units (90%). If the clinical impression of the drug being evaluated was that a 20% difference in dose (plasma levels) would not be clinically significant, in this example it must be concluded that the statistical test is too sensitive and the difference observed, even if real, is not significant clinically. Therefore, the drug products are bioequivalent in spite of the statistical findings.

Statistics should be used, in bioavailability testing, as a tool to determine if sufficient subjects have been included to minimize the effect of patient-to-patient variability in the data analysis. The results of statistical testing should not be used *as the decision* but to help *make the decision*. One must apply some statistical sense in order to avoid statistical nonsense.

A Common Pitfall: Cross-Study Comparisons—Perhaps the single most-common error made in interpreting bioavailability data is that of *cross-study comparison*. This occurs when the blood concentration-time curve of a drug product in one study is compared with the blood concentration-time curve of that drug product in another study. There are three reasons why such cross-study comparisons are dangerous and can lead to false conclusions. The following examples used to illustrate the three points are taken from actual bioavailability data.

Different Subject Population—In Fig 76-9, a research lot of potassium phenoxymethyl penicillin was compared with the appropriate reference standard for that product. The research-lot drug was found to be bioequivalent, with average peak-serum concentrations differing by 8% and the area differing by only 9%. In another study conducted with a full-manufacture lot of the test product, the same lot of the reference standard potassium phenoxymethyl penicillin was used. The results of this study are shown in Fig 76-10. Again, the two products were found to be bioequivalent as the peak and area parameters differed by less than 5%. In these two studies, identical test conditions were used and the same analytical procedure and laboratory was employed. However, if one compares the serum levels for the reference standard lot found in Fig 76-9, with the levels for the same lot of tablets in the study in Fig 76-10, sizable differences in blood levels are found as shown in Fig 76-11.

The average peak serum levels for this lot of tablets were found to be 8.5 units/mL and 12.5 units/mL in the two respective studies, a difference of approximately 31%. Likewise, the average AUC was found to differ by approximately 21%. Such differences are the sole result of cross-study

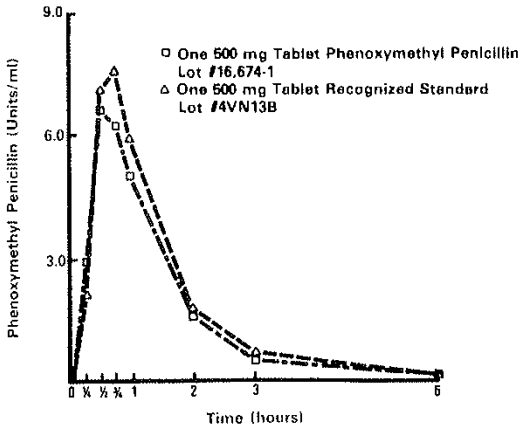

Fig 76-9. Average serum concentration of phenoxymethyl penicillin following oral administration of 500 mg given as one tablet of Recognized Standard (△), or of Test Product, Research Lot (□).

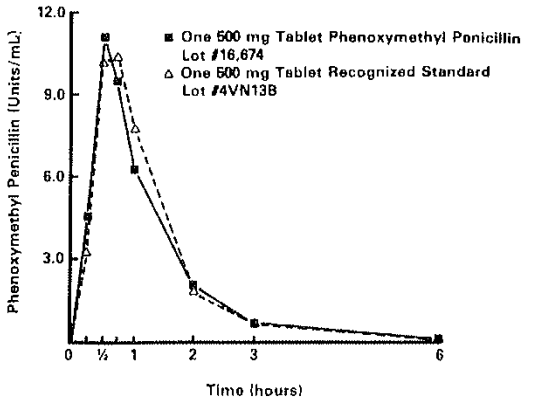

Fig 76-10. Average serum concentration of phenoxymethyl penicillin following oral administration of 500 mg given as one tablet of Recognized Standard (△), or of Test Product, Full Mfg Lot (■).

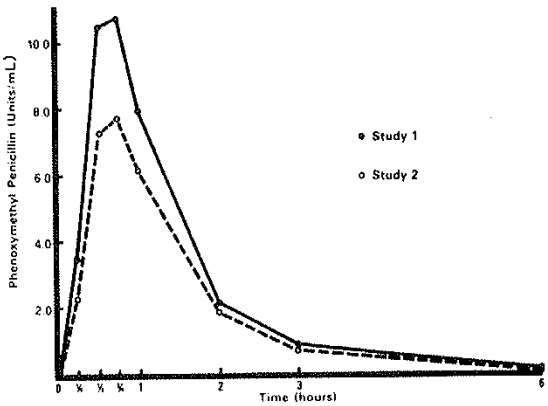

Fig 76-11. Average serum concentration of phenoxymethyl penicillin following a single oral 500-mg dose of Recognized Standard, in two different subject populations.

comparisons and are not due to differences in actual bioavailability.

The same lot of reference standard tablets was used in both studies. Hence, the difference must be due to the experimental variables which occur normally from study to study. The major difference between the two studies was the subject population involved. In the first study, healthy, adult, male, prison volunteers were used, whereas in the second study, there were 17 females and 7 males in a hospital clinic, also described as normal, healthy volunteers. An appreciable difference in sex distribution was obvious when comparing these studies. Adjustments for body weight and surface area alone did not correct for the apparent discrepancies in peak concentration or blood level AUC. It is difficult to determine the exact factors which caused the observed differences. This example should serve as a note of caution in comparing absolute bioavailability values of peak concentration and area under the curve from different studies.

Different Study Conditions—Parameters such as the food or fluid intake of the subject before, during and after drug administration can have dramatic effects on the absorption of certain drugs. Fig 76-12 shows the results of a three-way crossover test where the subjects were fasted 12 hr overnight and 2 hr after drug administration of an uncoated

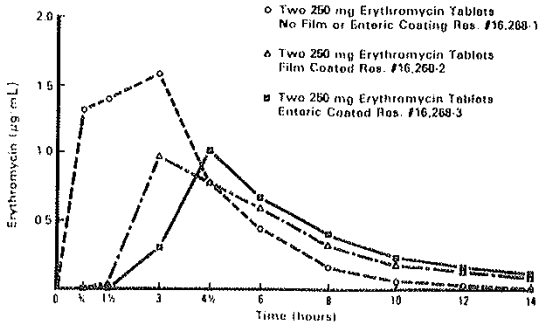

Fig 76-12. Average serum erythromycin concentration administered in 500-mg doses as three different tablet dosage forms. The results were obtained from 21 healthy adult subjects following an overnight fast of 12 hr before and 2 hr after drug administration.

