cellulose, methyl ether; Methocel

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

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

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

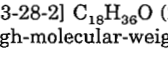
Solubility—Insoluble in ether, alcohol, or chloroform; soluble in glacial acetic acid or in a mixture of equal parts of alcohol and chloroform; swells in water, producing a clear to opalescent, viscous colloidal solution; insoluble in hot water and saturated salt solutions; salts of minerals, acids, and particularly polybasic acids, phenols, and tannins coagulate its solutions, but this can be prevented by the addition of alcohol or of glycol diacetate.

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

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

OLEYL ALCOHOL

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



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

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

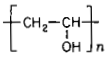
Description—Clear, colorless to light yellow, oily liquid; faint characteristic odor and bland taste; iodine value between 85 and 90; hydroxyl value between 205 and 215.

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

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

POLYVINYL ALCOHOL

Ethenol, homopolymer



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

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

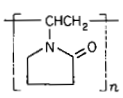
Description—White to cream-colored powder or granules; odorless.

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

Uses—A *suspending agent* and *emulsifier,* either with or without the aid of a surfactant. It commonly is employed as a lubricant and protectant in various ophthalmic preparations, such as decongestants, artificial tears, and contact-lens products (see page 832).

POVIDONE

2-Pyrrolidinone, 1-ethenyl-, homopolymer; Polyvinylpyrrolidone; PVP



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

viscous, depending upon the concentration and the molecular weight of the polymer used. It contains 12 to 13% nitrogen.

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

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

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

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

PROPYLENE GLYCOL MONOSTEARATE

Octadecanoic acid, monoester with 1,2-propanediol

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

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

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

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

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

SILICON DIOXIDE, COLLOIDAL—page 1046.

SODIUM LAURYL SULFATE

Sulfuric acid monododecyl ester sodium salt; Irium; Duponol C; Gardinol WA

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

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

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

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

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

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

SORBITAN ESTERS

Spans

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

Preparation—Sorbitol is dehydrated to form a hexitan that is then esterified with the desired fatty acid. See *Polysorbates,* page 1037, which are polyethylene glycol ethers of sorbitan fatty acid esters.

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

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

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

STEARIC ACID—page 1036.

STEARYL ALCOHOL

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

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

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

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

Uses—A surface-active agent used to *stabilize emulsions* and increase their ability to retain large quantities of water. See *Hydrophilic Ointment* (page 1036); *Hydrophilic Petrolatum* (page 1035).

TRAGACANTH

Gum Tragacanth; Hog Gum; Goat's Thorn

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

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

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

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

Solubility—Insoluble in alcohol.

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

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

XANTHAN GUM

Keltrol

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

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

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

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

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

OTHER EMULSIFYING AND SUSPENDING AGENTS

Chondrus [Irish Moss; Carrageenan]—The dried sun-bleached plant of *Chondrus crispus* (Linné) Stackhouse (Fam *Gigartinaceae*). *Uses:* Principally, as an emulsifying agent for liquid petrolatum and for cod liver oil. It is also a protective. See also page 1030.

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

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

Ointments

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

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

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

Oleaginous Ointment Bases

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

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

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

WHITE OINTMENT

Ointment USP XI; Simple Ointment

White Wax	50 g
White Petrolatum	950 g
To make	1000 g

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

Uses—An emollient and vehicle for other ointments.

YELLOW OINTMENT

Yellow Wax	50 g
Petrolatum	950 g
To make	1000 g

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

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

CETYL ESTERS WAX

Synthetic Spermaceti

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

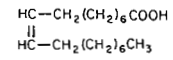
Description—White to off-white, somewhat translucent flakes; crystalline structure and pearly luster when caked; faint odor and a bland, mild taste; free from rancidity; specific gravity 0.820 to 0.840 at 50°; iodine value not more than 1; melts 43 to 47°.

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

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

OLEIC ACID

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



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

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

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

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

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

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

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

PARAFFIN

Paraffin Wax; Hard Paraffin

A purified mixture of solid hydrocarbons obtained from petroleum.

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

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

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

PETROLATUM

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

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

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

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

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

Solubility—Insoluble in water; almost insoluble in cold or hot alcohol or in cold dehydrated alcohol; freely soluble in benzene, carbon disulfide, chloroform, or turpentine oil; soluble in ether, solvent hexane, or in most fixed and volatile oils, the degree of solubility in these solvents varying with the composition of the petrolatum.

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

WHITE PETROLATUM

White Petroleum Jelly; White Soft Paraffin

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

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

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

Solubility—Similar to that described under *Petrolatum.*

Uses—Similar to yellow petrolatum but often is preferred because of its freedom from color. It is employed as a protective, as a base for ointments and cerates, and to form the basis for burn dressings. See *Petrolatum Gauze* (page 1201).

Absorbent Ointment Bases

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

LANOLIN ANHYDROUS

Anhydrous Lanolin; Wool Fat USP XVI; Refined Wool Fat

Lanolin that contains not more than 0.25% of water.

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

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

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

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

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

HYDROPHILIC PETROLATUM

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

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

Uses—A *protective* and *water-absorbable ointment base.* It will absorb a large amount of water from aqueous solutions of medicating substances, forming a W/O type of emulsion. See *Ointments* (page 845).

Emulsion Ointment Bases and Components

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

CETYL ALCOHOL

Cetostearyl Alcohol; Palmityl Alcohol; Aldol 52

$CH_3(CH_2)_{14}CH_2OH$

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

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

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

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

Uses—Similar to *Stearyl Alcohol* (page 1033). It also imparts a smooth texture to the skin and is used widely in cosmetic creams and lotions.

COLD CREAM

Petrolatum Rose Water Ointment USP XVI

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

Reduce the cetyl esters wax and the white wax to small pieces, melt them on a steam bath with the mineral oil, and continue heating until the temperature of the mixture reaches 70°. Dissolve the sodium borate in the purified water, warmed to 70°, and gradually add the warm solution to the melted mixture, stirring rapidly and continuously until it has congealed.

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

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

GLYCERYL MONOSTEARATE

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

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

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

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

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

Uses—A thickening and emulsifying agent for ointments. See *Ointments* (page 845).

HYDROPHILIC OINTMENT

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

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

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

LANOLIN

Hydrous Wool Fat

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

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

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

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

ROSE WATER OINTMENT

Cold Cream; Galen's Cerate

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

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

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

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

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

STEARIC ACID

Octadecanoic acid; Cetylacetic Acid; Stearophanic Acid

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

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

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

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

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

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

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

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

GLYCOL ETHERS AND DERIVATIVES

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

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

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

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

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

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

POLYETHYLENE GLYCOLS

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

$$H—[OCH_2CH_2—]_nOH$$

Polyethylene glycols [25322-68-3].

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

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

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

Uses—These possess a wide range of solubilities and compatibilities, which make them useful in pharmaceutical and cosmetic preparations. Their blandness renders them highly acceptable for hair dressings, hand lotions, sun-tan creams, leg lotions, shaving creams, and skin creams (eg, a peroxide ointment that is stable may be prepared using these compounds, while oil-type bases inactivate the peroxide). Their use in washable ointments is discussed under *Ointments* (page 845). They also are used in making suppositories, hormone creams, etc. See *Polyethylene Glycol Ointment* (below) and *Glycol Ethers* (above). The liquid polyethylene glycol 400 and the solid polyethylene glycol 3350, used in the proportion specified (or a permissible variation thereof) in the official Polyethylene Glycol Ointment, provide a water-soluble ointment base used in the formulation of many dermatological preparations. The solid, waxy, water-soluble glycols often are used to increase the viscosity of liquid polyethylene glycols and to stiffen ointment and suppository bases. In addition, they are used to compensate for the melting point-lowering effect of other agents, ie, chloral hydrate, etc, on such bases.

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

POLYOXYL 40 STEARATE

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

$RCOO(C_2H_4O)_nH$ ($RCOO$ is the stearate moiety; n is approximately 40).

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

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

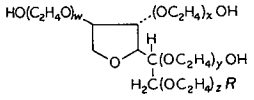
Description—White to light-tan waxy solid; odorless or has a faint fat-like odor; congeals between 37 and 47°.

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

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

POLYSORBATES

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



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

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

Preparation—These important nonionic surfactants (page 286) are prepared starting with sorbitol by (1) elimination of water-forming sorbitan (a cyclic sorbitol anhydride); (2) partial esterification of the sorbitan with a fatty acid such as oleic or stearic acid, yielding a hexitan ester known commercially as a *Span;* and (3) chemical addition of ethylene oxide, yielding a *Tween* (the polyoxyethylene derivative).

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

Solubility—*Polysorbate 80:* Very soluble in water, producing an odorless and nearly colorless solution; soluble in alcohol, cottonseed

oil,corn oil, ethyl acetate, methanol, or toluene; insoluble in mineral oil.

Uses—Because of their hydrophilic and lyophilic characteristics, these nonionic surfactants are very useful as emulsifying agents, forming O/W emulsions in pharmaceuticals, cosmetics, and other types of products. Polysorbate 80 is an ingredient in *Coal Tar Ointment* and *Solution*. See *Glycol Ethers* (page 1037).

PHARMACEUTICAL SOLVENTS

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

ACETONE

2-Propanone; Dimethyl Ketone

CH_3COCH_3

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

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

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

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

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

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

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

ALCOHOL

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

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

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

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

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

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

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

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

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

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

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

Alkalies cause a darkening in color because of the small amount of aldehyde usually present in it.

Uses—In pharmacy principally for its solvent powers (page 218). It also is used as the starting point in the manufacture of many important compounds, like ether, chloroform, etc. It also is used as a fuel, chiefly in the denatured form.

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

It is used widely and abused by lay persons as a sedative. It has, however, no medically approved use for this purpose. Moreover, alcohol potentiates the CNS effects of numerous sedative and depressant drugs. Hence, it should not be used by patients taking certain prescription drugs or OTC medications (see page 1746).

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

DENATURED ALCOHOL

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

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

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

Specially Denatured Alcohol—This alcohol is intended for use in a greater number of specified arts and industries than completely

denatured alcohol, and the character of the denaturant or denaturants used is such that specially denatured alcohol may be sold, possessed, and used only by those persons or firms that hold basic permits and are covered by bond.

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

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

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

DILUTED ALCOHOL

Diluted Ethanol

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

Preparation—

Alcohol	500 mL
Purified Water	500 mL

Measure the alcohol and the purified water separately at the same temperature, and mix. If the water and the alcohol and the resulting mixture are measured at 25°, the volume of the mixture will be about 970 mL.

When equal volumes of alcohol and water are mixed together, a rise in temperature and a contraction of about 3% in volume take place. In small operations the contraction generally is disregarded; in larger operations it is very important. If 50 gal of official alcohol are mixed with 50 gal of water, the product will not be 100 gal of diluted alcohol, but only 96 1/4 gal, a contraction of 3 3/4 gal. US *Proof Spirit* differs from this and is stronger; it contains 50%, by volume, of absolute alcohol at 15.56° (60°F). This corresponds to 42.5% by weight and has a specific gravity of 0.9341 at the same temperature. If spirits have a specific gravity lower than that of *proof spirit* (0.9341), they are said to be *above proof;* if greater, *below proof.*

It also may be prepared from the following:

Alcohol	408 g
Purified Water	500 g

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

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

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

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

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

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

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

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

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

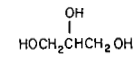
NONBEVERAGE ALCOHOL

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

CHLOROFORM—page 1042.

GLYCERIN

1,2,3-Propanetriol; Glycerol



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

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

Preparation—

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

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

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

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

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

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

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

Uses—One of the most valuable products known to pharmacy by virtue of its *solvent* property. It is useful as a *humectant* in keeping substances moist, owing to its hygroscopicity. Its agreeable taste and high viscosity adapt it for many purposes. Some modern ice collars and ice bags contain it and water hermetically sealed within vulcanized rubber bags. The latter are sterilized by dipping in a germicidal solution and are stored in the refrigerator until needed. It also has some therapeutic uses. In pure anhydrous form, it is used in the eye to reduce corneal edema and to facilitate ophthalmoscopic examination. It is used orally as an evacuant and, in 50 to 75% solution, as a systemic osmotic agent.

