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CHAPTER 80

Tonicity, Osmoticity, Osmolality, and Osmolarity

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It is generally 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, blood sugar, etc). 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 physiologic mechanisms which 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 is usually 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 whole body within this same short period of time. The reason for this is that fluid usually enters the body through the gut and must then be transported by the circulatory system to all tissues before complete equilibration can occur. In the normal person it may require 30–60 minutes to achieve reasonably good equilibration throughout the body after drinking water. Osmoticity is the property that largely determines the physiologic 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 to either formulating to avoid the side effects or 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 use of mannitol as a diuretic which 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 intravenous 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 and a 40% glucose ointment are used topically for corneal edema. Ophthalgan (*Ayerst*) is ophthalmic glycerin employed for its osmotic effect to clear edematous cornea to facilitate an ophthalmoscopic or genioscopic examination. Glycerin solutions in 50–75% concentrations [Glyrol (*Cooper Vision*), 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 which is a nonelectrolyte is a lactulose solution. Lactulose is a nonabsorbable disaccharide which 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 Cephulic (*Merrell-National*) 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 is ultimately coupled with the osmotic effect and laxation thus expelling undesirable levels of blood ammonia. This product is employed to prevent and treat frontal systemic encaphalopathy.

Osmotic laxation is known 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. A relatively new approach is the indirect application of the osmotic effect in therapy via osmotic pump drug delivery systems.[2]

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 is often called *semipermeable*. As the several types of membranes of the body vary in their permeability, it is well to note that they are *se-*

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lectively 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 a solution A on one side of the membrane, and a solution B of the same solute but of a higher concentration 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, which 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 (un-ionized 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 which is often 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 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 *isoosmotic* with physiologic fluids. The term *isotonic*, meaning equal tone, is in medical usage commonly used interchangeably with isoosmotic. However, terms such as isotonic and tonicity should be used *only* with reference to a physiologic fluid. Isoosmotic is actually a physical term which compares the osmotic pressure (or another colligative property, such as freezing point depression) of two liquids, neither of which may be a physiologic fluid, or which may be a physiologic fluid only under certain circumstances. For example, a solution of boric acid that is isoosmotic 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 physiologic compatibility where isoosmoticity need not. As another example, a "chemically defined elemental diet" or enteral nutritional fluid can be isoosmotic with the contents of the gastrointestinal tract, but would not be considered a physiologic 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. Physiologic solutions with an osmotic pressure lower than that of body fluids, or of 0.9% sodium chloride solution, are commonly referred to as being *hypotonic*. Physiologic 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 particles that may be present in a given system. The term used is *osmol*. An osmol is defined as the weight in grams of a solute, existing in a solution as molecules (and/or ions, macromolecules, aggregates, etc), that is osmotically equivalent to the gram-molecular-weight of an ideally behaving nonelectrolyte. Thus the osmol-weight of a nonelectrolyte, in a dilute solution, is generally 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 may also define an osmol in these following ways. It is the amount of solute which will provide one Avogadro's number, 6.02×10^{23} particles in solution and it is the amount of solute which on dissolution in one kg of water will result in an osmotic pressure increase of 22.4 atmospheres. This is derived from the gas equation, PV = nRT, assuming ideal conditions and standard temperature of 0°. This is equivalent to an increase of 17,000 mm Hg or 19,300 mm Hg at 37°. A milliosmol (mOsm) is one-thousandth of an osmol. For example, one mole of anhydrous dextrose is equal to 180 g. One Osm of this nonelectrolyte is also 180 g. One mOsm would be 180 mg. Thus 180 mg of this solute dissolved in one kg of water will produce an increase in osmotic pressure of 19.3 mm Hg 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, one mole will represent 2 osmols of sodium chloride theoretically. Accordingly, one Osm 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 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 is likely to be needed.

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 one osmol of solute per kilogram of water. A solution has an osmolality of n when it contains n osmols per kilogram of water. Osmolal solutions, like their counterpart molal solutions, reflect a weight to weight relationship between the solute and the solvent. All solutions with the same molal concentrations, irrespective of solute, contain the same mole fraction (f_m) of solute. In water

$$f_m = \frac{\text{moles solute}}{\text{moles solute} + \text{moles solvent}}$$

thus, for a one molal solution

$$f_m = \frac{1 \text{ mole solute}}{1 \text{ mole solute} + 55.5 \text{ moles water per kg}} = \frac{1}{56.5}$$

Since an osmol of any nonelectrolyte is equivalent to one mole of that compound, then a one osmolal solution is synonymous to a one molal solution for a typical nonelectrolyte.

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

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

Osmolarity—The relationship that we observed between molality and osmolality is similarly shared between molarity and osmolarity. A solution has an osmolar concentration of one when it contains one osmol of solute per liter of solution. Likewise, a solution has an osmolarity of *n* when it contains *n* osmols per liter of solution. Osmolar solutions, unlike osmolal solutions, reflect a weight in volume relationship between the solute and final solution. A one molar and one osmolar solutions would be synonymous for nonelectrolytes. For sodium chloride a one osmolar solution would contain one osmol of sodium chloride per liter which approximates a 0.5 molar solution. The advantage of employing osmolar concentrations over osmolal concentrations is the ability to relate a specific number of osmols or milliosmols to a volume, such as a liter or mL. Thus the osmolar concept is simpler and more practical. The osmolal concept does not allow for this convenience because of the w/w relationship. Also, additional data such as the density are usually not available. 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. This is partly due to the circumstance that until recent years most of the systems involved were body fluids in which the difference between the numerical values of the two concentration expressions is small and similar in magnitude to the error involved in their determination. The problem may partly center around the interpretation by some to view one kilogram of water in the osmolal concept as being equivalent to one liter, and more importantly, the interpretation that to make up to volume of one liter as in osmolarity is reasonably the same as plus one liter (a distortion of the osmolal concept). The essential difference resides in the error introduced which revolves around the volume of water occupied by the solute. A one osmolar solution of a solute will always be more concentrated than a one osmolal solution. With dilute solutions the difference may be acceptably small. Nine grams of sodium chloride per liter of aqueous solution is approximately equivalent to 9 g in 996.5 mL of water. This represents an error under one percent when comparing the osmoticity of 0.9% w/v solution to a solution of 9 g plus one kilogram of water. Using dextrose in a parallel comparison, errors range from approximately 3.5% in osmoticity with 50 g dextrose per liter versus 50 g plus one kilogram water to a difference of about 25% in osmoticity with 250 g dextrose per liter versus 250 g plus one kilogram water. The confusion appears to be without cause for concern at this time. However, one should be alerted to the sizeable errors 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 hypoosmotic. The significance of hyper- and hypo-osmoticity for medicinal and nutritional fluids will be discussed in later sections. The values which correspond to those terms for serum may be approximately visualized from the following example. *Assuming* normal serum osmolality to be *285 mOsm/kg*, as serum osmolality increases due to water *deficit* the following signs and symptoms usually are found to progressively accumulate at approximately these values: 294–298—thirst (if the patient is alert and communicative); 299–313—dry mucous membranes; 314–329—weakness, doughy skin; above 330—disorientation, postural hypotension, severe weakness, fainting, CNS changes, stupor, coma. As serum osmolality decreases due to water *excess* the following may occur: 275–261—headache; 262–251—drowsiness, weakness; 250–233—disorientation, cramps; below 233—seizures, stupor, coma.

As indicated previously, the body's mechanisms actively combat such major changes by limiting the variation in osmolality for normal individuals to less than about 1% (approximately in the range 282–288 mOsm/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 references. Serum osmolality is often loosely stated to be about 300 mOsm/L. Apart from that, and more specifically, two references state it as 280–295 mOsm/L; other references give it as 275–300 mOsm/L, 290 mOsm/L, 306 mOsm/L, and 275–295 mOsm/kg. There is a strong tendency to call it *osmolality* but to state it as *mOsm/L* (*not as mOsm/kg*). In the light of these varying values, one may ask about the reproducibility of the experimental measurements, assuming that is their source. It has been stated that most osmometers are accurate to 5 mOsm/L. With that type of reproducibility, the above variations may perhaps be expected. The difference between liter and kilogram is probably insignificant for serum and urine. It is difficult to measure kilograms of water in a solution, and easy to express body fluid quantities in liters. Perhaps no harm has been done to date by this practice for body fluids. However, loose terminology here may lead to loose terminology when dealing with the rather concentrated fluids used at times in parenteral and enteral nutrition.

Reference has been made to confusion in the use of the terms osmolality and osmolarity, a distinction of special importance for nutritional fluids. Awareness of high concentrations of formula should give warning as to possible risks. Unfortunately, the osmoticity of infant formulas, tube feedings, and total parenteral nutrition solutions has not been adequately described either in textbooks or in the literature,[3] and the labels of many commercial nutritional fluids do not in any way state their osmoticity. Only recently have enteral fluids been characterized in terms of osmoticity. Some product lines are now accenting isoosmotic enteral nutritional supplements. Often, when the term osmolarity is used, one cannot discern whether this is simply incorrect terminology, or if osmolarity has actually been calculated from osmolality.

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

The range of mOsm values found for serum raises the question as to what is really meant by the terms hypotonic and hypertonic for medicinal and nutritional fluids. One can find the statement that fluids with an osmolality of 50 mOsm or more above normal are hypertonic, and if 50 mOsm or more below normal are hypotonic. One can also find the statement that peripheral infusions should not have an osmolarity exceeding 700–800 mOsm/L.[4] Examples of osmol concentrations of solutions used in peripheral infusions are: D5W—252 mOsm/L; D10W—505 mOsm/L; Lactated Ringer's 5% Dextrose—525 mOsm/L. When a fluid is hypertonic, undesirable effects can often be decreased by using relatively slow rates of infusion, and/or relatively short periods of infusion. D25W—4.25% Amino Acids is a representative example 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 mOsm per kg of water over 4 hours.[3]

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 wt/vol concentration using one of the following equations:

(1) For a nonelectrolyte

$$\frac{\text{grams/liter}}{\text{mol wt}} \times 1000 = \text{mOsm/liter}$$

(2) For a strong electrolyte

$$\frac{\text{grams/liter}}{\text{mol wt}} \times \frac{\text{number of ions formed}}{} \times 1000 = \text{mOsm/liter}$$

(3) For individual ions, if desired

$$\frac{\text{grams of ion/liter}}{\text{ionic wt}} \times 1000 = \text{mOsm (of ion)/liter}$$

These are simple calculations; however, they omit consideration of factors such as solvation and interionic forces. By this method of calculation 0.9% sodium chloride has an osmolar concentration of 308 mOsm/L.

Two other methods compute osmolarity from values of osmolality. The determination of osmolality will be discussed in a later section. One method has a strong theoretical basis of physical-chemical principles;[5] it uses 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 mOsm/kg, was calculated to have an osmolarity of 280 mOsm/L, rather different from the value of 308 mOsm/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 the following relationship:[6,7] actual osmolarity = measured osmolality × (density − g solute/mL). This expression can be written:

$$\text{mOsm/L solution} = \text{mOsm/1000 g water} \times \text{g water/mL solution}$$

The experimental value for the osmolality of 0.9% sodium chloride solution was 292.7 mOsm/kg; the value computed for osmolarity was 291.4 mOsm/L. This method does not have as firm a theoretical basis as the preceding method but it has the advantage that it uses easily obtained values of density of the solution and of its solute content. Apparently it 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 mOsm/kg;[7] its osmolarity was calculated as 625 × 0.839 = 524 mOsm/L.

The USP requires that labels of pharmacopeial solutions which provide intravenous replenishment of fluid, nutrient(s), or electrolyte(s), as well as of the osmotic diuretic Mannitol Injection, state the osmolar concentration, in milliosmols per liter, except that where the contents are less than 100 mL, or where the label states the article is not for direct injection but is to be diluted before use, the label may alternatively state the total osmolar concentration in milliosmols per mL. This is a reasonable request from several standpoints, and intravenous fluids are being labeled in accordance with this stipulation, as shown in the next section.

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 (Travenol Solution), which is labeled to contain, per liter, dextrose (hydrous) 50 g, sodium chloride 6 g, potassium chloride 300 mg, calcium chloride 200 mg, sodium lactate 3.1 g. Also stated is that the total osmolar concentration of the solution is approximately 524 mOsm per liter, 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) above for the nonelectrolyte dextrose, and equation (2) for the electrolytes.

Dextrose

$$\frac{50 \text{ g} \times 1000}{198.17} = 252.3 \text{ mOsm/liter}$$

Sodium Chloride

$$\frac{6 \text{ g} \times 2 \times 1000}{58.44} = 205.33 \text{ mOsm/liter} \begin{cases} (102.66 \text{ mOsm } Na^+) \\ (102.66 \text{ mOsm } Cl^-) \end{cases}$$

Potassium Chloride

$$\frac{0.3 \text{ g} \times 2 \times 1000}{74.55} = 8.04 \text{ mOsm/liter} \begin{cases} (4.02 \text{ mOsm } K^+) \\ (4.02 \text{ mOsm } Cl^-) \end{cases}$$

Calcium Chloride

$$\frac{0.2 \text{ g} \times 3 \times 1000}{110.99} = 5.4 \text{ mOsm/liter} \begin{cases} (1.8 \text{ mOsm } Ca^{2+}) \\ (3.6 \text{ mOsm } Cl^-) \end{cases}$$

Sodium Lactate

$$\frac{3.1 \text{ g} \times 2 \times 1000}{112.06} = 55.32 \text{ mOsm/liter} \begin{cases} (27.66 \text{ mOsm } Na^+) \\ (27.66 \text{ mOsm lactate}) \end{cases}$$

The total osmolar concentration of the five solutes in the solution is 526.4, in good agreement with the labeled total osmolar concentration of approximately 524 mOsm/liter.

The mOsm of sodium in one liter of the solution is the sum of the mOsm of the ion from sodium chloride and sodium lactate, ie, 102.66 + 27.66 = 130.32 mOsm. Chloride ions come from the sodium chloride, potassium chloride, and calcium chloride, the total osmolar concentration being 102.66 + 4.02 + 3.6 = 110.3 mOsm. The mOsm values of potassium, calcium, and lactate are calculated to be 4.02, 1.8, and 27.66, respectively. Thus, with the possible exception of calcium, there is close agreement with the labeled mEq content of each of these ions.

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

The approximate osmolarity of mixtures of two solutions can be computed from the following relationship (the method is known as *alligation medial*):

$$\text{osm}_{\text{final}} = \frac{\text{osm}_a \times V_a}{V_{\text{final}}} + \frac{\text{osm}_b \times V_b}{V_{\text{final}}}$$

where

V_a = volume of component a
V_b = volume of component b
V_{final} = volume of final solution
osm_a = osmolarity of component a
osm_b = osmolarity of component b
$\text{osm}_{\text{final}}$ = osmolarity of final solution

For example, to calculate the osmolarity of a mixture of 500 mL of a solution of osmolarity 850 and 500 mL of a solution of osmolarity 252:

$$\text{osm}_{\text{final}} = \frac{850 \times 500}{1000} + \frac{252 \times 500}{1000}$$
$$= 425 \text{ mOsm/L} + 126 \text{ mOsm/L} = 551 \text{ mOsm/L}$$

This example illustrates the ease of calculating the osmoticity, by use of osmolarity, when solutions are mixed. Such a calculation would be much less valid if osmolality values were used. From the previous example one can see how to calculate the approximate effect if an additional solute is added.

Undesirable Effects of Abnormal Osmoticity

Ophthalmic Medication—It has been 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 87). It has also been

stated that abnormal tonicity of contact lens solutions can cause the lens to adhere to the eye and/or cause burning or dryness or photophobia.

Parenteral Medication—Osmoticity is of great importance in parenteral injections, its effects depending on the degree of deviation from tonicity, the concentration, the location of the injection, the volume injected, the speed of the injection, 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 are usually 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 are generally stated to cause tissue irritation, pain on injection, and electrolyte shifts, the effect depending on the degree of deviation from tonicity.

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

Excessive infusion of *hyper*tonic fluids leads to a wide variety of complications. For example, the sequence of events when the body is presented with a large intravenous 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 400–500 mg/kg/hr for an adult on total parenteral nutrition). A heavy load of nonmetabolizable dextrose increases the osmoticity of blood and acts as a diuretic; the increased solute load requires more fluid for excretion, 10–20 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 hours) 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 intravenous 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; 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.[3]

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) and venous pressure (VP) followed by a precipitous fall in CSF pressure. This may be particularly 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 1563 at 1 mEq/mL), that 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.[5]

As to other possibilities, there may be crenation of red blood cells and general cellular dehydration. Hypertonic dextrose or saline, etc. 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 intravenous injections, especially highly osmotic solutions, be performed slowly, usually being given preferably over a period not less than required for a complete circulation of the blood, e.g., *one minute*. The exact danger point varies with the state of the patient, the concentration 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 suddenly reversed by stopping the infusion and administering saline. It has also been shown that the CSF pressure in humans rises during treatment of diabetic ketoacidosis in association with fall in the plasma concentration of dextrose and 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.

Osmometry and the Clinical Laboratory

Osmometry is a fairly recent innovation in the clinical laboratory; an article in 1971 had the title: "Osmometry: A New Bedside Laboratory Aid for the Management of Surgical Patients." 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 generally used, but is usually reported as mOsm/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 50–1400 mOsm/L, and for a random specimen is 500–800 mOsm/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 due to 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 mOsm/L.

In a somewhat analogous fashion hypoosmotic serum is

likely to be due to decrease in serum sodium and/or excess of water. It may be associated with: (a) the postoperative state (especially with excessive water replacement therapy); (b) treatment with diuretic drugs and low-salt diet (as with patients with heart failure, cirrhosis, etc); (c) adrenal disease (eg, Addison's disease, adrenogenital syndrome); (d) SIADH (syndrome of inappropriate ADH secretion). There are many diseases that cause ADH to be released inappropriately (ie, in spite of the fact that serum osmoticity and volume may have been normal initially). These include oat-cell carcinoma of the lung, bronchogenic carcinoma, congestive heart failure, inflammatory pulmonary lesions, porphyria, severe hypothyroidism, cerebral disease (such as tumor, trauma, infection, vascular abnormalities). It may also be found with some patients with excessive diuretic use. Serum and urine osmoticity are measured when SIADH is suspected. In SIADH there is hypoosmoticity 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, etc. They may be of considerable value in an emergency situation.

(a) Serum osmolality may be estimated from the formula:

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

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

(b) A quick approximation is:

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

(c) 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 best measured 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 6–8 liters, or more. The normal urine osmolality depends on the clinical setting; normally, with maximum ADH stimulation, it can be as much as 1200 mOsm/kg, and with maximum ADH suppression as little as 50 mOsm/kg. Simultaneous determination of serum and urine osmolality is often 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 mOsm/kg. With severe impairment the value would be less than 400 mOsm/kg. Knowledge of urine osmolality may point to a problem even though other tests are normal (eg, the Fishberg concentration test, BUN, PSP excretion, creatinine clearance, IV pyelogram). Knowledge of its value may be especially useful in diabetes mellitus, essential hypertension, and silent pyelonephritis. The urine/serum osmolality ratio should be calculated; it should be equal to or greater than 3.

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. An example is the professional organization, ASPEN, "The American Society for Parenteral and Enteral Nutrition," with membership open to all of the above health practitioners. It is desirable, therefore, that pharmacists be able to discuss these matters with these other health professionals in terms of nutrition as well as medicine.

Osmoticity has been of special importance in the intravenous 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 seems to have led more recently to the use of rather similar formulations administered, not parenterally, but by instillation into some part of the gastrointestinal tract, usually, but not necessarily, by gavage. Of course, gavage feeding is not new. This method has given excellent total nutrition, for a period of time, to many patients. It has furnished an important part of their nutrition to others. It obviously avoids some of the problems associated with injections. Many of the reports on this topic refer to the use of a "Chemically Defined Elemental Diet." These are special nutritionally complete formulations that contain protein in so-called "elemental" or "predigested" form (protein hydrolysates or synthetic amino acids), and carbohydrate and fat in simple, easily digestible forms. 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.[8]

Although 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) in the

above formula 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 cause varying increases.

Commercial diets of this type are packaged as fluids or as powders for reconstitution. Reconstitution is usually with water. The labels of some preparations state the osmolality or osmolarity of the fluid obtained at standard dilution. However, the labels of many products do not state either their osmolality or osmolarity (or their osmoticity in any way). Often, as stated above, when the term osmolarity *is* used, one cannot discern whether this is simply incorrect terminology, or whether the osmolarity has actually been calculated from the osmolality. With concentrated infant formulas or tube feedings, the osmolarity may be only 80% of the osmolality. As mentioned earlier, the osmoticity (osmolality, etc.) of infant formulas, tube feedings, and total parenteral nutrition solutions are not adequately described either in textbooks or in the literature.

There are other areas of concern. A wide variation in osmolality was found when powdered samples from different containers were reconstituted in the same manner. This difference was found both within and among different lots of the same product. In addition, reconstitution of some powdered enteral formulas using the scoops supplied by the manufacturer gave formulas that had almost twice the osmolality of the same product when reconstituted accurately by weight.

This form of nutrition has been called, somewhat inaccurately, "Enteral Hyperalimentation."[1] It should be distinguished from (a) "Central Parenteral Nutrition" (which has also been called "Hyperalimentation," "Total Parenteral Nutrition" (TPN), and "Parenteral Hyperalimentation"); and from (b) the more recently reported "Peripheral Hyperalimentation." The terminology is in a state of flux due to the recent rapid progress in the forms of metabolic support.

The enteric route for hyperalimentation is frequently 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 gastrointestinal tract are frequently intact and, when challenged with appropriate nutrient fluids, can be effectively used. By using an intact GI tract for proper alimentation, the major problems of sepsis and metabolic derangement which relate to intravenous hyperalimentation are largely obviated, and adequate nutritional support is greatly simplified. Because of this increased safety and ease of administration, the enteric route for hyperalimentation should be used whenever possible.[9]

When ingested in large amounts or concentrated fluids, the osmotic characteristics of certain foods 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 follows:[10]

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 as follows:

	mOsm/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. Thus there is some analogy to the effect of hyperosmotic intravenous infusions.

Hyperosmotic feedings may result in mucosal damage in the GI tract. Rats given hyperosmotic feedings showed transient decrease in disaccharidase activities, and an increase in alkaline phosphatase activities. They also showed morphologic 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 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 delivered to the jejunum through a nasogastric tube.

The body attempts to keep the osmoticity of 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 better tolerated than one of higher osmoticity. As to tolerance, there is a great variation from one individual to another in sensitivity to 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 if administered slowly and if 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 post-operative patients, gastrostomy- and jejunostomy-fed patients, and patients whose GI tracts have not been challenged for an extended period of time. Thus osmoticity should always 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 isoosmotic formulas, feedings of reduced concentration (osmolality less than 400 mOsm/kg) may also be helpful initially if tolerance problems arise in sensitive individuals. Concentration and size of feeding can then be gradually increased 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 mOsm of solute. This requires the obligatory excretion of a volume of urine between 1200 and 1500 mL when the kidney is capable of concentration normally. As elderly individuals often have significant impairment in renal concentration ability, water loss as urine may exceed 2000–2500

mL per day. Such an individual would require 3–4 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 may rapidly 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 readings 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 have been considered to be impractical because of the elaborate apparatus required. However Zenk and Huxtable used a vapor pressure osmometer and state that it has much to recommend it for most of the systems under consideration here.[3] The method usually used is that of freezing point depression, which can be measured quite readily with a fair degree of accuracy (see *Freezing Point Depression*, Chapter 16). It should be noted that the data in Appendix A can be readily converted to vapor pressure lowering if desired.

Semiautomatic, high sensitivity osmometers that measure freezing point depression provide digital readouts or computer printouts of the results expressed in milliosmol units.

The results of investigations by Lund and coworkers[11] indicate that the freezing point of normal, healthy human blood is −0.52° and not −0.56°, as previously assumed.* 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 only rarely 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 isoosmotic; 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 with that of lacrimal fluid, namely, −0.52°.* Ophthalmic solutions with higher freezing points are usually 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.

* See discussion of Reliability of Data in this chapter.

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, giving 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, ie, 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, that figure which 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°). Since the adjustment to isotonicity need not be absolutely exact, approximations may be made. When it is recalled that for many years an 0.85% solution of sodium chloride, rather than the presently employed 0.90% concentration, was widely accepted and proved to be eminently satisfactory as the isotonic equivalent of blood serum, it is apparent that minor deviations are not of great concern. Also, formerly a 1.4% solution of sodium chloride was considered to be isotonic with lacrimal fluid and found to be relatively tolerable when applied to the eye. Nevertheless, adjustments to isotonicity should be as exact as practicable.

As a specific illustration of the manner in which the data in the table may be used, suppose it is required to calculate the quantity of sodium chloride needed to make 100 mL of a 1% solution of calcium disodium edetate isoosmotic with blood serum. Reference to the table indicates that the 1% solution provides for 0.12° of the necessary 0.52° of freezing point depression required of an isoosmotic solution, thus leaving 0.40° to be supplied by the sodium chloride. Again referring to the table, 0.52° is found to be the freezing point depression of a 0.9% solution of sodium chloride and by simple proportion it is calculated that a 0.69% solution will have a freezing point depression of 0.40°. Assuming additivity of the freezing point depressions, a solution of 0.69 g of sodium chloride and 1 g of calcium disodium edetate in sufficient water to make 100 mL will be isoosmotic with blood serum.

Likewise, to render a 1% solution of boric acid isotonic with lacrimal fluid by the addition of sodium chloride, one would proceed with the calculation as follows:

Freezing point depression of lacrimal fluid	0.52°
Freezing point depression of 1% boric acid solution	0.29°
Freezing point depression to be supplied by sodium chloride	0.23°
Freezing point depression of a 0.9% solution of sodium chloride	0.52°

Therefore

$$0.52:0.9 = 0.23:x$$

$$0.52x = 0.207$$

x = 0.4% sodium chloride to be incorporated with 1% boric acid to produce a solution which will be isotonic with lacrimal fluid.

Similarly, should a solution contain more than one ingredient, the sum of the respective freezing points of each ingredient would be determined and the difference between this sum and the required freezing point would represent the freezing point to be supplied by the added substance.

The preceding calculation can be expressed in the form of an equation, as follows:

$$x = \frac{(0.52° - a) \times c}{b}$$

where

- x = g of adjusting solute required for each 100 mL of solution.
- 0.52° = Freezing point depression of blood serum or lacrimal fluid.
- a = Freezing point depression of given ingredients in 100 mL of solution.
- b = Freezing point depression of c g of adjusting substance per 100 mL.
- c = g of adjusting solute per 100 mL, producing a freezing point depression of b.

L Values—In dilute solutions, the expression for freezing-point depression may be written as:

$$\Delta T_f = Lc$$

in which ΔT_f is the freezing-point depression in °C, L is a constant, and c is the molar concentration of the drug. L_{iso} is defined as the specific value of L at a concentration of drug which is isotonic with blood or lacrimal fluid.

For a more complete discussion of the use of L values, the reader is referred to RPS-14, page 1560.

Effect of Solvents—Besides water, certain other solvents are frequently 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 while these solvent components contribute to the freezing-point depression they may or may not have an effect on the "tone" of the tissue to which they are applied, ie, an *isoosmotic* solution may not be *isotonic*. It is apparent that in such cases, the utility of the methods described above or, for that matter, of any other method of evaluating "tonicity" is questionable.

Reliability of Data—While the freezing point of blood was formerly assumed to be −0.56°, later investigators[11] reported that in consequence of ice being disengaged in freezing-point determinations as ordinarily performed the observed freezing point of blood is low; according to them the correct freezing point is −0.52°. The same investigators found the freezing point of a 0.9% solution of sodium chloride to be correspondingly low; the correct freezing point in this case is also −0.52°. Presumably all solutions commonly considered to be isotonic with blood will freeze, when a correction for disengaged ice is applied, at −0.52°. It is apparent, therefore, that there is no need to change the isotonic concentration, if the reference temperature for both blood and the solution under consideration is always the same, and provided that the *method* of determining the freezing point is the same. Also, there appears to be no objection to using freezing-point data for solutions of other than isotonic concentration if the method of determining the freezing point is the same in all cases, since any differences that may be obtained when another method is used (such as that of Lund *et al*[11]), will probably be proportional to concentration.

In a discussion of the significance of freezing point data it is to be noted that there are some discrepancies in the literature concerning freezing points of solutions. An *exact* determination of freezing point is actually a difficult experiment, one which calls for the control of several variables that are commonly neglected, of which disengagement of ice is one. It is not possible at this time to select unequivocal freezing point data for most of the solutions listed in Appendix A included in this chapter. The comprehensive and valuable data of Lund, *et al*[11] referred to above, actually represent in most instances measurements of vapor pressure which have been *calculated* to corresponding freezing point depressions; it would seem to be desirable to have confirmatory evidence based on actual measurements of freezing point, determined more accurately than has generally been the case, before revisions of existing data are made. In the case of boric acid, which enters into the composition of many collyria, there is the further variable that a sterilized solution freezes at a higher temperature than a freshly prepared, unsterilized solution of the same strength; specifically, a freshly prepared solution containing 2.85% of boric acid was found to freeze at the same temperature (−0.82°) as a 3.1% solution which had been sterilized under pressure.

Earlier in this section it was stated that at one time lacrimal fluid was considered to have the same osmotic pressure as a 1.4% solution of sodium chloride, the freezing point of which was found to be, by the usual method of determination, −0.80°. The experiments of Krogh, *et al*[12] have indicated that lacrimal fluid has the same osmotic pressure as blood and that instead of assuming that the freezing point of solutions isotonic with lacrimal fluid is −0.80° it should be the same as that of blood, namely, −0.52°. Accordingly, the procedure for adjusting solutions to isotonicity with lacrimal fluid is qualitatively and quantitatively the same as the procedure for adjusting solutions to isotonicity with blood.

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 is often 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 cell volume produced by the solutions. This method appears to be more sensitive to small differences in tonicity than are methods based on observation of a hemolytic effect. Much useful information concerning the effect of various solutes on erythrocytes has been obtained by this procedure; a summary of many of these data is given in RPS-14, page 1562.

Other Methods of Adjusting Tonicity

Several methods for adjusting tonicity, other than those already described, are used.

Sodium Chloride Equivalent Methods—Sodium chloride equivalent is defined as the weight of sodium chloride that will produce the same osmotic effect as 1 g of the drug which is to be prepared as an isotonic solution. Appendix A lists the

sodium chloride equivalents for many drugs; some of the equivalents vary with the concentration of the drug (in certain cases because of changes of interionic attraction at different concentrations) but in every case the equivalent is for 1 g of drug. As an example of the use of these data, if the sodium chloride equivalent of boric acid is 0.5 at 1% concentration, this is interpreted to mean that 1 g of boric acid in solution will produce the same freezing-point depression as 0.5 g of sodium chloride, or that a 1% boric acid solution is equivalent in its colligative properties to a 0.5% solution of sodium chloride. From Appendix A it is found that for a 1.9% boric acid solution (ie, at isotonicity) the sodium chloride equivalent is 0.47, corresponding to a 0.9% sodium chloride solution (1.9 × 0.47).

Examples illustrating use of the sodium chloride equivalent method to adjust collyria to isotonicity follow. The same type of calculation may be used for other solutions that are to be made isotonic.

Example 1:

Homatropine Hydrobromide	1%
to make collyr isotonic	60 mL

0.6 g of homatropine hydrobromide is required. 1 g or 1% of the drug is equivalent in osmotic effect to 0.17 g or 0.17% of sodium chloride.

$$0.17 \times 0.6 = 0.102 \text{ g (sodium chloride)}$$

60 mL of an isotonic sodium chloride solution contains	0.54 g sodium chloride
0.6 g homatropine hydrobromide is equivalent to	0.102 g sodium chloride
	0.438 g sodium chloride

Therefore, 0.438 g of sodium chloride must be added to make 60 mL of a 1% homatropine hydrobromide solution isotonic with tear fluid. The same calculations may be made using percentage calculations. 1% of homatropine hydrobromide corresponds to 0.17% sodium chloride in colligative properties.

Thus, 0.9% minus 0.17% = 0.73% must be added, 0.73% of 60 mL = 0.438 g of sodium chloride to be added.

If boric acid is to be used as the adjusting substance the calculations have to be carried one step further. There is no "boric acid equivalent," but the sodium chloride equivalent of boric acid at 1% concentration is 0.5, meaning that 1 g of boric acid (or 1%) corresponds in colligative properties to 0.5 g sodium chloride (or 0.5%). Using the result obtained above, which was 0.438 g of sodium chloride to be added, it now follows that the sodium chloride equivalent of boric acid must be divided into the amount of sodium chloride or expressed as an equation:

$$1 \text{ g boric acid: } 0.5 \text{ g sodium chloride} = x \text{ g: } 0.438 \text{ g}$$
$$x = 0.876 \text{ g boric acid to be added}$$

For a prescription containing more than one active drug, the calculations for sodium chloride are carried out separately, the obtained quantities are added, and then the total is deducted from the 0.9% amount.

Example 2:

Epinephrine Hydrochloride	0.5%
Zinc Sulfate	0.3%
Sterile Preserved Water qs, to make	30 mL

M Ft Collyr isotonic SA

Sodium chloride equivalent of epinephrine HCl is 0.29
Sodium chloride equivalent of zinc sulfate is 0.15

150 mg epinephrine hydrochloride	~43.5 mg sodium chloride
90 mg zinc sulfate	~13.5 mg sodium chloride
Total ingredients are equivalent to	~57 mg sodium chloride

0.9% of 30 mL	270 mg sodium chloride
	57 mg
	213 mg

213 mg of sodium chloride must be added to make this solution isotonic with tear fluid. Since boric acid is the adjusting substance of choice for the solution 426 mg should be used (0.5 divided into 213 mg).

Isotonic Solution V-Values—These are the volumes of sterile water to be added to a specified weight of drug (often 0.3 g but sometimes 1 g) to prepare an isotonic solution. Appendix B gives such values for some commonly used drugs. The reason for providing data for 0.3 g drug is only that of convenience in preparing 30 mL (1 fl oz) of solution, as is often prescribed; if values for 100 mL of final solution are desired, the data in Appendix B should be multiplied by 100/30. The basic principle underlying the use of these values is to prepare an isotonic solution of the prescribed drug in sterile water and then dilute this solution to the required final volume with a suitable isotonic vehicle. For example, if 0.3 g of a drug is specified to be used (as in preparing 30 mL of 1% solution of the drug), it is first dissolved in the volume of sterile water stated in Appendix B and then diluted to 30 mL with a suitable isotonic vehicle. Isotonic solution values can be used, of course, for calculating tonicity-adjusting data for concentrations of drugs other than 1% and for volumes other than 30 mL. How this is done is illustrated in the following examples.