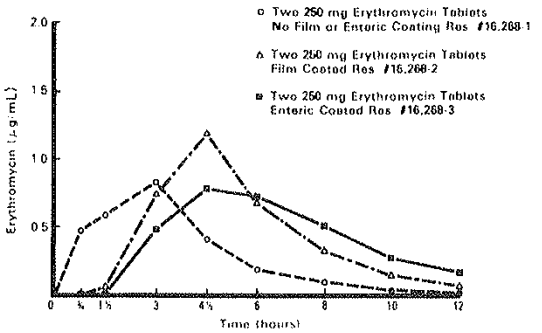

Fig 76-13. Average serum erythromycin concentration administered in 500-mg doses as three different tablet dosage forms. The results were obtained from 12 healthy adult subjects with only a 2-hr fast before drug administration.

tablet, a film-coated tablet or an enteric-coated tablet of erythromycin.

The results of this study suggest that the unprotected tablet is superior to both the film-coated and enteric-coated tablets in terms of blood-level performance. These results

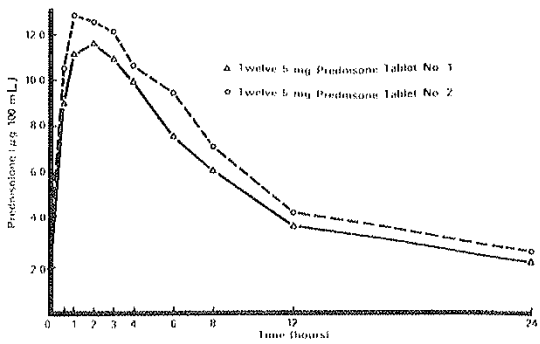

Fig 76-15. Average plasma prednisolone levels following 60 mg of prednisone administered to 24 normal adults as a single oral dose of twelve 5-mg prednisone tablets from two different manufacturers. Plasma levels were determined by a competitive protein-binding assay.

also suggest that neither film-coating nor enteric-coating is necessary for optimal blood-level performance. Figure 76-13 shows results with the same tablets when the study conditions were changed to only a 2-hr preadministration fast with a 2-hr postadministration fast. In this case, the blood levels of the uncoated tablet were depressed markedly while the film-coated and enteric-coated tablets showed relatively little difference in blood levels.

From this second study, it might be concluded that film-coating appears to impart the same degree of acid stability as an enteric coating. This might be acceptable if only one dose of the antibiotic was required. However, Fig 76-14 shows the results of a multiple-dose study in which the enteric-coated tablet and the film-coated tablet were administered 4 times a day, immediately after meals. The results show that the film coating does not impart the degree of acid stability as does the enteric coating when the tablets are administered immediately after food in a typical clinical situation.

Different Assay Methodology—Depending on the drug under study, there may be more than one assay method available. For example, some steroids can be assayed by a radioimmunoassay, competitive protein-binding, gas-liquid

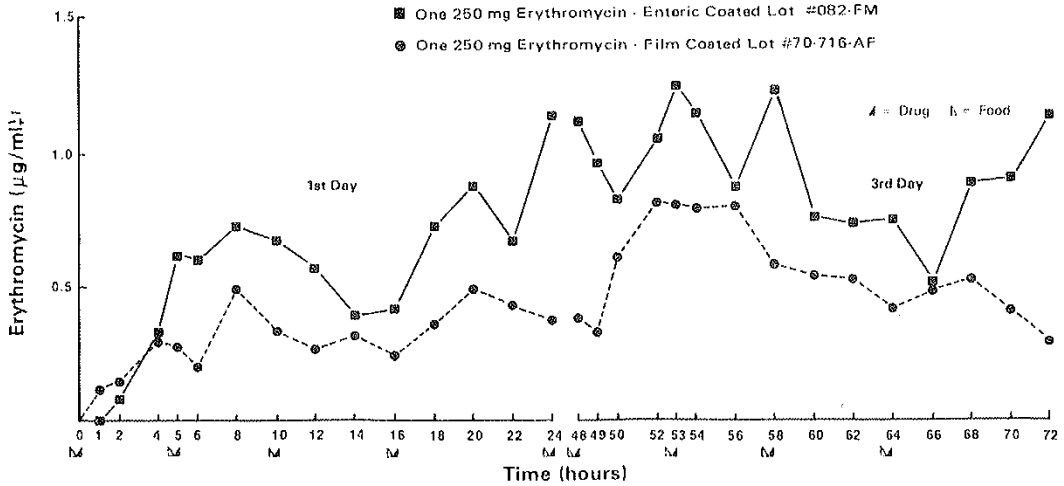

Fig 76-14. Average serum erythromycin concentration-time profiles administered in two different tablet dosage forms. The results were obtained from 24 healthy adult subjects following administration of 250 mg 4 times a day, with meals and at bedtime.

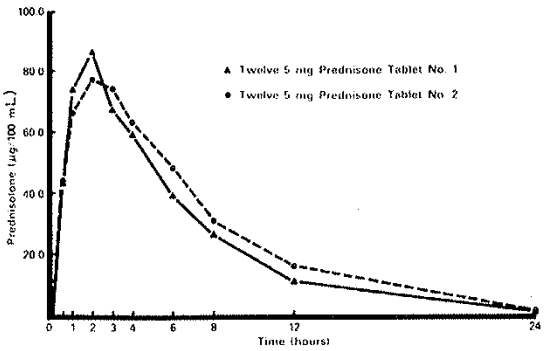

Fig 76-16. Average plasma prednisolone levels following 60 mg of prednisone administered to 24 normal adults as a single oral dose of 12 5-mg prednisone tablets from two different manufacturers. Plasma levels were determined by a radioimmunoassay procedure.

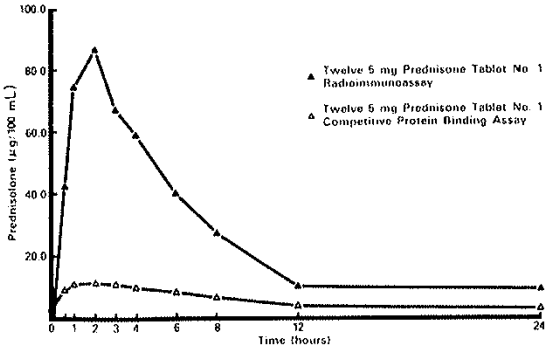

Fig 76-17. Average plasma prednisolone profiles administered as a single 60-mg dose to 24 normal adults. Plasma levels were determined by both a competitive protein binding assay and a radioimmunoassay.

chromatograph or, indirectly, by a 17-hydroxycorticosteroid assay.