ISOPROPYL ALCOHOL—page 1510.

METHYL ALCOHOL

Methanol; Wood Alcohol

CH_3OH

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

Caution—It is poisonous.

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

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

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

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

METHYL ISOBUTYL KETONE

2-Pentanone, 4-methyl-,

$(CH_3)_2CHCH_2COCH_3$ [108-10-1]; contains not less than 99% of $C_6H_{12}O$ (100.16).

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

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

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

MONOETHANOLAMINE

Ethanol, 2-amino-, Ethanolamine; Ethylolamine

$HOCH_2CH_2NH_2$ [141-43-5] C_2H_7NO (61.08).

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

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

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

Uses—A *solvent* for fats, oils, and many other substances, it is a pharmaceutical necessity for *Thimerosal Solution* (see RPS-17 page 1173). It combines with fatty acids to form soaps that find application in various types of emulsions such as lotions, creams, etc.

PROPYLENE GLYCOL

$CH_3CH(OH)CH_2OH$

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

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

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

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

Uses—A *solvent, preservative,* and *humectant*. See *Hydrophilic Ointment* (page 1036).

TROLAMINE

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

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

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

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

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

Uses—In combination with a fatty acid, eg, oleic acid (see *Benzyl Benzoate Lotion,* 748), as an *emulsifier*. See *Monoethanolamine*.

WATER—page 1027.

OTHER PHARMACEUTICAL SOLVENTS

Alcohol, Dehydrated, BP, PhI [Dehydrated Ethanol; Absolute Alcohol]—Transparent, colorless, mobile, volatile liquid; characteristic odor; burning taste; specific gravity not more than 0.798 at 15.56°; hygroscopic, flammable and boils about 78°. Miscible with water, ether, or chloroform. *Uses:* A pharmaceutical solvent; also used by injection for relief of pain (see *Alcohol,* pages 1038 and 1507).

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

ACETIC ACID

Acetic acid; a solution containing 36 to 37%, by weight, of $C_2H_4O_2$ (60.05).

Preparation—By diluting with distilled water an acid of higher concentration, such as the 80% product, or more commonly glacial acetic acid, using 350 mL of the latter for the preparation of each 1000 mL of acetic acid.

Description—Clear, colorless liquid, having a strong characteristic odor and a sharply acid taste; specific gravity about 1.045; congeals about −14°; acid to litmus.

Solubility—Miscible with water, alcohol, or glycerin.

Uses—In pharmacy as a *solvent* and *menstruum* and for making diluted acetic acid. It also is used as a starting point in the manufacture of many other organic compounds, eg, acetates, acetanilid, sulfonamides, etc. It is official primarily as a *pharmaceutic necessity* for the preparation of *Aluminum Subacetate Solution*.

DILUTED ACETIC ACID

Dilute Acetic Acid

A solution containing, in each 100 mL, 5.7 to 6.3 g of $C_2H_4O_2$.

Preparation—

Acetic Acid	158 mL
Purified Water, a sufficient quantity to make	1000 mL

Mix the ingredients.

Note—This acid also may be prepared by diluting 58 mL of glacial acetic acid with sufficient purified water to make 1000 mL.

Description—Essentially the same properties, solubility, purity, and identification reactions as *Acetic Acid,* but its specific gravity is about 1.008, and it congeals about −2°.

Uses—*Bactericidal* to many types of microorganisms and occasionally is used in 1% solution for surgical dressings of the skin. A 1% solution is *spermatocidal*. It also is used in vaginal douches for the management of *Trichomonas, Candida,* and *Haemophilus* infections.

GLACIAL ACETIC ACID

Concentrated Acetic Acid; Crystallizable Acetic Acid; Ethanolic Acid; Vinegar Acid

CH_3COOH

Glacial acetic acid [64-19-7] $C_2H_4O_2$ (60.05).

Preparation—This acid is termed *glacial* because of its solid, glassy appearance when congealed. In one process it is produced by distillation of weaker acids to which has been added a water-entraining substance such as ethylene dichloride. In this method, referred to as *azeotropic distillation,* the ethylene dichloride distills out with the water before the acid distills over, thereby effecting concentration of the latter.

In another process the aqueous acid is mixed with triethanolamine and heated. The acid combines with the triethanolamine to form a triethanolamine acetate. The water is driven off first; then, at a higher temperature, the triethanolamine compound decomposes to yield this acid.

A greater part of the acid now available is made synthetically from acetylene. When acetylene is passed into this acid containing a metallic catalyst such as mercuric oxide, ethylidene diacetate is produced, which yields, upon heating, acetic anhydride and acetaldehyde. Hydration of the former and air oxidation of the latter yield this acid.

Description—Clear, colorless liquid; pungent, characteristic odor; when well diluted with water, it has an acid taste; boils about 118°;

congeals at a temperature not lower than 15.6°, corresponding to a minimum of 99.4% of CH_3COOH; specific gravity about 1.05.

Solubility—Miscible with water, alcohol, acetone, ether, or glycerin; insoluble in carbon tetrachloride or chloroform.

Uses—A *caustic* and *vesicant* when applied externally and is often sold under various disguises as a *corn solvent*. It is an excellent solvent for fixed and volatile oils and many other organic compounds. It is used primarily as an *acidifying agent*.

ALUMINUM

Aluminum Al (26.98); the free metal in the form of finely divided powder. It may contain oleic acid or stearic acid as a lubricant. It contains not less than 95% Al and not more than 5% *Acid-insoluble substances,* including any added fatty acid.

Description—Very fine, free-flowing, silvery powder free from gritty or discolored particles.

Solubility—Insoluble in water or alcohol; soluble in hydrochloric and sulfuric acids or in solutions of fixed alkali hydroxides.

Uses—A *protective*. An ingredient in *Aluminum Paste*.

ALUMINUM MONOSTEARATE

Aluminum, dihydroxy(octadecanoato-*O*-)-,

Dihydroxy(stearato)aluminum [7047-84-9]; a compound of aluminum with a mixture of solid organic acids obtained from fats, and consists chiefly of variable proportions of aluminum monostearate and aluminum monopalmitate. It contains the equivalent of 14.5 to 16.5% of Al_2O_3 (101.96).

Preparation—By interaction of a hydroalcoholic solution of potassium stearate with an aqueous solution of potassium alum, the precipitate being purified to remove free stearic acid and some aluminum distearate simultaneously produced.

Description—Fine, white to yellowish white, bulky powder; faint, characteristic odor.

Solubility—Insoluble in water, alcohol, or ether.

Uses—A *pharmaceutical necessity* used in the preparation of *Sterile Procaine Penicillin G with Aluminum Stearate Suspension*.

STRONG AMMONIA SOLUTION

Stronger Ammonia Water; Stronger Ammonium Hydroxide Solution; Spirit of Hartshorn

Ammonia [1336-21-6]; a solution of NH_3 (17.03), containing 27.0 to 31.0% (w/w) of NH_3. Upon exposure to air it loses ammonia rapidly.

Caution—Use care in handling it because of the caustic nature of the Solution and the irritating properties of its vapor. Cool the container well before opening, and cover the closure with a cloth or similar material while opening. Do not taste it, and avoid inhalation of its vapor.

Preparation—Ammonia is obtained commercially chiefly by synthesis from its constituent elements, nitrogen and hydrogen, combined under high pressure and at high temperature in the presence of a catalyst.

Description—Colorless, transparent liquid; exceedingly pungent, characteristic odor; even when well diluted it is strongly alkaline to litmus; specific gravity about 0.90.

Solubility—Miscible with alcohol.

Uses—Only for chemical and pharmaceutical purposes. It is used primarily in making ammonia water by dilution and as a chemical reagent. It is too strong for internal administration. It is an ingredient in *Aromatic Ammonia Spirit*.

BISMUTH SUBNITRATE

Basic Bismuth Nitrate; Bismuth Oxynitrate; Spanish White; Bismuth Paint; Bismuthyl Nitrate

Bismuth hydroxide nitrate oxide [1304-85-4] $Bi_5O(OH)_9(NO_3)_4$ (1461.99); a basic salt that, dried at 105° for 2 hr, yields upon ignition not less than 79% of Bi_2O_3 (465.96).

Preparation—A solution of bismuth nitrate is added to boiling water to produce the subnitrate by hydrolysis.

Description—White, slightly hygroscopic powder; suspension in distilled water is faintly acid to litmus (pH about 5).

Solubility—Practically insoluble in water or organic solvents; dissolves readily in an excess of hydrochloric or nitric acid.

Incompatibilities—Slowly hydrolyzed in *water* with liberation of nitric acid; thus, it possesses the incompatibilities of the acid. *Reducing agents* darken it with the production of metallic bismuth.

Uses—A *pharmaceutical necessity* in the preparation of milk of bismuth. It also is used as an *astringent, adsorbent,* and *protective;* however, its value as a protective is questionable. This agent, like other insoluble bismuth salts, is used topically in lotions and ointments.

BORIC ACID

Boric Acid (H_3BO_3); Boracic Acid; Orthoboric Acid

Boric acid [10043-35-3] H_3BO_3 (61.83).

Preparation—Lagoons of the volcanic districts of Tuscany formerly furnished the greater part of this acid and borax of commerce. Borax is now found native in California and some of the other western states; calcium and magnesium borates are found there also. It is produced from native borax or from the other borates by reacting with hydrochloric or sulfuric acid.

Description—Colorless scales of a somewhat pearly luster, or crystals, but more commonly a white powder slightly unctuous to the touch; odorless and stable in the air; volatilizes with steam.

Solubility—1 g in 18 mL water, 18 mL alcohol, 4 mL glycerin, 4 mL boiling water, or 6 mL boiling alcohol.

Uses—A buffer, and it is this use that is recognized officially. It is a very weak *germicide (local anti-infective)*. Its nonirritating properties make its solutions suitable for application to such delicate structures as the cornea of the eye. Aqueous solutions are employed as an eye wash, mouth wash, and for irrigation of the bladder. A 2.2% solution is isotonic with lacrimal fluid. Solutions, even if they are made isotonic, will hemolyze red blood cells. It also is employed as a dusting powder, when diluted with some inert material. It can be absorbed through irritated skin, eg, infants with diaper rash.

Although it is not absorbed significantly from intact skin, it is absorbed from damaged skin and fatal poisoning, particularly in infants, has occurred with topical application to burns, denuded areas, granulation tissue, and serous cavities. *Serious poisoning can result from oral ingestion* of as little as 5 g. Symptoms of poisoning are nausea, vomiting, abdominal pain, diarrhea, headache, and visual disturbance. Toxic alopecia has been reported from the chronic ingestion of a mouth wash containing it. The kidney may be injured, and death may result. Its use as a preservative in beverages and foods is prohibited by national and state legislation. *There is always present the danger of confusing it with dextrose when compounding milk formulas for infants. Fatal accidents have occurred.* For this reason boric acid in bulk is colored, so that it cannot be confused with dextrose.

It is used to prevent discoloration of physostigmine solutions.

CALCIUM HYDROXIDE

Slaked Lime; Calcium Hydrate

Calcium hydroxide [1305-62-0] $Ca(OH)_2$ (74.09).

Preparation—By reacting freshly prepared calcium oxide with water.

Description—White powder; alkaline, slightly bitter taste; absorbs carbon dioxide from the air, forming calcium carbonate; solutions exhibit a strong alkaline reaction.

Solubility—1 g in 630 mL water or 1300 mL boiling water; soluble in glycerin or syrup; insoluble in alcohol; the solubility in water is decreased by the presence of fixed alkali hydroxides.