Example 1:

A prescription calls for:

Atropine Sulfate	0.3 g
Sterile Preserved Water qs	60 mL

M Ft Collyr isotonic and buffered SA
Sig: For Office Use.

This order is for a 0.5% solution of atropine sulfate. According to Appendix B, 0.3 g of atropine sulfate dissolved in 4.3 mL of sterile preserved water will produce a 1% isotonic solution when diluted to 30 mL with an isotonic vehicle. For 30 mL of 0.5% solution, half the quantities of atropine sulfate and sterile preserved water would be used, but for 60 mL of 0.5% solution the same quantities as for 30 mL of 1% solution are required.

Therefore, to fill this prescription order, 0.3 g of atropine sulfate should be dissolved in 4.3 mL of sterile preserved water and diluted with isotonic preserved Sørensen's pH 6.8 phosphate buffer to 60 mL.

* * * *

For more than one active ingredient in solution the quantity of water to be used is calculated for each ingredient separately. The values thus obtained are added, the total amount of sterile preserved water is then used to dissolve the active ingredients, and finally sufficient isotonic, buffered preserved solution (diluting solution) is used to make the required volume.

Example 2:

A prescription calls for:

Epinephrine Hydrochloride	0.5%
Zinc Sulfate	0.3%
Sterile Preserved Water qs to make	30 mL

M Ft Collyr isotonic

In this example the active ingredients are given in percentage. The ideal vehicle is 1.9% boric acid solution. Reference to the table for isotonic solution values shows the following:

Epinephrine hydrochloride 0.3 g (1%) will make 9.7 mL of an isotonic solution when dissolved in sterile preserved water. Zinc sulfate 0.3 g will make 5 mL of an isotonic solution with sterile water.

Therefore, the quantities called for in this prescription will make 4.85 mL and 1.5 mL of isotonic solutions, respectively. Dissolve the salts in sufficient sterile preserved water to make 6.35 mL and add sufficient 1.9% preserved boric acid solution to make 30 mL. The resulting solution is isotonic.

Since it is practically impossible to measure the required volumes accurately, it is feasible, in this instance, to use 6.35 mL of sterile preserved water as the total solvent for these two drugs. Graduated pipets, previously sterilized, are necessary for this work.

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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%		Isoosmotic 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											
Amobarbital sodium			0.25	0.143[c]			0.25				1.68	0.54	0.52	0	5.3
d-Amphetamine HCl											3.6	0.25	0.52	0	9.3
Amphetamine phosphate			0.34	0.20			0.27	0.47			2.64			98	5.7
Amphetamine sulfate			0.22	0.129[c]			0.21	0.36			3.47	0.26	0.52	0	4.5
Amprotropine phosphate											4.23	0.21	0.52	0	5.9
Amylcaine HCl			0.22				0.19				5.90			0	4.2
Anileridine HCl	0.19	0.052	0.19	0.104	0.19	0.212	0.18	0.316	0.18	0.509	4.98	0.18		100	5.6
Antazoline phosphate											5.13	0.18	0.52	12	2.6
Antimony potassium tartrate			0.18				0.13		0.10		6.05			90	4.0
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															
Atropine sulfate			0.13	0.075			0.11	0.19	0.11	0.32	6.52			0	5.2
Bacitracin			0.05	0.03			0.04	0.07	0.04	0.12	8.85	0.10	0.52	0	5.0
Barbital sodium			0.30	0.171[c]			0.29	0.50							
Benzalkonium chloride			0.16				0.14		0.13		3.12	0.29	0.52	0	9.8
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]											
Brompheniramine maleate	0.10	0.026	0.09	0.050	0.08	0.084					1.9	0.47	0.52	100	4.6
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

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration[e]				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
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
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											
Cephaloridine	0.09	0.023	0.07	0.041	0.06	0.074	0.06	0.106	0.05	0.145					
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

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration[e]				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
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									
Diperodon HCl	0.15	0.045	0.14	0.079	0.13	0.141					2.16	0.42	0.52	100	7.6
Diphenhydramine HCl				0.161[c]											
Diphenidol HCl	0.16	0.045	0.16	0.09	0.16	0.180					5.70			88*	5.5
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			
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 di-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									

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration[e]				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
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
Lincomycin 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
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									

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration[c]				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
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											3.67			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								
Phenylephrine tartrate											3.0	0.30		0	4.5
Phenylethyl alcohol	0.25	0.070	0.25	0.141	0.25	0.283					5.90			58*	5.4
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[c]			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
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												
Pralidoxime chloride	0.32	0.092	0.32	0.183	0.32	0.364					2.11	0.43		0	6.6
Prilocaine HCl	0.22	0.062	0.22	0.125	0.22	0.250	0.22	0.375			2.87	0.32	0.52	0	4.6
Procainamide HCl			0.22	0.13			0.19	0.33	0.17	0.49	4.18	0.22	0.52	45	4.6
Procaine HCl			0.21	0.122[c]			0.19	0.33	0.18						
Prochlorperazine edisylate	0.08	0.020	0.06	0.033	0.05	0.048	0.03	0.056	0.02	0.065	5.05	0.18	0.52	91	5.6
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

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration[e]				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
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
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					

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration[e]				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
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 ($\frac{1}{2}$ 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 diHCl	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 and co-workers,[13–16] and Sapp *et al.*[18]
[b] Adapted from Lund, *et al.*[11]
[c] Adapted from BPC.[19]
[d] Obtained from several sources.
[e] *E:* sodium chloride equivalents; *D:* freezing-point depression, °C; *H:* hemolysis, %, at the concentration which is isoosmotic 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[17–19]; †: pH determined after addition of blood.

Appendix B—Volumes of Water for Isotonicity[20,a]

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	Apomorphine hydrochloride	4.7	Bismuth potassium tartrate	3.0
Ammonium chloride	37.3	Ascorbic acid	6.0	Boric acid	16.7
Amobarbital sodium	8.3	Atropine methylbromide	4.7	Butacaine sulfate	6.7
Amphetamine phosphate	11.3	Atropine sulfate	4.3	Caffeine and sodium benzoate	8.7
Amphetamine sulfate	7.3	Bacitracin	1.7	Calcium chloride	17.0
Antipyrine	5.7	Barbital sodium	10.0	Calcium chloride (6 H_2O)	11.7

Appendix B—Continued

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
Chlorobutanol (hydrated)	8.0	Pentobarbital sodium	8.3	Sodium biphosphate	13.3
Chlortetracycline sulfate	4.3	Phenobarbital sodium	8.0	Sodium bisulfite	20.3
Cocaine hydrochloride	5.3	Physostigmine salicylate	5.3	Sodium borate	14.0
Cupric sulfate	6.0	Pilocarpine hydrochloride	8.0	Sodium iodide	13.0
Dextrose, anhydrous	6.0	Pilocarpine nitrate	7.7	Sodium metabisulfite	22.3
Dibucaine hydrochloride	4.3	Piperocaine hydrochloride	7.0	Sodium nitrate	22.7
Dihydrostreptomycin sulfate	2.0	Polymyxin B sulfate	3.0	Sodium phosphate	9.7
Ephedrine hydrochloride	10.0	Potassium chloride	25.3	Sodium propionate	20.3
Ephedrine sulfate	7.7	Potassium nitrate	18.7	Sodium sulfite, exsiccated	21.7
Epinephrine bitartrate	6.0	Potassium phosphate, monobasic	14.7	Sodium thiosulfate	10.3
Epinephrine hydrochloride	9.7			Streptomycin sulfate	2.3
Ethylmorphine hydrochloride	5.3	Procainamide hydrochloride	7.3	Sulfacetamide sodium	7.7
Fluorescein sodium	10.3	Procaine hydrochloride	7.0	Sulfadiazine sodium	8.0
Glycerin	11.7	Scopolamine hydrobromide	4.0	Sulfamerazine sodium	7.7
Holocaine hydrochloride	6.7	Scopolamine methylnitrate	5.3	Sulfapyridine sodium	7.7
Homatropine hydrobromide	5.7	Secobarbital sodium	8.0	Sulfathiazole sodium	7.3
Homatropine methylbromide	6.3	Silver nitrate	11.0	Tetracaine hydrochloride	6.0
Hyoscyamine sulfate	4.7	Silver protein, mild	5.7	Tetracycline hydrochloride	4.7
Neomycin sulfate	3.7	Sodium acetate	15.3	Viomycin sulfate	2.7
Oxytetracycline hydrochloride	4.3	Sodium bicarbonate	21.7	Zinc chloride	20.3
Penicillin G, potassium	6.0	Sodium biphosphate, anhydrous	15.3	Zinc sulfate	5.0
Penicillin G, sodium	6.0				

[a] Table of "Isotonic Solution Values" showing volumes in mL of solution that can be prepared by dissolving 300 mg of the specified drug in sterile water. 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 isoosmotic with 0.9% sodium chloride solution but may not be isotonic with blood (see Appendix A for hemolysis data).

CHAPTER 82

Stability of Pharmaceutical Products

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The use of kinetic and predictive studies for establishing credible expiration dates for pharmaceutical products is now accepted worldwide. However, prior to 1950 only qualitative or semiquantitative methods and procedures were used in pharmaceutical studies. As these rule-of-thumb methods are deficient; they have been replaced by rigorous, scientifically designed studies using reliable, meaningful, and specific stability-indicating assays, appropriate statistical concepts, and a computer to analyze the resulting data. In this way the maximum amount of valid information is obtained to establish a reliable, defendable expiration date for each formulation.

Stability information is ubiquitous. It may be in a well-planned rigorous kinetic study, in an obscure journal footnote, in a package insert, or label copy, or in a monograph in a book such as *The Merck Index* or *Physicians' Desk Reference.* Various journals periodically publish digests of compatibility studies. A comprehensive treatment of all aspects of pharmaceutical product stability has been published by Lintner.[1]

The main purpose of a quality assurance program is to devise and implement systems and procedures that provide a high probability that each dose or package of a pharmaceutical product will have homogeneous characteristics and properties (within reasonably acceptable limits) to insure both clinical safety and efficacy of the formulation. A broad, well-designed stability testing plan is an essential and pertinent expansion of the quality assurance program. The assigned expiration date is a direct application and interpretation of the knowledge gained from the stability study.

Stability of a pharmaceutical product may be defined as the capability of a particular formulation, in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic, and toxicological specifications. Assurances that the packaged product will be stable for its anticipated shelf life must come from an accumulation of valid data on the drug in its commercial package. These stability data involve selected parameters which, taken together, form the stability profile.

Stability of a drug can also be defined as the time from the date of manufacture and packaging of the formulation until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously. Although there are exceptions, 90% of labeled potency is generally recognized as the minimum acceptable potency level. Expiration dating is then defined as the time in which the preparation will remain stable when stored under recommended conditions.

An expiration date, which is expressed traditionally in terms of month and year, denotes the last day of the month. The expiration date should appear on the immediate container and the outer retail package. However, when single-dose containers are packaged in individual cartons, the expiration date may be placed on the individual carton instead of the immediate product container. If a dry product is to be reconstituted at the time of dispensing, expiration dates are assigned to both the dry mixture and the reconstituted product. Tamper resistant packaging is to be used where applicable.

A second quality assurance goal is drug or clinical safety and it, too, is closely related to pharmaceutical stability. Drug or clinical safety (ie, the nonoccurrence of harm), however, cannot be studied by itself. Rather, it is a negative concept which cannot be proven and must be expressed only in terms of the nonoccurrence of some harmful event. The latter probability, in turn, can be estimated only when the probability occurrence of the harmful event is known.

One type of time-related harmful event is a decrease in therapeutic activity of the preparation to below some arbitrary labeled content. A second type of harmful event is the appearance of a toxic substance, formed as a degradation product upon storage of the formulation. The number of published cases reflecting this second type is fortunately quite small. However, it is possible, though remote, for both types of harmful events to occur simultaneously within the same pharmaceutical product. Thus, the use of stability studies with the resulting application of expiration dating to pharmaceuticals is an attempt to predict the approximate time at which the probability of occurrence of a harmful event may reach an intolerable level. This estimate is subject to the usual Type 1 or alpha error (setting the expiration too early so that the product will be destroyed or recalled from the market at an appreciably earlier time than is actually necessary) and the Type 2 or beta error (setting the date too late so that the harmful event occurs in an unacceptably large proportion of cases). Thus, it is obligatory that the manufacturer clearly and succinctly define the method for determining the degree of change in a formulation and the statistical approach to be used in making the shelf-life prediction. An intrinsic part of the statistical methodology must be the statements of value for the two types of error. For the safety of the patient a Type 1 error can be accepted, but not a Type 2 error.

Requirements

Stability study requirements and expiration dating are covered in the Good Manufacturing Practices (GMPs), and the USP.

Good Manufacturing Practices—The GMPs[2] state that there shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used to determine appropriate storage conditions and expiration dating. The latter is to assure that the pharmaceutical product meets applicable standards of identity, strength, quality, and purity at time of use. These regulations, which apply to both human and veterinary drugs, are updated perodically in light of current knowledge and technology.

Compendiums—The compendiums also contain extensive stability and expiration dating information. Included are a discussion of stability considerations in dispensing practices and the responsibilities of both the pharmaceutical manufacturer and the dispensing pharmacist. It is now required that product labeling of official articles provide recommended storage conditions and an expiration date assigned to the specific formulation and package. Official storage conditions are defined as follows: "Cold" is any temperature not exceeding 8°, and "refrigerator" is a cold place where the temperature is maintained thermostatically between 2° and 8°; a "freezer" is a cold place maintained between −20° and −10°. "Cool" is defined as any temperature between 8° and 15°, and "room temperature" is that temperature prevailing in a working area. "Controlled room temperature" is that temperature maintained thermostatically between 15° and 30°. "Warm" is any temperature between 30° and

40°, while "excessive heat" is any heat above 40°. Should freezing subject a product to a loss of potency or to destructive alteration of the dosage form, the container label should bear appropriate instructions to protect the product from freezing. Bulk packages are exempt from storage requirements if the products are intended for manufacture or repacking for dispensing or distribution. Where no specific storage instructions are given in a monograph, it is understood that the product's storage conditions shall include protection from moisture, freezing, and excessive heat.

Product Stability

Many factors affect the stability of a pharmaceutical product, including the stability of the active ingredient(s), the potential interaction between active and inactive ingredients, the manufacturing process, the dosage form, the container-liner-closure system, the environmental conditions encountered during shipment, storage, handling, and length of time between manufacture and usage.

Classically, pharmaceutical product stability evaluations have been separated into studies of chemical, including biochemical, and physical stability of formulations. Realistically, there is no absolute division between these two arbitrary divisions. Physical factors—such as heat, light, and moisture—may initiate or accelerate chemical reactions, while every time a measurement is made on a chemical compound, physical dimensions are included in the study.

In this treatment, physical and chemical stability will be discussed along with those dosage form properties which can be measured and are useful in predicting shelf life. The effect of various physical and chemical phenomena of pharmaceuticals will also be treated.

Knowledge of the physical stability of a formulation is very important for three primary reasons. First, a pharmaceutical product must appear fresh, elegant, and professional, so long as it remains on the shelf. Any changes in physical appearance such as color fading or haziness can cause the patient or consumer to lose confidence in the product. Second, since some products are dispensed in multiple-dose containers, uniformity of dose content of the active ingredient over time must be assured. A cloudy solution or a broken emulsion can lead to a nonuniform dosage pattern. Third, the active ingredient must be available to the patient throughout the expected shelf life of the preparation. A breakdown in the physical system can lead to nonavailability of the medicament to the patient.

The chemical causes of drug deterioration have been classified into incompatibility, oxidation, reduction, hydrolysis, racemization, and others. In the latter category decarboxylation, deterioration of hydrogen peroxide and hypochlorites, and the formation of precipitates have been included.

Galenical Dosage Forms

As the various galenical dosage forms present unique stability problems, they will be discussed separately in the following section.

Suspensions—A stable suspension can be homogeneously redispersed with moderate shaking and can be easily poured throughout its shelf life, with neither the particle-size distribution, the crystal form, nor the physiological availability of the suspended active ingredient changing appreciably with time.

Most stable pharmaceutical suspensions are flocculated; that is, the suspended particles are physically bonded together to form a loose, semirigid structure. The particles are said to uphold each other while exerting no significant force on the liquid. Sedimented particles of a flocculated suspension can be easily redispersed at any time with only moderate shaking.

In nonflocculated suspensions, the particles remain as individuals unaffected by neighboring particles and are affected only by the suspension vehicle. These particles, which are smaller and lighter, settle slowly, but once they have settled, often form a rock-hard, difficult-to-disperse sediment. Nonflocculated suspensions can be made acceptable by decreasing the particle size of the suspended material or by increasing the density and viscosity of the vehicle.

When studying the stability of a suspension, first determine with a differential manometer if the suspension is flocculated. If the suspension is flocculated, the liquid will travel the same distance in the two side arms. With nonflocculated suspensions, the hydrostatic pressures in the two arms are unequal; hence the liquids will be at different levels.

The history of settling of the particles of a suspension may be followed by a Brookfield viscometer fitted with a Helipath attachment. This instrument consists of a rotating T-bar spindle which descends slowly into the suspension as it rotates. The dial reading on the viscometer is a measure of the resistance that the spindle encounters at various levels of the sedimented suspension. This test must be run only on fresh, undisturbed samples (see Chapter 22).

An electronic particle counter and sizer, such as a Coulter counter, or a microscope may be used to determine changes in particle-size distribution. Crystal form alterations can be detected by x-ray diffraction or by a microscopic examination.

All suspensions should be subjected to cycling temperature conditions to determine the tendency for crystal growth to occur within a suspension. Shipping tests, ie, transporting bottles across the country by rail or truck, are also used advantageously to study the stability of suspensions.

Emulsions—A stable emulsion can be homogeneously redispersed to its original state with moderate shaking and can be poured at any stage of its shelf life. Although most of the important pharmaceutical emulsions are of the O/W type, many stability test methods can be applied to either an O/W or a W/O emulsion.

Two simple tests are used to screen emulsion formulations. First, the stability of an emulsion can be determined by heating it to 50–70° and its gross physical stability observed visually or checked by turbidimetric measurements. Usually the emulsion that is the most stable to heat is the one most stable at room temperature. However, this may not always be true because an emulsion at 60° may not be the same as it is at room temperature. Second, the stability of the emulsion can be estimated by the "coalescence time" test. Although this is only a rough quantitative test, it is useful for detecting gross differences in emulsion stability at room temperature.

Emulsions should also be subjected to refrigeration temperatures. An emulsion stable at room temperature has been found to be unstable at 4°. It was reasoned that an oil-soluble emulsifier precipitated at the lower temperature and disrupted the system. An emulsion chilled to the extent that the aqueous base crystallizes is irreversibly damaged.

The ultracentrifuge is also used to determine emulsion stability. When the amount of separated oil is plotted against the time of centrifugation, a plateau curve is obtained. A linear graph results when the oil flotation (creaming) rate is plotted vs the square of the number of centrifuge revolutions per minute. The flotation rate is represented by the slope of the line resulting when the log distance of emulsion-water boundary from the rotor center is plotted against time for each resolution per minute.

For stability studies, two batches of an emulsion should be made at one time on production size equipment. One should be a bench-size lot and the other a larger, preferably production-size, batch. Different types of homogenizers produce different results and different sizes of the same kind of homogenizer can yield emulsions with different characteristics.

Solutions—A stable solution retains its original clarity, color, and odor throughout its shelf life. Retention of clarity of a solution is a main concern of a physical stability program. As visual observation alone under ordinary light is a poor test of clarity, a microscope light should be projected through a diaphragm into the solution. Undissolved particles will scatter the light and the solution will appear hazy. While the Coulter counter can also be used, light-scattering instruments are the most sensitive means of following solution clarity.

Solutions should remain clear over a relatively wide temperature range such as 4–47°. At the lower range an ingredient may precipitate due to its lower solubility at that temperature while at the higher temperature homogeneity may be destroyed by the flaking of particles from the glass containers or rubber closures. Thus, solutions should be subjected to cycling temperature conditions.

The stability program for solutions should also include the study of pH changes, especially when the active ingredients are soluble salts of insoluble acids or bases. Among other tests are observations for changes in odor, appearance, color, taste, light-stability, redispersibility, suspendibility, pourability, viscosity, isotonicity, gas evolution, microbial stability, specific gravity, surface tension, and pyrogen content in the case of parenteral products.

When solutions are filtered, the filter media may absorb some of the ingredients from the solution. Thus, the same type of filter should be used for preparing the stability samples as will be used to prepare the production-size batches.

For dry-packaged formulations intended to be reconstituted prior to use, the visual appearance should be observed on both the original dry material and on the reconstituted preparation. The color and odor of the cake, the color and odor of the solution, the moisture content of the cake, and the rate of reconstitution should be followed as a part of its stability profile.

Tablets—Stable tablets retain their original size, shape, weight, and color under normal handling and storage conditions throughout their shelf life. In addition, the *in vitro* availability of the active ingredients should not change appreciably with time.

Excessive powder or solid particles at the bottom of the container, cracks or chips on the face of a tablet, or appearance of crystals on the surface of tablets or on container walls are indications of physical instability of uncoated tablets. Hence, the effect of mild, uniform, and reproducible shaking and tumbling of tablets should be studied. After visual observation of the tablets for chips, cracks, and splits, the intact tablets are sorted and weighed to determine the amount of material worn away by abrasion. The results of these tests are comparative rather than absolute and should be correlated with actual stress experience. Packaged tablets should also be subjected to cross-country shipping tests as well as to various "drop tests."

Tablet hardness (or resistance to crushing or fracturing) can be followed by the commercially available hardness testers. As results will vary with the specific make of the test apparatus used, direct comparison of results obtained on different instruments cannot be made. Thus, the same instrument should be used consistently throughout a particular study.

Color stability of tablets can be followed by an appropriate colorimeter or reflectometer with heat, sunlight, and intense artificial light employed to accelerate the color deterioration. Caution must be used in interpreting the elevated temperature data as the system at that temperature may be different from that at a lower temperature. It is not always proper to assume that the same changes will occur at elevated temperatures as will happen later at room temperature. Evidence of instability of coated tablets is also indicated by cracks, mottling or tackiness of the coating.

For the more insoluble tableted active ingredients, the results of dissolution tests are more meaningful than disintegration results for making availability predictions. Dissolution rate tests should be run in an appropriate medium such as artificial gastric and/or intestinal juice at 37° (see Chapter 35). When no significant change (such as a change in the polymorphic form of the crystal) has occurred, an unaltered dissolution rate profile of a tablet formulation usually indicates constant *in vivo* availability.

Disintegration tests may be used to detect periodic gross changes in the physical characteristics of a tablet, but these tests must be correlated with the dissolution rate study of a particular tableted product. When there is no such correlation, *in vivo* tests must be run. The release pattern of sustained-release formulations should be determined periodically during the stability test period.

Uniformity of weight, odor, texture, drug and moisture contents, and humidity effect are also studied during a tablet stability test.

Gelatin Capsules—When stored under adverse conditions, capsule shells may soften and stick together or harden and crack under slight pressure. They should be protected from sources of microbial contamination. The shell of soft gelatin capsules should contain a preservative to prevent growth of fungi. Encapsulated products, like all other dosage forms, must be properly packaged.

Ointments—Ointments have been defined as high-viscosity suspensions of active ingredients in a nonreacting vehicle. A stable ointment is one which retains its homogeneity throughout its shelf-life period. The main stability problems seen in ointments are "bleeding" and changes in consistency due to aging or changes in temperature. When fluid components such as mineral oil separate at the top of an ointment, the phenomenon is known as "bleeding" and can be observed visually. Unfortunately, as there is no known way to accelerate this event, the tendency to "bleed" cannot be predicted.

An ointment which is too soft is messy to use while one which is very stiff is difficult to extrude and apply. Hence, it is important to be able to define quantitatively an ointment's consistency. This may be done with a penetrometer, an apparatus which allows a pointed weight to penetrate into the sample under a measurable force. The depth of the penetration is a measure of the consistency of an ointment. Consistency can also be measured by the Helipath attachment to a high viscosity viscometer or by a Burrell Severs rheometer. In the latter instrument the ointment is loaded into a cylinder and extruded with a measured force. The amount extruded is a measure of the consistency of the ointment.

Ointments have a considerable degree of structure which requires a minimum of 48 hours to develop after preparation. As rheological data on a freshly made ointment may be erroneous, such tests should be performed only after the ointment has achieved equilibrium.

Slight changes in temperature (1 or 2°) can greatly affect an ointment's consistency; hence rheological studies on ointments must be performed only at constant and controlled temperatures.

Among the other tests performed during the stability study of an ointment are a check of visual appearance, color, odor, viscosity, softening range, consistency, homogeneity, particle-size distribution, and sterility.

Undissolved components of an ointment may change in crystal form or in size with time. Microscopic examination or an X-ray diffraction measurement may be used to monitor these parameters.

In some instances it is necessary to use an ointment base that is less than ideal in order to achieve the stability required. For example, drugs that hydrolyze rapidly are more stable in a hydrocarbon base than in a base containing water, even though they may be more effective in the latter.

Incompatibility

Obvious sources of pharmaceutical instability include the incompatibility of various ingredients within a formulation. Numerous examples are described in other sections of this book and the literature is replete with illustrations. Thus the subject need not be treated in detail here.

While undesirable reactions between two or more drugs are said to result in a "physical," "chemical," or "therapeutic" incompatibility, physical incompatibility is somewhat of a misnomer. It has been defined as a physical or chemical interaction between two or more ingredients which leads to a visible recognizable change. The latter may be in the form of a gross precipitate, haze, or color change.

On the other hand, a chemical incompatibility is classified as a reaction in which a visible change does not occur. Since there is no visible evidence of deterioration, this type of incompatibility requires trained, knowledgeable personnel to recognize it, should it occur.

A therapeutic incompatibility has been defined as an undesirable pharmacological interaction between two or more ingredients which leads to (1) potentiation of the therapeutic effects of the ingredients, (2) destruction of the effectiveness of one or more of the ingredients, or (3) occurrence of a toxic manifestation within the patient.

Oxidation-Reduction

Oxidation is a prime cause of product instability and often, but not always, the addition of oxygen or the removal of hydrogen is involved. When molecular oxygen is involved, the reaction is known as autooxidation because it occurs spontaneously, though slowly, at room temperature.

Oxidation, or the loss of electrons from an atom, frequently involves free radicals and subsequent chain reactions. Only a very small amount of oxygen is required to initiate a chain reaction. In practice, it is easy to remove most of the oxygen from a container, but very difficult to remove all. Hence, nitrogen and carbon dioxide are frequently used to displace the headspace air in pharmaceutical containers to help minimize deterioration by oxidation.

As an oxidation reaction is complicated, it is difficult to perform a kinetic study on oxidative processes within a general stability program. The redox potential, which is constant and relatively easy to determine, can, however, provide valuable predictive information. In many oxidative reactions, the rate is proportional to the concentration of the oxidizing species but may be independent of the concentration of the oxygen present. The rate is influenced by temperature, radiation and the presence of a catalyst. An increase in temperature leads to an acceleration in the rate of oxidation. If the storage temperature of a preparation can be reduced to 0–5°, it can usually be assumed that the rate of oxidation will be at least halved.

Trace amounts of heavy metals such as cupric, chromic, ferrous, and ferric ions catalyze oxidation reactions. As little as 0.2 mg of copper ion/liter considerably reduces the stability of penicillin. Similar examples include the deterioration of epinephrine, phenylephrine, lincomycin, isoprenaline, and procaine hydrochloride. Adding chelating agents to water which is free of heavy metals and working in special manufacturing equipment (eg, glass) are some means used to reduce the influence of heavy metals on a formulation. Parenteral formulations should not come in contact with heavy metal ions during their manufacture, packaging, or storage.

Hydronium and hydroxyl ions catalyze oxidative reactions. The rate of decomposition for epinephrine, for example, is more rapid in a neutral or alkaline solution with maximum stability (minimum oxidative decomposition) at pH 3.4. There is a pH range for maximum stability for any antibiotic and vitamin preparation which can usually be achieved by adding an acid, alkali or buffer.

Oxidation may be inhibited by the use of antioxidants, called negative catalysts. They are very effective in stabilizing pharmaceutical products undergoing a free-radical-mediated chain reaction. These substances, which are easily oxidizable, act by possessing lower oxidation potentials than the active ingredient. Thus they undergo preferential degradation or act as chain inhibitors of free radicals by providing an electron and receiving the excess energy possessed by the activated molecule.

The ideal antioxidant should be stable and effective over a wide pH range, soluble in its oxidized form, colorless, nontoxic, nonvolatile, nonirritating, effective in low concentrations, thermostable, and compatible with the container-closure system and formulation ingredients.

The commonly used antioxidants for aqueous systems include sodium sulfite, sodium metabisulfite, sodium bisulfite, sodium thiosulfate, and ascorbic acid. For oil systems, ascorbyl palmitate, hydroquinone, propyl gallate, nordihydroguaiaretic acid, butylated hydroxytoluene, butylated hydroxyanisole, and alpha tocopherol are employed.

Synergists, which increase the activity of antioxidants, are generally organic compounds that complex small amounts of heavy metal ions (see Chapter 14). These include the ethylenediamine tetraacetic acid (EDTA) derivatives, dihydroethylglycine, and citric, tartaric, gluconic, and saccharic acids. EDTA has been used to stabilize ascorbic acid, oxytetracycline, penicillin, epinephrine, and prednisolone.

Reduction reactions are much less common than oxidative processes in pharmaceutical practice. Examples include the reduction of gold, silver, and mercury salts by light to form the corresponding free metal.

Hydrolysis

Drugs containing an ester or amide linkage are prone to hydrolysis. Some examples include cocaine, physostigmine, procaine, tetracaine, thiamine, and benzylpenicillin.

The rate of hydrolysis depends on the temperature and the pH of the solution. A much quoted rule-of-thumb is that for each 10° rise in storage temperature, the rate of reaction doubles or triples. As this is an empiricism, it is not always applicable.

When hydrolysis occurs, the concentration of the active ingredient decreases while the concentration of the decomposition products increases. The effect of this change on the rate of the reaction depends on the order of the reaction. With zero-order reactions the rate of decomposition is independent of concentration of the ingredient. Although weak solutions decompose at the same absolute rate as stronger ones, the weaker the solution, the greater the proportion of active ingredient destroyed in a given time, ie, the percentage of decomposition is greater in weaker solutions. Increasing the concentration of an active ingredient which is hydrolyzing by zero-order kinetics will slow the percentage decomposition.

With first-order reactions, which occur frequently in the hydrolysis of drugs, the rate of change is directly proportional to the concentration of the reactive substance. Thus changes in the concentration of the active ingredient have no influence on the percentage decomposition.

As many hydrolytic reactions are catalyzed by both hydronium and hydroxyl ions, pH is an important factor in determining the rate of a reaction. The pH range of minimum decomposition (or maximum stability) depends on the ion having the greatest effect on the reaction. If the minimum occurs at about pH 7, the two ions are of equal effect. A shift of the minimum toward the acid side indicates that the hydroxyl ion has the stronger catalytic effect and vice-versa in

the case of a shift toward the alkaline side. In general, hydroxyl ions have the stronger effect. Thus, the minimum is often found between pH 3 and 4.

Sometimes it is necessary to compromise between the optimum pH for stability and that for pharmacologic activity. For example, several local anesthetics are most stable at a distinctly acid pH, whereas for maximum activity they should be neutral or slightly alkaline.

Small amounts of acids, alkalies, or buffers are used to adjust the pH of a formulation. Buffers are used when small changes in pH are likely to cause major degradation of the active ingredient.

Obviously, the amount of water present can have profound effect on the rate of a hydrolysis reaction. When the reaction takes place fairly rapidly in water, other solvents can sometimes be substituted. For example, barbiturates are much more stable at room temperature in propylene glycol-water than in water alone.

Modification of chemical structure may be used to retard hydrolysis. In general, as it is only the fraction of the drug in solution that hydrolyzes, a compound may be stabilized by reducing its solubility. This can be done by adding various substituents to the alkyl or acyl chain of aliphatic or aromatic esters or to the ring of an aromatic ester. In some cases less-soluble salts or esters of the parent compound have been found to aid product stability. Steric and polar complexation have also been employed to alter the rate of hydrolysis. Caffeine complexes with local anesthetics such as benzocaine, procaine, and tetracaine to reduce their rate of hydrolysis and thus promotes stability.

Surfactants may also be used to stabilize drugs. For example, the half-life of benzocaine was increased 18 times by the addition of sodium lauryl sulfate.

Decarboxylation

Pyrolytic solid-state degradation through decarboxylation is not usually encountered in pharmacy as relatively high heats of activation (25 to 30 kcal) are required for the reaction. However, solid *p*-aminosalicylic acid undergoes pyrolytic degradation to *m*-aminophenol and carbon dioxide. The reaction, which follows first-order kinetics, is highly pH-dependent and is catalyzed by hydronium ions. The decarboxylation of *p*-aminobenzoic acid occurs only at extremely low pH values and at high temperatures.

Racemization

Racemization or the action or process of changing from an optically active compound into a racemic compound or an optically inactive mixture of corresponding dextro (*d*-) and levo (*l*-) forms is a major factor in pharmaceutical stability. Frequently, the *l*-form is more pharmacologically active than the *d*-form. For example, *l*-epinephrine is 15–20 times more active than its *d*-counterpart, while the activity of the racemic mixture is just over half that of the *l*-form. Current nomenclature practice uses (+) for *d*- and (−) for *l*-, therefore, *l*-ephinephrine would be named (−)-epinephrine, etc.

In general, racemization follows first-order kinetics and depends on temperature, solvent, catalyst, and the presence or absence of light. Racemization appears to depend on the functional group bound to the asymmetric carbon atom, with aromatic groups tending to accelerate the process.

Photochemical

Photolytic degradation can be an important limiting factor in the stability of pharmaceuticals.