Figures 76-15 and 76-16 show the results of a comparison of prednisone tablets using a competitive protein-binding method and a radioimmunoassay, respectively. The serum concentration-time curves resulting from each method lead to the same conclusion, that the products are bioequivalent. However, Fig 76-17 shows a comparison of the absolute values obtained by the two assay methods with the same product.

Obviously, the wrong conclusion would have been reached if one product had been assayed by one method and the other product by the other method and the results had been compared. Even in cases where only one assay method is employed, there are numerous modifications with respect to technique among laboratories which could make direct comparisons hazardous.

The backbone of any bioavailability study involving plasma (or urine) levels of drug, in addition to good study design and subject controls, is the analytical methodology used to determine the levels of a drug. In most cases one *probably* can assume that the precision and reliability of the method employed in a given study have been established to a sufficient degree to make the results of the study internally consistent. As demonstrated, major problems arise when, without careful evaluation of the analytical methodology employed, one attempts to compare the data of studies from different laboratories. Even with similar analytical methodology performed by the same laboratory, it would be unreasonable to expect agreement, using the same dosage form, of closer than 20 to 25% for plasma levels, AUCs, etc, from one study to the next.

Under the *best* conditions, cross-study comparisons are relatively insensitive, and at worst they can be misleading. Cross-study comparisons certainly cannot be used to make decisions or estimations of differences in drug products with the generally acceptable sensitivity of difference detection of 20% or less.

With insufficient data on the correlation of plasma levels with clinical response, it is difficult to decide if it is the peak plasma level or the total body load of a drug that is important. Changes in the rate of absorption require changes in the dose given (body load) for maintenance of similar peak plasma levels. Decisions as to which is more important, body load or peak level, are made with difficulty and tend to reduce the objective quantitation sought in bioavailability testing.

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CHAPTER 79

Tonicity, Osmoticity, Osmolality and Osmolarity

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

The physiological mechanisms 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 usually is corrected within a few seconds and, at most, within a minute or so. However, this rapid transfer of water does not mean that complete equilibration occurs between the extracellular and intracellular compartments throughout the entire body within this same short period of time. The reason is that fluid usually enters the body through the gut and then must be transported by the circulatory system to all tissues before complete equilibration can occur. In the normal person it may require 30 to 60 min to achieve reasonably good equilibration throughout the body after drinking water. Osmoticity is the property that largely determines the 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 or dispersions in an oleaginous base (Muro, *Bausch & Lomb*) 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 gonioscopic examination. Glycerin solutions in 50 to 75% concentrations [Glyrol (*IO Lab*), 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-Dow*) solution, which uses the acidification of the colon via lactulose degradation to serve as a trap for ammonia migrating from the blood to the colon. The conversion of ammonia of blood to the ammonium ion in the colon ultimately is coupled with the osmotic effect and laxation, thus expelling undesirable levels of blood ammonia. This product is employed to prevent and treat frontal systemic encephalopathy.

Osmotic laxation is 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 *selectively* permeable. Most normal living-cell membranes maintain various solute concentration gradients. A selectively permeable membrane may be defined either as one that does not permit free, unhampered diffusion of all

the solutes present, or as one that maintains at least one solute concentration gradient across itself. Osmosis, then, is the diffusion of water through a membrane that maintains at least one solute concentration gradient across itself.

Assume 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 (unionized molecules, ions, macromolecules, aggregates) of solute(s) in solution and thus is affected by the degree of ionization or aggregation of the solute. See Chapter 16 for review of colligative properties of solutions.

Body fluids, including blood and lacrimal fluid, normally have an osmotic pressure which often is described as corresponding to that of a 0.9% solution of sodium chloride. The body also attempts to keep the osmotic pressure of the contents of the gastrointestinal 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 physiological 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 actually is 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 physiological fluid, or which may be a physiological 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 physiological fluid, or suitable for parenteral use.

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

Such qualitative terms are of limited value, and it has become necessary to state osmotic properties in quantitative terms. To do so, a term must be used that will represent all the particles which 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), which is osmotically equivalent to a mole of an ideally behaving nonelectrolyte. Thus, the osmol-weight of a nonelectrolyte, in a dilute solution, generally is equal to its gram-molecular-weight. A milliosmol, abbreviated mOsm, is the weight stated in milligrams.

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

For a solution of an electrolyte such as sodium chloride, one molecule of sodium chloride represents one sodium and one chloride ion. Hence, one mole will represent 2 osmols of sodium chloride theoretically. Accordingly, 1 osmol NaCl = 58.5 g/2 or 29.25 g. This quantity represents the sum total of 6.02×10^{23} ions as the total number of particles. Ideal solutions infer very dilute solutions or infinite dilution. However, as the concentration is increased, other factors enter. With strong electrolytes, interionic attraction causes a decrease in their effect on colligative properties. In addition, and in opposition, for all solutes, including nonelectrolytes, solvation and possibly other factors operate to intensify their colligative effect. Therefore, it is very difficult and often impossible to predict accurately the osmoticity of a solution. It may be possible to do so for a dilute solution of a single, pure and well-characterized solute, but not for most parenteral and enteral medicinal and/or nutritional fluids; experimental determination likely is required.

Osmolality and Osmolarity

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

Osmolality—A solution has an osmolal concentration of one when it contains 1 osmol of solute/kg of water. A solution has an osmolality of n when it contains n osmols/kg 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 1 mole of that compound, then a 1 osmolal solution is synonymous to a 1 molal solution for a typical nonelectrolyte.

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

As in molal solutions, osmolal solutions usually are employed where quantitative precision is required, as in the

measurement of physical and chemical properties of solutions (ie, colligative properties). The advantage of the *w/w* relationship is that the concentration of the system is not influenced by temperature.