Uses—In the preparation of *Calcium Hydroxide Solution*.

CALCIUM HYDROXIDE TOPICAL SOLUTION

Calcium Hydroxide Solution; Lime Water

A solution containing, in each 100 mL, not less than 140 mg of $Ca(OH)_2$ (74.09).

Note—The solubility of calcium hydroxide varies with the temperature at which the solution is stored, being about 170 mg/100 mL at 15° and less at a higher temperature. The official concentration is based upon a temperature of 25°.

Preparation—

Calcium Hydroxide	3 g
Purified Water	1000 mL

Add the calcium hydroxide to 1000 mL of cool, purified water, and agitate the mixture vigorously and repeatedly during 1 hr. Allow the excess calcium hydroxide to settle. Dispense only the clear, supernatant liquid.

The undissolved portion of the mixture is not suitable for preparing additional quantities of the solution.

The object of keeping lime water over undissolved calcium hydroxide is to ensure a saturated solution.

Description—Clear, colorless liquid; alkaline taste; strong alkaline reaction; absorbs carbon dioxide from the air, a film of calcium carbonate forming on the surface of the liquid; when heated, it becomes turbid, owing to the separation of calcium hydroxide, which is less soluble in hot than in cold water.

Uses—Too dilute to be effective as a gastric antacid. It is employed *topically* as a *protective* in various types of lotions. In some lotion formulations it is used with olive oil or oleic acid to form calcium oleate,

which functions as an emulsifying agent. The USP classes it as an *astringent*.

CALCIUM PANTOTHENATE, RACEMIC—page 1814.

CALCIUM STEARATE

Octadecanoic acid, calcium salt

Calcium stearate [1592-23-0]; a compound of calcium with a mixture of solid organic acids obtained from fats, and consists chiefly of variable proportions of stearic and palmitic acids [calcium stearate, $C_{36}H_{70}CaO_4$ = 607.03; calcium palmitate, $C_{32}H_{62}CaO_4$ = 550.92]; contains the equivalent of 9 to 10.5% of CaO (calcium oxide).

Preparation—By precipitation from interaction of solutions of calcium chloride and the sodium salts of the mixed fatty acids (stearic and palmitic).

Description—Fine, white to yellowish white, bulky powder; slight, characteristic odor; unctuous and free from grittiness.

Solubility—Insoluble in water, alcohol, or ether.

Uses—A *lubricant* in the manufacture of compressed tablets. It also is used as a conditioning agent in food and pharmaceutical products. Its virtually nontoxic nature and unctuous properties makes it ideal for these purposes.

CALCIUM SULFATE

Sulfuric acid, calcium salt (1:1); Gypsum; Terra Alba

Calcium sulfate (1:1) [7778-18-9] $CaSO_4$ (136.14); *dihydrate* [10101-41-4] (172.17).

Preparation—From natural sources or by precipitation from interaction of solutions of calcium chloride and a soluble sulfate.

Description—Fine, white to slightly yellow-white, odorless powder.

Solubility—Dissolves in diluted HCl; slightly soluble in water.

Uses—A *diluent* in the manufacture of compressed tablets. It is sufficiently inert that few undesirable reactions occur in tablets made with this substance. It also is used for making plaster casts and supports.

CARBON TETRACHLORIDE

Methane, tetrachloro-, Tetrachloromethane

Carbon tetrachloride [56-23-5] CCl_4 (153.82).

Preparation—One method consists of catalytic chlorination of carbon disulfide.

Description—Clear, colorless liquid; characteristic odor resembling that of chloroform; specific gravity 1.588 to 1.590; boils about 77°.

Solubility—Soluble in about 2000 volumes water; miscible with alcohol, acetone, ether, chloroform, or benzene.

Uses—Officially recognized as a *pharmaceutical necessity* (solvent). Formerly it was used as a cheap *anthelmintic* for the treatment of *hookworm* infections, but it causes severe injury to the liver if absorbed.

CARNAUBA WAX

Obtained from the leaves of *Copernicia cerifera* Mart (Fam *Palmae*).

Preparation—Consists chiefly of myricyl cerotate with smaller quantities of myricyl alcohol, ceryl alcohol, and cerotic acid. It is obtained by treating the leaf buds and leaves of *Copernicia cerifera,* the so-called Brazilian Wax Palm, with hot water.

Description—Light-brown to pale-yellow, moderately coarse powder; characteristic bland odor; free from rancidity; specific gravity about 0.99; melts about 84°.

Solubility—Insoluble in water; freely soluble in warm benzene; soluble in warm chloroform or toluene; slightly soluble in boiling alcohol.

Uses—A pharmaceutic aid used as a *polishing agent* in the manufacture of coated tablets.

CELLULOSE ACETATE PHTHALATE

Cellulose, acetate, 1,2-benzenedicarboxylate

Cellulose acetate phthalate [9004-38-0]; a reaction product of the phthalic anhydride and a partial acetate ester of cellulose. When dried at 105° for 2 hr, it contains 19 to 23.5% of acetyl (C_2H_3O) groups and 30 to 36.0% of phthalyl (*o*-carboxybenzoyl, $C_8H_5O_3$) groups.

Preparation—Cellulose is esterified by treatment with acetic and phthalic acid anhydrides.

Description—Free-flowing, white powder; may have a slight odor of acetic acid.

Solubility—Insoluble in water or alcohol; soluble in acetone or dioxane.

Uses—An *enteric tablet-coating material*. Coatings of this substance disintegrate because of the hydrolytic effect of the intestinal esterases, even when the intestinal contents are acid. *In vitro* studies indicate that cellulose acetate phthalate will withstand the action of artificial gastric juices for long periods of time but will disintegrate readily in artificial intestinal juices.

MICROCRYSTALLINE CELLULOSE

Cellulose [9004-34-6]; purified, partially depolymerized cellulose prepared by treating alpha cellulose, obtained as a pulp from fibrous plant material, with mineral acids.

Preparation—Cellulose is subjected to the hydrolytic action of 2.5 *N* HCl at the boiling temperature of about 105 for 15 min, whereby amorphous cellulosic material is removed and aggregates of crystalline cellulose are formed. These are collected by filtration, washed with water and aqueous ammonia, and disintegrated into small fragments, often termed cellulose crystallites, by vigorous mechanical means such as a blender. US Pat 3,141,875.

Description—Fine, white, odorless, crystalline powder; consists of free-flowing, nonfibrous particles.

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

Uses—A tablet diluent and disintegrant. It can be compressed into self-binding tablets that disintegrate rapidly when placed in water.

Microcrystalline Cellulose and Sodium Carboxymethylcellulose—A colloid-forming, attrited mixture of microcrystalline cellulose and sodium carboxymethylcellulose. *Description and Solubility:* Tasteless, odorless, white to off-white, coarse to fine powder; pH (dispersion) 6 to 8; swells in water, producing, when dispersed, a white, opaque dispersion or gel. Insoluble in organic solvents or dilute acids. *Uses:* Pharmaceutic aid (suspending agent). *Grades Available* (amounts of sodium carboxymethylcellulose producing viscosities in the concentrations designated): 8.5%, 120 cps in 2.1% solution; 11%, 120 cps in 1.2% solution; 11%, 65 cps in 1.2% solution.

POWDERED CELLULOSE—page 1031.

CHLOROFORM

Methane, trichloro-,

Trichloromethane [67-66-3] $CHCl_3$ (119.38); contains 99 to 99.5% $CHCl_3$, the remainder consisting of alcohol.

Caution—Care should be taken not to vaporize it in the presence of a flame, because of the production of harmful gases (hydrogen chloride and phosgene).

Preparation—Made by the reduction of carbon tetrachloride with water and iron and by the controlled chlorination of methane.

The pure compound readily decomposes on keeping, particularly if exposed to moisture and sunlight, resulting in formation of phosgene (carbonyl chloride $COCl_2$) and other products. The presence of a small amount of alcohol greatly retards or prevents this decomposition; hence, the requirement that it contain 0.5 to 1% of alcohol. The alcohol combines with any phosgene, forming ethyl carbonate, which is nontoxic.

Description—Clear, colorless, mobile liquid; characteristic, ethereal odor; burning, sweet taste; not flammable, but its heated vapors burn with a green flame; affected by light and moisture; specific gravity 1.474 to 1.478, indicating 99 to 99.5% of $CHCl_3$; boils about 61°; not affected by acids but is decomposed by alkali hydroxide into alkali chloride and sodium formate.

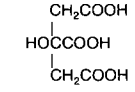
Solubility—Soluble in 210 volumes of water; miscible with alcohol, ether, benzene, solvent hexane, acetone, or fixed and volatile oils.

Uses—An obsolete *inhalation anesthetic*. Although it possesses advantages of nonflammability and great potency, it rarely is used because of the serious toxic effects it produces on the heart and liver. Internally, it has been used, in small doses, as a *carminative*. Externally, it is an *irritant* and when used in liniments it may produce blisters.

It is categorized as a pharmaceutic aid. It is used as a *preservative* during the aqueous percolation of vegetable drugs to prevent bacterial decomposition in the process of manufacture. In most instances it is evaporated before the product is finished. It is an excellent solvent for alkaloids and many other organic chemicals and is used in the manufacture of these products and in chemical analyses.

CITRIC ACID

1,2,3-Propanetricarboxylic acid, 2-hydroxy-,



Citric acid [77-92-9] $C_6H_8O_7$ (192.12); *monohydrate* [5949-29-1] (210.14).

Preparation—Found in many plants. It formerly was obtained solely from the juice of limes and lemons and from pineapple wastes. Since about 1925 the acid has been produced largely by fermentation of sucrose solution, including molasses, by fungi belonging to the *Aspergillus niger* group, theoretically according to the following reaction

$$\underset{\text{Sucrose}}{C_{12}H_{22}O_{11}} + \underset{\text{Oxygen}}{30_2} \rightarrow \underset{\text{Citric Acid}}{2H_3C_6H_5O_7} + \underset{\text{Water}}{3H_2O}$$

but in practice there are deviations from this stoichiometric relationship.

Description—Colorless, translucent crystals, or a white, granular to fine crystalline powder; odorless; strongly acid taste; the hydrous form effloresces in moderately dry air but is slightly deliquescent in moist air; loses its water of crystallization at about 50°; dilute aqueous solutions are subject to molding (fermentation), oxalic acid being one of the fermentation products.

Solubility—1 g in 0.5 mL water, 2 mL alcohol, or about 30 mL ether; freely soluble in methanol.

Uses—In the preparation of *Anticoagulant Citrate Dextrose Solution, Anticoagulant Citrate Phosphate Dextrose Solution, Citric Acid Syrup,* and *effervescent salts*. It also has been used to dissolve urinary bladder calculi and as a mild astringent.

COCOA BUTTER

Cacao Butter; Theobroma Oil; Oil of Theobroma

The fat obtained from the roasted seed of *Theobroma cacao* Linné (Fam *Sterculiaceae*).

Preparation—By grinding the kernels of the *chocolate bean* and expressing the oil in powerful, horizontal hydraulic presses. The yield is about 40%. It also has been prepared by dissolving the oil from the unroasted beans by the use of a volatile solvent.

Constituents—Chemically, it is a mixture of stearin, palmitin, olein, laurin, linolein, and traces of other glycerides.

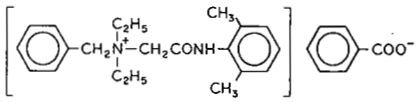
Description—Yellowish, white solid; faint, agreeable odor; bland (if obtained by extraction) or chocolate-like (if obtained by pressing) taste; usually brittle below 25°; specific gravity 0.858 to 0.864 at 100°/25°; refractive index 1.454 to 1.458 at 40°.

Solubility—Slightly soluble in alcohol; soluble in boiling dehydrated alcohol; freely soluble in ether or chloroform.