A drug can be chemically affected by radiation of a particular wavelength only if (1) it absorbs radiation at that wavelength and (2) the energy exceeds a threshold. Ultraviolet radiation, which has a large energy level, is the cause of many degradation reactions.

If the absorbing molecule reacts, the reaction is said to be photochemical in nature. Where the absorbing molecules do not participate directly in the reaction, but pass their energy to other reacting molecules, the absorbing substance is said to be a photosensitizer.

As many variables may be involved in a photochemical reaction, the kinetics may be quite complex. The intensity and wavelength of the light, the size, shape, composition, and color of the container may affect the velocity of the reaction.

The photodegradation of chlorpromazine through a semiquinone free-radical intermediate follows zero order kinetics. On the other hand, alcoholic solutions of hydrocortisone, prednisolone, and methylprednisolone degrade by reactions following first-order kinetics.

Colored-glass containers are most commonly used to protect light-sensitive formulations. Yellow-green glass gives the best protection in the ultraviolet region while amber confers considerable protection from ultraviolet radiation but little from infrared. Riboflavin is best protected by a stabilizer which has a hydroxyl group attached to or near the aromatic ring. The photodegradation of sulfacetamide solutions may be inhibited by an antioxidant such as sodium thiosulfate or metabisulfite.

Ultrasonic Energy

Ultrasonic energy, which consists of vibrations and waves with frequencies greater than 20,000/sec, promotes the formation of free radicals and alters drug molecules.

Changes in prednisolone, prednisone acetate, and deoxycorticosterone acetate suspensions in an ultrasonic field have been observed spectrophotometrically in the side chain at C-17 and in the oxo group of the A ring. With sodium alginate in an ultrasonic field, it has been reported that above a minimum power output, degradation increased linearly with increased power.

Ionizing Radiation

Ionizing radiation, particularly the gamma rays, has been used for the sterilization of certain pharmaceutical products. At the usual sterilizing dose, 2.5 Mrad, it seldom causes appreciable chemical degradation. In general, formulations which are in the solid or frozen state are more resistant to degradation from ionizing radiation than are those in liquid form. For example, many of the vitamins are little affected by irradiation in the solid state, but are appreciably decomposed in solution. On the other hand, both the liquid- and solid-state forms of atropine sulfate are seriously affected by radiation.

Predicting Shelf Life

The technique of estimating the shelf life of a formulation from its accumulated stability data has evolved from examining the data and making an educated guess through plotting the time-temperature points on appropriate graph paper and crudely extrapolating a regression line to the application of rigorous physical chemical laws, statistical concepts, and computers to obtain meaningful, reliable estimates.

A simple means of estimating shelf life from a set of computer-prepared tables has been described by Lintner, *et al.*[3] This system was developed to (1) select the best prototype formulation based on short-term stability data and (2) predict both estimated and minimum shelf-life values for the formulation. It is a middle-ground approach between the empirical methods and the modern, rigorous statistical concepts. All calculations can be made readily by hand and the esti-

mated values can be obtained easily from appropriate tables. The system assumes that:

1. Shelf-life predictions can be made satisfactorily for lower temperatures using the classical Arrhenius model from data obtained at higher temperatures.
2. The energy of activation of the degradation reaction is between 10 to 20 kcal/mole (this is a safe assumption as Kennon[4] has noted that rarely are drugs with energies of activation of less than 10 kcal/mole used in pharmacy and for values as high as 20 kcal/mole the error in the shelf-life prediction will be on the conservative side).
3. The rate of decomposition will not increase beyond that already observed.
4. The standard deviation of the replicated assays is known or can be estimated from the analytical data.

This concept further assumes that the degradation reaction follows zero or pseudo zero order kinetics. As shown in Fig 82-1, this is an excellent assumption. For data corresponding to a zero, first, or second order degradation pattern, it is impossible to distinguish one order from another with usual analytical procedures where the total degraded material is not large. In addition, shelf-life calculations assuming zero order kinetics are more conservative than those for higher orders.

This middle-ground system is useful in creating the experimental design for the stability study. The formulator has the opportunity to study various combinations of parameters to try to optimize the physical-statistical model. One can check the effect of improving the assay standard deviation, of running additional replicates, of using different time points, and of assuming various degradation rates and energies of activation on the stability of the test formulation.

McMinn and Lintner later developed and reported on an information processing system for handling product stability data.[5] This system saves the time of formulators in analyzing and interpreting their product stability data in addition to minimizing the amount of clerical help needed to handle an ever-increasing assay load. For products such as those of vitamins, for example, where large overages are required, the statistical portions of this advanced technique aid the manufacturer to tailor the formula composition to obtain the desired and most economical expiration dating.

This system stores both physical and chemical data, retrieves the information in three different formats (one of which was designed specifically for submitting to regulatory agencies), analyzes single-temperature data statistically by analysis of covariance and regression or multiple temperature data by weighted or unweighted analysis using the Arrhenius relationship, and provides estimates of the shelf life of the preparation with the appropriate confidence intervals, preprints the assay request cards which are used to record the results of the respective assay procedures and to enter the data into the system and produces a 5-year master-stability schedule as well as periodic 14-day schedules of upcoming assays.

As mentioned above, a portion of the advanced system analyzes the stability data obtained at a single temperature by analysis of covariance and regression. This analysis is based on the linear (zero-order) model

$$Y_{ij} = \beta_i X_{ij} + \alpha_i + \epsilon_{ij}$$

where Y_{ij} is the percent of label of the jth stability assay of the ith lot, X_{ij} is the time in months at which Y_{ij} was observed, β_i and α_i are the slope and intercept respectively of the regression line of the ith lot and ϵ_{ij} is a random error associated with Y_{ij}. The random errors are assumed to be identically and independently distributed normal variables with a zero mean and a common variance, σ^2.

A summary of the regression analysis for each individual lot and for the combination of these lots plus a summary of the analyses of covariance and deviation from regression are prepared by the computer.

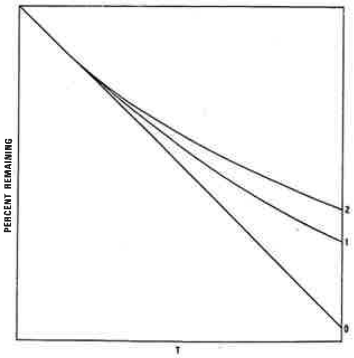

Fig 82-1. Zero order plots for reactions which are zero, first, and second order.

Because the computer combines or pools the stability data from the individual lots, irrespective of the statistical integrity of this step, the pooled data are examined for validity by the F test. The mean square of the regression coefficient (slope) is divided by the mean square of the deviation within lots, and similarly, the adjusted mean (y intercept) is divided by the common mean square to give the respective F ratios. The latter values are then compared to the critical 5% F values. When the calculated F values are smaller than the critical F values, the data may be combined and the pooled data analyzed.

A print-out for the combined lots as well as for each individual lot provides the estimated rate of degradation and its standard error in percent per month for each ingredient. The student t value is calculated from these estimates and tested for significance from zero. When the t value is significant, the print-out contains an estimate of the shelf life with the appropriate confidence interval. When the t value is not significantly different from zero, estimates of the minimum and projected shelf-life values are made. In addition, coordinates of the calculated least squares regression line with appropriate confidence limits for the mean and individual predicted assays are printed.

Plots of the resulting least squares line containing the individual data points are also printed by the computer. For the calculation of X_0, $\hat{Y}$ equals $\overline{Y} + \hat{\beta}(X_0 - \overline{X}..)$ where $\hat{\beta}$ is the least-squares estimate of the slope and $\overline{X}..$ is the mean time of assay.

The sample variance for this estimate, $S^2(\hat{Y})$, is equal to

$$S^2_{Y \cdot X}\left[\frac{1}{N} + \frac{(X_0 - \overline{X}..)^2}{\Sigma(X_{ij} - \overline{X}..)^2}\right]$$

where N is the number of assays. The 95% confidence interval is equal to $\hat{Y} \pm t_{0.05S(\hat{Y})}$.

For the cases where the slope of the best fitting line is positive and significantly different from zero (resulting, for example, from solvent evaporation), the statement "no degradation has been detected and hence no shelf-life estimate is made" is printed. Where the computed line has a positive slope but not significantly different from zero, only the minimum shelf-life value is calculated.

Traditionally, extensive stability data are collected at the recommended storage temperatures (usually refrigerator and/or room temperature) to be placed on the label of the package. However, elevated temperature data are very valuable in determining the shelf life of a product. In practice, multiple levels of thermal stress are applied to the formulation so that appropriate shelf-life estimates can be made for normally expected marketing conditions. In cases where data from accelerated studies are used to project a tentative

expiration date that is beyond the date supported by actual shelf-life studies, testing must continue until the tentative expiration date is verified.

It was noted in Chapter 18 that the effect of temperature variation on the rate of a reaction can be expressed by the Arrhenius equation

$$k = se^{-E_A/RT}$$

where k is the velocity or rate constant, s is the frequency factor, E_A is the activation energy, R is the gas constant, and T is the absolute temperature.

This relationship may be written in logarithmic form

$$\ln k = \ln s - \frac{E_A}{RT}$$

which on differentiation becomes

$$\frac{d \ln k}{dT} = \frac{E_A}{RT^2}$$

This can be integrated between the limits k_1 and k_2, and T_1 and T_2, and on subsequent transforming to the base 10 becomes

$$\log \frac{k_2}{k_1} = \frac{E_A}{2.303R}\left(\frac{T_2 - T_1}{T_2 \cdot T_1}\right)$$

A weighted modification of this model has been incorporated into the previously described computerized system. Each print-out contains a statement concerning the acceptability of the Arrhenius assumption with its appropriate probability level, the slope and intercept for the Arrhenius line, the estimated apparent energy of activation with its 95% confidence limits, plus estimated shelf-life values at selected temperatures.

The analysis of first-order stability data is based on the linear model

$$Y_{ij} = \alpha_i + \beta_i X_{ij} + \epsilon_{ij}$$

where Y_{ij} is the natural logarithm of the assay value for the jth observation of the ith temperature, X_{ij} is the elapsed time in months for the assay sample for the ith temperature, β_i and α_i are the slope and intercept respectively, and ϵ_{ij} is a random error associated with Y_{ij}. The errors are assumed to be identically and independently normally distributed with a zero mean and variance σ^2.

For orders other than first, Y_{ij}, represents the concentration raised to the power of 1 minus the order.

The estimated rate constant (ie, the negative slope) is

$$-b_i = -\sum_j (Y_{ij} - Y_{i\cdot})(X_{ij} - X_{i\cdot}) \Big/ \sum_j (X_{ij} - X_{i\cdot})^2$$

The standard error of the estimated rate constant is

$$S_{-b_i} = \frac{S(Y/X)}{[\Sigma(X_{ij} - X_{i\cdot})^2]^{1/2}}$$

where $S(Y/X)$, the residual standard error, is equal to

$$S(Y/X) = \left\{\frac{1}{N-2}\left[\sum_{j=1}^{12} (Y_{ij} - Y_{1\cdot})^2 - \frac{[\Sigma(X_{ij} - X_{i\cdot})(Y_{ij} - Y_{i\cdot})]^2}{\Sigma(X_{ij} - X_{i\cdot})^2}\right]\right\}^{1/2}$$

According to the Arrhenius relationship, faster degradation occurs at the higher temperatures; hence assays for the high-temperature data are usually run more often but for a shorter period of time. The effect of simple least-squares analysis of this type of data is to force the Arrhenius equation through the low temperature data and essentially ignore the high temperature information. Thus much more credence is placed in the point estimates of the low temperature than is warranted. In addition, the usual confidence limits on extrapolated degradation rates at refrigerator or room temperature cannot validly be made. For these reasons, Bentley[6] presented a method based on weighted least-squares analysis to replace the unweighted approximation. He also developed a statistical test for the validity of the Arrhenius assumption which is easily computed from the results of the unweighted method.

To make shelf-life estimates from elevated temperature data, two storage temperatures are obviously the minimum. As the accuracy of the extrapolation is enhanced by using additional temperatures, a minimum of four different temperatures is recommended for most product stability studies. With the current use of computers to do the bulk of stability calculations, including weighted least-squares analysis, the temperatures and storage conditions need not be selected for arithmetic convenience.

It is not necessary to determine the mechanism of the degradation reaction. In most cases, it is necessary only to follow some property of degradation and to linearize this function. Either the amount of undegraded drug or the amount of a formed decomposition product may be followed. It is usually impractical to determine the exact order of the reaction. With assay errors in the range of 2 to 5%, at least 50% decomposition must occur before the reaction order can be determined. As the loss with pharmaceuticals is generally less, zero-order kinetics should be assumed unless the reaction order is known from previous work. In any case, replication of stability assays is advisable.

The batches of drugs used for a stability study should be representative of production run material or at least of a known degree of purity. The quality of the excipients should also be known as their impurities or even their moisture content can deleteriously affect product stability. Likewise, the samples of the formulation taken for the stability study must be representative of the lot.

Specific assay methods must be used when at all possible. In any case, the reliability and specificity of the test method on the intact molecule and on the degradation products must be determined.

Addition of Overage

The problem of declining potency in an unstable preparation can be ameliorated by the addition of an excess or overage of the active ingredient. Overages, then, are added to pharmaceutical formulations to keep the content of the active ingredient within the limits compatible with therapeutic requirements for a predetermined period of time.

The amount of the overage depends upon the specific ingredient and the galenical dosage form. The International Pharmaceutical Federation has recommended that overages be limited to a maximum of 30% over the labeled potency of an ingredient.

Pharmaceutical Containers

Unless otherwise indicated in a compendial monograph, the official standards for containers apply to articles packaged either by the pharmaceutical manufacturer or the dispensing pharmacist. In general, repackaging of pharmaceuticals is inadvisable. However, if repackaging is necessary, the manufacturer of the product should be consulted for potential stability problems.

A pharmaceutical container has been defined as a device which holds the drug and is or may be in direct contact with the preparation. The immediate container is described as that which is in direct contact with the drug at all times. The liner and closure have traditionally been considered to be part of the container system. The container should not interact

physically or chemically with the formulation so as to alter the strength, quality, or purity of its contents beyond permissible limits.

The choice of containers and closures can have a profound effect on the stability of many pharmaceuticals. Now that a large variety of glass, plastics, rubber closures, tubes, tube liners, etc. are available, the possibilities for interaction between the packaging components and the formulation ingredients are immense. Some of the packaging elements themselves are subject to physical and chemical changes that may be time-temperature dependent.

Frequently it is necessary to use a well-closed or a tight container to protect a pharmaceutical product. A *well-closed container* is used to protect its contents from extraneous solids or a loss in potency of the active ingredient under normal commercial conditions. A *tight container* protects the contents from contamination by extraneous materials, loss of contents, and from efflorescence, deliquescence, or evaporation, and is capable of tight reclosure. When the packaging and storage of an official article in a well-closed or tight container is specified, water permeation tests should be performed on the selected container.

In a stability program, the appearance of the container with special emphasis on the inner walls, the migration of ingredients onto/into the plastic or into the rubber closure, the migration of plasticizer or components from the rubber closure into the formulation, the possibility of two-way moisture penetration through the container walls, the integrity of the tac-seal, and the back-off torque of the cap must be studied.

Glass, plastics, and metals are the commonly used components of pharmaceutical containers.

Traditionally, glass has been the most widely used container for pharmaceutical products to insure inertness, visibility, strength, rigidity, moisture protection, ease of reclosure, and economy of packaging. While glass has some disadvantages such as the leaching of alkali and insoluble flakes into the formulation, these can be offset by the choice of an appropriate glass. As the composition of glass formulations may be varied by the amounts and types of sand and silica added and the heat treatment conditions used, the proper container for any formulation can be selected.

New, unused glass containers are tested for resistance to attack by high-purity water using a sulfuric acid titration to determine the amount of released alkali. Both glass and plastic containers are used to protect light-sensitive formulations from degradation. The amount of transmitted light is measured using a spectrometer of suitable sensitivity and accuracy.

Glass is generally available in flint, amber, blue, emerald green, and certain light-resistant green and opal colors. The blue-, green-, and flint-colored glasses, which transmit ultraviolet and violet light rays, do not meet the official specifications for light-resistant containers.

Colored glass is not usually used for injectable preparations since it is difficult to detect the presence of discoloration, glass particles, and particulate matter in the formulations. Light-sensitive drugs for parenteral use are usually sealed in flint ampuls and placed in a box. Multiple-dose vials should be stored in a dark place.

Manufacturers of prescription drug products should include sufficient information on their product labels to inform the pharmacist of the type of dispensing container needed to maintain the identity, strength, quality, and purity of the product. This brief description of the proper container, eg, light-resistant, well-closed or tight, may be omitted for those products dispensed in the manufacturer's original container.

Plastics—Plastic containers have become very popular for storing pharmaceutical products. Polyethylene, polystyrene, polyvinyl chloride, and polypropylene are used to prepare plastic containers of various densities to fit specific formulation needs.

Factors such as plastic composition, processing and cleaning procedures, contacting media, inks, adhesives, absorption, adsorption, and permeability of preservatives also affect the suitability of a plastic for pharmaceutical use. Hence, biological test procedures are used to determine the suitability of a plastic for packaging products intended for parenteral use and for polymers intended for use in implants and medical devices. Systemic injection, intracutaneous, and implantation tests are employed. In addition, tests for nonvolatile residue, residue on ignition, heavy metals, and buffering capacity, were designed to determine the physical and chemical properties of plastics and their extracts.

The high-density polyethylene containers, which are used for packaging capsules and tablets, possess characteristic thermal properties, a distinctive infrared absorption spectrum and a density between 0.941 and 0.965 g/cm^3. In addition, these containers are tested for light transmission, water vapor permeation, extractable substances, nonvolatile residue, and heavy metals. Where a stability study has been performed to establish the expiration date for a dosage form in an acceptable high-density polyethylene container, any other high-density polyethylene container may be substituted provided that it, too, meets compendial standards and that the stability program is expanded to include the alternate container.

Materials from the plastic itself can leach into the formulation, and materials from the latter can be absorbed onto, into, or through the container wall. Various pharmaceutical preservatives are bound by the barrels of some plastic syringes. However, changing the composition of the syringe barrel from nylon to polyethylene or polystyrene has eliminated the binding in some cases.

A major disadvantage of plastic containers is the two-way permeation of "breathing" through the container walls. Volatile oils and flavoring and perfume agents are permeable through plastics to varying degrees. Components of emulsions and creams have been reported to migrate through the walls of some plastics causing either a deleterious change in the formulation or collapse of the container. Loss of moisture from a formulation is common. Gases, such as oxygen or carbon dioxide in the air, have been known to migrate through container walls and to affect a preparation.

Solid dosage forms, such as penicillin tablets, when stored in some plastics, are deleteriously affected by moisture penetration from the atmosphere into the container.

Metals—The pharmaceutical industry was, and to a degree still is, a tin stronghold. However, as the price of tin constantly varies, more aluminum tubes are being used. Lead tubes tend to have pinholes and are little used in the industry.

A variety of internal linings and closure or fold seals are available for both tin and aluminum tubes. Tin tubes can be coated with wax or with vinyl linings. Aluminum tubes are available with epoxy or phenolic resin, wax, vinyl, or a combination of epoxy or phenolic resin with wax. As aluminum is able to withstand the high temperatures required to cure adequately epoxy and phenolic resins, tubes made from this metal presently offer the widest range of lining possibilities.

Closure foldseals may consist of unmodified vinyl resin or plasticized cellulose and resin with or without added color.

Collapsible tubes are available in many combinations of diameters, lengths, openings, and caps. Custom-use tips for ophthalmic, nasal, mastitis, and rectal applications are also available. Only a limited number of internal liners and closure seals are available for tubes fitted with these special-use tips.

Lined tubes from different manufacturers are not necessarily interchangeable. While some converted resin liners may be composed of the same base resin, the actual liner may have been modified to achieve better adhesion, flow properties, drying qualities, or flexibility. These modifications may have been necessitated by the method of applying the liner, the curing procedure, or finally by the nature of the liner itself.

Closures

The closures for the formulations must also be studied as a portion of the overall stability program. While the closure must form an effective seal for the container, the closure must not react chemically or physically with the product. It must not absorb materials from the formulation or leach its ingredients into the contents.

The integrity of the seal between the closure and container depends on the geometry of the two, the materials used in their construction, the composition of the cap liner, and the tightness with which the cap has been applied. Torque is a measure of the circular force, measured in inch-pounds, which must be applied to open or close a container. When pharmaceutical products are set up on a stability study, the formulation must be in the proposed market package. Thus they should be capped with essentially the same torque to be used in the manufacturing step.

Rubber is a common component of stoppers, cap liners, and parts of dropper assemblies. Sorption of the active ingredient, preservative, or other formulation ingredients into the rubber and the extraction of one or more components of the rubber into the formulation are common problems.

The application of an epoxy lining to the rubber closure reduces the amount of leached extractives but has essentially no effect on the sorption of the preservative from the solution. Teflon-coated rubber stoppers may prevent most of the sorption and leaching.

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CHAPTER 84

Solutions, Emulsions, Suspensions and Extractives

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

The preparation of these dosage forms involves several considerations on the part of the pharmacist: purpose of the drug, internal or external use, concentration of the drug, selection of the liquid vehicle, physical and chemical stability of the drug, the preservation of the preparation, use of the appropriate excipients such as: buffers, solubilizers, suspending agents, emulsifying agents, viscosity controlling agents, colors, and flavors. The appropriate chapters (see the index) should be consulted for information on the preparation and characteristics of those liquid preparations that are intended for ophthalmic or parenteral use.

Much has been written during the past decade about the biopharmaceutical properties of, in particular, the solid dosage forms. In assessing the bioavailability of drugs in tablets and capsules, many researchers have first studied the absorption of drugs administered in solution. Since drugs are absorbed in their dissolved state, frequently it is found that the absorption rate of oral dosage forms decreases in the following order: aqueous solution > aqueous suspension > tablets or capsules. The bioavailability of a medicament, for oral ingestion and absorption, should be such that eventually all of the drug is absorbed as it passes through the gastrointestinal tract, regardless of the dosage form. There are a number of reasons for formulating drugs in forms in which the drug is not in the molecular state. These are: (a) improved stability, (b) improved taste, (c) low water solubility, (d) palatability, and (e) ease of administration. It becomes apparent, then, that each dosage form will have advantages and disadvantages.

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

The pharmacist, in the first instance, depends on the manufacturer to produce a product that is effective, elegant, and stable when stored under reasonably adverse conditions. Most drug manufacturers attempt to guarantee efficacy by evaluating their products in a scientifically acceptable manner but, in some instances, such efficacy is relative. For example, cough mixtures marketed by two different manufacturers may contain active ingredients in the same therapeutic class and it becomes difficult to assess the relative merits of the two products. In such instances the commercial advantage gained by one over the other may be based on product elegance. Thus, color, odor, taste, pourability, and homogeneity are important pharmaceutical properties.

The stability of the active ingredient in the final product is of prime concern to the formulator. In general, drug substances are less stable in aqueous media than in the solid dosage form and it is important, therefore, to properly buffer, stabilize, or preserve, in particular, those solutions, suspensions, and emulsions that contain water. Certain simple chemical reactions can occur in these products. These may involve an ingredient-ingredient interaction (which implies a poor formulation), a container-product interaction (which may alter product pH and thus, for pH-sensitive ingredients, be responsible for the subsequent formation of precipitates), or a direct reaction with water (ie, hydrolysis). The stability of pharmaceutical products is discussed in Chapter 82. The more complicated reactions usually involve oxygen. Vitamins, essential oils, and almost all fats and oils can be oxidized. Formulators usually use the word *autoxidation* when the ingredient(s) in the product react with oxygen but without drastic external interference. Such reactions must be first initiated by heat, light (including ultraviolet radiant energy), peroxides or other labile compounds, or heavy metals such as copper or iron. This initiation step results in the formation of a free radical (R*) which then reacts with oxygen.

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

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

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

reactions.

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

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

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

The effect of trace metals can be minimized by the use of citric acid or EDTA (ie, by use of sequestering agents). Antioxidants, on the other hand, may retard or delay oxidation by reacting with the free radicals formed in the product. Examples of antioxidants are the propyl, octyl, and dodecyl esters of gallic acid, butylated hydroxyanisole (BHA), and the tocopherols or vitamin E. For a more detailed approach to the prevention of oxidative deterioration in pharmaceuticals, the papers by Ostendorf[1] and Chalmers,[2] should be consulted. A description of many antioxidants is given in Chapter 68.

The problem of drug stability has been well defined by pharmaceutical scientists but, during the past few years, a secondary and, in some respects, more serious problem has confronted the manufacturer of liquid preparations. Such pharmaceutically diverse products as baby lotions and milk of magnesia have been recalled from the market because of microbial contamination. In a survey of retail packages of liquid antacid preparations containing magnesium hydroxide, it was found that 30.5% of the finished bottles were contaminated with *Pseudomonas aeruginosa.* The aerobic plate count ranged from less than 100 to 9,300,000 organisms/gram. Other examples could be cited but the range of microorganisms which can contaminate the liquid preparation includes the *Salmonella* sp, *E coli*, certain *Pseudomonas* sp, including *P aeruginosa* and *Staphylococcus aureus.* Bruch[3] describes the types of microorganisms found in various products and attempts to evaluate the hazards associated with the use of nonsterile pharmaceuticals. Coates[4] in a series of papers describes various interactions which must be considered when preservatives are selected.

The USP recommends that certain classes of products be routinely tested for microbial contamination, eg, natural plant and animal products, for freedom from *Salmonella* species; oral solutions and suspensions, for freedom from *E coli*; articles applied topically, for freedom from *P aeruginosa* and *S aureus*; articles for rectal, urethral or vaginal administration, for total microbial count.

Products may become contaminated for a number of reasons. First, the raw materials used in the manufacture of solutions, suspensions, and emulsions are excellent growth media for bacteria. Water, in particular, must be handled with care but substances such as gums, dispersing agents, surfactants, sugars, and flavors can be the carriers of bacteria which ultimately contaminate the product. A second source of contamination is equipment. Bacteria grow well in the nooks and crevices of pharmaceutical equipment (and in the simple equipment used in the dispensary). Such equipment should be thoroughly cleaned prior to use. Environment and personnel can contribute to product contamination. Hands and hair are the most important carriers of contaminants. General cleanliness is thus vital. Head coverings must be used by those involved in the manufacturing process and face masks should be used by those individuals suffering from colds, coughs, hay fever, and other allergic manifestations. Finally, packaging should be selected so that it will not contaminate the product and also will protect it from the environment.

The factors cited above relate to good manufacturing practice. However, the formulator can add a preservative to the product and decrease the probability of product contamination. If the product contains water, it is almost mandatory to include a preservative in the formulation. It must be stressed that this in no way replaces good in-plant control but merely provides further assurance that the product will retain its pharmaceutically acceptable characteristics to the patient level.

The major criteria that should be considered in selecting a preservative are: (a) it should be effective against a wide spectrum of microorganisms; (b) it should be stable for the shelf life of the product; (c) it should be nontoxic; (d) it should be nonsensitizing (e) it should be compatible with the ingredients in the dosage form; (f) it should be relatively free of taste and odor.

Preservatives may be used alone or in combination with each other to prevent the growth of microorganisms. Ethanol is a highly effective preservative. It is used at the 15% level in acidic media and at the 18% level in neutral or slightly alkaline media. Isopropyl alcohol is a fairly effective agent but it can be used only in topical preparations. Propylene glycol, a dihydric alcohol, has germicidal activity similar to that of ethanol. It is normally used at the 10% concentration level.

A 0.5% solution of phenol is a good preservative but it is toxic, has its own characteristic odor, and reacts chemically with many of the drugs and adjuvants which are incorporated into liquid preparations.

The use of hexachlorophene, a germicidal agent which is mainly effective against gram-positive organisms, is restricted to those preparations which are intended for external use only. Several years ago, an incorrectly formulated baby powder (which was found to contain 6.5% hexachlorophene) was responsible for the deaths of 30 French infants. Because of this and other evidence, this substance can be used as a preservative only if its concentration in the final product is 0.1% or less. However, certain liquid preparations (eg, Hexachlorophene Liquid Soap USP) are available. The hexachlorophene content is usually 0.25% in the USP product.

Organic mercury compounds are powerful biostatic agents. Their activity may be reduced in the presence of anionic emulsifying or suspending agents. They are not suitable for oral consumption but are used at the 0.005% concentration level in ophthalmic, nasal, and topical preparations.

Benzoic acid is effective only at pH 4 or less. Its solubility in certain aqueous preparations is poor and, in those instances, sodium benzoate may be utilized. Sorbic acid has a broad range of antimycotic activity but its antibacterial properties are more limited. It is effective only at a pH of less than 5.

Quaternary ammonium surface-active agents, eg, benzalkonium chloride, exhibit an objectionable off-taste and have been reported to be incompatible with a number of anionic substances. In concentrations of 1:5000 to 1:20,000 they are used in ophthalmic preparations.

3-Phenylpropan-1-ol (hydrocinnamyl alcohol) is claimed to be more effective than 2-phenylethanol and benzyl alcohol in inhibiting the growth of *P aeruginosa*, and it has been suggested that this substance may be a suitable preservative for oral suspensions and mixtures.

The methyl and propyl esters of para-hydroxybenzoic acid (the parabens) are widely used in the pharmaceutical industry. They are effective over a wide pH range (from about 3 to 9) and are used at up to about the 0.2% concentration level. The two esters are often used in combination in the same preparation. This achieves a higher total concentration and the mixture is active against a wide range of organisms. The hydroxybenzoates are effective against most organisms; however, their activity may be reduced in the presence of nonionic surface-active agents because of binding.

It should now be obvious that when the pharmacist dispenses or compounds the various liquid preparations he assumes responsibility, with the manufacturer, for the maintenance of product stability. The USP includes a section on stability considerations in dispensing practice. This section of the compendium should be studied in detail. Certain

points are self-evident. Stock should be rotated and replaced if expiration dates on the label so indicate. Products should be stored in the manner indicated in the compendium; eg, in a cool place, a tight, light-resistant container, etc. Further, products should be checked for evidence of instability. With respect to solutions, elixirs, and syrups, precipitation and evidence of microbial or chemical gas formation are the two major signs of instability. Emulsions may cream but if they break (ie, there is a separation of an oil phase) the product is considered to be unstable. Caking is a primary indication of instability in suspensions. The presence of large particles may mean that excessive crystal growth has occurred.

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

Aqueous Solutions

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

This section, and the chapter as a whole, must be considered as part of a broad subject that is based on principles presented in several chapters of Part 2, Pharmaceutics.

Water

The major ingredient in most of the dosage forms described herein is water. Water is used both as a vehicle and as a solvent for the desired flavoring or medicinal ingredients. Its tastelessness, freedom from irritating qualities, and lack of pharmacological activity make it ideal for such purposes. There is, however, a tendency to assume that its purity is constant and that it can be stored, handled, and used with a minimum of care. While it is true that municipal supplies must comply with Environmental Protection Agency regulations (or comparable regulations in other countries), drinking water *must* be repurified before it can be used in pharmaceuticals. For further information on water as H_2O, see Chapter 23.

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

A wide variety of commercially available stills are used to produce distilled water. The end use of the product dictates the size of the still and extent of pretreatment of the drinking water introduced into the system. A description of stills is provided in Chapter 85. Such water may be sterile provided the condenser is sterile, but to be called sterile, it must be subjected to a satisfactory sterilization process. However, it has been shown that *P aeruginosa* (and other microorganisms) can grow in the distilled water produced in hospitals. The implications of this are obvious. Sterile water may be sterile at the time of production but may lose this characteristic if it is improperly stored. Hickman *et al*,[5] by regrouping the components of conventional distillation equipment, have described a method for the continuous supply of sterile, ultrapure water.

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

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

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

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

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

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

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

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

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

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

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

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

Deionization processes do not necessarily produce *Purified Water* which will comply with US EPA requirements for drinking water. Resin columns retain phosphates and organic debris. Either alone or in combination, these substances can act as growth media for microorganisms. Observations have shown that deionized water containing 90 organisms/mL contained, after 24 hours storage, 10^6 organisms/mL. Columns can be partially cleaned of pseudomonads by recharging

but a 0.25% solution of formaldehyde will destroy most bacteria. The column must be thoroughly washed and checked for the absence of aldehyde (by use of Schiffs Reagent) before it can be used to generate deionized water.

Ultraviolet radiant energy (240–280 nm), heat, or filtration can be used to limit the growth, to kill or to remove microorganisms in water. The latter method employs membrane filters and can be used to remove bacteria from heat labile materials as described under membrane filters in Chapter 79.

The phenomenon of osmosis involves the passage of water from a dilute solution across a semipermeable membrane to a more concentrated solution. Flow of water can be stopped by applying pressure, equal to the osmotic pressure, to the concentrated solution. The flow of water can be reversed by applying a pressure, greater than the osmotic pressure. The process of reverse osmosis utilizes the latter principle; by applying pressure, greater than the osmotic pressure, to the concentrated solution, eg, tap water, pure water may be obtained (see *Reverse Osmosis* in Chapter 78).

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

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

Aromatic Waters

Aromatic waters, known also as medicated waters, are clear, saturated aqueous solutions of volatile oils or other aromatic or volatile substances. Their odors and tastes are similar to those of the drugs or volatile substances from which they are prepared, and the preparations should be free from empyreumatic (smoke-like) and other foreign odors. They are used principally as flavored or perfumed vehicles. The volatile substances from which aromatic waters are to be made should be of pharmacopeial quality or, in the case of nonofficial preparations, of the best quality if the finest flavors are to be obtained.

Aromatic waters may be prepared by one of two official processes.

Distillation—Distillation represents the most ancient and frequently the most satisfactory method for making this class of preparations. However, it is the slowest and the more expensive of the two methods.