Osmolarity—The relationship observed between molality and osmolality is shared similarly between molarity and osmolarity. A solution has an osmolar concentration of 1 when it contains 1 osmol of solute/L of solution. Likewise, a solution has an osmolarity of *n* when it contains *n* osmols/L of solution. Osmolar solutions, unlike osmolal solution, reflect a weight in volume relationship between the solute and final solution. A one molar and 1 osmolar solution would be synonymous for nonelectrolytes. For sodium chloride a 1 osmolar solution would contain 1 osmol of sodium chloride per liter which approximates a 0.5 molar solution. The advantage of employing osmolar concentrations over osmolal concentrations is the 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 usually are 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 due partly to the circumstance that, until recently, 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 partly may center around the interpretation by some to view one kilogram of water in the osmolal concept as being equivalent to 1 L, and, more importantly, the interpretation that to make up to volume of 1 L, as in osmolarity, is essentially the same as the weight of solute plus 1 liter (a distortion of the osmolal concept). The primary difference resides in the error introduced which revolves around the volume of water occupied by the solute. A 1 osmolar solution of a solute always will be more concentrated than a 1 osmolal solution. With dilute solutions the difference may be acceptably small. Nine grams of sodium chloride/L of aqueous solution is approximately equivalent to 9 g in 996.5 mL of water. This represents an error of under 1%, when comparing the osmoticity of 0.9% *w/v* solution to a solution of 9 g plus 1 kg of water. Using dextrose in a parallel comparison, errors range from approximately 3.5% in osmoticity with 50 g dextrose/L versus 50 g plus 1 kg of water to a difference of about 25% in osmoticity with 250 g dextrose/L versus 250 g plus 1 kg of water. The confusion appears to be without cause for concern at this time. However, one should be alerted to the sizeable errors which may occur with concentrated solutions or fluids, such as those employed in total parenteral nutrition, enteral hyperalimentation and oral nutritional fluids for infants.

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

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

The value given for normal serum osmolality above was described as an assumption because of the variety of values found in the literature. Serum osmolality often is stated loosely to be about 300 mOsmol/L. Apart from that, and more specifically, two references state it as 280 to 295 mOsmol/L; other references give it as 275 to 300 mOsmol/L, 290 mOsmol/L, 306 mOsmol/L, and 275 to 295 mOsmol/kg. There is a strong tendency to call it *osmolality* but to state it as *mOsmol/L* (*not as mOsmol/kg*). In the light of these varying values, one may ask about the reproducibility of the experimental measurements. It has been stated that most osmometers are accurate to 5 mOsmol/L. With that type of reproducibility, the above variations perhaps may be expected. The difference between a liter and kilogram probably is 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 infant-formula should give warning as to possible risks. Unfortunately, the osmoticity of infant formulas, tube feedings and total parenteral nutrition solutions has not been described adequately 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 now are accenting isoosmotic enteral nutritional supplements. Often, when the term osmolarity is used, one cannot discern whether this simply is incorrect terminology, or if osmolarity actually has been calculated from osmolality.

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

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

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:

For a nonelectrolyte

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

For a strong electrolyte

$$\frac{g/L}{\text{mol wt}} \times \frac{\text{number of ions formed}}{} \times 1000 = \text{mOsmol/L} \qquad (2)$$

For individual ions, if desired

$$\frac{g \text{ of ion/L}}{\text{ionic wt}} \times 1000 = \text{mOsmol (of ion)/L} \qquad (3)$$

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 mOsmol/L.

Two other methods compute osmolarity from values of osmolality. The determination of osmolality will be discussed later. One method has a strong theoretical basis of physical-chemical principles[6] using values of the partial molal volume(s) of the solute(s). A 0.9% sodium chloride solution, found experimentally to have an osmolality of 286 mOsmol/kg, was calculated to have an osmolarity of 280 mOsmol/L, rather different from the value of 308 mOsmol/L calculated as above. The method, using partial molal volumes, is relatively rigorous, but many systems appear to be too complex and/or too poorly defined to be dealt with by this method.

The other method is based on the following relationship:[6,7] actual osmolarity = measured osmolality × (density − g solute/mL). This expression can be written

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

The experimental value for the osmolality of 0.9% sodium chloride solution was 292.7 mOsmol/kg; the value computed for osmolarity was 291.4 mOsmol/L. This method 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 mOsmol/kg;[7] its osmolarity was calculated as 625 × 0.839 = 524 mOsmol/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/L, 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 alternatively may state the total osmolar concentration in milliosmols/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 (*Abbott*), which is labeled to contain, per L, dextrose (hydrous) 50 g, sodium chloride 6 g, potassium chloride 300 mg, calcium chloride 200 mg and sodium lactate 3.1 g. Also stated is that the total osmolar concentration of the solution is approximately 524 mOsmol per L, in part contributed by 130 mEq of Na^+, 109 mEq of Cl^-, 4 mEq of K^+, 3 mEq of Ca^{2+} and 28 mEq of lactate ion.

The derivation of the osmolar concentrations from the stated composition of the solution may be verified by calculations using Eq 1 above for the nonelectrolyte dextrose, and Eq 2 for the electrolytes.

Dextrose

$$\frac{50 \text{ g} \times 1000}{198.17} = 252.3 \text{ mOsmol/L}$$

Sodium Chloride

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

Potassium Chloride

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

Calcium Chloride

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

Sodium Lactate

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

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 mOsmol/L.

The mOsmol of sodium in 1 L of the solution is the sum of the mOsmol of the ion from sodium chloride and sodium lactate, ie, 102.66 + 27.66 = 130.32 mOsmol. 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 mOsmol. The mOsmol 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:

$$\text{osm}_{\text{final}} = \frac{850 \times 500}{1000} + \frac{252 \times 500}{1000}$$

$$= 425 \text{ mOsmol/L} + 126 \text{ mOsmol/L} = 551 \text{ mOsmol/L}$$

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 generally has been 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 86). It also has been stated that the abnormal tonicity of contact lens solutions can cause the lens to adhere to the eye and/or cause burning or dryness and photophobia.

Parenteral Medication—Osmoticity is of great importance in parenteral injections, its effects depending on 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 usually are administered slowly in small volumes, or into a large vein such as the subclavian, where dilution and distribution occur rapidly. Solutions that differ from the serum in tonicity generally are 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 to 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 to 20 mL of water being required to excrete each gram of dextrose. Solutions, such as those for total parenteral nutrition, should be administered by means of a metered constant-infusion apparatus over a lengthy period (usually more than 24 hr) to avoid sudden hyperosmotic dextrose loads. Such solutions may cause osmotic diuresis; if this occurs, water balance is likely to become negative because of the increased urinary volume, and electrolyte depletion may occur because of excretion of sodium and potassium secondary to the osmotic diuresis. If such diuresis is marked, body weight falls abruptly and signs of dehydration appear. Urine should be monitored for signs of osmotic diuresis, such as glycosuria and increased urine volume.