Uses—Valuable in pharmacy for making suppositories by virtue of its low fusing point and its property of becoming solid at a temperature just below the melting point. See *Suppositories* (page 851). In addition to this use, it is an excellent emollient application to the skin when inflamed; it also is used in various skin creams, especially the so-called *skin foods*. It also is used in massage.

DENATONIUM BENZOATE

Benzenemethanaminium *N*-2-(2,6-dimethylphenyl)amino-2-oxoethyl-*N,N*-diethyl-, benzoate;



Benzyldiethyl (2,6-xylylcarbamoyl)methylammonium benzoate [3734-33-6] $C_{28}H_{34}N_2O_3$ (446.59).

Preparation—2-(Diethylamino)-2′,6′-xylidide is quaternized by reaction with benzyl chloride. The quaternary chloride then is treated with methanolic potassium hydroxide to form the quaternary base that, after filtering off the KCl, is reacted with benzoic acid. The starting xylidide may be prepared by condensing 2,6-xylidine with chloroacetyl chloride and condensing the resulting chloroacetoxylidide with diethylamine. US Pat 3,080,327.

Description—White, odorless, crystalline powder; an intensely bitter taste; melts about 168°.

Solubility—1 g in 20 mL water, 2.4 mL alcohol, 2.9 mL chloroform, or 5000 mL ether.

Uses—A *denaturant* for ethyl alcohol.

DEXTRIN

British Gum; Starch Gum; Leiocom

Dextrin [9004-53-9] $(C_6H_{10}O_5)_n$.

Preparation—By the incomplete hydrolysis of starch with dilute acid or by heating dry starch.

Description—White or yellow, amorphous powder (*white:* practically odorless; *yellow:* characteristic odor); dextrorotatory; $[\alpha]_D^{20}$ generally above 200°; does not reduce Fehling's solution; gives a reddish color with iodine.

Solubility—Soluble in 3 parts of boiling water, forming a gummy solution; less soluble in cold water.

Uses—An *excipient* and *emulsifier*.

DEXTROSE

Anhydrous Dextrose; Dextrose Monohydrate; Glucose; D(+)-Glucose; α-D(+)-Glucopyranose; Medicinal Glucose; Purified Glucose; Grape Sugar; Bread Sugar; Cerelose; Starch Sugar; Corn Sugar

D-Glucose monohydrate [5996-10-1] $C_6H_{12}O_6 \cdot H_2O$ (198.17); *anhydrous* [50-99-7] (180.16). A sugar usually obtained by the hydrolysis of starch. For the structure, see page 411.

Preparation—See *Liquid Glucose* (page 1044).

Description—Colorless crystals or a white, crystalline or granular powder; odorless; sweet taste; specific rotation (anhydrous) +52.5 to +53; anhydrous dextrose melts at 146°; dextrose slowly reduces alkaline cupric tartrate TS in the cold and rapidly on heating, producing a red precipitate of cuprous oxide (difference from *sucrose*).

Solubility—1 g in 1 mL of water or 100 mL of alcohol; more soluble in boiling water or boiling alcohol.

Uses—See *Dextrose Injection* (page 1248). It also is used, instead of lactose as a supplement to milk for infant feeding.

DICHLORODIFLUOROMETHANE

Methane, dichlorodifluoro-, CCl_2F_2

Dichlorodifluoromethane [75-71-8] CCl_2F_2 (120.91).

Preparation—Carbon tetrachloride is reacted with antimony trifluoride in the presence of antimony pentafluoride.

Description—Clear, colorless gas; faint, ethereal odor; vapor pressure at 25° about 4883 torr.

Uses—A *propellant* (No 12, see page 968).

DICHLOROTETRAFLUOROETHANE

Ethane, 1,2-dichloro-1,1,2,2-tetrafluoro-, $CClF_2CClF_2$

1,2-Dichlorotetrafluoroethane [76-14-2] $C_2Cl_2F_4$ (170.92).

Preparation—By reacting 1,1,2-trichloro-1,2,2-trifluoroethane with antimony trifluorodichloride [SbF_3Cl_2], whereupon one of the 1-chlorine atoms is replaced by fluorine. The starting trichlorofluoroethane may be prepared from hexachloroethane by treatment with SbF_3Cl_2 (Henne AL: *Org Reactions II:* 65, 1944).

Description—Clear, colorless gas; faint, ethereal odor; vapor pressure at 25° about 1620 torr; usually contains 6 to 10% of its isomer, $CFCl_2$-CF_3.

Uses—A *propellant* (No 114 and 114a, see page 968).

EDETIC ACID

Glycine, *N,N′*-1,2-ethanediylbis[*N*-(carboxymethyl)], $(HOOCCH_2)_2NCH_2CH_2N(CH_2COOH)_2$

(Ethylenedinitrilo)tetraacetic acid [60-00-4] $C_{10}H_{16}N_2O_8$ (292.24).

Preparation—Ethylenediamine is condensed with sodium monochloroacetate with the aid of sodium carbonate. An aqueous solution of the reactants is heated to about 90° for 10 hr, then cooled and acidified with HCl whereupon the acid precipitates. US Pat 2,130,505.

Description—White, crystalline powder; melts with decomposition above 220°.

Solubility—Very slightly soluble in water; soluble in solutions of alkali hydroxides.

Uses—A *pharmaceutic aid* (metal complexing agent). The acid, rather than any salt, is the form most potent in removing calcium from solution. It may be added to shed blood to prevent clotting. It also is used in pharmaceutical analysis and the removal or inactivation of unwanted ions in solution. Salts of the acid are known as edetates. See *Edetate Calcium Disodium* (page 1267) and *Edetate Disodium* (page 1268).

ETHYLCELLULOSE

Cellulose ethyl ether [9004-57-3]; an ethyl ether of cellulose containing 44 to 51% of ethoxy groups. The *medium-type* viscosity grade contains less than 46.5% ethoxy groups; the *standard-type* viscosity grade contains 46.5% or more ethoxy groups.

Preparation—By the same general procedure described on page 1032 for *Methylcellulose* except that ethyl chloride or ethyl sulfate is employed as the alkylating agent. The 45 to 50% of ethoxy groups in the official ethylcellulose corresponds to from 2.25 to 2.61 ethoxy groups/$C_6H_{10}O_5$ unit, thus representing from 75 to 87% of the maximum theoretical ethoxylation, which is 3 ethoxy groups/$C_6H_{10}O_5$ unit.

Description—Free-flowing, white to light tan powder; forms films that have a refractive index of about 1.47; aqueous suspensions are neutral to litmus.

Solubility—The medium type is freely soluble in tetrahydrofuran, methyl acetate, chloroform, or mixtures of aromatic hydrocarbons with alcohol; the standard type is freely soluble in alcohol, methanol, toluene, chloroform, or ethyl acetate; both types are insoluble in water, glycerin, or propylene glycol.

Uses—A *pharmaceutic aid* as a tablet binder and for film-coating tablets and drug particles.

GELATIN—page 1031.

LIQUID GLUCOSE
GLUCOSE; STARCH SYRUP; CORN SYRUP

A product obtained by the incomplete hydrolysis of starch. It consists chiefly of dextrose [D-(+)-glucose, $C_6H_{12}O_6$ = 180.16] dextrins, maltose, and water.

Preparation—Commercially by the action of very weak H_2SO_4 or HCl on starch.

One of the processes for its manufacture is as follows: The starch, usually from corn, is mixed with 5 times its weight of water containing less than 1% of HCl, the mixture is heated to about 45° and then transferred to a suitable reaction vessel, into which steam is passed under pressure until the temperature reaches 120°. The temperature is maintained at this point for about 1 hr or until tests show complete disappearance of starch. The mass is then heated to volatilize most of the hydrochloric acid, sodium carbonate or calcium carbonate is added to neutralize the remaining traces of acid, the liquid is filtered, then decolorized in charcoal or bone-black filters, as is done in sugar refining, and finally concentrated in vacuum to the desired consistency.

When made by the above process, it contains about 30 to 40% of dextrose mixed with about an equal proportion of dextrin, together with small amounts of other carbohydrates, notably maltose. By varying the conditions of hydrolysis, the relative proportions of the sugars also vary.

If the crystallizable dextrose is desired, the conversion temperature is higher, and the time of conversion longer. The term *glucose,* as customarily used in the chemical or pharmaceutical literature, usually refers to dextrose, the crystallizable product.

The name *grape sugar* sometimes is applied to the solid commercial form of dextrose because the principal sugar of the grape is dextrose, although the fruit has never been used as a source of the commercial supply.

Description—Colorless or yellowish, thick, syrupy liquid; odorless, or nearly so; sweet taste; differs from sucrose in that it readily reduces hot alkaline cupric tartrate TS, producing a red precipitate of cuprous oxide.

Solubility—Miscible with water; sparingly soluble in alcohol.

Uses—As an ingredient of *Cocoa Syrup* (page 1027), as a tablet binder and coating agent, and as a diluent in pilular extracts; it has replaced glycerin in many pharmaceutical preparations. It is sometimes given *per rectum* as a *food* in cases when feeding by stomach is impossible. It should not be used in the place of dextrose for intravenous injection.

HYDROCHLORIC ACID

Chlorhydric Acid; Muriatic Acid; Spirit of Salt

Hydrochloric acid [7647-01-0] HCl (36.46); contains 36.5 to 38.0%, by weight, of HCl.

Preparation—By the interaction of NaCl and H_2SO_4 or by combining chlorine with hydrogen. It is obtained as a by-product in the manufacture of sodium carbonate from NaCl by the Leblanc process in which common salt is decomposed with H_2SO_4. HCl is also a by-product in the electrolytic production of NaOH from NaCl.

Description—Colorless, fuming liquid; pungent odor; fumes and odor disappear when it is diluted with 2 volumes of water; strongly acid to litmus even when highly diluted; specific gravity about 1.18.

Solubility—Miscible with water or alcohol.

Uses—Officially classified as a pharmaceutic aid that is used as an acidifying agent. It is used in preparing *Diluted Hydrochloric Acid.*

HYPOPHOSPHOROUS ACID

Phosphinic acid

Hypophosphorous acid [6303-21-5] HPH_2O_2 (66.00); contains 30 to 32% by weight, of H_3PO_2.

Preparation—By reacting barium or calcium hypophosphite with sulfuric acid or by treating sodium hypophosphite with an ion-exchange resin.

Description—Colorless or slightly yellow, odorless liquid; solution is acid to litmus even when highly diluted; specific gravity about 1.13.

Solubility—Miscible with water or alcohol.

Incompatibilities—Oxidized on exposure to air and by nearly all *oxidizing agents. Mercury, silver,* and *bismuth salts* are reduced partially to the metallic state as evidenced by a darkening in color. *Ferric compounds* are changed to ferrous.

Uses—An *antioxidant* in pharmaceutical preparations.

ISOPROPYL MYRISTATE

Tetradecanoic acid, 1-methylethyl ester

$CH_3(CH_2)_{12}COOCH(CH_3)_2$

Isopropyl myristate [110-27-0] $C_{17}H_{34}O_2$ (270.45).

Preparation—By reacting myristoyl chloride with 2-propanol with the aid of a suitable dehydrochlorinating agent.

Description—Liquid of low viscosity; practically colorless and odorless; congeals about 5° and decomposes at 208°; withstands oxidation and does not become rancid readily.

Solubility—Soluble in alcohol, acetone, chloroform, ethyl acetate, toluene, mineral oil, castor oil, or cottonseed oil; practically insoluble in water, glycerin, or propylene glycol; dissolves many waxes, cholesterol, or lanolin.

Uses—*Pharmaceutic aid* used in cosmetics and topical medicinal preparations as an emollient, as a lubricant, and to enhance absorption through the skin.

KAOLIN—page 1238.