Different authorities give different directions for the preparation of aromatic waters by distillation. For fresh drugs the proportions range from one part of drug to two of distillate, to two parts of drug to one part of distillate. For dried drugs such as cinnamon, anise, dill, caraway, and fennel the proportion is one part of drug to ten parts of distillate. In the case of dried leaf drugs such as peppermint, the proportion is three parts of drug to ten parts of distillate. Metallic distillation apparatus is usually employed, sometimes using a current of steam passed through the still. The drug should be contused or coarsely ground and combined with a sufficient quantity of *Purified Water*. On completion of the distillation process, any excess of oil in the distillate is removed and, if necessary, the clear water portion is filtered. Most distilled aromatic waters acquire an unpleasant empyreumatic odor as soon as they are distilled. This passes off gradually on exposure to air, if care has been taken not to expose the drug to direct heat during distillation. If precautions are not taken to protect the drug from partial burning, the odor of the carbonized substance will be noticeable in the distilled aromatic water. To avoid this difficulty, the drug should be placed in a partially filled round-bottomed copper wire cage, which is placed in the still to thus avoid any contact of the substance with the heated surface. The meshes of the cage are coarse enough to permit free passage of vapors and boiling water. If the volatile principles in the water are delicate and present in small quantities (eg, as in orange flower and rose waters), the distillate is returned several times to the still with fresh portions of flowers, thus giving rise to the commercial terms *double distilled*, *triple distilled*, or *quadruple distilled*, according to the number of redistillations. This process is called *cohobation*.

Stronger Rose Water is an example of an aromatic water prepared by distillation. It acquires a musty odor when stored in tightly closed containers over long periods of time. The odor of this water is best preserved by allowing limited access of fresh air to the container. Cotton plugs exclude foreign matter but, at the same time, permit air to enter the container. Stronger Rose Water, diluted with an equal volume of purified water, may be used when *Rose Water* is specified in a formulation.

Solution—Aromatic waters may be prepared by repeatedly shaking 2 g or 2 mL (if a liquid) of the volatile substance with 1000 mL of purified water over a period of 15 minutes. The mixture is set aside for 12 hours, filtered through wetted filter paper, and made to volume (1000 mL) by adding purified water through the filter. Peppermint Water USP can be prepared by either of the two official methods.

In terms of time and equipment this method is more convenient than that described above. However, making medicated waters by agitation with an excess of volatile oil, permitting the excess to remain and drawing off the water as required, is not recommended. Volatile oils may deteriorate through exposure to light and air and, because of this, may yield unsatisfactory aromatic waters.

Certain waters are prepared by dissolving well-defined substances in purified water. Camphor water is a saturated solution of camphor in purified water. Chloroform water is prepared by adding enough chloroform to purified water (in a dark amber-colored bottle) to maintain a slight excess after the mixture has been thoroughly agitated. The latter water has been used as a sedative in cough, asthma, and colic mixtures and as a vehicle for administering active ingredients.

Aromatic waters may also be prepared by thoroughly incorporating the volatile oil with 15 g of talc or with a sufficient quantity of purified siliceous earth or pulped filter paper.

Purified water (1000 mL) is added and the mixture is agitated for 10 min. The water is then filtered (and, if necessary, refiltered) and its volume adjusted to 1000 mL by passing purified water through the filter.

This is the process most frequently employed since the water can be prepared promptly, only 10 min of agitation being required. The use of talc, purified siliceous earth, or pulped filter paper greatly increases the surface of the volatile substance, insuring more rapid saturation of the water. These dispersing substances also form an efficient filter bed which produces a clear solution. They are also unreactive.

Other methods have been suggested for the preparation of aromatic waters. These are based on use of soluble concentrates or on incorporation of solubilizing agents such as polysorbate 20 (Tween 20, *Atlas*). However, such preparations are susceptible to mold growth and, in concentrations higher than 2%, impart an objectionable oily taste.

Concentrated waters (eg, peppermint, dill, cinnamon, caraway, and anise) may be prepared in the following manner.

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

If anise concentrate is being prepared, the volume of ethanol must be increased to 700 mL.

The aromatic water is prepared by diluting the concentrate with 39 times its volume of water. In general, these methods yield aromatic waters that are slightly inferior in quality to those prepared by distillation or solution.

The chemical composition of many of the volatile oils used in the preparation of pharmaceuticals and cosmetics is now known. Similarly, many synthetic aromatic substances have a characteristic odor. For example, geranyl phenyl acetate has a honey odor. Such substances, either alone or in combination, can be used in nonofficial preparations and, by combining them in definite proportions, it is possible to produce substitutes for the officially recognized oil. Imitation Otto Rose (which contains phenylethyl alcohol, rhodinol, citronellol, and other ingredients) is an example of the types of substitutes which are now available.

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

Preservation—Aromatic waters will deteriorate with time and should, therefore, be made in small quantities and protected from intense light and excessive heat, and stored in airtight, light-resistant containers. Deterioration may be due to volatilization, decomposition, or mold growth and will produce solutions that are cloudy and have lost all traces of their agreeable odor. Distilled water is usually contaminated with mold-producing organisms. *Recently* distilled and boiled water should, therefore, be used in the preparation of medicated waters. No preservative should be added to medicated waters. If they become cloudy or otherwise deteriorate, they should be discarded.

Aqueous Acids

The official inorganic acids and certain organic acids, although of minor significance as therapeutic agents, are of great importance in chemical and pharmaceutical manufacturing. This is especially true of acetic, hydrochloric, and nitric acids. The two latter acids, because of their relative completeness of ionization, are termed strong acids. These acids, and especially the last is very caustic and corrosive.

The inorganic acids are generally divided into two groups: (1) the *hydracids*, which contain no oxygen, eg, hydriodic, hydrobromic, hydrochloric, and hydrofluoric acids and (2) the oxygen-containing acids, eg, hypophosphorous, nitric, phosphoric, and sulfuric acids.

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

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

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

Incompatibilities—Although many of the reactions characteristic of acids offer opportunities for incompatibilities, only a few are of sufficient importance to require more than casual mention. Acids and acid salts decompose carbonates with liberation of carbon dioxide and, in a closed container, sufficient pressure may be developed to produce an explosion. Inorganic acids react with salts of organic acids to produce the free organic acid and a salt of the inorganic acid. If insoluble, the organic acid will be precipitated. Thus, salicylic acid and benzoic acid are precipitated from solutions of salicylates and benzoates. Boric acid is likewise precipitated from concentrated solutions of borates. By a similar reaction, certain soluble organic compounds are converted into an insoluble form. Sodium phenobarbital, for example, is converted into phenobarbital which in aqueous solution will precipitate.

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

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

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

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

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

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

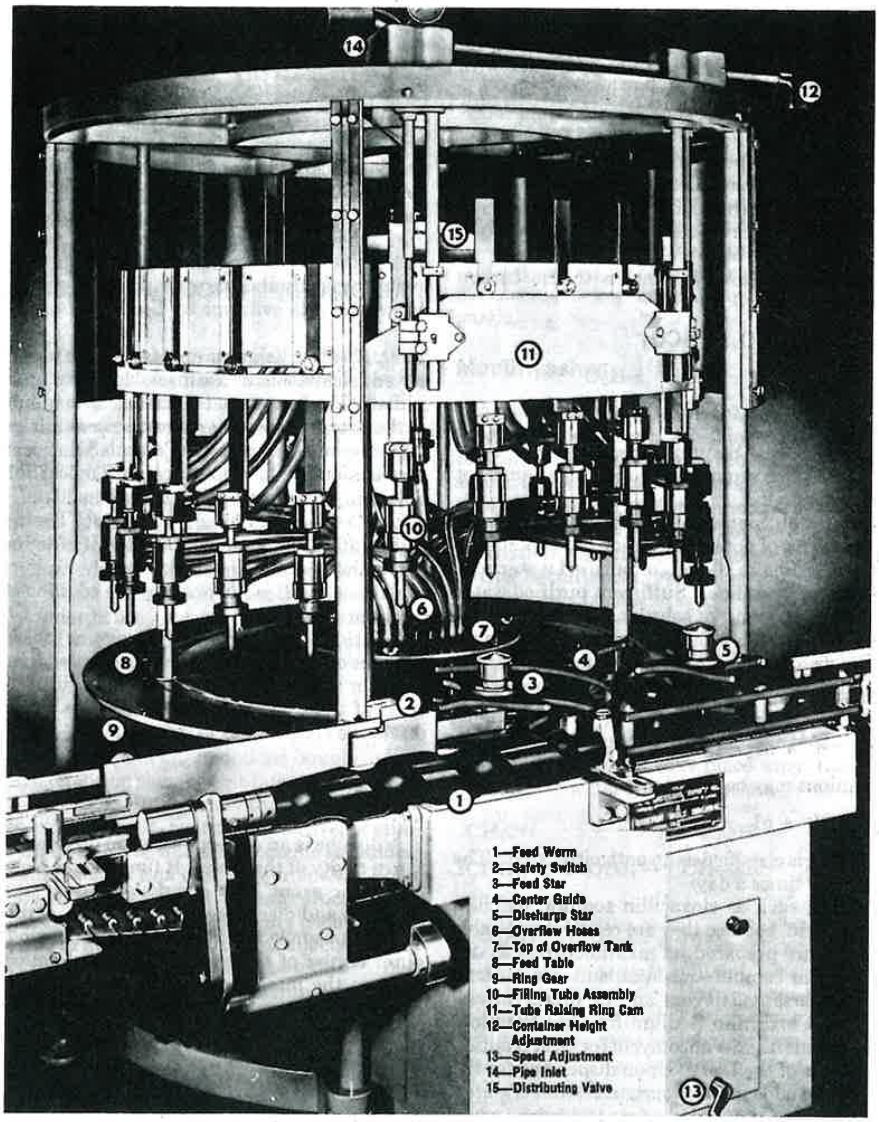


Fig 84-1. A rotary gravity bottle filler (courtesy, US Bottlers).

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

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

One of these diluted acids, Diluted Hydrochloric Acid USP is used in the treatment of achlorhydria. However, it may irritate the mucous membrane of the mouth and attack the enamel of the teeth. The usual dose is 5 mL, well diluted with water. In the treatment of achlorhydria no attempt is made to administer more than a relief-producing dose. The normal pH of the gastric juice is 0.9 to 1.5 and, in order to attain this level, particularly in severe cases of gastric malfunction, somewhat larger doses of the acid would be required.

Solutions

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

Solvents, solubility, and general methods for the incorporation of a solute in a solvent are discussed in Chapter 16. Solutions are usually bottled automatically by utilizing equipment of the type shown in Fig 84-1.

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

Simple Solutions—Solutions of this type are prepared by dissolving the solute in a suitable solvent. The solvent may contain other ingredients which stabilize or solubilize the active ingredient. Calcium Hydroxide Topical Solution (Lime Water), Sodium Phosphates Oral Solution, and Strong Iodine Solution are examples of solutions that are prepared in this way.

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

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

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

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

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

$$Ca^{2+} + CO_3^{2-} \rightarrow CaCO_3$$

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

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

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

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

Doubly charged anions may be found also

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

Strong Iodine Solution is classified as an antigoitrogenic. The usual dose is 0.3 mL 3 times a day.

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

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

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

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

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

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

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

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

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

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

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

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

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

Douches

A douche is an aqueous solution directed against a part or into a cavity of the body. It functions as a cleansing agent or antiseptic agent. An *eye douche*, used to remove foreign particles and discharges from the eyes, is directed gently at an oblique angle and is allowed to run from the inner to the outer corner of the eye. *Pharyngeal douches* are used to prepare the interior of the throat for an operation and to cleanse it in suppurative conditions. Similarly, there are *nasal douches* and *vaginal douches*. Douches are usually directed to the appropriate body part by using bulb syringes. These are described in Chapter 104.

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

Preparations of this type may contain alum, zinc sulfate, boric acid, phenol, or sodium borate. The ingredients in one douche are alum (4 g), zinc sulfate (4 g), liquefied phenol (5 mL), glycerin (125 mL), and water (a sufficient quantity to make 1000 mL of solution). Sodium borate (borax, sodium tetraborate) is used in the preparation of Compound Sodium Borate Solution NF XI (Dobell's Solution). A solution of sodium borate in water is alkaline to litmus paper. In the presence of water, sodium metaborate, boric acid, and sodium hydroxide are formed.

$$Na_2B_4O_7 + 3H_2O \rightarrow 2NaBO_2 + 2H_3BO_3$$

$$NaBO_2 + 2H_2O \rightarrow NaOH + H_3BO_3$$

The official solution contains sodium borate, sodium bicarbonate, liquefied phenol, and glycerin. The reaction between boric acid and glycerin is given in the section on *Mouthwashes.* See also the section on *Honeys* for a discussion on the toxic manifestations associated with the topical application of boric acid and borax.

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

Vaginal or urethral douches are occasionally referred to as Irrigations. These solutions may have an antiseptic, astringent, or soothing action and are prepared immediately before use by dissolving the medicament in the required amount of water. One example of such a preparation is Irrigation of Lactic Acid BPC 1963. This solution contains 3.75 mL of lactic acid in every 600 mL of aqueous product. There are a number of irrigations described in the USP: Acetic Acid Irrigation for bladder irrigation, Aminoacetic Acid Irrigation for urethral surgery, and Sodium Chloride Irrigation for washing wounds. These solutions are sterile and meet the same stringent standards used for parenteral preparations because they are used in areas of the body where it is essential that no microorganisms be introduced.

Enemas

Evacuation enemas are rectal injections employed to evacuate the bowel, retention enemas to influence the general system by absorption, or to affect locally the seat of disease. They may possess anthelmintic, nutritive, sedative, or stimulating properties, or they may contain radiopaque substances for roentgenographic examination of the lower bowel. Some official enemas are those of aminophylline, hydrocortisone, and methylprednisolone acetate. Enemas are usually given at body temperature in quantities of 1 to 2 pt injected slowly with a syringe. If they are to be retained in the intestine, they should not be used in larger quantities than 6 fluid ounces for an adult.

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

Barium sulfate enema contains 120 g of barium sulfate, 100 mL of acacia mucilage, and sufficient starch enema to make 500 mL.

Sodium chloride, sodium bicarbonate, sodium monohydrogen phosphate, and sodium dihydrogen phosphate are used in enemas. These substances may be used alone, in combination with each other, or in combination with irritants such as soap. Enema of Soap BPC 1963 is prepared by dissolving 50 g of soft soap in sufficient purified water to make 1000 mL of enema. Fleet Enema, a commercially available enema containing 16 g of sodium acid phosphate and 6 g of sodium phosphate in 100 mL, is marketed as a single-dose disposable unit. Sulfasalazine rectal enema has been administered for the treatment of ulcerative colitis and may be prepared by dispersing the tablets (1 g strength) in 250 mL water.

Gargles

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

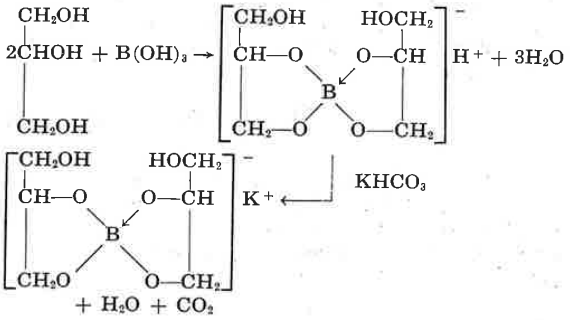
Phenol Gargle, and Potassium Chlorate and Phenol Gargle are official in the BPC. The former gargle contains 50 mL of phenol glycerin (16% *w/w* phenol and 84% *w/w* glycerin), 10 mL of amaranth solution (1% *w/v* in chloroform water), and water to make 1000 mL. This gargle should be diluted with an equal volume of warm water before use. The product should be so labeled that it cannot be mistaken for preparations intended for internal administration.

A flavored solution containing 1% povidone-iodine USP and 8% alcohol is commercially available as a mouthwash or gargle.

Mouthwashes

A mouthwash is an aqueous solution which is most often used for its deodorant, refreshing, or antiseptic effect. It may contain alcohol, glycerin, synthetic sweeteners, and surface-active, flavoring, and coloring agents. Commercial preparations contain such local anti-infective agents as hexetidine and cetylpyridinium chloride. They may be either acidic or basic in reaction and, in some instances, are fairly effective in reducing bacterial concentrations and odors in the mouth for short periods of time.

The products of commerce (eg, Cepacol, Listerine, Micrin, Scope, etc) vary widely in composition. Compound Sodium Borate Solution NF XI (Dobell's Solution) is used as an antiseptic mouthwash and gargle. Antiseptic Solution and Mouthwash are described in NF XII. The latter wash contains sodium borate, glycerin, and potassium bicarbonate. The reactions which take place when these substances are dissolved in water are given below.



Compound Sodium Chloride Mouthwash, and Zinc Sulphate and Zinc Chloride Mouthwash are described in the BPC. The former wash contains sodium chloride, sodium bicarbonate, concentrated peppermint emulsion, and double-strength chloroform water; the latter, zinc sulfate, and amaranth solution.

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

Juices

A juice is prepared from fresh ripe fruit, is aqueous in character, and is used in making syrups which are employed as vehicles. The freshly expressed juice is preserved with benzoic acid, and is allowed to stand at room temperature for

several days, until the pectins which are naturally present are destroyed by enzymatic action, as indicated by the filtered juice yielding a clear solution with alcohol. Pectins, if allowed to remain, would cause precipitation in the final syrup.

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

Artificial flavors have now replaced many of the natural fruit juices. Although they lack the flavor of the natural juice, they are more stable and are easier to incorporate into the final pharmaceutical form.

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

Nasal Solutions

Nasal solutions are usually aqueous solutions which are designed to be administered to the nasal passages in drops or spray form. While many of the drugs are administered for their local sympathomimetic effect such as Ephedrine Sulfate or Naphazoline Hydrochloride Nasal Solution, to reduce nasal congestion, a few other official preparations, Lypressin Nasal Solution and Oxytocin Nasal Solution are administered in spray form for systemic effect for the treatment of diabetes insipidus and *milk let down* prior to breast feeding, respectively.

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

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

A formula for Ephedrine Nasal Drops BPC is:

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

Otic Solutions

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

The main classes of drugs used for topical administration to the ear include analgesics, eg, benzocaine; antibiotics, eg, neomycin, and anti-inflammatory agents, eg, cortisone. The USP preparations include Glycerin Otic Solution which incorporates the drugs antipyrine and benzocaine in a glycerin solvent. The Neomycin and Polymyxin B Sulfates and Cortisol Otic Solutions contain appropriate buffers, dispersants usually in an aqueous solution. These otic preparations include the main types of solvents used, namely glycerin or water. The viscous glycerin vehicle, permits the drug to remain in the ear for a long time. Anhydrous glycerin being hygroscopic tends to remove moisture from surrounding tissues thus reducing swelling.

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

Sweet or Other Viscid Aqueous Solutions

Solutions which are sweet or viscid include Syrups, Honeys, Mucilages, and Jellies. All of these preparations are viscous liquids or semisolids. The basic sweet or viscid substances giving body to these preparations are sugars, polyols, or polysaccharides (gums).

Syrups

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

Flavored syrups offer unusual opportunities as vehicles in extemporaneous compounding and are readily accepted by both children and adults. Because they contain no or very little alcohol, they are vehicles of choice for many of the drugs that are prescribed by pediatricians. Their lack of alcohol makes them superior solvents for water-soluble substances. However sucrose based medicines continuously administered to children apparently cause an increase in dental caries and gingivitis; consequently, alternate formulations of the drug either unsweetened or sweetened with non-cariogenic substances should be considered. A knowledge of the sugar content of liquid medicines is useful for patients who are on a restricted calorie intake; such a list may be found in the literature[6].

Syrups possess remarkable masking properties for bitter and saline drugs. Glycyrrhiza Syrup has been recommended for disguising the salty taste of bromides, iodides, and chlorides. This has been attributed to its colloidal character and to its double sweetness—the immediate sweetness of the sugar and the lingering sweetness of the glycyrrhizin. This syrup is also of value in masking bitterness in preparations containing the B complex vitamins. Acacia Syrup, because of its colloidal character, is of particular value as a vehicle for masking the disagreeable taste of many medicaments. Raspberry Syrup is one of the most efficient flavoring agents and is especially useful in masking the taste of bitter drugs. Many factors, however, enter into the choice of a suitable flavoring agent. Literature reports are often contradictory and there appears to be no substitute for the taste panel. The literature on this subject has been reviewed by Meer,[7] and this reference and Chapter 68 should be consulted for further information on the flavoring of pharmaceuticals and the preparation of a number of official syrups. A series of papers is

available in improving the palatability of bulk compounded products using flavoring and sweetening agents.[8]

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

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

When heat is used in the preparation of syrups, there is almost certain to be an inversion of a slight portion of the sucrose.

$$\underset{\text{Sucrose}}{C_{12}H_{22}O_{11}} + H_2O \rightarrow \underset{\text{Invert sugar}}{2C_6H_{12}O_6}$$

Sucrose solutions rotate polarized light to the right but, as hydrolysis proceeds, the optical rotation decreases and becomes negative when the reaction is complete. This reaction is termed *inversion* because *invert sugar* (dextrose plus levulose) is formed. The speed of inversion is greatly increased by the presence of acids; the hydrogen ion acts as a catalyst in this hydrolytic reaction. Invert sugar is more readily fermentable than sucrose and tends to darken in color. Nevertheless its two reducing sugars are of value in retarding the oxidation of other substances.

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

The levulose formed during inversion is sweeter than sucrose and therefore the resulting syrup is sweeter than the original syrup. The relative sweetness of levulose, sucrose, and dextrose is in the ratio 173:100:74. Thus invert sugar is $1/100\ (173 + 74)^{1/2} = 1.23$ times as sweet as sucrose. The levulose formed during the hydrolysis is also responsible for the darkening of syrup. It is sensitive to heat and darkens readily, particularly in solution. When syrup or sucrose is overheated, it caramelizes. See *Caramel* (page 1282). Occasionally it is appropriate to use a sugar free liquid preparation, a list of these has recently been published[9].

Preparation—Syrups are prepared in various ways, the choice of the proper method depending on the physical and chemical characteristics of the substances entering into the preparation. Four methods which are employed may be summarized as follows: (1) solution with heat; (2) agitation without heat; (3) addition of a medicating liquid to syrup; and (4) percolation.

Solution with Heat—This is the usual method of making syrups when the valuable constituent is neither volatile nor injured by heat, and when it is desirable to make the syrup rapidly. The sucrose is usually added to the purified water or aqueous solution and heated until solution is effected, then strained, and sufficient purified water added to make the desired weight or volume. If the syrup is made from an infusion, a decoction, or an aqueous solution containing organic matter, it is usually proper to heat the syrup to the boiling point to coagulate albuminous matter; this is separated subsequently by straining. If the albumin or other impurities were permitted to remain in the syrup, fermentation would probably be induced in warm weather. Saccharometers are very useful in making syrups by the hot process in cases where the proper specific gravity of the finished syrup is known. The saccharometer may be floated in the syrup while boiling, and thus the exact degree of concentration determined without waiting to cool the syrup and having to heat it again to concentrate it further. When taking a reading of the specific gravity of the hot syrup allowance must be made for the variation from the official temperature (specific gravities in the USP are taken at 25°).

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

The formula and procedure given for Acacia Syrup (page 1293) illustrate this method of preparation.

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

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

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

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

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

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

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

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

Sorbitol Solution is the sweetening agent and contains 70% *w/w* of total solids, consisting mainly of D-sorbitol. It has about half the sweetening power of syrup.[10]

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

Many other active ingredients (eg, ephedrine sulfate, dicyclomine hydrochloride, chloral hydrate, chlorpromazine hydrochloride, etc) are marketed as syrups. Like the cough syrups, these preparations are flavored and colored and are recommended in those instances where the patient cannot swallow the solid dosage form. An example of such a preparation is Ephedrine Sulfate Syrup USP XVIII. Besides the active ingredient, the syrup contains citric acid, amaranth solution, caramel, lemon and orange oils, benzaldehyde, vanillin, ethanol, and sucrose. Amaranth has been banned as an ingredient in manufactured products in a number of countries, including the US.

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

The formula and procedure given for Aromatic Eriodictyon Syrup (page 1293) illustrate this method of preparation.

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

To be successful in using this process, care in several particulars must be exercised: (1) the percolator used should be cylindrical or semicylindrical, and cone-shaped as it nears the lower orifice; (2) a coarse granular sugar must be used, otherwise it will form into a compact mass, which the liquid cannot permeate; (3) the purified cotton must be introduced with care. If pressed in too tightly, it will effectually stop the process; if inserted too loosely, the liquid will pass through the cotton rapidly and the filtrate will be weak and turbid (from imperfect filtration); it should be inserted completely within the neck of the percolator, since a protruding end, inside the percolator, up through the sucrose, will permit the last portions of water to pass out at the lower orifice without dissolving all of the sucrose. For specific directions see *Syrup* (page 1500). The process of percolation is applied on a commercial scale for the making of official syrups as well as those for confectionary use.

Percolation is the preferred method for the preparation of Syrup USP (page 1293). The sucrose, in this instance, is placed in the percolator. However, a slightly modified approach must be used if a drug of vegetable origin is to be incorporated into the syrup. For example, wild cherry bark is first percolated with water; the collection vessel contains sucrose (800 g) and glycerol (50 mL). When the total volume is 1000 mL, the percolate is agitated to produce Wild Cherry Syrup BPC.

Preservation—Syrups should not be made in larger quantities than can be used within a few months, except in those cases where special facilities can be employed for their preservation. A low temperature is the best method of preservation for syrups. The USP indicates that syrups not be exposed to excessive heat. Concentration without supersaturation is also a condition favorable to preservation. The USP states that syrups may contain preservatives to prevent bacterial and mold growth. Preservatives such as glycerin, methylparaben, benzoic acid, and sodium benzoate may be added, particularly when the concentration of sucrose in the syrup is low. Combinations of alkyl esters of *p*-hydroxybenzoic acid are effective inhibitors of yeasts which have been implicated in the contamination of commercial syrups.[11] Any attempt to restore syrups which have been spoiled through fermentation by heating them and "working them over" is reprehensible.

The official syrups should be preserved in well-dried bottles, preferably those which have been sterilized. These bottles should not hold more than is likely to be required during four to six weeks and should be completely filled, carefully stoppered, and stored in a cool, dark place.

Syrups Prepared from Juices

Blackberry syrup, pineapple syrup, and strawberry syrup may be prepared by following the directions given in the BPC for Raspberry Syrup. One volume of the concentrated raspberry juice is diluted with 11 volumes of syrup. Syrup of Black Currant BPC is prepared in a similar manner but with certain modifications. The pectin in the juice is destroyed with pectinase. The syrup is prepared from 700 g of sucrose and 560 mL of clarified juice and is preserved with sulfurous acid or sodium metabisulfite. The addition of a dye is permitted, provided it complies with the pertinent government regulations. Cherry Syrup USP is prepared from cherry juice by the addition of alcohol, sucrose, and water (page 1293).

Honeys

Honeys are thick liquid preparations somewhat allied to the syrups, differing in the use of honey, instead of syrup, as a base. They are unimportant as a class of preparations today but at one time, before sugar was available and honey was the most common sweetening agent, they were widely used. BPC lists two preparations containing honey. The first, Oxymel, or "acid honey," is a mixture of acetic acid (150 mL), purified water (150 mL), and honey (sufficient to produce 1000 mL of product). Squill Oxymel contains squill, water, acetic acid, and honey and is prepared by a maceration process.

One nonofficial preparation contains borax (10.5 g), glycerin (5.25 g), and sufficient honey to make 1000 g. It has been indicated that this type of product can cause serious boric acid intoxication in babies. It should not be used in pharmaceutical practice.

Mucilages

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

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

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

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

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

Several synthetic mucilage-like substances such as *polyvinyl alcohol*, *methylcellulose*, *carboxymethylcellulose*, and related substances, as described in Chapter 68, are used as mucilage substitutes, emulsifying and suspending agents. Methylcellulose (page 1297) is widely used as a bulk laxative since it absorbs water and swells to a hydrogel in the intestine in much the same manner as *psyllium* or *karaya gum*. Methylcellulose Oral Solution is a flavored solution of the agent. The solution may be prepared by slowly adding the methylcellulose to about one-third the amount of water, boiling, with stirring until it is thoroughly wetted. Cold water should then be added and the wetted material allowed to dissolve while stirring. The viscosity of the solution will depend upon the concentration and the specifications of the methylcellulose. The synthetic gums are nonglycogenetic and may be used in the preparation of diabetic syrups. Several formulas for such syrups, based on sodium carboxymethylcellulose, have been proposed.

Jellies

Jellies are a class of gels in which the structural coherent matrix contains a high portion of liquid, usually water. They are similar to mucilages, in that they may be prepared from gums similar to those used for mucilage, but they differ from the latter in having a jelly-like consistency. A whole gum of the best quality rather than a powdered gum is desirable in order to obtain a clear preparation of uniform consistency. Tragacanth is the gum used in the preparation of Ephedrine Sulfate Jelly NF XII. These preparations may also be formulated from acacia, chondrus, gelatin, carboxymethylcellulose, and similar substances, with water.

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

Jellies are prone to microbial contamination and therefore contain preservatives, eg, methyl *p*-hydroxybenzoate is used as a preservative in a base for medicated jellies. This base contains sodium alginate, glycerin, calcium gluconate, and water. The calcium ions cause a cross-linking with sodium alginate to form a gel of firmer consistency.[12] A discussion of gels is provided later in the chapter.

Nonaqueous Solutions

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

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

Although the lines between aqueous and nonaqueous preparations tend to blur in those cases where the solvent is water-soluble, it is possible to categorize a number of products as nonaqueous. This section is, therefore, devoted to five

groups of nonaqueous solutions; the first includes the alcoholic or hydroalcoholic solutions, examples of these being elixirs and spirits; the second, the ethereal solutions, an example being the collodions; the third, the glycerin solutions, as exemplified by the glycerins; the oleaginous solutions, as represented by the liniments, oleovitamins, toothache drops, inhalations, and inhalants.

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

Collodions

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

Elixirs

Elixirs are clear, pleasantly flavored, sweetened hydroalcoholic liquids intended for oral use. They are used as flavors and vehicles such as Aromatic Elixir (page 1294) for drug substances and, when such substances are incorporated into the specified solvents, they are classified as medicated elixirs, eg, Dexamethasone Elixir USP and Phenobarbital Elixir USP. The main ingredients in the elixir are ethanol and water but glycerin, sorbitol, propylene glycol, flavoring agents, preservatives, and syrups are often used in the preparation of the final product.

The distinction between some of the medicated syrups and elixirs is not always clear. For example, Ephedrine Sulfate Syrup USP contains between 20 and 40 mL of alcohol in 1000 mL of product. Ephedrine Elixir BPC contains syrup and 100 mL of ethanol in the same final volume. Definitions are, therefore, inconsistent and, in some instances, not too important with respect to the naming of the articles of commerce. The exact composition must, however, be known if the presence or absence of an ingredient (eg, sucrose) is of therapeutic significance or when an additional ingredient must be incorporated in the product.

Elixirs contain ethyl alcohol. However, the alcoholic content will vary greatly, from elixirs containing only a small quantity, to those that contain a considerable portion as a necessary aid to solubility. For example, Aromatic Elixir USP contains 21 to 23% C_2H_5OH; Compound Benzaldehyde Elixir, on the other hand, contains 3 to 5% C_2H_5OH.

Elixirs may also contain glycerin and syrup. These may be added to increase the solubility of the medicinal agent or for sweetening purposes. Some elixirs contain propylene glycol. Claims have been made that this solvent is a satisfactory substitute for both glycerin and alcohol. Sumner,[13] in his paper on terpin hydrate preparations, summarized the advantages and disadvantages of this solvent and suggested several formulations with therapeutic characteristics superior to those of the elixir described in NF XIII.

One usual dose of the elixir (5 mL) contains 85 mg of terpin hydrate. This substance is used in bronchitis in doses of 125 to 300 mg as an expectorant. The elixir is, therefore, ineffective for the treatment of bronchitis. However, the elixir is used as a vehicle for the drugs in many commercially available cough syrups. These may contain dextromethorphan hydrobromide, codeine phosphate, chlorpheniramine maleate, pyrilamine maleate, ammonium chloride, creosote, chloroform, and a wide variety of other drugs with expectorant and antitussive properties.

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

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

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

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

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

An elixir may contain water and alcohol soluble ingredients. If such is the case, the following procedure is indicated:

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

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

One of the official elixirs, Iso-Alcoholic Elixir (page 1319), is actually a combination of two solutions, one containing 8 to 10% ethanol and the other containing 73 to 78% ethanol. The elixir is used as a vehicle for various medicaments that require solvents of different alcohol strengths. For example, the alcohol strength of the elixir to be used with a single liquid galenical is approximately the same as that of the galenical. When different alcohol strengths are used in the same prescription, the elixir to be used is the one that produces the best solution. This is usually the average of the alcohol strengths of the several ingredients. For nonextractive substances, the lowest alcohol strength of elixir that will produce a clear solution should be used.

The formula for High-Alcoholic Elixir is:

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

This elixir and many other liquid preparations intended for internal use (eg, the diabetic syrups thickened with sodium

carboxymethylcellulose or similar substances) contain saccharin. During the past few years, scientists have been studying the toxic effects of this sweetening agent and of the cyclamates. The cyclamate studies showed that the sweetener could produce cancer in animals and, as a result, this substance was removed from a wide variety of products. Similar studies have been carried out on saccharin.

Cyclamates and saccharin have been banned in some countries as ingredients in manufactured products. However, these substances may still be purchased as OTC products themselves. Much research has been done to find a safe synthetic substitute for sucrose. As a result aspartame (methyl *N*-L-α-aspartyl-L-phenylalaninate), which is about 200 times sweeter than sucrose, is now being used in many commercial preparations as the sweetening agent. It is sparingly soluble in water and is most stable at a pH of 4.3. This compound will likely be used in a number of pharmaceutical formulations in the near future.[14]

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

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

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

Glycerins

Glycerins or glycerites are solutions or mixtures of medicinal substances in not less than 50% by weight of glycerin. Most of the glycerins are extremely viscous and some of them are of a jelly-like consistency. Few of the glycerins are extensively used.

Glycerin is a valuable pharmaceutical solvent forming permanent and concentrated solutions not otherwise obtainable. Some of these solutions are used in their original form as medicinal agents while others are used to prepare aqueous and alcoholic dilutions of substances which are not readily soluble in water or alcohol. Glycerin Otic Solution of the USP is discussed previously under Otic solutions. One of the glycerins, Phenol Glycerin BPC is diluted with glycerin to form the pharmaceutical preparation, Phenol Ear-Drops BPC.

Phenol Glycerin BPC

Phenol	**160 g**
Glycerin	**840 g**

Dissolve the phenol in the glycerin.