If the 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 and there may be heart failure and pulmonary edema. Probably the precipitating factor is a bolus of concentrated solute suddenly reaching the myocardium and the chemoreceptors in the aortic arch and carotid sinus.[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) pressure and venous pressure (VP) followed by a precipitous fall in CSF pressure. This particularly may be conducive to intracranial hemorrhage, as the rapid infusion produces an increase in plasma volume and venous pressure at the same time the CSF pressure is falling. During the CSF pressure rise, there is a drop in hemoglobin and hematocrit, reflecting a marked increase in blood volume.

Hyperosmotic medications, such as sodium bicarbonate (osmolarity of 1563 at 1 mEq/mL), which are administered intravenously, should be diluted prior to use and should be injected slowly to allow dilution by the circulating blood. Rapid "push" injections may cause a significant increase in blood osmoticity.[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 that required for a complete circulation of the blood, *eg, 1 min.* 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 reversed suddenly by stopping the infusion and administering saline. It also has been shown that the CSF pressure in humans rises during treatment of diabetic ketoacidosis in association with a fall in the plasma concentration of dextrose and a fall in plasma osmolality. These observations may be explained by the different rates of decline in dextrose content of the brain and of plasma. The concentration of dextrose in the brain may fall more slowly than in the plasma, causing a shift of fluid from the extracellular fluid space to the intracellular compartment of the CNS, resulting in increased intracranial pressure.

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 used generally, but usually is reported as mOsmol/L. It may seem unnecessary to mention that osmolality depends not only on the number of solute particles, but also on the quantity of water in which they are dissolved. However, it may help one to understand the statement that the normal range of urine osmolality is 50 to 1400 mOsmol/L, and for a random specimen is 500 to 800 mOsmol/L.

Serum Osmoticity

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

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

moticity is a comatose diabetic with a serum osmoticity of 365 mOsmol/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 the postoperative state (especially with excessive water replacement therapy), treatment with diuretic drugs and low-salt diet (as with patients with heart failure, cirrhosis, etc), adrenal disease (eg, Addison's disease, adrenogenital syndrome) or SIADH (syndrome of inappropriate ADH secretion). There are many diseases which 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 or cerebral disease (such as tumor, trauma, infection, vascular abnormalities, etc). It also may be found with some patients with excessive diuretic use. Serum and urine osmoticity are measured when SIADH is suspected. In SIADH there is 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.

1. Serum osmolality may be estimated from the formula

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

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

2. A quick approximation is

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

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

Urine Osmoticity

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

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

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

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 causing 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, when the term osmolarity *is* used, one cannot discern whether this is simply incorrect terminology, or whether the osmolarity actually has been calculated from the osmolality. With concentrated infant formulas or tube feedings, the osmolarity may be only 80% of the osmolality. The osmoticity (osmolality, etc) of infant formulas, tube feedings and total parenteral nutrition solutions are not described adequately 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 also has 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 frequently is overlooked in many diseases or posttrauma 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 used effectively. By using an intact GI tract for proper alimentation, the major problems of sepsis and metabolic derangement which relate to intravenous hyperalimentation largely are obviated, and adequate nutritional support is simplified greatly. Because of this increased safety and ease of administration, the enteric route for hyperalimentation should be used whenever possible.[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[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

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

When nutrition of high osmoticity is ingested, large amounts of water will transfer to the stomach and intestines from the fluid surrounding those organs in an attempt to lower the osmoticity. The higher the osmoticity, the larger the amount of water required; a large amount of water in the GI tract can cause distention, cramps, nausea, vomiting, hypermotility and shock. The food may move through the tract too rapidly for the water to be reabsorbed, and result in diarrhea; severe diarrhea can cause dehydration. The hyperosmotic enteral effects have been observed by the administration of undiluted hypertonic oral medication;[11] Table 1 from this work lists average osmolality values of some commercially available drug solutions and suspensions. Thus, there is some analogy to the effect of hyperosmotic intravenous infusions.

Hyperosmotic feedings may result in mucosal damage in the GI tract. Rats given hyperosmotic feeding showed transient decrease in disaccharidase activity, and an increase in alkaline phosphatase activity. They also showed 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 frequency of diarrhea. Infant formulas that are hyperosmotic may affect preterm infants adversely during the early neonatal period, and they may produce or predispose neonates to necrotizing enterocolitis when delivered to the jejunum through a nasogastric tube.

The body attempts to keep the osmoticity of the contents of the stomach and intestines at approximately the same level as that of the fluid surrounding them. As a fluid of lower osmoticity requires the transfer of less water to dilute it, it should be tolerated better than one of higher osmoticity. As to tolerance, there is a great variation from one individual to another in sensitivity to the osmoticity of foods. The majority of patients receiving nutritional formulas, either orally or by tube, are able to tolerate feedings with a wide range of osmoticities 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 postoperative 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 mOsmol/kg) also may be helpful initially if tolerance problems arise in sensitive individuals. Concentration and size of feeding then can be increased gradually to normal as tolerance is established.

A common disturbance of intake encountered in elderly individuals relates to excess solid intake rather than to reduced water intake. For example, an elderly victim of a

cerebral vascular accident who is being fed by nasogastric tube may be given a formula whose solute load requires a greatly increased water intake. Thus, tube feeding containing 120 g of protein and 10 g of salt will result in the excretion of more than 1000 mOsmol of solute. This requires the obligatory excretion of a volume of urine between 1200 and 1500 mL when the kidneys are capable of normal concentration ability. As elderly individuals often have significant impairment in renal function, water loss as urine may exceed 2000 to 2500 mL per day. Such an individual would require 3 to 4 L 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 which rapidly may become critical. The importance of knowing the complete composition of the tube feeding formulas used for incapacitated patients cannot be overemphasized.