LACTIC ACID

Propanoic acid, 2-hydroxy-, 2-Hydroxypropionic Acid; Propanoloic Acid; Milk Acid

$CH_3CH(OH)COOH$

Lactic acid [50-21-5] $C_3H_6O_3$ (90.08); a mixture of lactic acid and lactic acid lactate ($C_6H_{10}O_5$) equivalent to a total of 85 to 90%, by weight, of $C_3H_6O_3$.

Discovered by Scheele in 1780, it is the acid formed in the souring of milk, hence the name *lactic,* from the Latin name for milk. It results from the decomposition of the lactose (milk sugar) in milk.

Preparation—A solution of glucose or of starch previously hydrolyzed with diluted sulfuric acid is inoculated, after the addition of suitable nitrogen compounds and mineral salts, with *Bacillus lactis.* Calcium carbonate is added to neutralize the lactic acid as soon as it is formed, otherwise the fermentation stops when the amount of acid exceeds 0.5%. When fermentation is complete, as indicated by failure of the liquid to give a test for glucose, the solution is filtered, concentrated, and allowed to stand. The calcium lactate that crystallizes is decomposed with dilute sulfuric acid and filtered with charcoal. The lactic acid in the filtrate is extracted with ethyl or isopropyl ether, the ether is distilled off, and the aqueous solution of the acid is concentrated under reduced pressure.

Description—Colorless or yellowish, nearly odorless, syrupy liquid; acid to litmus; absorbs water on exposure to moist air; when a dilute solution is concentrated to above 50%, lactic acid lactate begins to form; in the official acid the latter amounts to about 12 to 15%; specific gravity about 1.20; decomposes when distilled under normal pressure but may be distilled without decomposition under reduced pressure.

Solubility—Miscible with water, alcohol, or ether; insoluble in chloroform.

Uses—In the preparation of *Sodium Lactate Injection* (page 1265). It also is used in babies' milk formulas, as an acidulant in food preparations, and in 1 to 2% concentration in some spermatocidal jellies. A 10% solution is used as a bactericidal agent on the skin of neonates. It is corrosive to tissues on prolonged contact. A 16.7% solution in flexible collodion is used to remove warts and small cutaneous tumors.

LACTOSE

D-Glucose, 4-*O*-β-D-galactopyranosyl-, Milk Sugar

Lactose [63-42-3] $C_{12}H_{22}O_{11}$ (342.30); *monohydrate* [10039-26-6] (360.31); a sugar obtained from milk.

For the structural formula, see page 411.

Preparation—From skim milk, to which is added diluted HCl to precipitate the casein. After removal of the casein by filtration, the reaction of the whey is adjusted to a pH of about 6.2 by addition of lime, and the remaining albuminous matter is coagulated by heating; this is filtered out and the liquid set aside to crystallize. Animal charcoal is used to decolorize the solution in a manner similar to that used in purifying sucrose.

Another form of lactose, known as β-lactose, also is available on the market. It differs in that the D-glucose moiety is β instead of α. It is reported that this variety is sweeter and more soluble than ordinary lactose and for that reason is preferable in pharmaceutical manufacturing where lactose is used. Chemically, β-lactose does not appear to differ from ordinary α-lactose. It is manufactured in the same way as α-lactose up to the point of crystallization, then the solution is heated to a temperature above 93.5°, the temperature at which the α form is

converted to the β variety. The β form occurs only as an anhydrous sugar, whereas the α variety may be obtained either in the anhydrous form or as a monohydrate.

Description—White or creamy white, hard, crystalline masses or powder; odorless; faintly sweet taste; stable in air, but readily absorbs odors; pH (1 in 10 solution) 4 to 6.5; specific rotation +54.8 to +55.5.

Solubility—1 g in 5 mL water or 2.6 mL boiling water; very slightly soluble in alcohol; insoluble in chloroform or ether.

Uses—A *diluent* largely used in medicine and pharmacy. It is generally an ingredient of the medium used in penicillin production. It is used extensively as an addition to milk for infant feeding.

MAGNESIUM CHLORIDE

Magnesium chloride hexahydrate [7791-18-6] $MgCl_2 \cdot 6H_2O$ (203.30); *anhydrous* [7786-30-3] (95.21).

Preparation—By treating magnesite or other suitable magnesium minerals with HCl.

Description—Colorless, odorless, deliquescent flakes or crystals, which lose water when heated to 100° and lose HCl when heated to 110°; pH (1 in 20 solution in carbon dioxide-free water) 4.5 to 7.

Solubility—Very soluble in water; freely soluble in alcohol.

Uses—*Electrolyte replenisher; pharmaceutical necessity* for hemodialysis and peritoneal dialysis fluids.

MAGNESIUM STEARATE

Octadecanoic acid, magnesium salt

Magnesium stearate [557-04-0]. A compound of magnesium with a mixture of solid organic acids obtained from fats, which consists chiefly of variable proportions of magnesium stearate and magnesium palmitate. It contains the equivalent of 6.8 to 8.0% MgO (40.30).

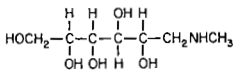
Description—Fine, white, bulky powder; faint, characteristic odor; unctuous, adheres readily to the skin and free from grittiness.

Solubility—Insoluble in water, alcohol, or ether.

Uses—A *pharmaceutical necessity (lubricant)* in the manufacture of compressed tablets.

MEGLUMINE

D-Glucitol, 1-deoxy-1-(methylamino)-,



1-Deoxy-1-(methylamino)-D-glucitol [6284-40-8] $C_7H_{17}NO_5$ (195.21).

Preparation—By treating glucose with hydrogen and methylamine under pressure and in the presence of Raney nickel.

Description—White to faintly yellowish white, odorless crystals or powder; melts about 130°.

Solubility—Freely soluble in water; sparingly soluble in alcohol.

Uses—In forming salts of certain pharmaceuticals, surface-active agents and dyes. See *Diatrizoate Meglumine Injections* (page 1195), *Iodipamide Meglumine Injection* (page 1187) and *Iothalamate Meglumine Injection* (page 1197).

LIGHT MINERAL OIL

Light Liquid Petrolatum NF XII; Light Liquid Paraffin; Light White Mineral Oil

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

Description—Colorless, transparent, oily liquid, free, or nearly free, from fluorescence; odorless and tasteless when cold, and develops not more than a faint odor of petroleum when heated; specific gravity 0.818 to 0.880; kinematic viscosity not more than 33.5 centistokes at 40°.

Solubility—Insoluble in water or alcohol; miscible with most fixed oils, but not with castor oil; soluble in volatile oils.

Uses—Officially recognized as a *vehicle*. Once it was used widely as a vehicle for nose and throat medications; such uses are now considered dangerous because of the possibility of lipoid pneumonia. It sometimes is used to cleanse dry and inflamed skin areas and to facilitate removal of dermatological preparations from the skin. It should never be used for internal administration because of *leakage*. See *Mineral Oil* (page 1233).

NITRIC ACID

Nitric acid [7697-37-2] HNO_3 (63.01); contains about 70%, by weight, of HNO_3.

Preparation—May be prepared by treatment of sodium nitrate (Chile saltpeter) with sulfuric acid, but usually produced by catalytic oxidation of ammonia.

Description—Highly corrosive fuming liquid; characteristic, highly irritating odor; stains animal tissues yellow; boils about 120°; specific gravity about 1.41.

Solubility—Miscible with water.

Uses—*Pharmaceutic aid* (acidifying agent).

NITROGEN

Nitrogen [7727-37-9] N_2 (28.01); contains not less than 99%, by volume, of N_2.

Preparation—By the fractional distillation of liquefied air.

Uses—A diluent for medicinal gases. Pharmaceutically, is employed to replace air in the containers of substances that would be affected adversely by air oxidation. Examples include its use with fixed oils, certain vitamin preparations, and a variety of injectable products. It also is used as a propellant.

PHENOL

Carbolic Acid

C_6H_5OH

Phenol [108-95-2] C_6H_6O (94.11).

Preparation—For many years made only by distilling crude carbolic acid from coal tar and separating and purifying the distillate by repeated crystallizations; it now is prepared synthetically.

One process uses chlorobenzene as the starting point in the manufacture. The chlorobenzene is produced in a vapor phase reaction, with benzene, HCl, and oxygen over a copper catalyst, followed by hydrolysis with steam to yield HCl and phenol (which is recovered).

Description—Colorless to light pink, interlaced, or separate, needle-shaped crystals, or a white or light pink, crystalline mass; characteristic odor; when undiluted, it whitens and cauterizes the skin and mucous membranes; when gently heated, phenol melts, forming a highly refractive liquid; liquefied by the addition of 10% of water; vapor is flammable; gradually darkens on exposure to light and air; specific gravity 1.07; boils at 182°; congeals not lower than 39°.

Solubility—1 g in 15 mL water; very soluble in alcohol, glycerin, chloroform, ether, or fixed and volatile oils; sparingly soluble in mineral oil.

Incompatibilities—Produces a liquid or soft mass when triturated with *camphor, menthol, acetanilid, acetophenetidin, aminopyrine, antipyrine, ethyl aminobenzoate, methenamine, phenyl salicylate, resorcinol, terpin hydrate, thymol,* and several other substances including some *alkaloids*. It also softens *cocoa butter* in suppository mixtures.

It is soluble in about 15 parts of water; stronger solutions may be obtained by using as much glycerin as phenol. Only the crystallized form is soluble in fixed oils and liquid petroleum, the liquefied form is not all soluble because of its content of water. *Albumin* and *gelatin* are precipitated by it. *Collodion* is coagulated by the precipitation of pyroxylin. Traces of *iron* in various chemicals such as *alum, borax,* etc, may produce a green color.

Uses—A *caustic, disinfectant, topical anesthetic,* and pharmaceutical necessity as a *preservative* for injections, etc. At one time widely used as a germicide and still the standard against which other antiseptics are compared, it has few legitimate uses in modern medicine. Nevertheless, it is still used in several proprietary antiseptic mouthwashes, hemorrhoidal preparations, and burn remedies. In full strength, a few drops of the liquefied form may be used to cauterize small wounds, dog bites, snake bites, etc. It commonly is employed as an *antipruritic,* in the form of either phenolated calamine lotion (1%), phenol ointment (2%), or a simple aqueous solution (0.5 to 1%). It has been used for sclerosing hemorrhoids, but more effective and safer drugs are available. A 5% solution in glycerin is used in simple earache. Crude carbolic acid is an effective, economical agent for disinfecting excrement. It is of some therapeutic value as a *fungicide,* but more effective and less toxic agents are available. If accidentally spilled, it should be removed promptly from the skin by swabbing with alcohol.

Liquefied Phenol [Liquefied Carbolic Acid]—Phenol maintained in a liquid condition by the presence of 10.0% of water. It contains not less than 89.0%, by weight, of C_6H_6O. *Note—When it is to be mixed with a fixed oil, mineral oil, or white petrolatum, use the crystalline Phenol, not Liquefied Phenol. Preparation:* Melt phenol (a convenient quantity) by placing the unstoppered container in a steam bath and applying heat gradually. Transfer the liquid to a tared vessel, weigh, add 1 g of purified water for each 9 g of phenol, and mix thoroughly. *Description:* Colorless liquid, which may develop a red tint upon exposure to air and light; characteristic, somewhat aromatic odor; when undiluted it cauterizes and whitens the skin and mucous membranes; specific gravity about 1.065; when it is subjected to distillation, the boiling temperature does not rise above 182°, which is the boiling temperature of phenol; partially solidifies at about 15°. *Solubility:* Miscible with alcohol, ether,

or glycerin; a mixture of liquefied phenol and an equal volume of glycerin is miscible with water. *Uses:* A formulation that facilitates the dispensing of concentrated phenol. Its therapeutic uses are described above under *Phenol*. It is a *pharmaceutical necessity for Phenolated Calamine Lotion* (see RPS-18 page 762).