Phenol Ear-Drops BPC

Phenol Glycerin	**40 mL**
Glycerin, a sufficient quantity, to make	**100 mL**

Add the glycerin to the glycerite.

Water must not be added to this preparation. It reacts with the phenol to produce a preparation which is caustic and, consequently, damaging to the area of application.

Although not within the context of the definitions given in this section, certain aqueous and nonaqueous preparations are used to remove wax (cerumen) from the ear. One commercially available preparation contains benzocaine, chlorbutol, *p*-dichlorobenzene, and turpentine; others contain olive oil, dioctyl sodium sulfosuccinate, or triethanolamine polypeptide oleate-condensate. Sodium Bicarbonate Ear-Drops BPC should be used if wax is to be removed from the ear. This preparation contains sodium bicarbonate (5 g), glycerin (30 mL), and purified water (a sufficient quantity to make 100 mL).

Starch Glycerin, an emollient, contains starch (100 g), benzoic acid (2 g), purified water (200 mL), and glycerin (700 mL).

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

Inhalations and Inhalants

Inhalations

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

> Inhalations are drugs or solutions of drugs administered by the nasal or oral respiratory route for local or systemic effect. Examples in this Pharmacopeia are Epinephrine Inhalation and Isoproterenol Hydrochloride Inhalation. Nebulizers are suitable for the administration of inhalation solutions only if they give droplets sufficiently fine and uniform in size so that the mist reaches the bronchioles.
>
> Another group of products, also known as inhalations and sometimes called insufflations, consists of finely powdered or liquid drugs that are carried into the respiratory passages by the use of special delivery systems such as pharmaceutical aerosols that hold a solution or suspension of the drug in a liquefied gas propellant (see Aerosols). When released through a suitable valve and oral adapter, a metered dose of the inhalation is propelled into the respiratory tract of the patient. Powders may also be administered by mechanical devices that require a manually produced pressure or a deep inspiration by the patient, eg, *Cromolyn Sodium*.
>
> Solutions may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizer, or the nebulizer may be attached to a plastic face mask, tent, or intermittent positive-pressure breathing (IPPB) machine.

As stated in the pharmacopeia, particle size is of major importance in the administration of this type of preparation. The various types of mechanical devices that are used in conjunction with inhalations are described in some detail in Chapter 104. It has been reported in the literature that the optimum particle size for penetration into the pulmonary cavity is of the order of ½ to 7 μm. Fine mists are produced by pressurized aerosols and hence possess basic advantages over the older nebulizers. In addition to this, metered aerosols deliver more uniform doses than those obtained with the older mechanical devices. Chapter 93 should be consulted for further details on this subject.

The term *Inhalation* is used commonly by the layman to represent preparations intended to be vaporized with the aid of heat, usually steam, and inhaled. Benzoin Inhalation BPC contains benzoin, storax, and alcohol. The vapors from a preparation containing 1 teaspoonful of the tincture and 1 qt of boiling water may be inhaled. The device known as a *vaporizer* is used with a number of commercially available preparations of this type.

Epinephrine Inhalation and Isoproterenol Hydrochloride Inhalation are described in USP.

Inhalants

The USP defines inhalants as follows:

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

Propylhexedrine Inhalant and Tuaminoheptane Inhalant are described as consisting of cylindrical rolls of suitable fibrous material impregnated with propylhexedrine or tuaminoheptane (as carbonate) usually aromatized, and contained in a suitable inhaler. Propylhexedrine is the active ingredient in the widely used Benzedrex Inhaler. Both of these drugs are vasoconstrictors and are used to relieve nasal congestion.

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

Liniments

Liniments are solutions or mixtures of various substances in oil, alcoholic solutions of soap, or emulsions. They are intended for external application and should be so labeled. They are applied with rubbing to the affected area and, because of this, were once called *embrocations*. Dental liniments, which are no longer official, are solutions of active substances and are rubbed into the gums. Most dentists question their usefulness and, consequently, this type of preparation is relatively unimportant as a pharmaceutical form.

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

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

White Liniment BPC

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

Mix the oleic acid with the turpentine oil. Add the dilute ammonia solution mixed with 45 mL of previously warmed water. Shake. Dissolve the ammonium chloride in the remainder of the water, add to the emulsion, and mix.

Other liniments contain antipruritics, astringents, emollients, and analgesics and are classified on the basis of the active ingredient in the formulation. An example of a liniment in this category is:

Compound Calamine Application BPC
(Compound Calamine Liniment)

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

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

Dermatologists prescribe products of this type but only those containing the rubefacients are extensively advertised and used by consumers for treatment of minor muscular aches and pains.

Because of the confusion of camphorated oil (camphor liniment) with castor oil resulting in ingestion and leading to poisoning, camphorated oil has been banned from the market. It is essential that these applications be clearly marked for external use only. (Camphorated Oil is presently classified as a new drug by the Food and Drug Administration).

Oleovitamins

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

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

The indicated vitamins are unstable in the presence of rancid oils and, therefore, these preparations, and in particular, Oleovitamin A, should be stored in small, tight containers, preferably under vacuum or under an atmosphere of an inert gas, protected from light.

Spirits

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

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

Spirits should be stored in tight, light-resistant containers, and in a cool place. This prevents evaporation and volatilization of either the alcohol or the active principle.

Preparation—There are four classic methods for the preparation of this official group: These are *simple solution, solution with maceration, chemical reaction*, and *distillation*.

Simple Solution—This is the method by which the majority of spirits are prepared. The formula and procedure

given for Aromatic Ammonia Spirit illustrate this method of preparation.

Aromatic Ammonia Spirit

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

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

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

Ammonium carbonate is a mixture of ammonium bicarbonate and ammonium carbamate (NH_2COONH_4). The carbamate reacts with water to form the carbonate.

$$NH_2COONH_4 + H_2O \rightarrow (NH_4)_2CO_3$$

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

Solution with Maceration—In this procedure, leaves of the drug are macerated in purified water to extract water-soluble matter. They are then expressed, and the moist macerated leaves are added to a prescribed quantity of alcohol. The volatile oil is added to the filtered liquid. Peppermint Spirit is made by this process. Peppermint Spirit BPC differs from the official product in that it is a solution of the volatile oil in alcohol only. The concentration of volatile oil in the final product is about the same but the official preparation possesses a green color. The ready availability of soluble chlorophyll and other coloring agents has led to the frequent suggestion that a more uniform product could be obtained through their use. However, these agents cannot be used in preparing the official article.

The formula and procedure for Peppermint Spirit (page 814) illustrate this method of preparation.

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

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

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

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

Toothache Drops

Toothache drops are preparations used for temporary relief of toothache by application of a small pledget of cotton saturated with the product into the tooth cavity. Anesthetic compounds include clove oil, eugenol, and benzocaine; other ingredients include camphor, creosote, menthol, and alcohol.

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

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

Emulsions

An emulsion is a two-phase system prepared by combining two immiscible liquids, one of which is uniformly dispersed throughout the other and consists of globules that have diameters equal to or greater than those of the largest colloidal particles. The globule size is, of course, critical and must be such that the system achieves maximum stability. However, even under the best of conditions, separation of the two phases will occur unless a third substance, an *emulsifying agent*, is incorporated. The basic emulsion must, therefore, contain three components but the products of commerce may consist of a number of therapeutic agents dissolved in either of the two phases of the preparation.

Most emulsions are so prepared as to incorporate an aqueous phase into a nonaqueous phase (or *vice versa*). However, it is possible to prepare emulsions that are basically nonaqueous. For example, investigations of the emulsifying effects of anionic and cationic surfactants on the nonaqueous immiscible system, glycerin and olive oil, have shown that certain amines and three cationic agents produced stable emulsions. This broadening of the basic definition for the term *emulsion* is recognized in the USP.

An emulsion is a two-phase system in which one liquid is dispersed in the form of small droplets throughout another liquid. The dispersed

liquid is known as the internal or discontinuous phase, whereas the dispersion medium is known as the external or continuous phase. Where oil is the dispersed phase and an aqueous solution is the continuous phase, the system is designated as an oil-in-water (O/W) emulsion and this can be easily and uniformly diluted with water. Conversely, where water or an aqueous solution is the dispersed phase and oil or oleaginous material is the continuous phase, the system is designated as a water-in-oil (W/O) emulsion.

Many emulsifying agents are available for use in preparing emulsions, among them the following:

Natural Emulsifying Agents—These substances may be derived from either animal or vegetable sources. Examples of those obtained from the former source are gelatin, egg yolk, casein, wool fat, and cholesterol. Acacia, tragacanth, chondrus, and pectin are representative of those obtained from vegetable sources. Various cellulose derivatives, eg, methylcellulose and carboxymethylcellulose, are used to increase viscosity of the aqueous phase and thereby enhance emulsion stability.

Finely Divided Solids—Examples of emulsifying agents of this type are bentonite, magnesium hydroxide, aluminum hydroxide, and magnesium trisilicate.

Synthetic Emulsifying Agents—This group may be further subdivided into the anionic, cationic, and nonionic agents. Examples of these three types of emulsifying agents are, in order of presentation, sodium lauryl sulfate, benzalkonium chloride, and polyethylene glycol 400 monostearate.

Many of these emulsifying agents are described in greater detail in Chapter 68.

NF XIII suggested that only O/W emulsions are suitable for oral use because these are water-miscible and thus their oiliness is masked. This compendium gave specific directions for the preparation of emulsions utilizing gelatin as an emulsifying agent. These preparations are based on either type A or type B gelatin. Type A gelatin is prepared from acid-treated precursors and is used at a pH of about 3.2. It is incompatible with anionic emulsifying agents such as the vegetable gums. The following formula was recommended:

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

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

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

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

The emulsion type (O/W or W/O) is of lesser significance if the final preparation is to be applied to the skin. If there are no breaks in the skin, a W/O emulsion can be applied more evenly since the skin is covered with a thin film of sebum. The latter substance favors the oily phase and contributes to the ease of application. The choice of emulsion type will, however, depend on many other factors. This is particularly true for those preparations which have basic cosmetic characteristics. It may be advantageous to formulate an O/W emulsion if ease of removal is an important consideration to the patient.

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

Mineral Oil	500 mL
Acacia, very fine powder	125 g
Syrup	100 mL
Vanillin	40 mg
Alcohol	60 mL
Purified Water, to make	1000 mL

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

Very few emulsions are now included in the official compendia. The BPC states that the term "emulsion" should be restricted to oil-in-water preparations intended for internal use and lists the following: Liquid Paraffin Emulsion, Liquid Paraffin and Magnesium Hydroxide Emulsion, Liquid Paraffin and Phenolphthalein Emulsion, and Concentrated Peppermint Emulsion.

This, however, should not lead the student to the conclusion that emulsions are a relatively unimportant class of pharmaceuticals. While it is true that few preparations carry the term *emulsion* in their titles, they are of great significance as bases for other types of preparations, particularly in the dermatological and cosmetic areas. Academically, they illustrate the importance of the relationship between the theory and practice of emulsion technology and, practically, they possess a number of important advantages over other liquid forms. These may be summarized in the following way:

1. In an emulsion, the therapeutic properties and the spreading ability of the constituents are increased.
2. The unpleasant taste or odor of the oil can be partially or wholly masked by the process of emulsification. Secondary masking techniques are available to the formulator but these must be used with caution. If flavors and sweetening agents are added to the emulsion, only minimal amounts should be used in order to prevent the nausea or gastric distress that results on ingestion of larger quantities of these formulation aids.
3. The absorption and penetration of medicaments are more easily controlled if they are incorporated into an emulsion.
4. Emulsion action is more prolonged and the emollient effect is greater than that observed with comparable preparations.
5. Water is not only an inexpensive diluent but is a good solvent for the many drugs and flavors that are incorporated into the emulsion.

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

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

While emphasis concerning preservation of emulsions deals with the aqueous phase, microorganisms can reside also in the lipid (oil) phase. Consequently, it has been recommended

that pairs of preservatives be used to ensure adequate concentration in both phases.[15] Esters of *p*-hydroxybenzoic acid can be used to ensure appropriate concentrations in both phases because of their difference in oil and water solubilities.

An emulsion can be diluted with the liquid that constitutes or is miscible with the external phase. The diluting liquid will, however, decrease the viscosity of the preparation and, in certain instances, will invert the emulsion. The latter phenomena may occur if the emulsifier-in-water method (see below) is used to prepare the emulsion.

Preparation

The theory of emulsion preparation is discussed in Chapter 21. The following procedures are those suggested by Griffin *et al.*[16]

The formulator must first determine the physical and chemical characteristics of the active ingredient. He must know the following:

1. Structural formula
2. Melting point
3. Solubility
4. Stability
5. Dose
6. Specific chemical incompatibilities

It is also necessary, at this stage, to decide on the type of emulsion required. Washable emulsions are of the O/W type; nonwashable, the W/O type. In general, O/W emulsions contain over 70% water. W/O emulsions will usually contain higher concentrations of oils and waxes. The preparation of cream and ointment emulsions for topical use is given in Chapter 88.

Experimental formulations may be prepared by the following procedure:

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

The technique of emulsification of pharmaceutical preparations has been described by White.[17] The preparation of an emulsion requires work to reduce the internal phase into small droplets and disperse them through the external phase: this can be accomplished by a mortar and pestle or a high speed emulsifier. The addition of emulsifying agents not only reduces this work but also stabilizes the final emulsion. Emulsions may be prepared by four principle methods.

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

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

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

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

A recent innovation in emulsion technology is the development of multiple emulsions. The dispersed phase of these emulsions contains even smaller droplets which are miscible with the continuous phase. Thus the multiple emulsion may be O/W/O where the aqueous phase is between two oil phases, or W/O/W where the internal and external aqueous phases are separated by an oil phase. While the technique of preparing these emulsions is more complicated, recent research indicates potential use of these emulsions for prolonged action, more effective dosage forms, parenteral preparations, protection against the external environment, and enzyme entrapment.[18]

Equipment

When emulsions are prepared, energy must be expended to form an interface between the oily and aqueous phases. Emulsification equipment includes, therefore, a wide variety of agitators, homogenizers, colloid mills, and ultrasonic devices. Griffin, *et al*,[16] Becher,[19] and Peck, *et al*,[20] have evaluated the emulsification equipment used by pharmacists and drug manufacturers. These publications should be consulted for further details on the use of such apparatus for the preparation of emulsions and related products.

The preparation of emulsions on a large scale usually requires the expenditure of considerable amounts of energy for heating and mixing. Careful consideration of these processes has led to the development of low energy emulsification by using an appropriate emulsification temperature and selective heating of the ingredients. This process involves the preparation of an emulsion concentrate subsequently diluted with the external phase at room temperature.[21]

Agitators—Ordinary agitation or shaking may be used to prepare the emulsion. This method is frequently employed

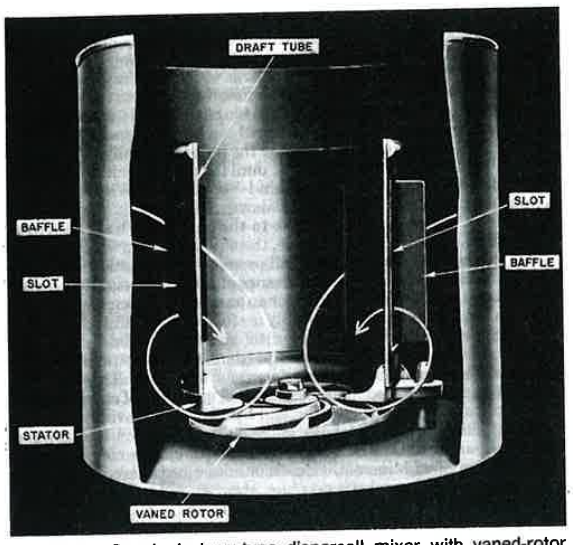


Fig 84-2. Standard slurry-type dispersall mixer with vaned-rotor "mixing" element and slotted draft-tube circulating element (courtesy, Abbe Eng).

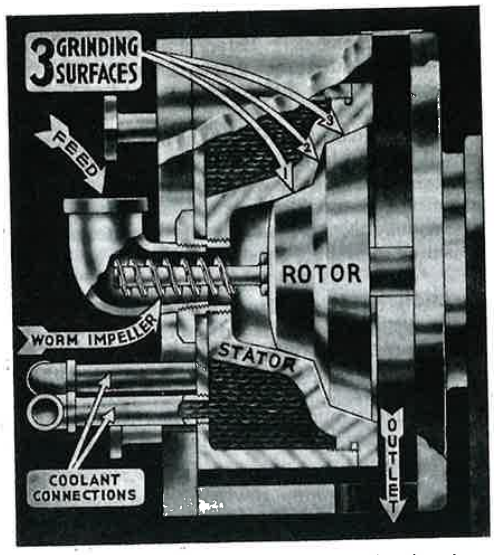


Fig 84-4. A colloid mill shown in cross section (courtesy, Tri-Homo).

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

The mortar and pestle are widely used by the prescription pharmacist in extemporaneous preparation of emulsions. This equipment has very definite limitations because its usefulness depends largely on the viscidity of the emulsifying agent. A mortar and pestle cannot be used to prepare an emulsion if the emulsifying agent lacks viscidity (eg, gelatin solutions). These emulsifying agents will produce stable emulsions only if other types of equipment are used to mix the ingredients and the agent together.

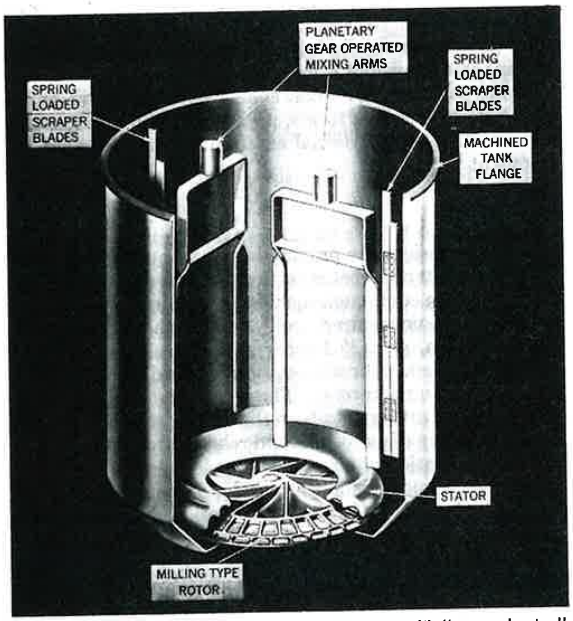


Fig 84-3. Standard paste-type dispersall mixer with "cupped-rotor" milling element and double-rotating mixing arm circulating element (courtesy, Abbe Eng).

Small electric mixers may be used to prepare emulsions at the prescription counter. These mixers will save time and energy and produce satisfactory emulsions when the emulsifying agent is acacia or agar. However, the mixers cannot be used if the emulsifying agent is gelatin.

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

Production-size agitators include high-powered propeller shaft stirrers immersed in a tank or self-contained units with propeller and paddle systems. The latter units are usually so constructed that the contents of the tank may be either heated or cooled during the production process. Baffles are often built into a tank and these increase the efficiency of agitation. Two mixers manufactured by the same company are shown in Figs 84-2 and 84-3.

Colloid Mills—The principle of operation of the colloid mill is the passage of the mixed phases of an emulsion formula between a stator and a high-speed rotor revolving at speeds of 2000–18,000 rpm. The clearance between the rotor and the stator is adjustable, usually from 0.001 in. upward. The emulsion mixture, in passing between the rotor and stator, is subjected to a tremendous shearing action which effects a fine dispersion. Two of the many types of colloid mills on the market are shown in Figs 84-4 and 84-5. The operating principle is the same for all but each manufacturer incorporates specific features which result in changes in operating efficiency. The shearing forces applied in the colloid mill may result in a temperature increase within the emulsion. It may be necessary, therefore, to cool the equipment when the emulsion is being produced.

Homogenizers and Viscolizers—In the viscolizer and the homogenizer, the mixed phases are passed between a finely ground valve and seat under high pressure. This, in effect,

Fig 84-5. Types of rotors used in colloid mills. These may be smooth (for emulsification of most emulsions), serrated (for the emulsification of ointments and very viscous products), or of vitrified stone (for the emulsifications of paints and pigment dispersions) (courtesy, Tri-Homo).

produces an atomization which is enhanced by the impact received by the atomized mixture as it strikes the valve head. This type of apparatus operates at pressures of 1000–5000 lb/sq in. and produces some of the finest dispersions obtainable in an emulsion.

Homogenizers may be used in one of two ways: (1) the ingredients in the emulsion are mixed and then passed through the homogenizer to produce the final product; or (2) an emulsion is prepared in some other way and is then passed through a homogenizer for the purpose of decreasing the particle size and obtaining a greater degree of uniformity and stability.

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

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

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

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

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

The Marco Flow-Master Kom-bi-nator employs a number of different actions, each of which takes the ingredients a little further along in the process of subdividing droplets until complete homogenization results. The machine is equipped with a pump which carries the liquid through the various stages of the process. In the first stage, the ingredients are forced between two specially designed rotors (gears) which shoot the liquid in opposite directions in a small chamber and, in this way, mixed thoroughly. These rotors also set up a swirling action in the next chamber into which the liquid is forced and swirled back and forth in eddies and cross currents. The second stage is a pulsing or vibrating action at rapid frequency. The product then leaves this chamber, goes through a small valve opening, and is dashed against the wall of the homogenizing chamber. Pressure is applied but is not as great as that used in other types of homogenizers. Pressure is accurately controlled by adjusting devices on the front of the machine, and temperature is controlled by passing coolants through the stators.

Ultrasonic Devices—The preparation of emulsions by the use of ultrasonic vibrations is also possible. An oscillator of high frequency (100,000–500,000/sec) is connected to two electrodes between which is placed a piezoelectric quartz plate. The quartz plate and electrodes are immersed in an oil bath and, when the oscillator is operating, high-frequency waves flow through the fluid. Emulsification is accomplished by simply immersing a tube containing the emulsion ingredients into this oil bath. Considerable research has been done on ultrasonic emulsification, particularly with regard to the mechanism of emulsion formation by this method. Limited data indicate that these devices will produce stable emulsions only with liquids of low viscosity. The method is not, however, practical for large-scale production of emulsions.

Special techniques and equipment will, in certain instances, produce superior emulsions, including rapid cooling, reduction in particle size, ultrasonic devices, etc. A wide selection of equipment for processing both emulsions and suspensions has been recently described[22]. A number of improvements have been made to make the various processes more effective and energy efficient.

Suspensions

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

Certain authors also include liniments and the newer sustained-release suspensions in any discussion of this particular subject. The former preparations are now usually considered as solutions although a number of older liniments were, in fact,

suspensions. The sustained-release suspensions represent a very specialized class of preparation, and as such, are discussed in more detail in Chapter 92. Some insoluble drugs are also administered in aerosol form. One example of such a preparation is dexamethasone phosphate suspended in a propellant mixture of fluorochlorocarbons. More detail on aerosols is available in Chapter 93.

Suspension formulation and control is based on the principles outlined in Chapters 19 to 22. Formulation involves more than suspending a solid in a liquid. A knowledge of the behavior of particles in liquids, of suspending agents, and of flavors and colors is required to produce a satisfactory suspension.

Briefly, the preparation of a stable suspension depends upon the appropriate dispersion of the drug in the suspending medium. To ensure that the particles are wetted by the dispersion medium a surface-active agent should be used, especially if the dispersed phase is hydrophobic. The suspending agent in the aqueous medium can then be added. Alternatively, the dry suspending agent can be thoroughly mixed with the drug particles and then triturated with the diluent. Other approaches to suspension preparation include the formation of a flocculated suspension and also a flocculated preparation in a suspending vehicle. Details of these procedures are given in Chapter 21.

The most efficient method of producing fine particles is by dry milling prior to suspension. Suspension equipment such as colloid mills or homogenizers are normally used in wet milling finished suspensions to reduce particle agglomerates. These machines (Fig 84-4) usually have a stator and a rotor which effects the dispersion action. Several methods of producing small uniform dry particles are: micropulverization fluid energy grinding, spray drying, and controlled precipitation with ultrasound.[23]

The choice of an appropriate suspending agent depends upon the use of the products, external or internal, facilities for preparation, and the duration of product storage.

Preparations made extemporaneously for internal use may include as suspending agents: acacia, methylcellulose and other cellulose derivatives, sodium alginate, and tragacanth. Agents suitable for external use include bentonite, methylcellulose and other cellulose derivatives, sodium alginate, and tragacanth. Agents which may require high speed equipment and which are suitable for internal or external use include aluminum magnesium silicates and carbomer.[24]

Preparations such as those mentioned above possess certain advantages over other dosage forms. Some drugs are insoluble in all acceptable media and must, therefore, be administered as a tablet, capsule, etc, or as a suspension. Because of its liquid character, the last preparation insures some uniformity of dosage but does present some problems in maintenance of a consistent dosage regimen. Disagreeable tastes can be covered by use of a suspension of the drug or a derivative of the drug, an example of the latter being the drug chloramphenicol palmitate. Suspensions are also chemically more stable than solutions. This is particularly important with certain antibiotics and the pharmacist is often called on to prepare such a suspension just prior to the dispensing of the preparation. In addition to this, a suspension is an ideal dosage form for patients who have difficulty swallowing tablets or capsules. This factor is of particular importance in administration of drugs to children.

Suspensions should possess certain basic properties. The dispersed phase should settle slowly and should be readily redispersed on shaking. They should not cake on settling and the viscosity should be such that the preparation pours easily. As with all dosage forms, there should be no question as to the chemical stability of the suspension. Appropriate preservatives should be incorporated in order to minimize microbiological contamination. Lastly, the suspension must be acceptable to the patient on the basis of its taste, color, and cosmetic qualities, the latter two factors being of particular importance in preparations intended for external use.

Gels

Pharmaceutical terminology is, at best, confusing and no two authors will classify Gels, Jellies, Magmas, Milks, and Mixtures in the same way. The NF described Gels as a special class of pharmaceutical preparations but considered Jellies under the same heading. The latter preparations usually contain water-soluble active ingredients and are, therefore, considered in another part of this chapter. The USP definition for Gels is given below.

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

The USP states that each 100 g of Aluminum Hydroxide Gel contains the equivalent of not less than 3.6 and not more than 4.4 g of aluminum oxide (Al_2O_3), in the form of aluminum hydroxide and hydrated oxide, and it may contain varying quantities of basic aluminum carbonate and bicarbonate. The gel itself is usually prepared by the interaction of a soluble aluminum salt, such as a chloride or sulfate, with ammonia solution, sodium carbonate or bicarbonate. The reactions which occur during the preparation are:

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

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

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

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

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

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

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

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

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

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

Aluminum hydroxide gels may also contain peppermint oil, glycerin, sorbitol, sucrose, saccharin, and various preservatives. Sorbitol improves the acid-consuming capacity, apparently by inhibiting a secondary polymerization that takes place on aging. In addition polyols such as mannitol, sorbitol,

and inositol have been shown to improve the stability of aluminum hydroxide and aluminum hydroxycarbonate gels.

Aluminum Hydroxide and Belladonna Mixture BPC

Belladonna Tincture	100 mL
Chloroform Spirit	50 mL
Aluminum Hydroxide Gel to	1000 mL

It should be noted, however, that the addition of other drugs (e.g., antibiotics) to the gel may result in a loss of the activity anticipated for that active ingredient.

Generally, if left undisturbed for some time, gels may become semisolid or gelatinous. With some gels, small amounts of water may separate on standing.

The single phase gels are being used more frequently in pharmacy and cosmetics because of several properties: semi-solid state, high degree of clarity, ease of application, ease of removal, and use. The gels often provide a faster release of drug substance, independent of the water solubility of the drug, as compared to creams and ointments. Some drugs used in medication gels include: urea, hydrogen peroxide, ephedrine sulphate, erythromycin, and povidone iodine.

The gels may be used as lubricants for catheters, bases for patch testing, sodium chloride gels for electrocardiography, fluoride gels for topical dental use, and prostaglandin-E_2 gel for intravaginal administration.

The gels can be prepared from a number of pharmaceutical agents such as tragacanth 2–5%, sodium alginate 2–10%, gelatin 2–15%, methylcellulose 2–4%, sodium carboxymethylcellulose 2–5%, carbomer 0.3–5%, polyvinyl alcohols 10–20%.[25] The percentages indicate the concentration ranges of the gelling agent. The lower percentage preparations may be used as lubricants and the higher percentage preparations are used as dermatological bases. Some of the gelling agents are available in different grades indicating the viscosity at a definite concentration. In general, high viscosity grades result in gels at lower concentrations.

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

The preparation of a few gel bases is given below:

Sodium Alginate Gel Base

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

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

Carbomer Jelly

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

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

The USP lists a number of gels: Sodium Fluoride and Phosphoric Acid Gel for application to the teeth to reduce cavities, Betamethasone Benzoate Gel and Fluocinonide Gel, anti-inflammatory corticosteroids, Tolnaftate Gel, an antifungal agent, and Tretinoin Gel for acne treatment.

Lotions

Lotions are usually liquid suspensions or dispersions intended for external application to the body. They may be prepared by triturating the ingredients to a smooth paste and then cautiously adding the remaining liquid phase. High-speed mixers or homogenizers produce better dispersions and are, therefore, the tools of choice in the preparation of larger quantities of lotion. Calamine Lotion USP is the classical example of this type of preparation and consists of finely powdered, insoluble solids held in more or less permanent suspension by the presence of suspending agents and/or surface-active agents. Many investigators have studied Calamine Lotion and this had led to the publication of many formulations, each possessing certain advantages over the others but none satisfying the collective needs of all dermatologists. The formula for the official lotion is given on page 779.

Phenolated Calamine Lotion USP (page 780) contains 10 mL of liquefied phenol in sufficient calamine lotion to make the product measure 1000 mL. Formulations containing Avicel R (hydrated microcrystalline cellulose, *FMC Corp.*) and carboxymethylcellulose settle less than do the official preparations.

Calamine Lotion

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

Phenolated Calamine Lotion

Calamine	8 g
Zinc Oxide	8 g
Glycerin	2 mL
Avicel R Gel	2 g
Carboxymethylcellulose	2 g
Liquefied Phenol	1 mL
Calcium Hydroxide Solution, a sufficient quantity, to make	100 mL

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

Suspensions may also be formed by chemical interaction in the liquid. White Lotion is an example of this type of preparation.

White Lotion

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

Dissolve the zinc sulfate and the sulfurated potash separately, each in 450 mL of purified water, and filter each solution. Add slowly the sulfurated potash solution to the zinc sulfate solution with con-

stant stirring. Then add the required amount of purified water, and mix.

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

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

This lotion must be freshly prepared and does not contain a suspending agent. Bentonite Magma has been used in some formulations. Coffman and Huyck[26] include a detailed discussion of the chemistry and the problems involved in the preparation of a suitable product.

The USP recognizes a second type of lotion. These are emulsions of the O/W type stabilized by a surface-active agent. Benzyl Benzoate Lotion is an example of this type of preparation. Lastly, some lotions are clear solutions and, in fact, the active ingredient of one official lotion, Dimethisoquin Hydrochloride Lotion, is a water-soluble substance. However, one unofficial formulation for this lotion lists dimethisoquin hydrochloride, menthol, and zinc oxide as active ingredients and the preparation thus becomes a suspension. Several lotions are listed in the USP and contain for example: antibiotics, steroids, keratolytics, and scabicides.

A formula for hydrocortisone lotion is given in the BPC 1973:

Hydrocortisone, finely powdered	10.0 g
Chlorocresol	0.5 g
Glyceryl Monostearate, self-emulsifying	40.0 g
Glycerin	63.0 g
Purified Water, to make	1000.0 g

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

Lotions are usually applied without friction. Even so, the insoluble matter should be very finely divided. Particles approaching colloidal dimensions are more soothing to inflamed areas and are more effective in contact with infected surfaces. A wide variety of ingredients may be added to the preparation to produce better dispersions or to accentuate the cooling, soothing, drying, or protective properties of the lotion. Bentonite is a good example of a suspending agent used in the preparation of lotions. Methylcellulose or sodium carboxymethylcellulose will localize and hold the active ingredient in contact with the affected site. A formulation containing glycerin will keep the skin moist for a considerable period of time. The drying and cooling effect may be accentuated by the addition of alcohol to the formula.

Dermatologists frequently prescribe lotions containing anesthetics, antiseptics, astringents, germicides, protectives, or screening agents, to be used in treating or preventing various types of skin diseases and dermatitis. Antihistamines, benzocaine, calamine, resorcin, steroids, sulfur, zinc oxide, and zirconium oxide are common ingredients in unofficial lotions. In many instances the cosmetic aspects of the lotion are of great importance. Many lotions compare badly with cosmetic preparations of a similar nature. The manufacture of fine lotions to meet the specialized needs of the dermatologist provides the pharmacist with an excellent opportunity to demonstrate his professional competence. Recent extensive studies on lotions will assist the pharmacist to gain this goal.[27]

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

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

Magmas and Milks

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

Bentonite Magma USP (page 1297) is prepared by simple hydration. Two procedures are given in the compendium for the preparation of this product.

Magmas may also be prepared by chemical reaction. Magnesium hydroxide is prepared by the hydration of magnesium oxide.

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

Milk of Magnesia USP (page 795) is a suspension of magnesium hydroxide containing 7.0–8.5% $Mg(OH)_2$. It has an unpleasant alkaline taste. This taste can be masked with 0.1% citric acid and 0.05% of a volatile oil or a blend of volatile oils. The citric acid reduces the alkalinity of the preparation.

Milk of Bismuth (page 797) contains bismuth hydroxide and basic bismuth carbonate in suspension in water. The Magma is prepared by reacting bismuth subnitrate with nitric acid and ammonium carbonate with ammonia solution and then mixing the resulting two solutions.

The following reactions occur during the preparation of the magma.

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

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

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

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

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

For the most part, magmas and milks are intended for internal use, although Bentonite Magma is used primarily as a suspending eg, Milk of Magnesia USP and Dihydroxy Aluminum Aminoacetate Magma USP, agent for insoluble substances either for local application or for internal use. All magmas require a label directing that they be shaken well before use. Freezing must be avoided.

Mixtures

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

rations. The BPC uses the term *mixtures* and includes suspensions in this category, for example:

Ammonium Chloride Mixture BPC

Ammonium Chloride	100 g
Aromatic Ammonia Solution	50 mL
Liquorice Liquid Extract	100 mL
Purified Water, to make	1000 mL

It should be recently prepared.