Osmolality Determination

The need for experimental determination of osmolality has been established. In regard to this there are four properties of solutions that depend only on the number of "particles" in the solution. They are osmotic pressure elevation, boiling point elevation, vapor pressure depression and freezing point depression. These are called colligative properties and if one of them is known, the others can be calculated from its value. Osmotic pressure elevation is the most difficult to measure satisfactorily. The boiling-point elevation may be determined but the values are rather sensitive to changes in barometric pressure. Also, for an aqueous solution the molal boiling-point elevation is considerably less than the freezing-point depression. Thus, it is less accurate than the freezing-point method. Determinations of vapor-pressure lowering 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] A vapor-pressure osmometer with a precision of <2 mOsmol/kg is reported by Dickerson, *et al.*[11] The method usually used is that of freezing-point depression, which can be determined 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 converted readily to vapor pressure lowering if desired.

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

The results of investigations by Lund *et al*[12] indicate that the freezing point of normal, healthy human blood is −0.52° and not −0.56°, as previously assumed (see *Reliability of Data*, page 1489). Inasmuch as water is the medium in which the various constituents of blood are either suspended or dissolved in this method, it is assumed that *any aqueous solution* freezing at −0.52° is *isotonic with blood*. Now it is rare that a simple aqueous solution of the therapeutic agent to be injected parenterally has a freezing point of −0.52°, and to obtain this freezing point it is necessary either to add some other therapeutically inactive solute if the solution is hypotonic (freezing point above −0.52°) or to dilute the solution if it is hypertonic (freezing point below −0.52°). The usual practice is to add either sodium chloride or dextrose to adjust hypotonic parenteral solutions to isotonicity. Certain solutes, including ammonium chloride, boric acid, urea, glycerin and propylene glycol, cause hemolysis even when they are present in a concentration that is isoosmotic and such solutions obviously are not isotonic. See Appendix A.

In a similar manner solutions intended for ophthalmic use may be adjusted to have a freezing point identical to that of lacrimal fluid, namely, −0.52° (see *Reliability of Data*, page 1489). Ophthalmic solutions with higher freezing points usually are made isotonic by the addition of boric acid or sodium chloride.

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

Freezing-Point Calculations

As explained in the preceding section, freezing-point data often may be employed in solving problems of isotonicity adjustment. Obviously, the utility of such data is limited to those solutions where the solute does not penetrate the membrane of the tissue, eg, red blood cells, with which it is in contact. In such cases, Appendix A, 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 accepted widely 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 addi-

tivity 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 (in degrees).
- 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. The term, 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 frequently are employed in nose drops, ear drops and other preparations to be used in various parts of the body. Liquids such as glycerin, propylene glycol or alcohol may compose part of the solvent. In solving isotonicity adjustment problems for such solutions it should be kept in mind that 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 formerly was assumed to be −0.56°, later investigators[12] reported that as a consequence of ice being disengaged in freezing-point determinations, as ordinarily performed, the observed freezing point of blood is too low and 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 obtained when another method is used (such as that of Lund *et al*[12]), probably will 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 which commonly are neglected, such as the disengagement of ice. It is not possible, at this time, to select unequivocal freezing point data for most of the solutions listed in Appendix A at the end of this chapter. The comprehensive and valuable data of Lund, *et al*,[12] 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 generally has 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*[13] 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 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 often is far more important in producing hemolysis than is the osmotic effect. There is no certain evidence that any single mechanism of action causes hemolysis. The process appears to involve such factors as pH, lipid solubility, molecular and ionic sizes of solute particles and possibly inhibition of cholinesterase

in cell membranes and denaturing action on plasma membrane protein.

Some investigators test the tonicity of injectable solutions by observing variations of red-blood-cell volume produced by these solutions. This method appears to be more sensitive to small differences in tonicity than those based on observation of a hemolytic effect. Much useful information concerning the effect of various solutes on erythrocytes has been obtained by this procedure and 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—A sodium chloride equivalent is defined as the weight of sodium chloride which will produce the same osmotic effect as 1 g of the drug 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% − 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 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 for the convenience of preparing 30 mL (1 fl oz) of solution, as is prescribed often. 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 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 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 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 separately for each ingredient. The values thus obtained are added, the total amount of sterile water then is 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 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 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[f]
Acetylcysteine	0.20	0.055	0.20	0.113	0.20	0.227	0.20	0.341			4.58	0.20	0.52	100[e]	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[e]	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[e]	6.2
Aminohippuric acid	0.13	0.035	0.13	0.075											
Aminophylline				0.098[c]											
Ammonium carbonate	0.70	0.202	0.70	0.405							1.29	0.70	0.52	97	7.7
Ammonium chloride			1.12								0.8	1.12	0.52	93	5.0
Ammonium lactate	0.33	0.093	0.33	0.185	0.33	0.370					2.76	0.33	0.52	98	5.9
Ammonium nitrate	0.69	0.200	0.69	0.400							1.30	0.69	0.52	91	5.3
Ammonium phosphate, dibasic	0.58	0.165	0.55	0.315							1.76	0.51	0.52	0	7.9
Ammonium sulfate	0.55	0.158	0.55	0.315							1.68	0.54	0.52	0	5.3
Amobarbital sodium			0.25	0.143[c]			0.25				3.6	0.25	0.52	0	9.3
d-Amphetamine HCl											2.64			98	5.7
Amphetamine phosphate			0.34	0.20			0.27	0.47			3.47	0.26	0.52	0	4.5
Amphetamine sulfate			0.22	0.129[c]			0.21	0.36			4.23	0.21	0.52	0	5.9
Amprotropine phosphate											5.90			0	4.2
Amylcaine HCl			0.22				0.19				4.98	0.18		100	5.6
Anileridine HCl	0.19	0.052	0.19	0.104	0.19	0.212	0.18	0.316	0.18	0.509	5.13	0.18	0.52	12	2.6
Antazoline phosphate											6.05			90	4.0
Antimony potassium tartrate			0.18				0.13		0.10						
Antipyrine			0.17	0.10			0.14	0.24	0.14	0.40	6.81	0.13	0.52	100	6.1
Apomorphine HCl			0.14	0.080[c]											
Arginine glutamate	0.17	0.048	0.17	0.097	0.17	0.195	0.17	0.292	0.17	0.487	5.37	0.17	0.52	0	6.9
Ascorbic acid				0.105[c]							5.05		0.52[b]	100[e]	2.2
Atropine methylbromide			0.14				0.13		0.13		7.03	0.13			
Atropine methylnitrate											6.52			0	5.2
Atropine sulfate			0.13	0.075			0.11	0.19	0.11	0.32	8.85	0.10	0.52	0	5.0
Bacitracin			0.05	0.03			0.04	0.07	0.04	0.12					
Barbital sodium			0.30	0.171[c]			0.29	0.50			3.12	0.29	0.52	0	9.8
Benzalkonium chloride			0.16				0.14		0.13						
Benztropine mesylate	0.26	0.073	0.21	0.115	0.15	0.170	0.12	0.203	0.09	0.242					
Benzyl alcohol			0.17	0.09[c]			0.15								