PHOSPHORIC ACID

Orthophosphoric Acid; Syrupy Phosphoric Acid; Concentrated Phosphoric Acid

Phosphoric acid [7664-38-2] H_3PO_4 (98.00); contains 85 to 88%, by weight, of H_3PO_4.

Preparation—Phosphorus is converted to phosphorus pentoxide P_2O_5 by exposing it to a current of warm air, then the P_2O_5 is treated with water to form phosphoric acid. The conversion of the phosphorus to the pentoxide takes place while the phosphorus, distilling from the phosphorus manufacturing operation, is in the vapor state.

Description—Colorless, odorless liquid of a syrupy consistency; specific gravity about 1.71.

Solubility—Miscible with water or alcohol, with the evolution of heat.

Uses—To make the diluted acid and as a weak acid in various pharmaceutical preparations. Industrially, it is used in dental cements and in beverages as an acidulant.

Diluted Phosphoric Acid [Dilute Phosphoric Acid]—Contains, in each 100 mL, 9.5 to 10.5 g of H_3PO_4 (98.00). *Preparation:* Mix phosphoric acid (69 mL) and purified water (qs) to make 1000 mL. *Description and Solubility:* Clear, colorless, odorless liquid; specific gravity about 1.057. Miscible with water or alcohol. *Uses:* A *pharmaceutical necessity*. It also has been employed in *lead poisoning* and in other conditions in which it is desired to administer large amounts of phosphate and at the same time produce a mild acidosis. It has been given in the dosage of 60 mL a day (5 mL/hr) under carefully controlled conditions.

POTASSIUM METAPHOSPHATE

Metaphosphoric acid (HPO_3), potassium salt

Potassium metaphosphate [7790-53-6] KPO_3 (118.07); a straight-chain polyphosphate, having a high degree of polymerization; contains the equivalent of 59 to 61% P_2O_5.

Preparation—By thermal dehydration of monopotassium phosphate (KH_2PO_4).

Description—White, odorless powder.

Solubility—Insoluble in water; soluble in dilute solutions of sodium salts.

Uses—*Pharmaceutic aid* (buffering agent).

MONOBASIC POTASSIUM PHOSPHATE

For the full monograph, see page 1264.

Comments—A component of various buffer solutions. Medicinally, it has been used as a urinary acidifier.

PUMICE

Pumex

A substance of volcanic origin, consisting chiefly of complex silicates of aluminum, potassium, and sodium.

Description—Very light, hard, rough, porous, grayish masses or a gritty, grayish powder of several grades of fineness; odorless, tasteless, and stable in the air.

Three powders are available:

Pumice Flour or Superfine Pumice—Not less than 97% passes through a No 200 standard mesh sieve.

Fine Pumice—Not less than 95% passes through a No 150 standard mesh sieve, and not more than 75% passes through a No 200 standard mesh sieve.

Coarse Pumice—Not less than 95% passes through a No 60 standard mesh sieve, and not more than 5% passes through a No 200 standard mesh sieve.

Solubility—Insoluble in water and is not attacked by acids or alkali hydroxide solutions.

Uses—A *filtering* and *distributing medium* for pharmaceutical preparations. Because of its grittiness the powdered form is used in certain types of soaps and cleaning powders and also as a *dental abrasive*.

PYROXYLIN

Cellulose, nitrate; Soluble Guncotton

Pyroxylin [9004-70-0]; a product obtained by the action of a mixture of nitric and sulfuric acids on cotton, which consists chiefly of cellulose tetranitrate $(C_{12}H_{16}N_4O_{18})_n$.

Note—The commercially available form is moistened with about 30% of alcohol or other suitable solvent. The alcohol or solvent must be allowed to evaporate to yield the dried substance described in the Pharmacopeia.

Preparation—Shönbein, in 1846, found that nitric acid acts on cotton and produces a soluble compound. It subsequently was proved that this substance belongs to a series of closely related nitrates in which the nitric acid radical replaces the hydroxyl of the cellulose formula. This usually is indicated by taking the double empirical formula for cellulose $C_{12}H_{20}O_{10}$ and indicating replacement of four of the OH groups thus

$$\underset{\text{Cellulose}}{C_{12}H_{20}O_{10}} + 4HNO_3 \rightarrow \underset{\substack{\text{Cellulose}\\\text{Tetranitrate}}}{C_{12}H_{16}O_6(NO_3)_4} + 4H_2O$$

The compound used in preparing collodion is a varying mixture of the di-, tri-, tetra-, and pentanitrates, but is mainly tetranitrate. The hexanitrate is the true explosive guncotton and is insoluble in ether, alcohol, acetone, or water.

Description—Light yellow, matted mass of filaments, resembling raw cotton in appearance but harsh to the touch; *exceedingly flammable,* burning, when unconfined, very rapidly and with a luminous flame; when kept in well-closed bottles and exposed to light, it is decomposed with the evolution of nitrous vapors, leaving a carbonaceous residue.

Solubility—Insoluble in water; dissolves slowly but completely in 25 parts of a mixture of 3 volumes of ether and 1 volume of alcohol; soluble in acetone or glacial acetic acid and precipitated from these solutions by water.

Uses—A *pharmaceutical necessity* for *Collodion*.

ROSIN

Resina; Colophony; Georgia Pine Rosin; Yellow Pine Rosin

A solid resin obtained from *Pinus palustris* Miller and from other species of *Pinus* Linné (Fam *Pinaceae*).

Constituents—American rosin contains *sylvic acid* $[C_{20}H_{30}O_2]$, α-, β-, and γ-*abietic acids* $[C_{20}H_{30}O_2]$, *γ-pinic acid* (from which α- and β-pinic acids are gradually formed), and *resene*. Some authorities also include *pimaric acid* $[C_{30}H_{20}O_2]$ as a constituent. French rosin is called *galipot*.

Description—Sharply angular, translucent, amber-colored fragments, frequently covered with a yellow dust; fracture brittle at ordinary temperatures, shiny and shallow-conchoidal; odor and taste are slightly terebinthinate; easily fusible and burns with a dense, yellowish smoke, specific gravity 1.07 to 1.09.

Solubility—Insoluble in water; soluble in alcohol, ether, benzene, glacial acetic acid, chloroform, carbon disulfide, dilute solutions of sodium hydroxide and potassium hydroxide, or some volatile and fixed oils.

Uses—A pharmaceutical necessity for *Zinc-Eugenol Cement*. Formerly, and to some extent still, used as a component of plasters, cerates, and ointments, to which it adds adhesive qualities.

PURIFIED SILICEOUS EARTH

Purified Kieselguhr; Purified Infusorial Earth; Diatomaceous Earth; Diatomite

A form of silica $[SiO_2]$ [7631-86-9] consisting of the frustules and fragments of diatoms, purified by boiling with acid, washing, and calcining.

Occurrence and Preparation—Large deposits of this substance are found in Virginia, Maryland, Nevada, Oregon, and California, usually in the form of masses of rocks, hundreds of feet in thickness. Under the microscope it is seen to consist largely of the minute siliceous frustules of diatoms. It must be purified carefully in a manner similar to that directed for *Talc* (page 1048) and thoroughly calcined. The latter treatment destroys the bacteria that are present in large quantities in the native earth.

Description—Very fine, white, light-gray or pale-buff mixture of amorphous powder and lesser amounts of crystalline polymorphs, including quartz and cristobalite; gritty, readily absorbs moisture and retains about four times its weight of water without becoming fluid.

Solubility—Insoluble in water, acids, or dilute solutions of alkali hydroxides.

Uses—Introduced into the USP as a distributing and *filtering medium* for aromatic waters; also suitable for filtration of elixirs. Like talc, it does not absorb active constituents.

COLLOIDAL SILICON DIOXIDE

Silica [7631-86-9] SiO_2 (60.08); a submicroscopic fumed silica prepared by the vapor-phase hydrolysis of a silicon compound.

Description—Light, white, nongritty powder of extremely fine particle size (about 15 nm).

Solubility—Insoluble in water or acids (except hydrofluoric); dissolved by hot solutions of alkali hydroxides.

Uses—A *tablet moisture adsorber, glidant,* and as a *suspending* and *thickening agent* in pharmaceutical preparations.

SODA LIME

A mixture of calcium hydroxide and sodium or potassium hydroxide or both.

It may contain an indicator that is inert toward anesthetic gases such as ether, cyclopropane, and nitrous oxide and that changes color when the soda lime no longer can absorb carbon dioxide.

Description—White or grayish white granules; if an indicator is added, it may have a color; absorbs carbon dioxide and water on exposure to air.

Uses—Neither a therapeutic nor a pharmaceutical agent. It is a *reagent for the absorption of carbon dioxide* in anesthesia machines, oxygen therapy, and metabolic tests. Because of the importance of the proper quality for these purposes it has been made official and standardized.

SODIUM BORATE

Sodium Tetraborate; Sodium Pyroborate; Sodium Biborate

Borax [1303-96-4] $Na_2B_4O_7 \cdot 10H_2O$ (381.37); *anhydrous* [1330-43-4] $Na_2B_4O_7$ (201.22).

Preparation—Found in immense quantities in California as a crystalline deposit. The earth, which is strongly impregnated with borax, is lixiviated; the solution is evaporated and crystallized.

Calcium borate, or *cotton balls,* also occurs in the borax deposits of California, and sodium borate is obtained from it by double decomposition with sodium carbonate.

Description—Colorless, transparent crystals, or a white, crystalline powder; odorless; the crystals often are coated with white powder because of efflorescence; solution alkaline to litmus and phenolphthalein; pH about 9.5.

Solubility—1 g in 16 mL water, 1 mL glycerin, or 1 mL boiling water; insoluble in alcohol.

Incompatibilities—Precipitates many *metals* as insoluble borates. In aqueous solution it is alkaline and precipitates *aluminum salts* as aluminum hydroxide, *iron salts* as a basic borate, and ferric hydroxide and *zinc sulfate* as zinc borate and a basic salt. *Alkaloids* are precipitated from solutions of their salts. Approximately equal weights of *glycerin* and boric acid react to produce a decidedly acid derivative generally called glyceroboric acid. Thus, the addition of glycerin to a mixture containing it overcomes incompatibilities arising from an alkaline reaction.

Uses—As a pharmaceutical necessity, it is used as an alkalizing agent and as a buffer for alkaline solutions. Its alkalizing properties provide the basis for its use in denture adhesives and its buffering action for its use in eyewash formulations.

SODIUM CARBONATE

Carbonic acid, disodium salt, monohydrate; Monohydrated Sodium Carbonate USP XVII

Disodium carbonate monohydrate [5968-11-6] $Na_2CO_3 \cdot H_2O$ (124.00); *anhydrous* [497-19-8] (105.99).

Preparation—The initial process for its manufacture was devised by Leblanc, a French apothecary, in 1784, and consists of two steps: first, the conversion of common salt [NaCl] into sodium sulfate by heating it with sulfuric acid and, second, the decomposition of the sulfate by calcium carbonate (limestone) and charcoal (coal) at a high temperature to yield this salt and calcium sulfide. The carbonate then is leached out with water.

It currently is prepared by the electrolysis of sodium chloride, whereby sodium and chlorine are produced, the former reacting with water to produce sodium hydroxide and this solution treated with carbon dioxide to produce the salt. The process is used most extensively in localities where electric power is very cheap.

The monohydrated form is made by crystallizing a concentrated solution of this salt at a temperature above 35° (95°F) and stirring the liquid so as to produce small crystals. It contains about 15% water of crystallization.

Soda ash is a term designating a commercial quality of the anhydrous salt. Its annual production is very large, and it has a wide variety of applications, among which are the manufacture of glass, soap, and sodium salts; it also is used for washing fabrics.

Washing soda, or *sal soda,* is the salt with 10 molecules of water. It is in the form of colorless crystals that rapidly effloresce in the air.