The term mixture occurs in the expression dry mixture which may be used to describe many official USP products, in particular antibiotic powders for oral solutions which have been previously described on page 1498.

The pectin and the tragacanth in Kaolin Mixture with Pectin (page 812) act as suspending agents. An alternate formula, based on Veegum (*Vanderbilt*) and sodium carboxymethylcellulose, has been proposed.[28]

Kaolin Mixture with Pectin

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

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

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

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

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

Mixtures, including suspensions, are subject to contamination by microorganisms that remain viable and are a potential health hazard during the period of use of the products. Survival times of organisms depend on the preservative used in the formulation. A kaolin pediatric mixture that contains benzoic acid kills organisms rapidly, whereas organisms survived for more than a week in a magnesium trisilicate mixture that contained no more than a trace of peppermint oil.[29]

Occasionally it is necessary to prepare suspensions from crushed tablets. A general formula for this purpose is given.[24]

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

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

Cimetidine 300 mg tablets	24 (7,200 mg)
Glycerin	10 mL
Simple Syrup, to make	120 mL

The tablets are triturated using a mortar to a fine powder, the mixture is levigated with the glycerin, the simple syrup is added and mixed well. The mixture is placed in a blender until smooth and is then refrigerated.[30]

Official Suspensions

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

> Suspensions are preparations of finely divided, undissolved drugs dispersed in liquid vehicles. Powders for suspension are preparations of finely powdered drugs intended for suspension in liquid vehicles. An example of the ready-to-use type is *Trisulfapyrimidines Oral Suspension*, in which the three sulfapyrimidines are already suspended in a liquid, flavored vehicle in a form suitable for oral administration. *Tetracycline for Oral Suspension* is finely divided tetracycline mixed with suspending and dispersing agents. It is intended to be constituted with the prescribed volume of purified water and mixed before it is dispensed by the pharmacist for oral administration to the patient.

Neither this definition nor the monographs give specific directions for the preparation of the suspension although pharmacopeias usually permit the addition of suitable flavoring agents, suspending agents, preservatives, and certified color additives. One procedure for the preparation of the commonly used *Trisulfapyrimidines Oral Suspension* is given below.

Trisulfapyrimidines Oral Suspension

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

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

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

Many formulations for suspensions are given in the BPC under the heading of *mixtures*. A properly prepared suspension has a number of desirable properties: (a) the suspended material should not settle rapidly; (b) particles that do settle should not form a hard cake and should easily be uniformly resuspended on shaking; (c) the suspension should pour freely from the container. Insoluble powders that do not disperse evenly throughout the suspending medium, when shaken, should be finely powdered and levigated with a small amount of an agent such as glycerin or alcohol or a portion of the dispersion of the suspending agent. The other ingredients are incorporated and the remainder of the dispersion of the suspending agent is gradually incorporated by trituration to produce the appropriate volume.

Suspensions intended for parenteral or ophthalmic use are also described in the USP. For a discussion of these suspensions, reference should be made to Chapters 85 and 87.

Extraction

Extraction, as the term is used pharmaceutically, involves the separation of medicinally active portions of plant or animal tissues from the inactive or inert components by use of selective solvents in standard extraction procedures. The products so obtained from plants are relatively impure liquids, semisolids, or powders, intended only for oral or external use; they include classes of preparations known as decoctions, infusions, fluidextracts, tinctures, pilular (semisolid) extracts and powdered extracts. Such preparations have been popularly called galenicals, after Galen, the 2nd century Greek physician. For additional information concerning extraction and extractives, which are briefly discussed in the following, see RPS 15, Chapter 86.

In this discussion we are concerned primarily with basic extraction procedures for crude drugs to obtain the therapeutically desirable portion and eliminate the inert material by treatment with a selective solvent, known as the menstruum. Extraction differs from solution in that the presence of insoluble matter is implied in the former process. The principal methods of extraction are: (1) maceration, (2) percolation, (3) digestion, (4) infusion, and (5) decoction.

The processes of particular importance, insofar as the USP is concerned, are those of maceration and percolation; most pharmacopeias refer to such processes for extraction of active principles from crude drugs.

Maceration—In this process the solid ingredients are placed in a stoppered container with the whole of the solvent and allowed to stand for a period of at least three days (until soluble matter is dissolved), with frequent agitation. The mixture is then strained, the marc (the damp solid material) pressed, and the combined liquids are clarified by filtration or by decantation after standing.

Percolation—This is the procedure most frequently used to extract the active ingredients in the preparation of tinctures and fluidextracts. Certain specific procedural details are provided in USP, which should be consulted for such information. In the BPC general procedure, a percolator (a narrow cone-shaped vessel open at both ends) is used. The solid ingredient(s) are moistened with an appropriate amount of specified menstruum and allowed to stand for approximately four hours in a well-closed container, after which the drug mass is packed into the percolator. Sufficient menstruum is added to saturate the mass and the top of the percolator is closed. When the liquid is about to drip from the neck (bottom) of the percolator, the outlet is closed. Additional menstruum is added to give a shallow layer above the mass and the mixture is allowed to macerate in the closed percolator for 24 hours. The outlet of the percolator is then opened and the liquid contained therein is allowed to drip slowly, additional menstruum being added as required, until the percolate measures about three-quarters of the required volume of the finished product. The marc is pressed and the expressed liquid is added to the percolate. Sufficient menstruum is added to produce the required volume, and the mixed liquid is clarified by filtration or by allowing it to stand and then decanting.

For a detailed discussion of various aspects of percolation see RPS 15, Chapter 86.

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

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

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

Extracts

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

Tinctures—Tinctures are defined in the USP as being alcoholic or hydroalcoholic solutions prepared from vegetable materials or from chemical substances, an example of the latter being Iodine Tincture. Traditionally, tinctures of potent vegetable drugs essentially represent the activity of 10 g of the drug in each 100 mL of tincture, the potency being adjusted following assay. Most other tinctures of vegetable drugs represent the extractive from 20 g of the drug in 100 mL of tincture.

The USP specifically describes two general processes for preparing tinctures, one by percolation designated as Process P, and the other by maceration designated as Process M. These utilize the methods described above, on this page. Process P includes a modification so that tinctures that require assay for adjustment to specified potency may be thus tested before dilution to final volume. A tincture prepared by Process P as modified for assayed tinctures is Belladonna Tincture. Examples of tinctures prepared by Process M are Compound Benzoin Tincture and Sweet Orange Peel Tincture (the latter contains the extractive from 50 g of sweet orange peel in 100 mL of tincture).

Fluidextracts—The USP defines fluidextracts as being liquid preparations of vegetable drugs, containing alcohol as a solvent or as a preservative, or both, so made that each mL contains the therapeutic constituents of 1 g of the standard drug that it represents. While the USP states that pharmacopeial fluidextracts are made by percolation, the official compendia have previously described general procedures for three percolation methods used in making fluidextracts. Process A is a percolation method that can be modified for fluidextracts that must be assayed. Process E is an alternative for Process A in which percolation is conducted on a column of drug much greater in length than in diameter. Process D is used for preparing fluidextracts with boiling water as the menstruum, alcohol being added as a preservative to the concentrated percolate; this is the procedure used for preparing Cascara Sagrada Fluidextract.

The BP and BPC use the designation *Liquid Extracts* for the category of fluidextracts.

* For a discussion of *resins* and *oleoresins* obtained by solvent extraction of plant exudates see Chapter 25, under *Plant Exudates*.

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

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

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

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

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CHAPTER 89

Powders

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Powders are encountered in almost every aspect of pharmacy, both in industry and in practice. Drugs and other ingredients, when they occur in the solid state in the course of being processed into a dosage form, usually are in a more or less finely divided condition. Frequently this is a powder whose state of subdivision is critical in determining its behavior both during processing and in the finished dosage form. Apart from their use in the manufacture of tablets, capsules, suspensions, etc, powders also occur as a pharmaceutical dosage form. While use of powders as a dosage form has declined, the properties and behavior of finely divided solids material are of considerable importance in pharmacy.

This chapter is intended to provide an introduction to the fundamentals of powder mechanics and to the primary means of powder production and handling. The relationships of the principles of powder behavior to powders as dosage forms are discussed.

Production Methods

Molecular Aggregation

Precipitation and Crystallization—These two processes are fundamentally similar and depend on achieving three conditions in succession: (1) a state of supersaturation (supercooling in the case of crystallization from a melt), (2) formation of nuclei, and (3) growth of crystals or amorphous particles.

Supersaturation can be achieved through evaporation of solvent from a solution, cooling of the solution if the solute has a positive heat of solution, by production of additional solute as a result of a chemical reaction, or by a change in the solvent medium by addition of various soluble secondary substances. In the absence of seed crystals, significant supersaturation is required to initiate the crystallization process through formation of nuclei. A nucleus is thought to consist of from ten to a few hundred molecules having the spatial arrangement of the crystals that will ultimately be grown from them. Such small particles are shown by the Kelvin equation to be more soluble than large crystals and, therefore, to require supersaturation, relative to large crystals, for their formation and subsequent growth. It is a gross oversimplification to assume that, for a concentration gradient of a given value, the rate of crystallization is the negative of the rate of dissolution. The latter is generally somewhat greater.

Depending on the conditions of crystallization, it is possible to control or modify the nature of the crystals obtained. When polymorphs exist, careful temperature control and seeding with the desired crystal form are often necessary. The habit or shape of a given crystal form is often highly dependent on impurities in solution, pH, rate of stirring, rate of cooling, and the solvent. Very rapid rates of crystallization can result in impurities being included in the crystals by entrapment.

Spray Drying—Atomization of a solution of one or more solids *via* a nozzle, spinning disk, or other device, followed by evaporation of the solvent from the droplets is termed spray drying. The nature of the powder that results is a function of several variables, including the initial solute concentration, size distribution of droplets produced, and rate of solvent removal. The weight of a given particle is determined by the volume of the droplet from which it was derived and by the solute concentration. The particles produced are aggregates of primary particles consisting of crystals and/or amorphous solids, depending on the rate and conditions of solvent removal. This approach to the powdered state provides the opportunity to incorporate multiple solid substances into individual particles at a fixed composition, independent of particle size, and avoiding difficulties that can arise in attempting to obtain a uniform mixture of several powdered ingredients by other procedures.

Particle Size Reduction

Comminution in its broadest sense is the mechanical process of reducing the size of particles or aggregates. Thus, it embraces a wide variety of operations including cutting, chopping, crushing, grinding, milling, micronizing, and trituration, which depend primarily on the type of equipment employed. The selection of equipment in turn is determined by the characteristics of the material, the initial particle size, and the degree of size reduction desired. For example, very large particles may require size reduction in stages simply because the equipment required to produce the final product will not accept the initial feed, as in crushing prior to grinding. In the case of vegetable and other fibrous material, size reduction generally must be, at least initially, accomplished by cutting or chopping. Chemical substances used in pharmaceuticals, in contrast, generally need not be subjected to either crushing or cutting operations prior to reduction to the required particle size. However, these materials do differ considerably in melting point, brittleness, hardness, and moisture content, all of which affect the ease of particle size reduction and dictate the choice of equipment. The heat generated in the mechanical grinding, in particular, presents problems with materials which tend to liquefy or stick together and with the thermolabile products which may degrade unless the heat is dissipated by use of a flowing stream of water or air. The desired particle size, shape, and size distribution must also be considered in the selection of grinding or milling equipment. For example, attrition mills tend to produce spheroidal, more free-flowing particles than do impact-type mills, which yield more irregular-shaped particles.

Fracture Mechanics—Reduction of particle size through fracture requires application of mechanical stress to the material to be crushed or ground. Materials respond to stress by yielding, with consequent generation of strain. Depending on the time course of strain as a function of applied stresses, materials can be classified according to their behavior over a continuous spectrum ranging from brittle to plastic. In the case of a totally brittle substance, complete rebound would occur on release of applied stress at stresses up to the yield point, where fracture would occur. In contrast, a totally

plastic material would not rebound nor would it fracture. The vast majority of pharmaceutical solids lie somewhere between these extremes and thus possess both elastic and viscous properties. Linear and, to a lesser extent, nonlinear viscoelastic theory has been well developed to account for quantitatively and explain the simultaneous elastic and viscous deformations produced in solids by applied stresses.

The energy expended by comminution ultimately appears as surface energy associated with newly created particle surfaces, internal free energy associated with lattice changes, and as heat. Most of the energy expressed as heat is consumed in the viscoelastic deformation of particles, friction, and in imparting kinetic energy to particles. Energy is exchanged among these modes and some is, of course, effective in producing fracture. It has been estimated that 1% or less of the total mechanical energy used is associated with newly created surface or with crystal lattice imperfections.

While the grinding process has been described mathematically, the theory of grinding has not been developed to the point where the actual performance of the grinding equipment can be predicted quantitatively. However, three fundamental laws have been advanced:

Kick's Law—The work required to reduce the size of a given quantity of material is constant for the same reduction ratio regardless of the original size of the initial material.

Rittinger's Law—The work used for particulate size reduction is directly proportional to the new surface produced.

Bond's Law—The work used to reduce the particle size is proportional to the square root of the diameter of the particles produced.

In general, however, these laws have been useful only in providing trends and qualitative information on the grinding process. Usually laboratory testing is required to evaluate the performance of particular equipment. A work index, developed from Bond's Law, is a useful way of comparing the efficiency of milling operations.[1] A grindability index, which has been developed for a number of materials, also can be used to evaluate mill performance.[2]

A number of other factors must also be considered in equipment selection. Abrasion or mill wear is an important factor in the grinding of hard materials, particularly in high-speed, close-clearance equipment (eg, hammer mills). In some instances mill wear may be so extensive as to lead to highly contaminated products and excessive maintenance costs that make the milling process uneconomical. Hardness of the material, which is often related to abrasiveness, must also be considered. This is usually measured on the Moh's Scale. Qualitatively, materials from 1 to 3 are considered as soft and from 8 to 10 as hard. Friability (ease of fracture) and fibrousness can be of equal importance in mill selection. Fibrous materials, eg, plant products, require a cutting or chopping action and cannot usually be reduced in size effectively by pressure or impact techniques. A moisture content above about 5% will in most instances also create a problem and can lead to agglomeration or even liquefaction of the milled material. Hydrates will often release their water of hydration under the influence of a high-temperature milling process and thus may require cooling or low-speed processing.

Methods and Equipment—When a narrow particle size distribution with a minimum of fines is desired, closed-circuit milling is advantageous. This technique combines the milling equipment with some type of classifier (see *Particle Size Measurement and Classification*). In the simplest arrangement, a screen is used to make the separation, and the oversize particles are returned to the mill on a continuous basis while the particles of the desired size pass through the screen and out of the grinding chamber. Overmilling, with its subsequent production of fines, is thereby minimized.

In order to avoid contamination or deterioration, the equipment used for pharmaceuticals should be fabricated of materials which are chemically and mechanically compatible with the substance being processed. The equipment should be readily disassembled for ease in cleaning to prevent cross-contamination. Dust-free operation, durability, simplified construction and operation, and suitable feed and outlet capacities are additional considerations in equipment selection.

While there is no rigid classification of large-scale comminution equipment, it generally is divided into three broad categories based on feed and product size:

1. *Coarse crushers* (eg, jaw; gyratory; roll and impact crushers).
2. *Intermediate grinders* (eg, rotary cutters; disk; hammer, roller, and chaser mills).
3. *Fine grinding mills* (eg, ball, rod, hammer, colloid, and fluid energy mills; high-speed mechanical screen and centrifugal classifier).

Machines in the first category are ordinarily employed where the size of the feed material is relatively large, ranging from 1½ to 60″ in diameter. These are used most frequently in the mineral crushing industry and will not be considered further. The machines in the second category are used for feed materials of relatively small size and provide products which fall between 20- and 200-mesh. Those in the third category produce particles, most of which will pass through a 200-mesh sieve, though, often the particle size of the products from fine grinding mills is well into the micron range.

The comminution effect of any given operation can be described mathematically in terms of a matrix whose elements represent the probabilities of transformation of the various-size particles in the feed material to the particle sizes present in the output. The numerical values of the elements in the transition matrix can be determined experimentally and the matrix serves to characterize the mill. Matrices of this type are frequently a function of feed rate and feed particle size distribution but are useful in predicting mill behavior. Multiplication of the appropriate comminution matrix with the feed size distribution line-matrix yields the predicted output size distribution.

Intermediate and Fine Grinding Mills—The various types of comminuting equipment in this class generally employ one of three basic actions or, more commonly, a combination of these actions.

1. *Attrition*—This involves breaking down of the material by a rubbing action between two surfaces. The procedure is particularly applicable to the grinding of fibrous materials where a tearing action is required to reduce the fibers to powder.
2. *Rolling*—This uses a heavy rolling member to crush and pulverize the material. Theoretically, only a rolling-crushing type of action is involved, but in actual practice some slight attrition takes place between the face of the roller and the bed of the mill.
3. *Impact*—This involves the operation of hammers (or bars) at high speeds. These strike the lumps of material and throw them against each other or against the walls of the containing chamber. The impact causes large particles to split apart, the action continuing until small particles of required size are produced. In some instances high-velocity air or centrifugal force may be utilized to generate high impact velocities.

Roller Mills in their basic form consist of two rollers revolving in the same direction at different rates of speed. This principle, which provides particle size reduction mainly through compression (crushing) and shear has been applied to the development of a wide variety of roller mills. Some use multiple smooth rollers or corrugated, ribbed, or saw-toothed rollers to provide a cutting action. Most allow adjustment of the gap between rollers to control the particle size of the product. The roller mill is quite versatile and can be used to crush a variety of materials.

Hammer Mills consist of a rotating shaft on which are mounted either rigid or swing hammers (beaters). This unit is enclosed with a chamber containing a grid or removable screen through which the material must pass. On the upper part is the feed hopper. As the material enters the chamber, the rapidly rotating hammers strike against it and break it into

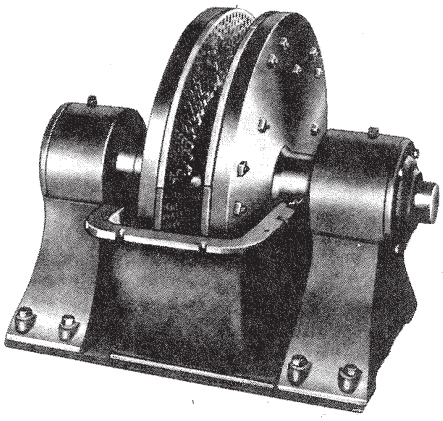

Fig 89-1. Sprout-Waldron double attrition mill.

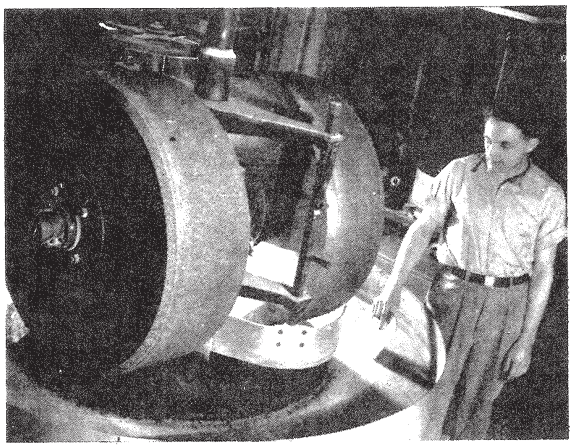

Fig 89-2. Chaser mill (courtesy, MSD).

smaller fragments. These are swept downward against the screen where they undergo additional "hammering" action until they are reduced to a size small enough to pass through the openings and out. Oversize particles are hurled upward into the chamber where they also undergo further blows by the revolving hammers.

These mills operate at high speed and generally with controlled feed rate. Both impact and attrition provide the grinding action. Particle size is regulated by rotor speed, feed rate, type and number of hammers, clearance between hammers and chamber wall, and discharge openings. The higher the speed, the steeper the approach angle of the particle to the screen hole. Thus, for any screen size opening, the higher the blade speed, the smaller the particle obtained. Increasing the screen thickness will have a similar effect. In general flat-edged blades are most effective for pulverizing, while sharp-edged blades will act to chop or cut fibrous materials.

A wide range of particle sizes down to the micron size can be produced by these mills. The particle shape, however, is generally sharper and more irregular than that produced by compression methods. When very fine particles are desired, hammer mills can be operated in conjunction with an air classifier. Under such conditions a narrower particle size distribution and lower grinding temperatures are obtained. Fine pulverizing of plastic material can be accomplished in these mills by embrittlement with liquid N_2 or CO_2 or by jacketing the grinding chamber.

Cutter Mills are useful in reducing the particle size of fibrous material and act by a combined cutting and shearing action. They consist of a horizontal rotor in which are set a series of knives or blades. This rotor turns within a housing into which are set stationary bed knives. The feed is from the top and a perforated plate or screen is set into the bottom of the housing through which the finished product is discharged. The particle size and shape is determined by the plate size, gap between rotor and bed knives, and size of the openings. A number of rotor styles are available to provide different particle shapes and sizes, though cutter mills are normally not designed to produce particles finer than 80 to 100 mesh.

Attrition Mills make use of two stone or steel grinding plates, one or both of which revolve to provide grinding mainly through attrition. These mills are most suitable for friable or medium-hard, free-flowing material.

The Sprout-Waldron double runner attrition mill (Fig 89-1) is an example of a mill which utilizes two rotating disks revolving in opposite directions. The particle size reduction is controlled by varying the speed at which the disks revolve, the space between the disks, and the size and number of ridges and indentations in the face of the disks. By using other plates and shell construction, these mills can be adapted for coarse granulating, pulverizing, shredding, and cutting. Projecting spikes, when added to the rotating plates to mesh with spikes on the stationary plate, provide a milling action that is similar to that obtained with a hammer mill. By appropriate combination with a classifier, particle sizes ranging from 10 mesh to 20 μm can be obtained by these attrition mills.

Chaser Mills are so called because two heavy granite stones, mounted vertically like wheels and connected by a short horizontal shaft, are made to revolve or *chase* each other upon a granite base (Fig 89-2). In practice chasers are enclosed in a tight box or small room with airtight doors and the substances to be powdered are fed in from the top by an elongated funnel, the spout of which delivers the material in the path of the stones. The height of a curb in the mill may be increased and the fineness of the powder thereby influenced by its height. Revolution of the chasers produces an upward current of air; this carries over the lighter particles, which fall outside the curb and are subsequently collected as a fine powder.

Pebble or Ball Mills, sometimes called "pot mills" or "jar mills," are operated on the principle of attrition and impact, the grinding being effected by placing the substance in jars or cylindrical vessels, lined with porcelain or a similar hard substance and containing "pebbles" or "balls" of flint, porcelain, steel, or stainless steel. These cylindrical vessels revolve horizontally on their long axis and the tumbling of the pebbles or balls over one another and against the sides of the cylinder produces pulverization with a minimum loss of material. Ball milling is a relatively slow process and generally requires many hours to produce material of suitable fineness. In order to keep the grinding time within reasonable limits, coarse material (>10-mesh) should be preground before introduction into a ball mill. Fig 89-3 shows a sectional view of a single jar mill. Rod mills are a modification in which rods about 3″ shorter than the length of the mill are used in place of balls. This results in a lower production of fines and a somewhat more granular product.

Vibrating Ball Mills, which also combine attrition and impact, consist of a mill shell containing a charge of balls similar to rotating ball mills. However, in this case the shell is vibrated at some suitable frequency, rather than rotated. These mills offer the advantage of being free of rotating parts, and thus can be integrated readily into a particle classifying system or other ancillary equipment. Furthermore, there have been several studies which have demonstrated that the vibrating ball mill will grind at rates often as high as 20 to 30 times that of the conventional tumbling mill and offer a higher order of grinding rate and efficiency than other prevailing milling procedures.

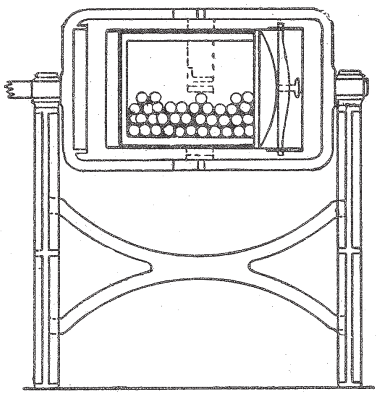

Fig 89-3. Single jar mill.

Fluid-Energy Mills are used for pulverizing and classifying extremely small particles of many materials. The mills have no moving parts, grinding being achieved by subjecting the solid material to streams of high velocity elastic fluids, usually air, steam or an inert gas. The material to be pulverized is swept into violent turbulence by the sonic and supersonic velocity of the streams. The particles are accelerated to relatively high speeds and when they collide with each other the impact causes violent fracture of the particles.

A schematic representation of one type of fluid-energy mill is shown in Fig 89-4. The elastic grinding fluid is introduced through nozzles in the lower portion of the mill under pressures ranging from 25 to 300 pounds per square inch. In this way, a rapidly circulating flow of gas is generated in the hollow, doughnut-shaped mill. A Venturi feeder introduces the coarse material into the mill and the particles enter into the jet stream of rapidly moving gas. The raw material is quickly pulverized by mutual impact in the reduction chamber. As the fine particles form they are carried upward in the track. Particles are simultaneously ground and classified in this process. The smaller particles are entrapped by the drag of gas leaving the mill and are carried out to a collecting chamber or bag. Centrifugal force at the top of the chamber stratifies the larger, heavy particles and their greater momentum carries them downward and back to the grinding chamber.

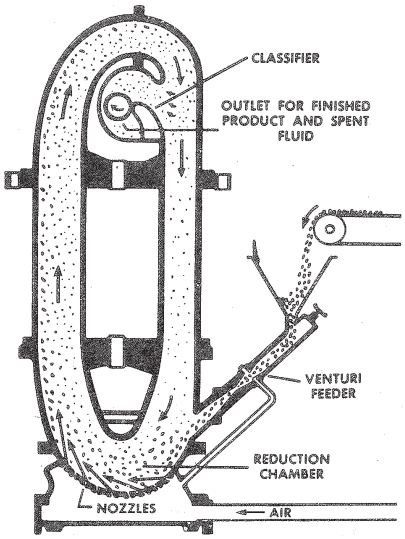

Fig 89-4. The Jet-O-Mizer fluid energy mill (courtesy, Fluid Energy).

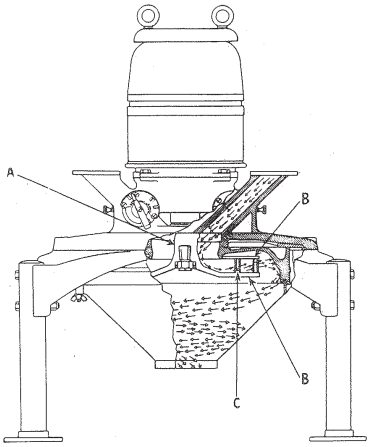

Fig 89-5. CentriMil, a centrifugal-impact mill, available in models ranging from 2 to 250 hp. A: Spinning rotor; B: rotor hub disks; C: impacters (courtesy, Entoleter).

A major advantage of the fluid-energy mill lies in the fact that the cooling effect of the grinding fluid as it expands in the grinding chamber more than compensates for the moderate heat generated during the grinding process. Another advantage in the use of these mills is the rather narrow range of particle sizes produced. When precise control of particle size is an important factor, the fluid-energy mill produces very narrow ranges of particles with minimum effort.

One major disadvantage is the necessity of controlling the feeding of the coarse, raw material into the jet stream. Often the feeding device becomes clogged by a clump of material, and special feeding devices must be built to produce a uniform rate of feed.

Centrifugal-Impact Pulverizers also have been found to be effective for the reduction of the particle size of a wide variety of materials ranging from very soft organic chemicals to hard abrasive minerals. In addition, this type of mill is well suited for the size reduction of heat-sensitive substances. Basically, in these pulverizers, the material is fed into the center of a spinning rotor which applies a high centrifugal force to the particles. The material, thus accelerated, moves toward the impactor set at the periphery of the rotor. On striking these impactors the material is hurled against the outer casing where final reduction is achieved. Processed material is removed from the bottom of the conical discharge hopper (Fig 89-5). Particle size reduction in the range of 10- to 325-mesh can be obtained with this type of mill with a minimum of fines.

Particle Size Measurement and Classification

Size and Distribution

Statistical Parameters—Monodisperse systems of particles of regular shape, such as perfect cubes or spheres, can be completely described by a single parameter, ie, length of a side or diameter. However, when either nonuniform size distributions or anisometric shapes exist, any single parameter is incapable of totally defining the powder. Measurements must be made over the total range of sizes present. Statistical diameters, for example, are useful measures of central size tendency and are computed from some measured property that is a function of size and related to a linear dimension. For irregular particles the assigned size will be strongly dependent on the method of measurement.

Once a method of assignment of numerical value for the

Table I—Definition of Statistical Diameters*

Type of Mean Diameter	Statistical Definition	Description
Arithmetic	$\Sigma nd/\Sigma n$	Mean diameter weighted by number
Diameter moment	$\Sigma nd^2/\Sigma nd$	Mean diameter weighted by particle diameter
Surface moment	$\Sigma nd^3/\Sigma nd^2$	Mean diameter weighted by particle surface
Volume moment	$\Sigma nd^4/\Sigma nd^3$	Mean diameter weighted by particle volume
Surface	$(\Sigma nd^2/\Sigma n)^{1/2}$	Root mean square
Volume	$(\Sigma nd^3/\Sigma n)^{1/3}$	

* When grouped data are used, n is the number of particles in a size interval characterized by a diameter, d.

diameter, surface area, or other parameter has been established, the average value computed for the parameter is dependent on the weighting given the various sizes. Mean particle diameter is the most important single statistical parameter since, if the proper diameter is chosen, the various other parameters of interest such as specific surface area, number, mean particle weight, etc, often may be calculated. Thus the choice of the mean diameter to be measured or calculated is based on its intended use. For example, specific surface area, which may control drug dissolution, frequently can be related to the root mean square diameter. Depending on the method of measurement, various diameters are obtained; these will be discussed later. The particle diameters most commonly used are listed in Table I.

Size Distributions—As has been pointed out, size distributions are often complex and no single particle size parameter is sufficient to characterize or permit prediction of the many bulk properties of pharmaceutical interest, eg, flow characteristics, packing densities, compressibility, segregation tendencies. Thus, descriptions beyond the central tendency provided by the various mean diameters are needed. These generally take the form of equations or charts that describe in detail the distribution of particle size. In measuring particle size it is important first to select the parameter that is related to the ultimate use of the product, and then select the method that will measure this parameter.

Certainly more useful information would be gained if the particle size of a powder used in a suspension were determined by sedimentation than by microscopy, or if the total surface area of the particles were the critical factor (as in use as an adsorbant) by the more useful method of permeability or gas adsorption.

Particles can be classified by determining the number of particles in successive size ranges. The distribution can be represented by a bar graph or histogram (Fig 89-6), where the widths of the bars represent the size range and the heights represent the frequency of occurrence in each range. A smooth curve drawn through the midpoints of the tops of the bars in this case results in a normal probability size distribution curve. A line drawn through the center of the curve to the abscissa divides the area into two equal parts and represents the mean value. Since a number of other symmetrical distributions could have this same midpoint a term to describe the scatter about the mean value is needed. Standard deviation (the root-mean square deviation about the mean) serves to define the spread of the curve on either side of the midpoint.

Most particulate material cannot, however, be described by a normal distribution curve. The resultant curves are usually skewed as shown in Fig 89-7, making mathematical

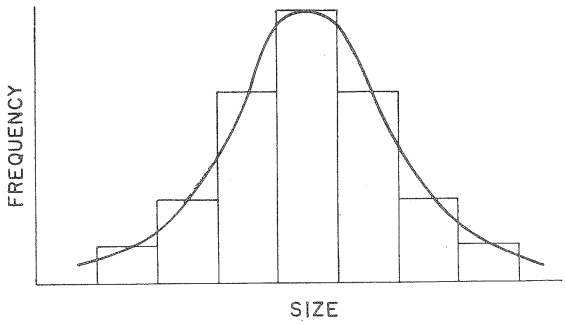

Fig 89-6. Symmetrical particle size distribution curve.

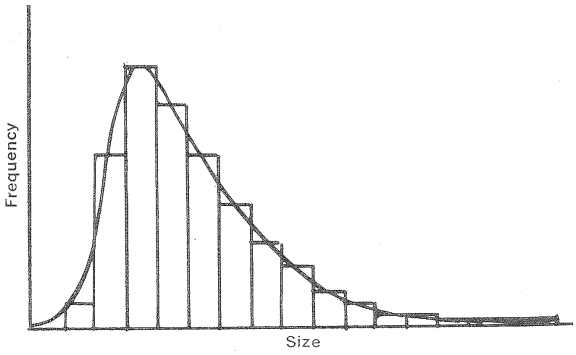

Fig 89-7. Skewed particle size distribution curve.

analysis complex. In a skewed size distribution the mean value is affected by very large or very small values. In these cases the median (ie, the central value of a series of observations) is a more useful average. In a symmetrical distribution the mean and the median values are the same. Most asymmetrical size distribution curves relating to powders can be converted into symmetrical curves by using the logarithm of the size, ie, Log Normal Distribution curve. The symmetrical shape of the latter curve allows for simplified mathematical analysis.

Cumulative plots are also useful for particle size distribution analysis. Here the cumulative percent of the particles which are finer (or larger) than a given size is plotted against the size. By use of logarithmic–probability paper the median size (geometric mean) and standard deviation (geometric standard deviation) can be readily obtained by graphical solution. The median is the 50% size and the standard deviation is the slope of the line and equal to the ratio 50% size/15.87% size (Fig 89-8).

Size Measurement

Frequently, particle size measurements are made in conjunction with separation of the powder into fractions on the basis of size. Methods that lead primarily to size distribution analysis only are discussed first, followed by methods in which classification by size is a central feature.

The basic processes employed for measurement, classification or fractionation of fine solid particles involve direct and indirect techniques. Direct methods measure the actual dimensions of the particle by use of a calibration scale as in microscopy and sieving. Indirect measurements make use of some characteristic of the particle that can be related to particle size; eg, sedimentation rates, permeability, and optical properties.