Appendix A—Continued

	0.5%		1%		2%		3%		6%		Isoosmotic concentration[a]				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
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	0.289[c]							1.9	0.47	0.52	100	4.6
Brompheniramine maleate	0.10	0.026	0.09	0.050	0.08	0.084									
Bupivacaine HCl	0.17	0.048	0.17	0.096	0.17	0.193	0.17	0.290	0.17	0.484	5.38	0.17	0.52	83	6.8
Butabarbital sodium	0.27	0.078	0.27	0.155	0.27	0.313	0.27	0.470			3.33	0.27	0.52	0	6.8
Butacaine sulfate			0.20	0.12			0.13	0.23	0.10	0.29					
Caffeine and sodium benzoate			0.26	0.15			0.23	0.40			3.92	0.23	0.52	0	7.0
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			3.56			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	0.316	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							

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isosmotic concentration[a]				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Diethanolamine	0.31	0.089	0.31	0.177	0.31	0.358					2.90	0.31	0.52	100	11.3
Dihydrostreptomycin sulfate			0.06	0.03			0.05	0.09	0.05	0.14	19.4	0.05	0.52	0	6.1
Dimethpyrindene maleate	0.13	0.039	0.12	0.070	0.11	0.120									
Dimethyl sulfoxide	0.42	0.122	0.42	0.245	0.42	0.480					2.16	0.42	0.52	100	7.6
Diperodon HCl	0.15	0.045	0.14	0.079	0.13	0.141									
Diphenhydramine HCl				0.161[c]							5.70			88*	5.5
Diphenidol HCl	0.16	0.045	0.16	0.09	0.16	0.180									
Doxapram HCl	0.12	0.035	0.12	0.070	0.12	0.140	0.12	0.210							
Doxycycline hyclate	0.12	0.035	0.12	0.072	0.12	0.134	0.11	0.186	0.09	0.264					
Dyphylline	0.10	0.025	0.10	0.052	0.09	0.104	0.09	0.155	0.08	0.245					
Echothiophate iodide	0.16	0.045	0.16	0.090	0.16	0.179									
Edetate disodium	0.24	0.070	0.23	0.132	0.22	0.248	0.21	0.360			4.44	0.20	0.52	0	4.7
Edetate trisodium monohydrate	0.29	0.079	0.29	0.158	0.28	0.316	0.27	0.472			3.31	0.27	0.52	0	8.0
Emetine HCl				0.058[c]				0.17		0.29					
Ephedrine HCl			0.30	0.165[c]			0.28				3.2	0.28		96	5.9
Ephedrine sulfate			0.23	0.13			0.20	0.36			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]							6.83			0	5.2
Ferric ammonium citrate (green)															
Floxuridine	0.14	0.040	0.13	0.076	0.13	0.147	0.12	0.213	0.12	0.336	8.47	0.12	0.52	3*	4.5
Fluorescein sodium			0.31	0.181[c]			0.27	0.47			3.34	0.27	0.52	0	8.7
Fluphenazine 2-HCl	0.14	0.041	0.14	0.082	0.12	0.145	0.09	0.155							
d-Fructose											5.05			0*	5.9
Furtrethonium iodide	0.24	0.070	0.24	0.133	0.22	0.250	0.21	0.360			4.44	0.20	0.52	0	5.4
Galactose											4.92			0	5.9
Gentamicin sulfate	0.05	0.015	0.05	0.030	0.05	0.060	0.05	0.093	0.05	0.153					
D-Glucuronic acid											5.02			48*	1.6
Glycerin				0.203[c]							2.6			100	5.9
Glycopyrrolate	0.16	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*	2.6
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%		Isosmotic concentration[a]				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Indigotindisulfonate sodium	0.30	0.085	0.30	0.172							4.97			85	5.0
Intracaine HCl											9.58			100	9.4
Iodophthalein sodium				0.07[c]							4.95	0.18	0.52	0	6.2
Isometheptene mucate	0.18	0.048	0.18	0.095	0.18	0.196	0.18	0.302			6.65	0.14	0.52	trace	4.5
Isoproterenol sulfate	0.14	0.039	0.14	0.078	0.14	0.156	0.14	0.234	0.14	0.389					
Kanamycin sulfate	0.08	0.021	0.07	0.041	0.07	0.083	0.07	0.125	0.07	0.210	2.30			100*	2.1
Lactic acid				0.230[c]							9.75	0.09		0*	5.8
Lactose			0.07	0.040[c]			0.08		0.09		9.40	0.10	0.52	69*	6.9
Levallorphan tartrate	0.13	0.036	0.13	0.073	0.13	0.143	0.12	0.210	0.12	0.329					
Levorphanol tartrate	0.12	0.033	0.12	0.067	0.12	0.136	0.12	0.203			4.42			85	4.3
Lidocaine HCl				0.13[c]							6.60	0.14	0.52	0	4.6
Lincomycin HCl	0.16	0.045	0.16	0.090	0.15	0.170	0.14	0.247	0.14	0.400					
Lobeline HCl				0.09[b]							9.96	0.09	0.52	0	6.5[f]
Lyapolate sodium	0.10	0.025	0.09	0.051	0.09	0.103	0.09	0.157	0.09	0.263	2.02	0.45		0	6.3
Magnesium chloride				0.45							6.3	0.14	0.52	0	6.2
Magnesium sulfate			0.17	0.094[c]			0.15	0.26	0.15	0.43	3.18	0.28	0.52	0	7.0
Magnesium sulfate, anhydrous	0.34	0.093	0.32	0.184	0.30	0.345	0.29	0.496							
Mannitol				0.096[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	5.0
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	0.068	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	0.166	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				3.00	0.22		100	5.3
Neoarsphenamine											2.32			17	7.8
Neomycin sulfate			0.11	0.063[c]			0.09	0.16	0.08	0.232					
Neostigmine bromide			0.22	0.127[c]			0.19				4.98			0	4.6
Neostigmine methylsulfate			0.20	0.115[c]			0.18		0.17		5.22	0.17			
Nicotinamide			0.26	0.148[c]			0.21	0.36			4.49	0.20	0.52	100	7.0
Nicotinic acid			0.25	0.144[c]											
Nikethamide				0.100[c]							5.94			100	6.9
Novobiocin sodium	0.12	0.033	0.10	0.057	0.07	0.073									
Oleandomycin phosphate	0.08	0.017	0.08	0.038	0.08	0.084	0.08	0.129	0.06	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[e]	2.3