Description—Colorless crystals or a white, crystalline powder; stable in air under ordinary conditions; when exposed to dry air above 50° it effloresces, and at 100° it becomes anhydrous; decomposed by weak acids, forming the salt of the acid and liberating carbon dioxide; aqueous solution alkaline to indicators (pH about 11.5).

Solubility—1 g in 3 mL water or 1.8 mL boiling water; insoluble in alcohol.

Incompatibilities—*Acids, acid salts,* and *acidic preparations* cause its decomposition. Most *metals* are precipitated as carbonates, hydroxides, or basic salts. *Alkaloids* are precipitated from solutions of their salts.

Uses—Occasionally, for dermatitides topically as a lotion; it has been used as a mouthwash and a vaginal douche. It is used in the preparation of the sodium salts of many acids. The USP recognizes it as a pharmaceutic aid used as an alkalizing agent.

SODIUM HYDROXIDE

Caustic Soda; Soda Lye

Sodium hydroxide [1310-73-2] NaOH (40.00); includes not more than 3% Na_2CO_3 (105.99).

Caution—Exercise great care in handling it, as it rapidly destroys tissues.

Preparation—By treating sodium carbonate with milk of lime or by the electrolysis of a solution of sodium chloride as explained under *Potassium Hydroxide* (page 1211). It now is produced largely by the latter process. See also *Sodium Carbonate,* above.

Description—White, or nearly white, fused masses, small pellets, flakes, sticks, and other forms; hard and brittle and shows a crystalline fracture; exposed to the air, it rapidly absorbs carbon dioxide and moisture; melts at about 318°; specific gravity 2.13; when dissolved in water or alcohol or when its solution is treated with an acid, much heat is generated; aqueous solutions, even when highly diluted, are strongly alkaline.

Solubility—1 g in 1 mL water; freely soluble in alcohol or glycerin.

Incompatibilities—Exposed to air, it absorbs *carbon dioxide* and is converted to sodium carbonate. With *fats* and *fatty acids* it forms soluble soaps; with *resins* it forms insoluble soaps. See *Potassium Hydroxide* (page 1211).

Uses—Too alkaline to be of medicinal value but occasionally used in veterinary practice as a caustic. It is used extensively in pharmaceutical processes as an alkalizing agent and is generally preferred to potassium hydroxide because it is less deliquescent and less expensive; in addition, less of it is required, since 40 parts of it are equivalent to 56 parts of KOH. It is a pharmaceutical necessity in the preparation of *Glycerin Suppositories.*

SODIUM STEARATE

Octadecanoic acid, sodium salt

Sodium stearate [822-16-2] $C_{18}H_{35}NaO_2$ (306.47) consists chiefly of sodium stearate and sodium palmitate $C_{16}H_{31}NaO_2$ = 278.41).

Preparation—Stearic acid is reacted with an equimolar portion of NaOH.

Description—Fine, white powder, soapy to the touch; usually has a slight, tallow-like odor; affected by light; solutions are alkaline to phenolphthalein TS.

Solubility—Slowly soluble in cold water or cold alcohol; readily soluble in hot water or hot alcohol.

Uses—Officially, a pharmaceutic aid used as an emulsifying and stiffening agent. It is an ingredient of glycerin suppositories. In dermatological practice it has been used topically in sycosis and other skin diseases.

STARCH

Corn Starch; Wheat Starch; Potato Starch

Starch [9005-25-8] consists of the granules separated from the mature grain of corn *Zea mays* Linné (Fam *Gramineae*) or of wheat *Triticum aestivum* Linné] (Fam *Gramineae*) or from tubers of the potato *Solanum tuberosum* Linné (Fam *Solanaceae*).

Preparation—In making starch from corn, the germ is separated mechanically, and the cells softened to permit escape of the starch granules. This generally is done by permitting it to become sour and decomposed, stopping the fermentation before the starch is affected. On the small scale, it may be made from wheat flour by making a stiff ball of dough and kneading it while a small stream of water trickles upon it. It is carried off with the water, while the *gluten* remains as a soft, elastic mass; the latter may be purified and used for various purposes to which gluten is applicable. Commercially, its quality largely depends on the purity of the water used in its manufacture. It may be made from potatoes by first grating them, and then washing the soft mass upon a

sieve, which separates the cellular substances and permits the starch granules to be carried through. It then must be washed thoroughly by decantation, and the quality of this starch also depends largely on the purity of the water that is used in washing it.

Description—Irregular, angular, white masses or fine powder; odorless; slight, characteristic taste. *Corn starch:* Polygonal, rounded, or spheroidal granules up to about 35 μm in diameter, which usually have a circular or several-rayed central cleft. *Wheat starch:* Simple lenticular granules 20 to 50 μm in diameter and spherical granules 5 to 10 μm in diameter; striations faintly marked and concentric. *Potato starch:* Simple granules, irregularly ovoid or spherical, 30 to 100 μm in diameter, and subspherical granules 10 to 35 μm in diameter; striations well marked and concentric.

Solubility—Insoluble in cold water or alcohol; when it is boiled with about 20 times its weight of hot water for a few minutes and then cooled, a translucent, whitish jelly results; aqueous suspension neutral to litmus.

Uses—Has absorbent and demulcent properties. It is used as a dusting powder and in various dermatological preparations; also as a pharmaceutic aid (filler, binder, and disintegrant). *Note—Starches obtained from different botanical sources may not have identical properties with respect to their use for specific pharmaceutical purposes, eg, as a tablet-disintegrating agent. Therefore, types should not be interchanged unless performance equivalency has been ascertained.*

Under the title *Pregelatinized Starch* the NF recognizes starch that has been processed chemically or mechanically to rupture all or part of the granules in the presence of water and subsequently dried. Some types may be modified to render them compressible and flowable.

STORAX

Liquid Storax; Styrax; Sweet Gum; Prepared Storax

A balsam obtained from the trunk of *Liquidambar orientalis* Miller, known in commerce as Levant Storax, or of *Liquidambar styraciflua* Linné, known in commerce as American Storax (Fam *Hamamelidaceae*).

Constituents—The following occur in both varieties: *styracin (cinnamyl cinnamate), styrol (phenylethylene,* C_8H_8*), α- and β-storesin* (the cinnamic acid ester of an alcohol called *storesinol*), *phenylpropyl cinnamate,* free *cinnamic acid,* and *vanillin*. In addition to these, Levant storax contains *ethyl cinnamate, benzyl cinnamate,* free *storesinol, isocinnamic acid, ethylvanillin, styrogenin,* and *styrocamphene*. This variety yields from 0.5 to 1% of volatile oil; from this have been isolated *styrocamphene, vanillin,* the cinnamic acid esters of *ethyl, phenylpropyl, benzyl,* and *cinnamyl alcohols, naphthalene,* and *styrol*.

The American variety contains, in addition to the aforementioned substances common to both varieties, *styaresin* (the cinnamic acid ester of the alcohol *styresinol,* an isomer of storesinol) and *styresinolic acid*. It yields up to 7% of a dextrorotatory volatile oil, the composition of which has not been investigated completely; styrol and traces of vanillin have been isolated from it.

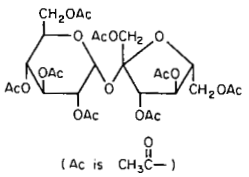
Description—Semiliquid, grayish to grayish brown, sticky, opaque mass, depositing on standing a heavy dark brown layer (Levant storax); or a semisolid, sometimes a solid mass, softened by gently warming (American storax); transparent in thin layers; characteristic odor and taste; more dense than water.

Solubility—Insoluble in water, but soluble, usually incompletely, in an equal weight of warm alcohol; soluble in acetone, carbon disulfide, or ether, some insoluble residue usually remaining.

Uses—An *expectorant* but is used chiefly as a local remedy, especially in combination with benzoin; eg, it is an ingredient of *Compound Benzoin Tincture* (page 1203). It may be used, like benzoin, to protect fatty substances from rancidity.

SUCROSE OCTAACETATE

α-D-Glucopyranoside, 1,3,4,6-tetra-*O*-acetyl-β-D-fructofuranosyl-, tetraacetate



Sucrose octaacetate [126-14-7] $C_{28}H_{38}O_{19}$ (678.60).

Preparation—Sucrose is subjected to exhaustive acetylation by reaction with acetic anhydride in the presence of a suitable condensing agent such as pyridine.

Description—White, practically odorless powder; intensely bitter taste; hygroscopic; melts not lower than 78°.

Solubility—1 g in 1100 mL water, 11 mL alcohol, 0.3 mL acetone, or 0.6 mL benzene; very soluble in methanol or chloroform; soluble in ether.

Uses—A *denaturant* for alcohol.

SULFURATED POTASH

Thiosulfuric acid, dipotassium salt, mixt with potassium sulfide ($K_2(S_x)$); Liver of Sulfur

Dipotassium thiosulfate mixture with potassium sulfide (K_2S_x) [39365-88-3]; a mixture composed chiefly of potassium polysulfides and potassium thiosulfate. It contains not less than 12.8% S (sulfur) in combination as sulfide.

Preparation—By thoroughly mixing 1 part of sublimed sulfur with 2 parts of potassium carbonate and gradually heating the mixture in a covered iron crucible until the mass ceases to swell and is melted completely. It then is poured on a stone or glass slab and, when cold, is broken into pieces and preserved in tightly closed bottles. When the heat is regulated properly during its production, the reaction is represented approximately by

$$3K_2CO_3 + 8S \rightarrow 2K_2S_3 + K_2S_2O_3 + 3CO_2$$

As this product rapidly deteriorates on exposure to moisture, oxygen, and carbon dioxide, it is important that it be prepared recently to produce satisfactory preparations.

Description—Irregular pieces, liver-brown when freshly prepared, changing to a greenish yellow; decomposes upon exposure to air; an odor of hydrogen sulfide and a bitter, acrid, alkaline taste; even weak acids cause the liberation of H_2S from sulfurated potash; 1 in 10 solution light brown in color and alkaline to litmus.

Solubility—1 g in about 2 mL water, usually leaving a slight residue; alcohol dissolves only the sulfides.

Uses—Extensively in dermatological practice, especially in the official *White Lotion* or *Lotio Alba* (page 1207). It is used as an opacifier.

The equation for the reaction of the potassium trisulfide in preparing the lotion is

$$ZnSO_4 + K_2S_3 \rightarrow ZnS + 2S + K_2SO_4$$

TALC

Talcum; Purified Talc; French Chalk; Soapstone; Steatite

A native, hydrous magnesium silicate, sometimes containing a small proportion of aluminum silicate.

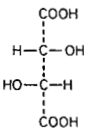
Occurrence and Preparation—The native form, called *soapstone* or *French chalk,* is found in various parts of the world. An excellent quality is obtained from deposits in North Carolina. Deposits of a high grade, conforming to the USP requirements, also are found in Manchuria. The native form usually is accompanied by variable amounts of mineral substances. These are separated from it by mechanical means, such as flotation or elutriation. It then is powdered finely, treated with boiling dilute HCl, washed well, and dried.

Description—Very fine, white, or grayish white crystalline powder; unctuous to the touch, adhering readily to the skin, and free from grittiness.

Uses—Officially, as a dusting powder and pharmaceutic aid; in both categories it has many specific uses. Its medicinal use as a dusting powder depends on its desiccant and lubricant effects. When perfumed, and sometimes medicated, it is used extensively for toilet purposes under the name *talcum powder;* for such use it should be in the form of an impalpable powder. When used as a filtration medium for clarifying liquids, a coarser powder is preferred to minimize passage through the pores of the filter paper; for this purpose it may be used for all classes of preparations with no danger of adsorption or retention of active principles. It is used as a lubricant in the manufacture of tablets and as a dusting powder when making handmade suppositories. Although it is used as a lubricant for putting on and removing rubber gloves, it should not be used on surgical gloves because even small amounts deposited in organs or healing wounds may cause granuloma formation.