Microscopy—Microscopic techniques have been classified as one of the most accurate of *direct* methods. Here, particles

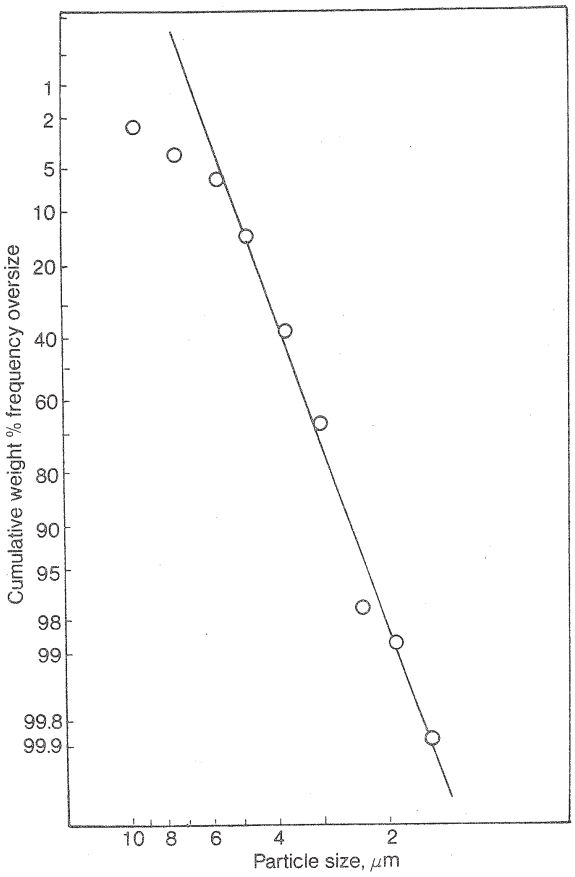

Fig 89-8. Log-probability plot of particle size vs cumulative weight % frequency oversize.

are sized directly and individually, rather than being grouped statistically by some other means of classification. The linear measurement of particles is made by comparison with a calibrated scale usually incorporated into the microscope. For spherical particles the size is defined by the measurement of the diameter. However, for other-shaped particles some other single size designation is generally used; eg, the diameter of a sphere with the same projected area as the nonspheroidal particle being measured. Other characteristic diameters based on various aspects of the projected particle outline as seen through the microscope also have been reported in the literature to describe nonspheroidal particles.

The method is rather tedious and other limitations are found in the techniques required for preparation of the slides and in the maximum resolution which sets the lower limits of particle size measurement using visible light. White light can resolve particles within the range of 0.2 to 100 μm. This lower limit can be decreased to about 0.1 μm by the use of ultraviolet light and to about 0.01 μm by the use of the ultramicroscope. The electron microscope finds its greatest usefulness in particle size measurements in the range of 0.2 to 0.001 μm.

While microscopic methods for particle size determination are time consuming, tedious, and generally require more skill than some of the other techniques, they do offer a number of advantages. They supply information about the shape and thickness that cannot be obtained by other methods and, in addition, supply a permanent record through use of photomicrographs.

A variety of semiautomated procedures have been developed to reduce the fatigue and tedium associated with manual counting of particles. These are represented by instruments such as the Imanco Quantimet 720 and the πMC System (*Millipore*) which scan the powder image in a manner similar to a TV scanner. The signal obtained is analyzed by a pulse-height analyzer and is expressed as a particle size distribution.

Adsorption of Gases—Adsorption of a solute from solution or of a gas at low temperatures onto powdered material serves as a measure of the particle surface area, generally reported as specific surface (area/unit mass). Common adsorption techniques utilize the adsorption of nitrogen and krypton at low temperatures. The volume of the gas adsorbed by a powdered sample is determined as a function of gas pressure, and an appropriate plot is prepared. The point at which a monomolecular layer of adsorbate occurs is estimated from the discontinuity that shows in the curve. The specific surface area then can be calculated from a knowledge of the volume of gas required to achieve this monolayer, and the area/molecule occupied by the gas, its molecular weight, and density. Frequently, more complex expressions such as the Brunauer, Emmett, and Teller (BET) equation must be used to describe the surface adsorption of some materials, and to determine the volume of gas required to produce an adsorbed monolayer. The surface properties of a number of pharmaceuticals have been investigated by this technique.

Permeability—When a gas or liquid is allowed to flow through a powdered material, the resistance to this flow is found to be a function of such factors as specific surface of the powder, area of the bed, pore space, pressure drop across the bed, and viscosity of the fluid. This resistance can be described and the specific surface calculated by the Kozeny-Carmen equation which relates these factors. This method, while it does not provide a size distribution analysis, does offer a rapid and convenient means of size estimation that is useful for some industrial operations.

Instruments that measure the rate of flow of a gas through a powder bed under controlled pressure differential are available commercially. The Fisher *Sub-Sieve Sizer* permits the reading of average particle size directly. The Blaine *Permeameter* produced by Precision Scientific Company utilizes the principle of filling the void spaces in a powder with mercury and then weighing it. The void fraction is calculated from the known density of mercury at different temperatures.

The calculations involved in permeability techniques are often complicated and yield only an average size of particles. In measuring particles in the subsieve ranges, rather large deviations may be encountered. With larger mesh sizes, some good agreement is found between the results obtained by techniques employing permeability and microscopy, particularly if the powders are made up of spherical or near-spherical particles.

Impaction and Inertial Techniques—The laws that govern the trajectories of particles in fluid streams are utilized in several methods of particle size measurement. Impaction devices are based on the dynamics of deposition of fine particles in a moving air stream when directed past obstacles of defined geometric form, or when forced from a jet device onto a plane surface.

The *cascade impactor*, described by Pilcher and his coworkers,[3] forces particle laden air at a very high speed and fixed rate through a series of jets (each smaller than the preceding one) onto glass slides; impaction takes place in a series of stages. The velocities of the air stream and the particles suspended in it are increased as they advance through the impactor. As a result, the particles are classified by impaction on the different slides, with the larger particles on the top slides and the smaller ones on the downstream slides. Fig 89-9 illustrates the principle of the cascade impactor. The exact size of impacted particles on each slide must subse-

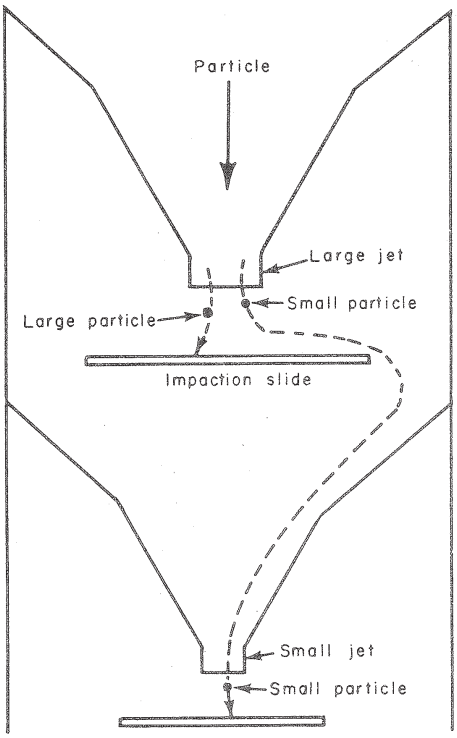

Fig 89-9. The principle of the cascade impactor.[3]

quently be determined. Size analyses may be obtained directly by theoretical treatment or prior calibration of the instrument.

Tillotson[4] has described an instrument based on inertial principles similar to those of the cascade impactor. This instrument may be adapted for automatic readout of size distribution by means of light-scattering techniques and electronic counters. The method is claimed to provide complete particle size distribution data in a few minutes.

Automatic Particle Size Counters—The Coulter Counter, HIAC Counter, and Gelman Automatic Particle Counter represent three examples of automatic counting equipment.

The *Coulter Counter* will determine the particle volume distribution of material suspended in an electrolyte-containing solution. A table of size ranges of several methods compared with the Coulter principle is shown in Fig 89-10. The principle underlying use of this instrument is described on page 560.

The *HIAC Counter* measures the size distribution of particles suspended in either liquids or gases. The standard models will measure sizes from 2 to 2500 μm at pressures up to 3000 psi. Basically, in this instrument the particles pass

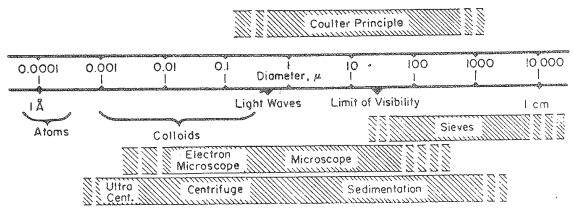

Fig 89-10. Size range of Coulter method compared with coverage of sieve, sedimentation, and microscopic methods, and overlap of electron microscope and centrifuge ranges (courtesy, Coulter).

a window one-by-one. Each particle as it passes, depending on its size, interrupts some portion of a light beam. This causes an instantaneous reduction in the voltage from a photodetector which is proportional to the size of the particle. Several counting circuits with preset thresholds tally the particles by size.

The *Gelman Counter* uses the principles of light-scattering to count particles in the air in the range of 0.5 μm and larger.

Size Classification

Sieving—This is one of the simplest and probably the most frequently used method for determining particle size distribution. The technique basically involves size classification followed by the determination of the weight of each fraction.

In this technique, particles of a powder mass are placed on a screen made up of uniform apertures. By application of some type of motion to the screen, the particles smaller than the apertures are made to pass through. The sieve motion generally is either (a) horizontal, which tends to loosen the packing of the particles in contact with the screen surface, permitting the entrapped subsieve particles to pass through or (b) vertical, which serves to agitate and mix the particles as well as to bring more of the subsieve particles to the screen surface.

One major difficulty associated with this method is the production of screens with uniform apertures, particularly in the very fine mesh sizes. As a result the practical lower limit for woven-wire mesh screens is about 43 μm (325-mesh). However, with the introduction of electroformed screens, sieves capable of analyzing particles in the 5-μm range are now available. In addition, "blinding" of the openings by oversize or irregular particles and inefficient presentation of the particles to the screen surface are problems associated with this technique. The use of horizontal and vertical screening motions, airjets, sudden periodic reversal of the sieve motion, and continuous cycling all have been used in an attempt to eliminate these problems.

For continuous operations, the screens are attached to mechanical or electromagnetic devices which supply the energy required to shake the particles through the openings in the screen and also prevent accumulation of fines within the openings as this tends to clog them and slow down the operation. The use of an electromagnetic instead of mechanical drive provides a more gentle sieving action with a resultant decrease in sieve wear, blinding, and less machine noise. Sieves may be used either in a sequence of sizes through which the material must pass or singly in the required size.

This apparatus is useful in obtaining size analysis data under controlled conditions. The sample is placed in the top of the nest of standard sieves arranged in a descending order. The length of time and force of vibration to which the sample is subjected may be preset by variable time and voltage controls. The controlled vibration causes the powder particles to pass through the sieves, each fraction coming to rest in the sieve through which it cannot pass. For the purpose of analysis, the weight of each fraction is determined and the percentage calculated.

The Sonic Sifter (*Allen-Bradley* and *ATM*) is a laboratory sifter that utilizes sonic oscillation to classify particles. A mechanical pulse action is used to reduce blinding and agglomeration in the subsieve sizes. This combination of sonic and mechanical agitation permits dry sifting down to 5 μm. US Standard Sieves are available for this unit from $3\frac{1}{2}$- to 400-mesh and in precision electroformed mesh sizes from 150 to 5 μm.

Industrial-size mechanical sieves are varied in design and capacity, and include the gyratory, circular rotatory, vibrating, shaking, and revolving sifters. In gyratory sifters the motion

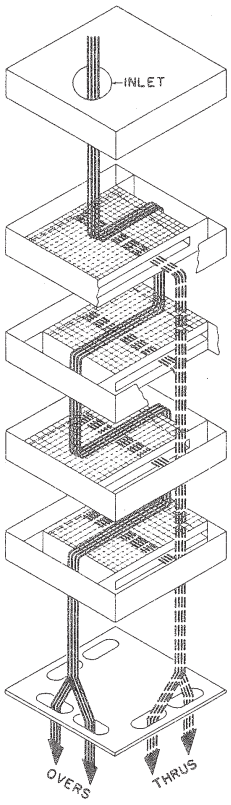

Fig 89-11. Gyro-Whip sifter (courtesy, Sprout-Waldron).

is in a single horizontal plane, but may vary from circular to reciprocal from the feed to the discharge end. The circular sifter also confines the screen motion to a horizontal plane, but in this case the total motion applied to the sieve is circular. The Sprout-Waldron *Gyro-Whip* is an example of such a sifter in which the material enters the top and spreads over the first sieve. Some of the finer particles drop through and are discharged into the "throughs" channel. The remaining powder moves to the next sieve in order, the process is repeated until complete separation is accomplished (Fig 89-11).

Centrifugal screening is utilized in the Symons *V-Screen* developed by Nordberg. Here the material is pushed through a spinning vertical wire cloth cylinder. Sharp cuts in particle size can be obtained with this equipment. Downward air flow, instead of shaking and tapping, has been used to move the particles through the screen openings; alternating with a reverse air flow serves to prevent "blinding," particularly with fine-mesh sieves.

Wet Screening—The addition of water is sometimes employed to dissolve out any unwanted binders, remove fines or surface contamination, and to reduce surface forces, particularly in micro-mesh sieves, that oppose the flow of particles through the sieve. Particles that tend to agglomerate or react with oxygen or moisture and thus cannot be dry-sieved often can be handled by wet-sieving. Particles in the 6 to 150-μm range have been classified with good precision using electroformed sieves. Some hydrophobic substances which resist wetting by water may be wet screened by the use of organic liquids such as petroleum ether, acetone, or alcohol. Wet screening may be accomplished by spraying both the screen surface and the material as it is fed onto the screen or by feeding a slurry of material directly onto the screen.

Screening Surfaces—A number of factors must be considered in selecting screening surfaces. Primary consideration is given to the size and shape of the aperture opening, selection of which is determined by the particle size that is to be separated. Screens commonly used in pharmaceutical processing include *woven wire screens*, *bolting cloth*, *closely spaced bars*, and *punched plates*. Punched plates are used for coarse sizing; their holes may be round, oval, square, or rectangular. The plates must be sturdy and withstand rough service. Sizes in common use range upward from $\frac{1}{4}$ inch.

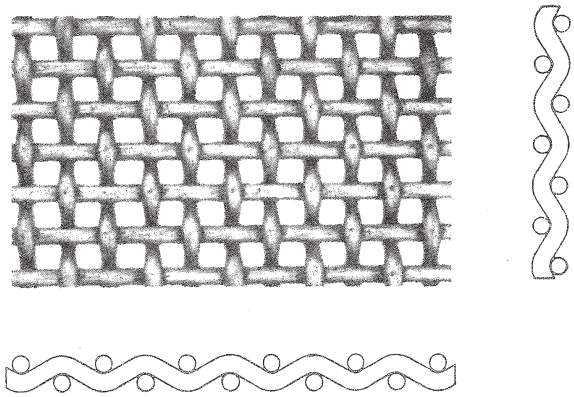

Fig 89-12. Plain weave screen.

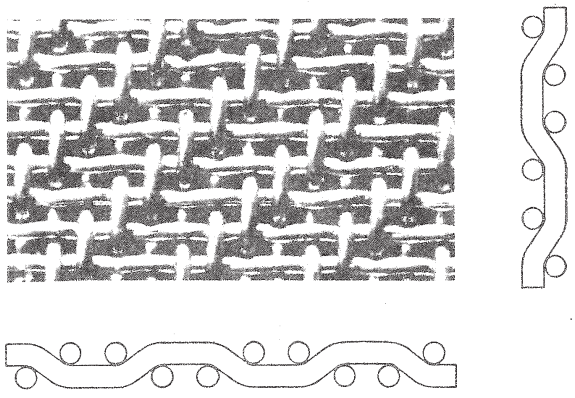

Fig 89-13. Twilled weave screen.

Most screening, however, is accomplished with woven wire screens ranging in size from those with 400 openings to the inch to screens with 4-inch square openings or larger. There are numerous types of woven wire screens, including plain, twilled and braided weave. An example of the plain and twilled weave is shown in Figs 89-12 and 89-13.

In the US, the two common standards are the *Tyler Standard* and *US Standard* sieves. In both these series the sieve number refers to the number of openings per linear inch. For most purposes, screens from the two series are interchangeable, though in a few instances the number designations are different. Since these numbers do not define the size of the openings the Bureau of Standards has established specifications for *Standard Sieves*, as given in Table II. These specifications also establish tolerances for the evenness of weaving, as irregularities from careless weaving might permit much larger particles to pass the sieve than would be indicated. The standard sieves used for pharmaceutical testing are of wire cloth.

Sedimentation—This method employs the settling of particles in a liquid of a relatively low density, under the influence of a gravitational or centrifugal field. In free settling (ie, no particle–particle interference) the particles are supported by hydraulic forces and their fall can be described by

Table II—Nominal Dimensions of Standard Sieves

No	Sieve opening, mm	Sieve opening, μm	Permissible variation in average opening, %	Permissible variation in maximum opening, %	Wire diameter, mm
2	9.52	9520	±3	+ 5	2.11 to 2.59
4	4.76	4760	±3	+10	1.14 to 1.68
8	2.38	2380	±3	+10	0.74 to 1.10
10	2.00	2000	±3	+10	0.68 to 1.00
20	0.84	840	±5	+15	0.38 to 0.55
30	0.59	590	±5	+15	0.29 to 0.42
40	0.42	420	±5	+25	0.23 to 0.33
50	0.297	297	±5	+25	0.170 to 0.253
60	0.250	250	±5	+25	0.149 to 0.220
70	0.210	210	±5	+25	0.130 to 0.187
80	0.177	177	±6	+40	0.114 to 0.154
100	0.149	149	±6	+40	0.096 to 0.125
120	0.125	125	±6	+40	0.079 to 0.103
200	0.074	74	±7	+60	0.045 to 0.061

Stokes' law. However, in most real situations particle–particle interference, nonuniformity, and turbulence are all present, resulting in more complex settling patterns. The Andreason pipet, which is based on sampling near the bottom of a glass sedimentation chamber, is perhaps the best known of the early instruments. With centrifugation, entrainment of particles in the currents produced by other particles may also interfere with fractionation.

Gravitational settling chambers are often used for large-scale separation of relatively coarse particles in the range of 100 μm. Centrifugal devices are useful for the separation of much smaller particles (5–10 μm).

Sedimentation balances are available which provide a means of directly weighing particles at selected time intervals as they fall in a liquid system. For continuous observations, automatic recording balances are also available. A commercially available instrument called a *Micromerograph* utilizes the principle of sedimentation in an air column. This instrument and others related to it in principle offer more rapid determinations than those which utilize a liquid medium. There are, however, serious uncertainties in the method which must be taken into consideration. Deviations from Stokes' law and impaction of particles against the inner wall of the settling chamber are sources of possible error.

The Carey and Stairmand *photosedimentometer* photographs the tracks of particles as they fall in a dispersion medium. The size determination is derived from the length of the photographic track, which is an indication of the distance traveled by the particles, and the time of exposure of the photograph.

Elutriation—In this process the particles are suspended in a moving fluid, generally water or air. In vertical elutriation at any particular velocity of the fluid, particles of a given size will move upwards with the fluid, while larger particles will settle out under the influence of gravity. In horizontal elutriation a stream of suspended particles is passed over a settling chamber. Particles that leave the stream are collected in the bottom of the chamber. Normally, for all elutriation techniques, both undersize and oversize particles appear in each fraction and recycling is required if a clean cut is desired. By varying the fluid velocities stepwise the sample may be separated into fractions. The amount in each fraction then can be determined and the size limits calculated by the use of the Stokes' equation or measured directly by microscopy. Air elutriation usually will give a sharper fractionation in a shorter time than will water elutriation.

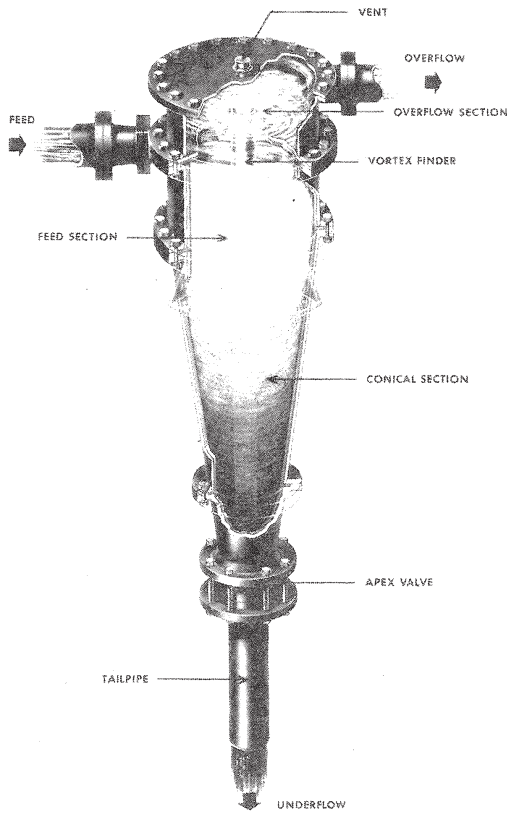

Fig 89-14. DorrClone, a hydrocentrifugal classifier (courtesy, Dorr-Oliver).

Centrifugal elutriation is basically the same process, except in this case the fluid stream is caused to spin so as to impart a high centrifugal force to the suspended particles. Those particles which are too large to follow the direction of flow separate out on the walls or bottom of the elutriator or cyclone. The finer particles escape with the discharge stream. Separation down to about 0.5 μm can be achieved with some centrifugal classifiers.

The DorrClone (*Dorr-Oliver*) shown in Fig 89-14 is an example of a centrifugal type classifier. The feed enters tangentially into the upper section. Centrifugal forces in the vortex throw the coarser particles to the wall where they collect and then drop down and out of the unit. The fine particles move to the inner spiral of the vortex and are displaced upward and finally out of the top of the unit.

The Sharples *Super Classifier* (Fig 89-15) is another example of a centrifugal classifier useful for the high-speed separation of fine particles. It has a capacity of about 250 lb/hr and operates at an air flow of about 100 cu ft/min at a maximum rotor speed of about 15,000 rpm.

The Donaldson air classifier subjects the feed particles to a high degree of dispersion just prior to classification and thus is able to make sharp separations in production quantities as low as 0.5 μm.

Inertial elutriators, which utilize an abrupt change in direction of the fluid stream to produce separation, are effective down to about 200-mesh. However, as with other elutriators a clean cut cannot usually be obtained without recycling.

Felvation is a unique process that combines elutriation and sieving along with a varying fluid flow rate and a turbulent fluidized bed to achieve particle separation. The particles are fluidized within the felvation column. By gradually in-

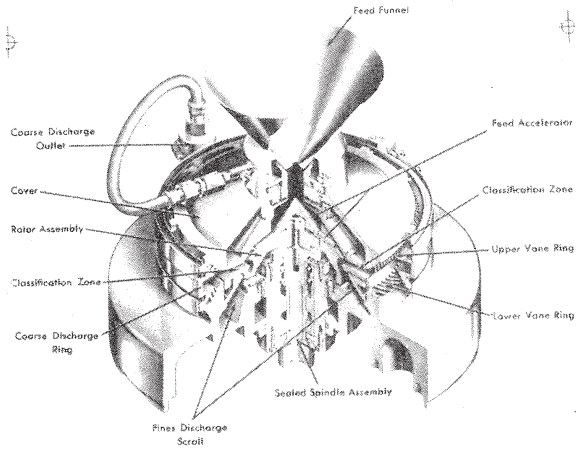

Fig 89-15. The Sharples K-8 Super Classifier (courtesy, Sharples).

creasing the fluid flow rate the very fine particles are brought up to and then through a sieve surface set into the upper section of the column. These fines are subsequently filtered out of the fluid stream. A further increase in the fluid flow rate causes larger and larger particles to move through the sieve. The final stage is reached when particles just larger than the sieve aperture are elutriated up to the sieve. Because of the way in which the particles are presented to the sieve, very little blinding of the openings occur. Furthermore, since the sieve need only serve as a "go, no go" gauge and not as a supporting surface for the powder, a relatively small sieve surface is required. Thus, the more uniform but more expensive electroform sieves, even down to a 10-μm size, can be utilized in this process.

Miscellaneous Methods—Numerous other methods have been applied to particle size determination, including X-ray and electron diffraction, ultrasound, flotation, and electrostatic, magnetic, and dielectrophoretic methods. These techniques either are used principally as research tools or are industrial-scale methods of use outside the pharmaceutical industry. Detailed descriptions of their principles of operation and their applications can be found in the texts listed at the end of this chapter.

Solids Handling

Packing and Bulk Properties

Bulk Density; Angles of Repose—Systems of particulate solids are the most complex physical systems encountered in pharmacy. No two particles in a powder are identical and the nature of momentum and energy exchange between particles defies description except in the most idealized and approximate terms. Bulk properties of powders are determined in part by the chemical and physical properties of their component solids and in part by the manner in which the various components interact. These interactions in turn frequently depend on the past history of the powder bed as well as on the ambient conditions.

The static properties of a particulate bed are dependent on particle–particle interactions and in particular on the way in which applied stresses are distributed through the bed. The number of contacts between particles and hence the average number of interparticulate contact points per particle increases as bed packing increases. Packing may be expressed in terms of porosity, percent voids, or fraction of solids by volume. Packings for regular arrangements of uniform spheres can be calculated and range in fractional solids from 0.53 for cubic to 0.74 for tetrahedral lattices. Powders comprised of irregular-shaped particles in a distribution of sizes can pack to fractional densities approaching unity.

The manner in which stresses are transmitted through a bed and the bed's response to applied stress are reflected in the various angles of friction and repose. The most commonly used of these is the angle of repose which may be experimentally determined by a number of methods, with slightly differing results. The typical method is to pour the powder in a conical heap on a level flat surface and to measure the included angle with the horizontal. Angles of repose range from 23 degrees for smooth uniform glass beads to 64 degrees for granular limestone. Cohesive materials frequently behave in an anomalous manner yielding values in excess of 90 degrees.

The angle of internal friction is a measure of internal stress distributions and is the angle at which an applied stress diverges as it passes through the bed. This angle together with the angle of slide are useful parameters in the design of storage/discharge bins. The latter angle is defined as the least slope at which a powder will slide down an inclined plane surface. Various other angles are in lesser use and will not be discussed here.

Statics—Powders at rest experience stresses that vary with location throughout their volume and that arise from pressures exerted by the container as well as from the weight of the bed above. Each point within the bed experiences both normal and shear stresses in general. Normal stresses may be either tensile or compressive. The powder bed will remain motionless and no flow will occur unless the normal and/or the shear strength is exceeded at some point within the bed. In general, the yield strengths, both normal and shear, are functions of the normal and shear stresses at the point of interest and depend upon the orientation of the axes of reference and the nature of the powder itself. It is apparent that to understand powder flow it is necessary to understand the conditions under which bed failure occurs and powder flow is initiated and sustained.

Consider the stresses which are applied to the faces of a small cube that is centered about a point chosen at random within a powder bed. Normal stresses are designated σ_i, where the subscript indicates the axis normal to the face and shear stresses are designated τ_{ij}, where the first subscript indicates the face and the second indicates the direction of the applied force. If the cube has an edge length, 1, which is not infinitesimal, and if a stress gradient exists within the region, the corresponding stresses on opposite faces of the cube will not be equal. However, if the cube is made progressively smaller and as 1 approaches zero, the stress values will converge to those at the point of interest. These forces are illustrated in Fig 89-16. It can be seen from this diagram that the state of stress at a point can be described by nine stress components.

If the system is in static equilibrium, and is not being accelerated translationally or rotationally, the forces which would otherwise result in movement must be in balance and have the effect of canceling each other. For example, τ_{xy} must equal τ_{yx} if rotation about the z-axis is not to occur. In a similar manner, shear and normal stresses, which would lead to translational movement along any of the three axes, must also balance.

Because the directions of the mutually perpendicular axes in Fig 89-16 were chosen arbitrarily, any other orientation of the cube corresponding to another set of axes must also result in a balance of forces. However, the distribution of stress among normal and shear components will depend on the particular axes selected. Thus, the stress condition of a powder can be analyzed in terms of the dependence of the normal and shear stresses on the direction chosen for the

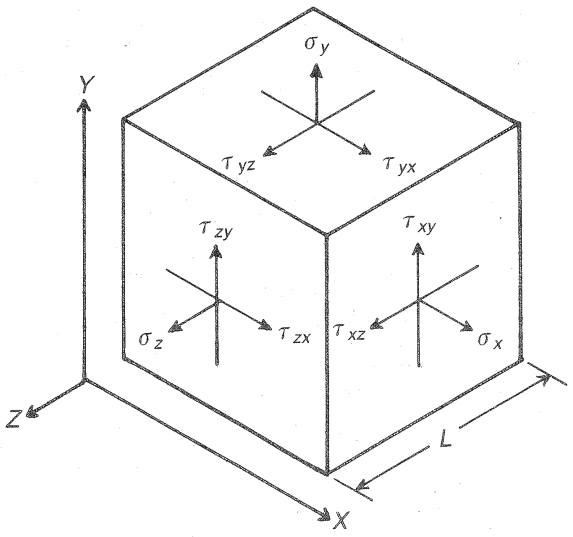

Fig 89-16.

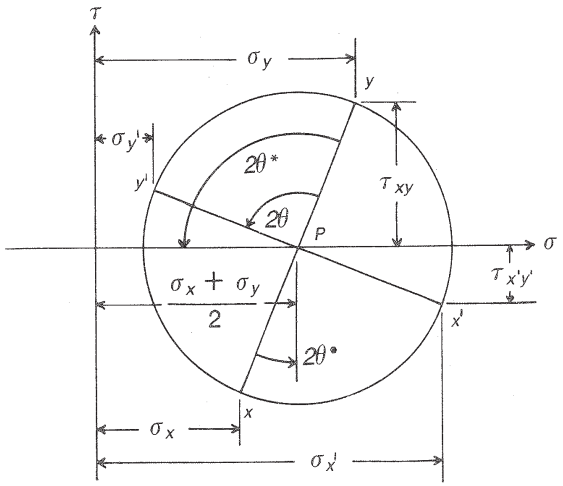

Fig 89-18.

reference axes. This can be done by a method of analysis devised by Mohr, and can be visualized using a Mohr circle diagram. The Mohr diagram permits stresses at any given point within a powder bed to be graphically resolved into normal, σ, and shear, τ, stresses for any arbitrary choice of axes.

For simplicity, assume that stress in the z-direction is not a function of z and that stress gradients exist in the x and y directions only. Stresses then can be analyzed in the xy plane without reference to the z-axis. Fig 89-17 shows the relationship between stresses relative to two xy coordinate systems at an angle θ to each other. If the condition of stress in the powder remains constant and only the angle θ between the two sets of reference axes is allowed to change, the resolution of stress into normal and shear components will be different for each set of axes and will depend on θ. By means of trigonometry, the relationships between these two sets of stresses is shown to be:

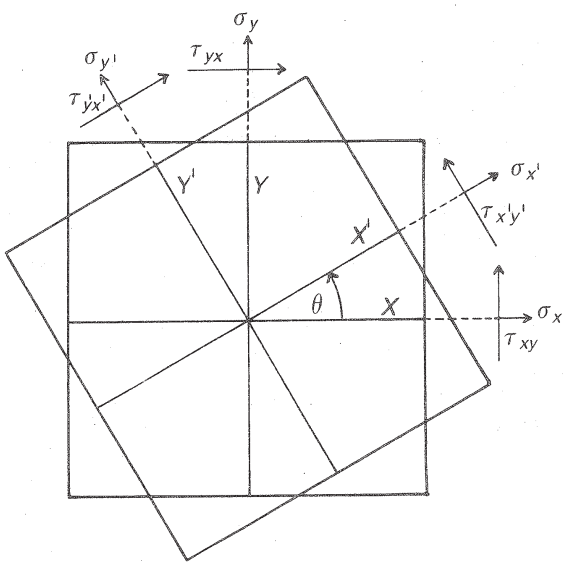

Fig 89-17.

$$\sigma_{x'} = \frac{\sigma_x + \sigma_y}{2} + \frac{\sigma_x - \sigma_y}{2} \cos 2\theta + \tau_{xy} \sin 2\theta$$

$$\sigma_{y'} = \frac{\sigma_x + \sigma_y}{2} - \frac{\sigma_x - \sigma_y}{2} \cos 2\theta - \tau_{xy} \sin 2\theta$$

$$\tau_{x'y'} = -\frac{\sigma_x - \sigma_y}{2} \sin 2\theta - \tau_{xy} \cos 2\theta$$

These equations permit the calculation of σ and τ values for any desired set of axes if the values are known for any given set of axes. In particular, if θ is chosen properly, $\tau_{x'y'}$ can be made to vanish and normal stresses only will remain. The set of axes for which this is true are called the *principal axes* of stress and the corresponding σ's are called the *principal stresses*. All points within static beds of powders can be characterized by principal axes and stresses which will, in general, vary from point to point throughout the bed. The principal axes do not necessarily correspond to the orientation of the walls of the powder container.

These concepts can be extended to three dimensions. Thus, it is possible to find a set of three mutually perpendicular planes, on which there are no shear stresses acting, for each location within the powder. The normals to these planes are the principal axes. It is also possible to find a set of planes for which the shear stresses are a maximum and the normal stresses are equal. The associated axes are called the axes of maximum shear. These two sets of axes are important since they represent directions of bed failure were it to occur.

The relationships between stresses, as functions of θ, can be illustrated and determined graphically. Fig 89-18 is an example of a Mohr's circle diagram for stress. Such diagrams are based on the stress equations. This can be seen by comparison of Fig 89-18 with the equations, noting the relationships of the stresses of θ. A Mohr diagram can be constructed for any point within the powder, permitting stresses to be graphically resolved into normal and shear components for any arbitrary choice of axes.

Steps in constructing a diagram are as follows. (1) Plot the center of the circle, p, on the σ axis at the average normal stress, $(\sigma_x + \sigma_y)/2$. (2) Plot point x and y with coordinates (σ_x, τ_{xy}) and (σ_y, τ_{xy}), respectively. Note that these three points lie on a diameter of the circle. (3) Draw a circle with its center at p and passing through points x and y. (4) Locate the $x'y'$ diameter using the angle 2θ. The stress components corresponding to the new axes can be read off the graph. Both

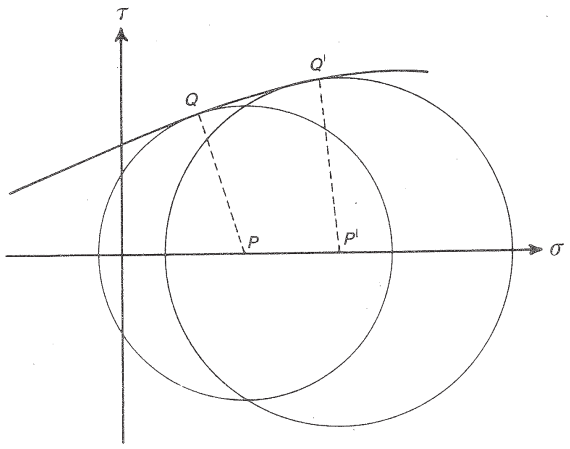

Fig 89-19.

$\sigma_{x'}$ and $\sigma_{y'}$ are read off the same axes on the graph since both are normal stresses.

For the particular case in Fig 89-18, the principal axes lie at an angle of θ^* to the original axes. The axes of maximum shear stress lie at an angle of θ from the original axes since the xy line corresponding to maximum shear is perpendicular to the σ axis. Depending on the state of the powder, it is possible to have negative σ values, where the Mohr circle passes to the left of the τ axis.

The application of stress normal to a plane of shear influences the shear stress at which the powder fails. Because of this, a given powder will fail at various combinations of normal and shear stresses. These combinations can be expressed graphically by a line in the σ,τ plane which separates regions on the graph at which the powder either flows or is stable. This is shown in Fig 89-19 for a typical powder. Various powders will display curves which uniquely define their failure characteristics. Each point on such a curve corresponds to a σ,τ combination at which failure occurs and can be analyzed by constructing a Mohr circle which passes through the point and is centered on the intersection of a line perpendicular to the point, q, and the σ axis. An example is shown in Fig 89-19.

Bulk Properties—In addition to the angles of repose and friction which reflect bulk behavior, tensile and shear strength and dilatancy are of interest. Tensile strength is measured by forming a powder bed on a roughened and split plate. Half of the plate is laterally movable and the force necessary to rupture the bed by pulling the plate halves apart, minus sliding plate friction corrections, represents the bed tensile strength. Various methods of applying force to the movable plate are used, including tipping the plate from the horizontal and allowing it to react to gravity by rolling on steel balls.

Shear strength is determined from the force necessary to shear horizontally a bed of known cross section. The Jenike shear cell is typical of those in use. It permits various loads to be applied normal to the plane of shear, whereby a shear failure locus can be determined. With the desired normal load applied, a steadily increasing shearing force is applied until failure occurs. These measurements are the basis for constructing powder failure curves such as that in Fig 89-19.

When packed powder beds are deformed, local expansion occurs along the failure planes, barring fracture of the particles themselves. This phenomenon is termed dilatancy and is a direct consequence of the micromechanics of interparticulate movement. For one particle to move past another it is necessary for it to move to the side in order to move forward when the particles are in an "interlocked" arrangement. Such arrangements predominate in packed beds with the consequence that the collective sideways movements in the failure zone produce bed expansion. Room for expansion must therefore be provided when packed beds are forced to flow.

Mixing of Powders

Degree of Homogeneity—Many mathematical expressions have been proposed and used to express the degree of homogeneity of powders comprised of two or more components. For the most part measures of mixture uniformity have been statistical and based on either the standard deviation or variance of the composition from its mean value. It should be recognized that these indices of mixing are scalar quantities and are incapable of uniquely describing the composition profile of a given powder bed. A practical definition of mixing uniformity should be selected to relate as closely as possible to the desired properties of the mix. The manner in which samples are taken (number, size, and location of samples) largely determines the validity and interpretation of the derived index.

The standard deviation is presented here as a representative index. It can be estimated solely from a set of n samples. If sample number i has composition x_i, and all samples are of uniform size, then the sample standard deviation is defined in the usual way as:

$$s = \sqrt{\sum_{i=1}^{n} (x_i - \bar{x})^2/(n-1)}$$

where $\bar{x}$ is the mean composition estimated from the samples alone.

In sampling a bed, there should be assurance that the bed is sampled uniformly over its entirety. This can be done either by use of a sampling "thief" designed to probe the bed and collect samples at selected points or serially as the powder is discharged from the mixer.

The "scale of scrutiny" at which the powder is examined for uniformity is determined by the sample size. This should be chosen based on the ultimate use of the powder. For a tablet or capsule formulation the appropriate sample size is that of the dosage form.

Two important concepts related to mixing uniformity have been described by Danckwerts as the scale and the intensity of segregation. Assuming that zones having uniform but differing compositions exist in a powder bed, the scale of segregation is a function of the size of the zones. The intensity of segregation is in turn a function of the composition differences among zones. Generally, the process of mixing tends to reduce the intensity of segregation while the scale of segregation passes through a minimum.

Mechanisms of Mixing and Segregation—Three primary mechanisms are responsible for mixing: (i) convective movement of relatively large portions of the bed, (ii) shear failure which primarily reduces the scale of segregation, and (iii) diffusive movement of individual particles. Most efficient mixers operate to induce mixing by all three mechanisms. Thus, mixing can be considered to be a random shuffling-type operation involving both large and small particle groups and even individual particles. However, it should be noted that the use of random motion to achieve random distribution assumes that no other factors influence this distribution. This is rarely if ever the case in practice. Instead, a variety of properties of the powders being mixed influence this approach to complete randomness. Stickiness or slipperiness of particles must be considered, among other factors. As might be expected, the stickier the material the less readily it mixes and demixes. Electrostatic forces on the particle surface also can produce marked effects on the mixing process, and in fact may produce sufficient particle–particle repulsion to make random mixing impossible.

By enabling particles to undergo movement relative to each other, mixers also provide the conditions necessary for segregation to occur. Any manipulation of a powder bed for purposes of conveying, discharge from a hopper, etc. provides the opportunity for segregation. Thus, many of the so-called mechanisms of segregation are actually conditions under which segregation can happen.

The segregation that occurs in free-flowing solids usually does so as a result of differences in particle size and, to a lesser extent, to differences in particle density and shape. The circumstances leading to segregation can be generalized from a fundamental physical standpoint. The necessary and sufficient conditions for segregation to occur are twofold: (i) that various mixture components exhibit mobilities for interparticulate movement which differ and (ii) that the mixture experience either a field which exerts a directional motive force on the particles or a gradient in a mechanism capable of inducing or modifying interparticulate movement. The combination of these conditions results in asymmetric particle migrations and leads to segregation.

Rates of Mixing and Segregation—Rate expressions analogous to those of chemical kinetics can be derived using any of the various indices of mixing as time dependent variables. When this is done, it is usually found that mixing follows a first-order approach to an equilibrium state of mixedness. More recently, mixing has been described as a stochastic process (by means of stationary and nonstationary Markov chains) in which the probabilities of particle movement from place to place in the bed are determined. When applied to a mixer, this approach is capable of indicating zones of greater and lesser mixing intensity.

Large-Scale Mixing Equipment—The ideal mixer should produce a complete blend rapidly with as gentle as possible a mixing action to avoid product damage. It should be easily cleaned and discharged, be dust-tight, and require low maintenance and low power consumption. All of these assets generally are not found in any single piece of equipment, thus requiring some compromise in the selection of a mixer.

Rotating Shell Mixers—The drum-type, cubical-shaped, double-cone, and twin-shell blenders are all examples of this class of mixers. Drum-type blenders with their axis of rotation horizontal to the center of the drum are used quite commonly. These, however, suffer from poor crossflow along the axis. The addition of baffles or inclining the drum on its axis increases crossflow and improves the mixing action. Cubical- and polyhedron-shaped blenders with the rotating axis set at various angles also are available. However, in the latter, because of their flat surfaces, the powder is subjected more to a sliding than a rolling action, a motion which is not conducive to the most efficient mixing.

Double-cone blenders, an important class of rotating shell or tumbling mixers, were developed in an attempt to overcome some of the shortcomings of the previously discussed mixers. Here, the mixing pattern provides a good crossflow with a rolling rather than a sliding motion. Normally, no baffles are required so that cleaning is simplified. The twin-shell blender is another important tumbling-type blender. This blender combines the efficiency of the inclined drum-type with the intermixing that occurs when two such mixers combine their flow. The Zig-Zag blender, an extension of the twin-shell blender, provides efficient continuous precision blending.

Fixed-Shell Mixers—The ribbon mixer, one of the oldest mechanical solid–solid blending devices, exemplifies this type of mixer. The ribbon mixer consists of a relatively long troughlike shell with a semicircular bottom. The shell is fitted with a shaft on which are mounted spiral ribbons, paddles, or helical screws, alone or in combination. These mixing blades produce a continuous cutting and shuffling of the charge by circulating the powder from end to end of the trough as well as rotationally. The shearing action that develops between the moving blade and the trough serves to break down powder agglomerates. However, ribbon mixers are not precision blenders; in addition, they suffer from the disadvantage of being more difficult to clean than the tumbler-type blenders and of having a higher power requirement.

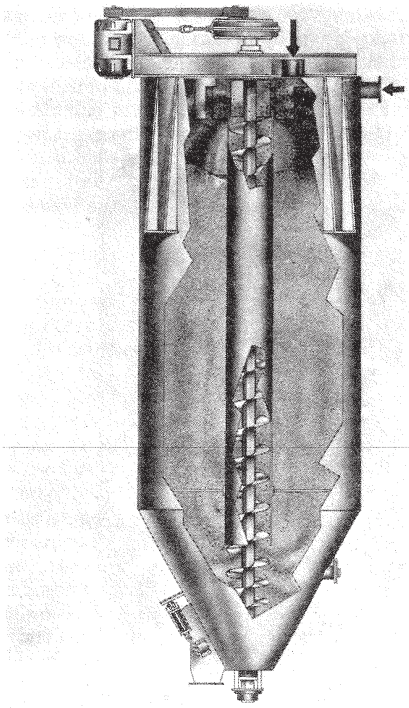

Fig 89-20. Sprout-Waldron vertical mixer.

Sigma-Blade and Planetary Paddle Mixers are also used for solid–solid blending, although most generally as a step prior to the introduction of liquids. Mixers with high-speed impeller blades set into the bottom of a vertical or cylindrical shell have been shown to be very efficient blenders. This type of mixer, in addition to its ability to produce precise blends, serves also to break down agglomerates rapidly. The mechanical heat buildup produced by this mixer within the powder mix, and the relatively high power requirement are often drawbacks to the use of this type of mixer.

Muller Mixers are a specialized class of mixers, useful for heavy-duty operations requiring high shearing forces. The mulling action is a shearing mechanism, and is the closest to the type of mixing achieved by the hand-operated mortar and pestle. *Vertical Impeller Mixers*, which have the advantage of requiring little floor space, employ a screw type of impeller which constantly overturns the batch (Fig 89-20). The fluidized mixer is a modification of the vertical impeller type. The impeller is replaced by a rapidly moving stream of air fed into the bottom of the shell. The body of the powder is fluidized and mixing is accomplished by circulation and overtumbling in the bed (Fig 89-21). Generally, when precision solid–solid blending is required, the rotating twin shell or the double cone type blenders are recommended.

Motionless Mixers—These are in-line continuous processing devices with no moving parts. They consist of a series of fixed flow-twisting or flow-splitting elements. The Ross Blendex (*Ross & Son*), designed for blending of free-flowing solids, is constructed to operate in a vertical plane. Four pipes interconnect with successive tetrahedral chambers, the number of chambers needed depending on the quality of mix desired. The powders enter the mixer from overhead hoppers

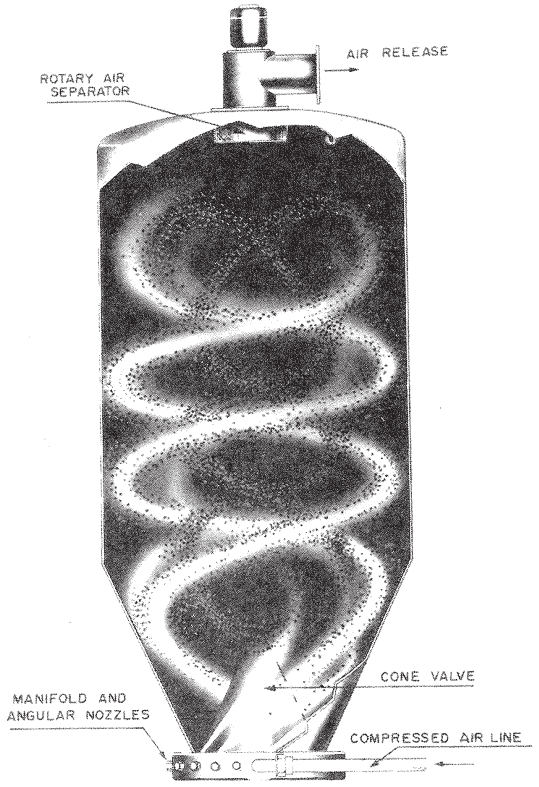

Fig 89-21. Air Mix mixer (courtesy, Sprout-Waldron).

and free fall through the mixer and are mixed by what is described as Interfacial Surface Generation. For two input streams entering this mixer the number of layers, L, emerging from each of the successive chambers, C, is $L = 2(4)^C$. Thus for 10 chambers over 2 million layers are generated. This type of blender provides efficient batch or continuous mixing for a wide variety of solids without particle size reduction or heat generation and essentially no maintenance. Units are available to mix quantities ranging from 100 to 5000 lb/hr.

Small-Scale Mixing Equipment—The pharmacist most generally employs the mortar and pestle for the small-scale mixing usually required for prescription compounding. However, the use of spatulas and sieves also may be utilized on occasion. The mortar and pestle method combines comminution and mixing in a single operation. Thus, it is particularly useful where some degree of particle size reduction as well as mixing is required as in the case of mixtures of crystalline material.

The blending of powders with a spatula on a tile or paper, a relatively inefficient method, is sometimes used for small quantities of powders often as an auxiliary blending technique or when the compaction produced by the mortar and pestle technique is undesirable.

Sieving is usually employed as a pre- or post-mixing method to reduce loosely held agglomerates and to increase the overall effectiveness of a blending process. When used alone as a solid–solid blending technique, several passes through the sieve are required to produce a reasonably homogeneous mix.

Storage and Flow

Flow Patterns—Discharge of powders from large-scale mixers, storage bins, or machine-feed hoppers primarily generates flow in the form of shear failure. That is, the powder behaves in a manner analogous to a viscous liquid in laminar flow. The analogy ends at that point since conditions are then present in the powder bed conducive to segregation. The overall pattern of discharge from a bin takes the form of either funnel-flow or mass-flow. Bin design characteristics, which take into account the powder's angles of slide and internal friction and its yield locus in terms of normal and shear stresses, determine which flow pattern will occur.

In funnel flow the powder moves in a column down the center of the bin toward the exit orifice at the bottom. Material surrounding this relatively rapidly moving core remains stationary or is slowly drawn into the core. The core is primarily fed from the top where powder moves to the center and then down in the manner of a funnel.

The powder in a mass flow bin moves downward toward the orifice as a coherent mass. When it reaches the tapered section of the bin leading to the orifice it is compressed and flows in shear analogous to a plastic mass being compressed. This type of bin is advantageous for use with powders having a strong tendency to segregate.

The rate of discharge from a hopper varies as a function of the cube of the orifice diameter and is nearly independent of the height of the bed. An arch forms over the orifice which in effect is a boundary between material in essentially free fall and material in the closely packed condition of the powder bed. The rate of mass transport across this constantly renewed surface determines the rate of orifice flow. It has been shown that flow can be substantially increased if gas is pumped through the bed and across the orifice in the direction of solids flow. Flow conditioners are also an important means of improving flow and are discussed in Chapter 21.

Pneumatic Transport—This method of transporting powders is of interest since it can be used to mix powders at the same time as they are being conveyed. The method consists of propelling a solids–gas mixture along a conduit *via* a gas pressure drop. The solids are held in suspension by the turbulence of the gas stream. At low solids concentrations where the particles are relatively small, the solids are uniformly dispersed over the pipe cross-section. However, at higher solids content or with larger particles some stratification will occur in a horizontal pipe and solids will settle out if the pipe is overloaded.

As mentioned before, gas flow must be turbulent so as to suspend the solids; however, the solids behave as in laminar flow. Slippage between gas and solid occurs, particularly in vertical pipes, with the consequence that gas and solids flow rates are not in proportion to flow stream composition. Further, smaller and less dense particles flow more rapidly than large and dense material and a chromatographic-like separation occurs. This is not a problem, however, once steady state is achieved. Because of the industrial importance of this process in many fields it has been extensively investigated and a number of useful theoretical and empirical expressions have been derived and may be used to predict conditions necessary for satisfactory pneumatic transport.

Powders as a Dosage Form

Historically, powders represent one of the oldest dosage forms. They are a natural outgrowth of man's attempt to prepare crude drugs and other natural products in a more conveniently administered form. However, with declining use of crude drugs and increasing use of many highly potent compounds, powders as a dosage form have been replaced largely by capsules and tablets.

In certain situations powders possess advantages and thus still represent a portion (although small) of the solid dosage forms currently being employed. These advantages are flexibility in compounding and relatively good chemical sta-

bility. The chief disadvantages of powders as a dosage form are (1) they are time-consuming to prepare and (2) they are not well suited for the dispensing of many unpleasant-tasting, hygroscopic, or deliquescent drugs.

Bulk powders have another serious disadvantage when compared with divided and individually weighed powders—inaccuracy of dose. The dose is influenced by many factors including size of measuring spoon, density of powder, humidity, degree of settling, fluffiness due to agitation, and personal judgment. Not only do patients measure varying amounts of powder when using the same spoon but they often select one differing in size from that specified by their physician.

Extemporaneous Techniques

In both the manufacturing and extemporaneous preparation of powders the general techniques of weighing, measuring, sifting, mixing, etc, as described previously are applied. However, the following procedures should receive special attention.

1. Use of geometric dilution for the incorporation of small amounts of potent drugs.
2. Reduction of particle size of all ingredients to the same range to prevent stratification of large and small particles.
3. Sieving when necessary to achieve mixing or reduction of agglomerates, especially in the preparation of dusting powders or powders into which liquids have been incorporated.
4. Heavy trituration, when applicable, to reduce the bulkiness of a powder.
5. Protection against humidity, air oxidation, and loss of volatile ingredients.

Powders are most commonly prepared either as divided powders and bulk powders which are mixed with water or other suitable material prior to administration, or as dusting powders which are applied locally. They also may be prepared as dentifrices, products for reconstitution, insufflations, aerosols, and other miscellaneous products.

The manually operated procedures usually employed by the prescription pharmacist today are *trituration*, *pulverization by intervention*, and *levigation*.

Trituration—This term refers to the process of reducing substances to fine particles by rubbing them in a mortar with a pestle. The term also designates the process whereby a mixture of fine powders is intimately mixed in a mortar. The circular mixing motion of the pestle on the powders contained in a mortar results in blending them and in also breaking up soft aggregates of powders. By means of the application of pressure on the pestle, crushing or grinding also can be effected.

When granular or crystalline materials are to be incorporated into a powdered product, these materials are comminuted individually and then blended together in the mortar.

Pulverization by Intervention—This is the process of reducing the state of subdivision of solids with the aid of an additional material which can be removed easily after the pulverization has been completed. This technique is often applied to substances which are gummy and tend to reagglomerate or which resist grinding. A prime example is camphor which cannot be pulverized easily by trituration because of its gummy properties. However, on the addition of a small amount of alcohol or other volatile solvent, this compound can be reduced readily to a fine powder. Similarly, iodine crystals may be comminuted with the aid of a small quantity of ether. In both instances the solvent is permitted to evaporate and the powdered material is recovered.

Levigation—In this process a paste is first formed by the addition of a suitable nonsolvent to the solid material. Particle size reduction is then accomplished by rubbing the paste in a mortar with a pestle or on an ointment slab using a spatula. Levigation is generally used by the pharmacist to incorporate solids into dermatologic and ophthalmic ointments and suspensions.

The Mortar and Pestle—These are the most frequently used utensils in small-scale comminution. Mortars made of various materials and in diverse shapes are available and while these are often used interchangeably the different kinds of mortars have specific utility in preparing or grinding different materials.

Modern mortars and pestles are usually prepared from Wedgwood ware, porcelain, or glass. While pharmacists often use different mortars interchangeably, each type has a preferential range of utility which makes its use more efficient. Glass mortars, for example, are designed primarily for use in preparing solutions and suspensions of chemical materials in a liquid. They also are suitable for preparing ointments which require the reduction of soft aggregates of powdered materials or the incorporation of relatively large amounts of liquid. Glass also has the advantage of being comparatively nonporous and of not staining easily and thus is particularly useful when substances such as flavoring oils or highly colored substances are used. Glass cannot be used for comminuting hard solids.

Wedgwood mortars are well suited for comminution of crystalline solids or for the reduction in particle size of most materials used in modern prescription practice. They are capable of adequately powdering most substances which are available only as crystals or hard lumps. However, Wedgwood is relatively porous and will stain quite easily. A Wedgwood mortar is available with a roughened interior which aids in the comminution process but which requires meticulous care in washing since particles of the drugs may be trapped in the rough surface and cause contamination of materials subsequently comminuted in the mortar.

Porcelain mortars are very similar to Wedgwood except that the exterior surface of the former is usually glazed and thus less porous than the Wedgwood mortar. Porcelain mortars may be used for comminution of soft aggregates or crystals but are more generally used for the blending of powders of approximately uniform particle size.

Pestles are made of the same material as the mortar. Pestles for Wedgwood or porcelain mortars are available with hard rubber or wooden handles screwed into the head of the pestle. Also available are one-piece Wedgwood pestles. Pestles made entirely of porcelain are objectionable, because they are easily broken.

Pestles and mortars should not be interchanged. The efficiency of the grinding or mixing operation depends largely on a maximum contact between the surfaces of the head of the pestle and the interior of the mortar. The pestle should have as much bearing on the interior surface of the mortar as its size will permit. A pestle which does not "fit" the mortar will result in a waste of labor.

Divided Powders

Divided powders (*chartula* or *chartulae*) are dispensed in the form of individual doses and are generally dispensed in papers, properly folded. They also may be dispensed in metal foil, small heat-sealed plastic bags, or other containers.

Dividing Powders—After the weighing, comminuting, and mixing of ingredients are completed, the powders must be accurately divided into the prescribed number of doses. In order to achieve accuracy consistent with the other steps in the preparation, *each dose should be weighed individually* and transferred to a powder paper. Following completion of this step the powder papers are folded.

Folding Powders—The operations of folding powder papers are illustrated in Fig 89-22. Care in making the several

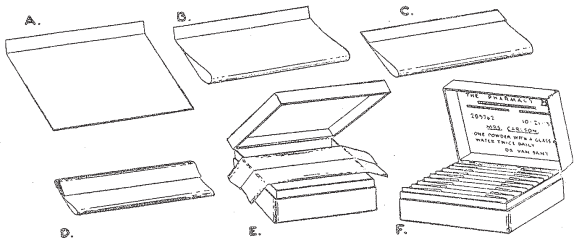

Fig 89-22. Folding powder papers.

folds, and experience gained by repetition, are necessary to obtain uniformity when the powders are finally placed in the box for dispensing. Deviation from any of the three main folds will result in powders of varying height being formed, and variations in the folded ends will likewise be noticeable when the powders are placed side by side.

All of the powder papers for the prescription being filled should be creased by folding down a margin on the top. For a standard 3- by 4-inch powder paper, the fold should be about ½ inch wide; for other powder papers it should be in proportion.

After the powder has been distributed over the papers as described, the additional folds are made as follows. The lower edge of the paper is lifted and folded over until it lies exactly in the crease of the original top fold (Fig 89-22*B*) which is then pressed down over this lower edge (Fig 89-22*C*). The top of the paper, as it now appears, is folded toward the operator until it exactly divides the folded paper in the center (Fig 89-22*D*). The three folds mentioned will so regulate the height of the powders in a low-style powder box that they will just protrude slightly, thus making it possible to pick out one powder with the fingers without disturbing the others. For the old-style boxes having greater depth the final fold should be adjusted to make the powder at least even with the edge of the box.

When the individual powder paper has been folded lengthwise, it is picked up in both hands by the ends and pressed down over the ends of the box so that both ends are turned over exactly the same length. At the same time the end of the box is pressed in slightly so that the powder when finally completed will fit and slide evenly in the box (Fig 89-22*E*).

The turned ends are simultaneously and firmly pressed between the thumb and finger to complete the folding. The top of the powder paper, at the center, should not be creased with the fingers or with a spatula, as the "roll edge" adds materially to the appearance of the finished box of powders, and creasing may unnecessarily cake the powder. However, where a large number of powders must be placed in a comparatively small box, creasing may help.

When all the powders are folded they may be assembled in one hand, with the lengthwise folds uppermost and toward the operator, and placed in the box. Some pharmacists prefer to alternate the folds, having one forward and one backward, and some even prefer to turn every other powder upside down to lessen the likelihood of the powders springing from the box when a powder is removed. This occurs most frequently when the powder is bulky, and it is possible to adjust this partially by tapping the assembled powders down, first from one side or end and then from the other to effect a more uniform distribution of the powder.

Packaging Divided Powders—Specially manufactured paper and boxes are available for dispensing divided powders.

Powder Papers—Four basic types of powder papers are available.

1. Vegetable parchment, a thin semiopaque moisture-resistant paper.
2. White bond, an opaque paper with no moisture-resistant properties.
3. Glassine, a glazed, transparent moisture-resistant paper.
4. Waxed, a transparent waterproof paper.

Hygroscopic and volatile drugs can be protected best by use of a waxed paper, double-wrapped with a bond paper to improve the appearance of the completed powder. Parchment and glassine papers offer limited protection for these drugs.

A variety of sizes of powder papers are available. The selection of the proper size depends on the bulk of each dose and the dimensions of the powder box required to hold the number of doses prescribed.

Powder Boxes—Various types of boxes are supplied in several sizes for dispensing divided powders. The hinged-shoulder boxes shown in Fig 89-22*F* are the most popular and have the advantage of preventing the switching of lids with the directions for use when several boxes of the same size are in the same home. The prescription label may be pasted directly on top of the lid or inside the lid. In the latter case the name of the pharmacy is lithographed on top of the lid.

Special Problems

The incorporation of volatile substances, eutectic mixtures, liquids, and hygroscopic or deliquescent substances into powders presents problems that require special treatment.

Volatile Substances—The loss of camphor, menthol, and essential oils by volatilization when incorporated into powders may be prevented or retarded by use of heat-sealed plastic bags or by double wrapping with a waxed or glassine paper inside of bond paper.

Eutectic Mixtures—Liquids result from the combination of phenol, camphor, menthol, thymol, antipyrine, phenacetin, acetanilid, aspirin, salol, and related compounds at ordinary temperatures. These so-called eutectic mixtures may be incorporated into powders by addition of an inert diluent. Magnesium carbonate or light magnesium oxide are commonly used and effective diluents for this purpose, although kaolin, starch, bentonite, and other absorbents have been recommended. Silicic acid prevents eutexia with aspirin, phenyl salicylate, and other troublesome compounds; incorporation of about 20% silicic acid (particle size, 50 μm) prevented liquefaction even under the compression pressures required to form tablets.

In handling this problem each eutectic compound should be first mixed with a portion of the diluent and gently blended together, preferably with a spatula on a sheet of paper. Generally, an amount of diluent equal to the eutectic compounds is sufficient to prevent liquefaction for about two weeks. Deliberate forcing of the formation of the liquid state, by direct trituration, followed by absorption of the moist mass, will also overcome this problem. This technique requires use of more diluent than previously mentioned methods but offers the advantage of extended product stability. Thus the technique is useful for dispensing a large number of doses that normally would not be consumed over a period of one or two weeks.

Liquids—In small amounts, liquids may be incorporated into divided powders. Magnesium carbonate, starch, or lactose may be added to increase the absorbability of the powders if necessary. When the liquid is a solvent for a nonvolatile heat-stable compound, it may be evaporated gently on a water bath. Lactose may be added during the course of the evaporation to increase the rate of solvent loss by increasing the surface area. Some fluidextracts and tinctures may be treated in this manner, although use of an equivalent amount of a powdered extract, when available, is a more desirable technique.

Hygroscopic and Deliquescent Substances—Substances that become moist because of affinity for moisture in the air may be prepared as divided powders by adding inert diluents. Double wrapping is desirable for further protection. Extremely deliquescent compounds cannot be satisfactorily prepared as powders.

Bulk Powders

Bulk powders may be classified as (1) oral powders, (2) dentifrices, (3) douche powders, (4) dusting powders, (5) insufflations, and (6) triturations.

Oral Powders—These are generally supplied as *finely divided powders* or as *effervescent granules*.

The finely divided powders are intended to be suspended or dissolved in water or mixed with soft foods, eg, applesauce, prior to administration. Antacids and laxative powders are frequently administered in this form.

Effervescent granules contain sodium bicarbonate and either citric acid, tartaric acid, or sodium biphosphate in addition to the active ingredients. On solution in water carbon dioxide is released as a result of the acid–base reaction. The effervescence from the release of the carbon dioxide serves to mask the taste of salty or bitter medications.

Granulation is generally accomplished by producing a moist mass, forcing it through a coarse sieve, and drying it in an oven. The moisture necessary for massing the materials is readily obtained by heating them sufficiently to drive off the water of hydration from the uneffloresced citric acid. The completed product must be dispensed in tightly closed glass containers to protect it against the humidity of the air. For a formerly official general formula for preparing effervescent salts see RPS-15, page 1574.

Effervescent powders may be prepared also by adding small amounts of water to the dry salts in order to obtain a workable mass. The mass is dried and ground to yield the powder or granule. Care must be utilized in this procedure to ensure that the reaction which occurs in the presence of water does not proceed too far before it is stopped by the drying process. Should this happen, the effervescent properties of the product will be destroyed.

Other preparative techniques have been reported for effervescent powders such as a fluidized bed procedure in which the powders are blended and then suspended in a stream of air in a Wurster chamber. Water is sprayed into the chamber resulting in a slight reaction and an expansion of the particles to form granules ranging in size from 10- to 30-mesh. This approach apparently offers a number of advantages over the older techniques. The extent of reaction and particle size are controlled during the manufacture. A drying oven, trays, and even grinding devices are not required. Furthermore, the technique lends itself to a continuous as well as a batch operation.

The heat generated from the blending and mixing operation also has been used to mass the powders by causing the release of the water of hydration from the citric acid. The massed materials can be dried and sieved through a coarse sieve. This technique thus eliminates the need of an external heat source or a granulating solution.

Dentifrices—These may be prepared in the form of a bulk powder, generally containing a soap or detergent, mild abrasive, and an anticariogenic agent. These products are considered in more detail in Chapter 109.

Douche Powders—These products are completely soluble and are intended to be dissolved in water prior to use as antiseptics or cleansing agents for a body cavity. They are most commonly intended for vaginal use, although they may be formulated for nasal, otic, or ophthalmic use. Generally, since aromatic oils are included in these powders, they are passed through a No 40 or 60 sieve to eliminate agglomeration and to insure complete mixing. Dispensing in wide-mouth glass jars serves to protect against loss of volatile materials and permits easy access by the patient. Bulk powder boxes may be used for dispensing douche powders, although glass containers are preferred because of the protection afforded by these containers against air and moisture.

Dusting Powders—These are locally applied nontoxic preparations that are intended to have no systemic action. They always should be dispensed in a very fine state of subdivision to enhance effectiveness and minimize irritation. When necessary, they may be micronized or passed through a No 80 or 100 sieve.

Extemporaneously prepared dusting powders should be dispensed in sifter-top packages. Commercial dusting powders are available in sifter-top containers or pressure aerosols. The latter, while generally more expensive than the other containers, offer the advantage of protection from air, moisture, and contamination, as well as convenience of application. Foot powders and talcum powders are currently available as pressure aerosols.

Dusting powders are applied to various parts of the body as lubricants, protectives, absorbents, antiseptics, antipruritics, antibromhidrosis agents, astringents, and antiperspirants.

While in most cases dusting powders are considered nontoxic, absorption of boric acid through large areas of abraded skin has caused toxic reactions in infants. Accidental inhalation of zinc stearate powder has led to pulmonary inflammation of the lungs of infants. The pharmacist should be aware of the possible dangers when the patient uses these compounds as well as other externally applied products. See also Chapter 40.

Insufflations—These are finely divided powders introduced into body cavities such as the ears, nose, throat, tooth sockets, and vagina. An insufflator (powder blower) is usually employed to administer these products. However, the difficulty in obtaining a uniform dose has restricted their general use.

Specialized equipment has been developed for the administration of micronized powders of relatively potent drugs. The Norisodrine Sulfate Aerohaler Cartridge (*Abbott*) is an example of such a product. In the use of this Aerohaler, inhalation by the patient causes a small ball to strike a cartridge containing the drug. The force of the ball shakes the proper amount of the powder free, permitting its inhalation. Another device, the Spinhaler turbo-inhaler (*Fisons*), is a propeller-driven device designed to deposit a mixture of lactose and micronized cromolyn sodium into the lung as an aid in the management of bronchial asthma.

Pressure aerosols have also been employed as a means of administering insufflations, especially for potent drugs. This method offers the advantage of excellent control of dose, through metered valves, as well as product protection.

Triturations—These are dilutions of potent powdered drugs, prepared by intimately mixing them with a suitable diluent in a definite proportion by weight. They were at one time official as 1–10 dilutions. The pharmacist sometimes prepares triturations of poisonous substances, e.g., atropine, in a convenient concentration using lactose as the diluent, for use at the prescription counter. These medicinal substances are more accurately and conveniently weighed by using this method.

The correct procedure for preparing such triturations or any similar dilution of a potent powder medicament, to insure uniform distribution of the latter, is as follows: (1) reduce the drug to a moderately fine powder in a mortar; (2) add about an equal amount of diluent and mix well by thorough trituration in the mortar; (3) successively add portions of diluent, triturating after each addition, until the entire quantity of diluent has been incorporated. Under no circumstance

should the entire quantity of diluent be added at once to the drug that is to be diluted in the expectation that uniform dispersion of the latter will be more expeditiously achieved on brief trituration of the mixture.

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