TARTARIC ACID

Butanedioic acid, *R*-(*R,*R**) 2,3-dihydroxy-,**



L-(+)-Tartaric acid [87-69-4] $C_4H_6O_6$ (150.09).

Preparation—From *argol,* the crude cream of tartar (potassium bitartrate) deposited on the sides of wine casks during the fermentation

of grapes, by conversion to calcium tartrate, which is hydrolyzed to tartaric acid and calcium sulfate.

Description—Large, colorless or translucent crystals, or a white granular to fine crystalline powder; odorless; acid taste; stable in the air; solutions acid to litmus; dextrorotatory.

Solubility—1 g in 0.8 mL water, 0.5 mL boiling water, 3 mL alcohol, or 250 mL ether; freely soluble in methanol.

Uses—Chiefly, as the acid ingredient of preparations in which it is neutralized by a bicarbonate, as in effervescent salts, and the free acid is completely absent or present only in small amounts in the finished product. It also is used as a buffering agent.

TITANIUM DIOXIDE—page 1217.

TRICHLOROMONOFLUOROMETHANE

Methane, trichlorofluoro-,

$CFCl_3$

Trichlorofluoromethane [75-69-4] CCl_3F (137.37).

Preparation—Carbon tetrachloride is reacted with antimony trifluoride in the presence of a small quantity of antimony pentachloride. The reaction produces a mixture of CCl_3F and CCl_2F_2, which readily is separable by fractional distillation.

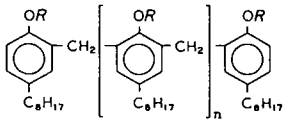
Description—Clear, colorless gas; faint, ethereal odor; vapor pressure at 25° is about 796 torr; boils about 24°.

Solubility—Practically insoluble in water; soluble in alcohol, ether, or other organic solvents.

Uses—A *propellant* (No 11, see page 968).

TYLOXAPOL

Phenol, 4-(1,1,3,3-tetramethylbutyl)-, polymer with formaldehyde and oxirane



[*R* is $CH_2CH_2O(CH_2CH_2O)_mCH_2CH_2OH$; *m* is 6 to 8; *n* is not more than 5]

p-(1,1,3,3-Tetramethylbutyl)phenol polymer with ethylene oxide and formaldehyde [25301-02-4].

Preparation—*p*-(1,1,3,3-Tetramethylbutyl)phenol and formaldehyde are condensed by heating in the presence of an acidic catalyst, and the polymeric phenol thus obtained is reacted with ethylene oxide at elevated temperature under pressure in the presence of NaOH. US Pat. 2,454,541.

Description—Amber, viscous liquid; may show a slight turbidity; slight aromatic odor; specific gravity about 1.072; stable at sterilization temperature and in the presence of acids, bases, and salts; oxidized by metals; pH (5% aqueous solution) 4 to 7.

Solubility—Slowly but freely soluble in water; soluble in many organic solvents, including acetic acid, benzene, carbon tetrachloride, carbon disulfide, chloroform, or toluene.

Uses—A nonionic detergent that depresses both surface tension and interfacial tension. It also is used in contact-lens-cleaner formulations.

ISO-ALCOHOLIC ELIXIR

Iso-Elixir

Low-Alcoholic Elixir	
High-Alcoholic Elixir	of each a calculated volume

Mix the ingredients.

LOW-ALCOHOLIC ELIXIR

Compound Orange Spirit	10 mL
Alcohol	100 mL
Glycerin	200 mL
Sucrose	320 g
Purified Water, a sufficient quantity, to make	1000 mL

Alcohol Content—8 to 10%.

HIGH-ALCOHOLIC ELIXIR

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

Alcohol Content—73 to 78%.

Uses—Intended as a general *vehicle* for various medicaments that require solvents of different alcoholic strengths. When it is specified in a prescription, the proportion of its two ingredients to be used is that which will produce a solution of the required alcohol strength.

The alcoholic strength of the elixir to be used with a single liquid galenical in a prescription is approximately the same as that of the galenical. When galenicals of different alcoholic strengths are used in the same prescription, the elixir to be used is to be of such alcoholic strength as to secure the best solution possible. This generally will be found to be the average of the alcoholic strengths of the several ingredients.

For nonextractive substances, the lowest alcoholic strength of the elixir that will yield a perfect solution should be chosen.

UREA

For the full monograph, see page 1346.

Comments—A protein denaturant that promotes hydration of keratin and mild keratolysis in dry and hyperkeratotic skin. It is used in 2 to 20% concentrations in various dry-skin creams.

OTHER MISCELLANEOUS PHARMACEUTICAL NECESSITIES

Bucrylate [Propenoic acid, 2-cyano-, 2-methylpropyl ester; Isobutyl 2-cyanoacrylate [1069-55-2] $C_{80}H_{11}NO_2$ (153.18)]—*Preparation:* One method reacts isobutyl 2-chloroacrylate with sodium cyanide. *Uses:* Surgical aid (tissue adhesive).

Ceresin [Ozokerite; Earth Wax; Cerosin; Mineral Wax; Fossil Wax]—A hard, white odorless solid resembling spermaceti when purified, occurring naturally in deposits in the Carpathian Mountains, especially in Galicia. It is a mixture of natural complex paraffin hydrocarbons. Melts between 61 and 78°; specific gravity 0.91 to 0.92; stable toward oxidizing agents. Soluble in 30% alcohol, benzene, chloroform, petroleum, benzin, or hot oils. *Uses:* Substitute for beeswax; in dentistry, for impression waxes.

Ethylenediamine Hydrate BP, PhI [$H_2NCH_2CH_2NH_2 \cdot H_2O$]—Clear, colorless or slightly yellow liquid with an ammoniacal odor and characteristic alkaline taste; solidifies on cooling to a crystalline mass (mp 10); boils 118 to 119°; specific gravity about 0.96; hygroscopic and absorbs CO_2 from the air; aqueous solutions alkaline to litmus. Miscible with water or alcohol; soluble in 130 parts of chloroform; slightly soluble in benzene or ether. *Uses:* In the manufacture of aminophylline and in the preparation of aminophylline injections. See *Ethylenediamine* (page 1016).

Ferric Oxide, Red—Contains not less than 90% Fe_2O_3. It is made by heating native ferric oxide or hydroxide at a temperature that will yield a product of the desired color. The color is governed by the temperature and time of heating, the presence and kind of other metals, and the particle size of the oxide. A dark-colored oxide is favored by prolonged heating at high temperature and the presence of manganese. A light-colored oxide is favored by the presence of aluminum and by finer particle size. *Uses:* Imparting color to neocalamine and cosmetics.

Ferric Oxide, Yellow—Contains not less than 97.5% Fe_2O_3. It is prepared by heating ferrous hydroxide or ferrous carbonate in air at a low temperature. *Uses:* As for *Red Ferric Oxide* (above).

Honey NF XII [Mel; Clarified Honey; Strained Honey]—The saccharine secretion deposited in the honeycomb by the bee, *Apis mellifera* Linné (Fam *Apidae*). It must be free from foreign substances such as parts of insects, leaves, etc, but may contain pollen grains. *History:* Honey is one of the oldest of food and medicinal products. During the 16th and 17th centuries it was recommended as a cure for almost everything. *Constituents: Invert sugar* (62 to 83%), *sucrose* (0 to 8%), and *dextrin* (0.26 to 7%). *Description:* Thick, syrupy liquid of a light yellowish to reddish brown color; translucent when fresh but frequently becomes opaque and granular through crystallization of dextrose; characteristic odor and a sweet, faintly acrid taste. *Uses:* A sweetening agent and pharmaceutic necessity.

Hydriodic Acid, Diluted—Contains, in each 100 mL, 9.5 to 10.5 g of HI (127.91) and 600 mg to 1 g of HPH_2O_2 (66.00). The latter is added to prevent the formation of free iodine. *Caution: Diluted Hydriodic Acid must not be dispensed or used in the preparation of other products if they contain free iodine. Preparation:* On a large scale, by the interaction of iodine and hydrogen sulfide. *Description and Solubility:* Colorless or not more than pale-yellow, odorless liquid; specific gravity about 1.1. Miscible with water or alcohol. *Uses:* In *Hydriodic Acid Syrup* (page 1028). The latter has been used as an expectorant. It also is used in the manufacture of inorganic iodides and disinfectants. The 57% acid also is used for analytical purposes, such as methoxyl determinations.

Lime [Calx; Calcium Oxide; Quicklime; Burnt Lime; Calx Usta; CaO (56.08)]—*Preparation:* By calcining *limestone* (a native calcium carbonate) in kilns with strong heat. *Description and Solubility:* Hard, white or grayish white masses or granules, or a white or grayish white

powder; odorless; solution strongly alkaline; 1 g is soluble in about 840 mL water and 1740 mL boiling water; soluble in glycerin or syrup; insoluble in alcohol. *Uses:* In making mortar, whitewash, and various chemicals and products. It is an ingredient in *Sulfurated Lime Solution*. In the USP, calcium hydroxide has replaced it, as it is more stable and more readily available in a quality suitable for medicinal use than the lime usually obtainable. Unless protected from air, lime soon becomes unfit for use, due to the action of carbon dioxide and moisture in the air. See *Calcium Hydroxide* (page 1041).

Peach Oil—An oil resembling almond oil, obtained from *Persica vulgaris* (Fam *Rosaceae*).

Polacrilin Potassium—Methacrylic acid polymer with divinylbenzene, potassium salt [39394-76-5]; Amberlite IRP-88. Prepared by polymerizing methacrylic acid with divinylbenzene, and the resulting resin is neutralized with KOH. Dry, buff-colored, odorless, tasteless, free-flowing powder; stable in light, air, and heat; insoluble in water. *Uses: Pharmaceutic aid* (tablet disintegrant).

Poloxalene—Glycols, polymers, polyethylene-polypropylene [9003-11-6]. Polypropylene glycol is reacted with ethylene oxide. *Uses: Pharmaceutic aid* (surfactant).

Raspberry Juice—The liquid expressed from the fresh ripe fruit of *Rubus idaeus* Linné or of *Rubus strigosus* Michaux (Fam *Rosaceae*); contains not less than 1.5% of acids calculated as citric acid. *Preparation:* Express the juice from the washed, well-drained, fresh, ripe, red raspberries. Dissolve 0.1% of benzoic acid in the expressed juice and allow it to stand at room temperature (possibly for several days) until a small portion of the filtered juice produces a clear solution when mixed with ½ of its volume of alcohol, the solution remaining clear for not less than 30 min. Strain the juice from the mixture or filter it, if necessary. *Description:* Clear liquid with an aromatic, characteristic odor and a characteristic sour taste; the freshly prepared juice is red to reddish orange; affected by light. *Uses:* In the preparation of *Raspberry Syrup*, a *flavored vehicle*.

Sodium Glutamate—Sodium Acid Glutamate [142-47-2] $HOOCCH(NH_2)CH_2CH_2COONa$. White or nearly white, crystalline powder. Very soluble in water; sparingly soluble in alcohol. *Uses:* Imparts a meat flavor to foods.

Sodium Thioglycollate [Sodium Mercaptoacetate; $HSCH_2COONa$]—Hygroscopic crystals that discolor on exposure to air or iron. Freely soluble in water; slightly soluble in alcohol. *Uses:* Reducing agent in Fluid Thioglycollate Medium for sterility testing.

Suet, Prepared [Mutton Suet]—Internal fat of the abdomen of the sheep, *Ovis aries* (Fam *Bovidae*), purified by melting and straining. White, solid fat with a slight, characteristic odor and taste when fresh; melts between 45 and 50° and congeals between 37 and 40°; must be preserved in a cool place in tight containers. *Uses:* In ointments and cerates.