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration[a]				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
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[b]											
Paraldehyde	0.25	0.071	0.25	0.142	0.25	0.288	0.25	0.430			3.65	0.25	0.52	97	5.3
Pargyline HCl	0.30	0.083	0.29	0.165	0.29	0.327	0.28	0.491			3.18	0.28	0.52	91	3.8
Penicillin G, potassium			0.18	0.102[c]			0.17	0.29	0.16	0.46	5.48	0.16	0.52	0	6.2
Penicillin G, procaine				0.06[d]											
Penicillin G, sodium			0.18	0.100[c]			0.16	0.28	0.16	0.46	5.90			18	5.2
Pentazocine lactate	0.15	0.042	0.15	0.085	0.15	0.169	0.15	0.253	0.15	0.420					
Pentobarbital sodium				0.145[c]							4.07			0	9.9
Pentolinium tartrate											5.95			55*	3.4
Phenacaine HCl				0.09[d]											
Pheniramine maleate				0.09[d]											
Phenobarbital sodium			0.24	0.135[c]			0.23	0.40			3.95	0.23	0.52	0	9.2
Phenol			0.35	0.20							2.8	0.32	0.52	0*	5.6
Phentolamine mesylate	0.18	0.052	0.17	0.096	0.16	0.173	0.14	0.244	0.13	0.364	8.23	0.11	0.52	83	3.5
Phenylephrine HCl			0.32	0.184[c]			0.30				3.0	0.30		0	4.5
Phenylephrine tartrate											5.90			58*	5.4
Phenylethyl alcohol	0.25	0.070	0.25	0.141	0.25	0.283									
Phenylpropanolamine HCl			0.38	0.219[c]							2.6	0.35		95	5.3
Physostigmine salicylate			0.16	0.090[c]											
Physostigmine sulfate				0.074[c]											
Pilocarpine HCl			0.24	0.138[c]			0.22	0.38			4.08	0.22	0.52	89	4.0
Pilocarpine nitrate			0.23	0.132[c]			0.20	0.36			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	0.006	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	7.0
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								2.11	0.43		0	6.6
Pralidoxime chloride	0.32	0.092	0.32	0.183	0.32	0.364					2.87	0.32	0.52	0	4.6
Prilocaine HCl	0.22	0.062	0.22	0.125	0.22	0.250	0.22	0.375			4.18	0.22	0.52	45	4.6
Procainamide HCl			0.22	0.13			0.19	0.33	0.17	0.49					
Procaine HCl			0.21	0.122[c]			0.19	0.33	0.18		5.05	0.18	0.52	91	5.6
Prochlorperazine edisylate	0.08	0.020	0.06	0.033	0.05	0.048	0.03	0.056	0.02	0.065					
Promazine HCl	0.18	0.050	0.13	0.077	0.09	0.102	0.07	0.112	0.05	0.137					
Proparacaine HCl	0.16	0.044	0.15	0.086	0.15	0.169	0.14	0.247	0.13	0.380	7.46	0.12	0.52		
Propiomazine HCl	0.18	0.050	0.15	0.084	0.12	0.133	0.10	0.165	0.08	0.215					
Propoxycaine HCl											6.40			16	5.3
Propylene glycol											2.00			100	5.5
Pyrathiazine HCl	0.22	0.065	0.17	0.096	0.11	0.123	0.08	0.140	0.06	0.170					
Pyridostigmine bromide	0.22	0.062	0.22	0.125	0.22	0.250	0.22	0.377			4.13	0.22	0.52	0	7.2
Pyridoxine HCl											3.05			31*	3.2
Quinacrine methanesulfonate				0.06[c]											
Quinine bisulfate			0.09	0.05			0.09	0.16							
Quinine dihydrochloride			0.23	0.130[c]			0.19	0.33	0.18		5.07	0.18	0.52	trace*	2.5
Quinine hydrochloride			0.14	0.077[c]			0.11	0.19							
Quinine and urea HCl			0.23	0.13			0.21	0.36			4.5	0.20	0.52	64	2.9

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration[a]				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
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	par-tial	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	0.156	0.13	0.219	0.10	0.285					
Sodium nitrate			0.68								1.36	0.66		0	6.0
Sodium nitrite			0.84	0.460[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					
Sodium tartrate	0.33	0.098	0.33	0.193	0.33	0.385					2.72	0.33	0.52	0	7.3
Sodium thiosulfate			0.31	0.181[c]							2.98	0.30	0.52	0	7.4
Sodium warfarin	0.18	0.049	0.17	0.095	0.16	0.181	0.15	0.264	0.15	0.430	6.10	0.15	0.52	0	8.1
Sorbitol (½ H_2O)											5.48			0	5.9
Sparteine sulfate	0.10	0.030	0.10	0.056	0.10	0.111	0.10	0.167	0.10	0.277	9.46	0.10	0.52	19*	3.5
Spectinomycin HCl	0.16	0.045	0.16	0.092	0.16	0.185	0.16	0.280	0.16	0.460	5.66	0.16	0.52	3	4.4
Streptomycin HCl			0.17	0.10[c]			0.16	0.16							
Streptomycin sulfate			0.07	0.036[c]			0.06	0.10	0.06	0.17					

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration[a]				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Sucrose			0.08	0.047[c]			0.09	0.16	0.09	0.26	9.25	0.10	0.52	0	6.4
Sulfacetamide sodium			0.23	0.132[c]			0.23	0.40			3.85	0.23	0.52	0	8.7
Sulfadiazine sodium			0.24	0.14			0.24	0.38			4.24	0.21	0.52	0	9.5
Sulfamerazine sodium			0.23	0.13			0.21	0.36			4.53	0.20	0.52	0	9.8
Sulfapyridine sodium			0.23	0.13			0.21	0.36			4.55	0.20	0.52	5	10.4
Sulfathiazole sodium			0.22	0.13			0.20	0.35			4.82	0.19	0.52	0	9.9
Tartaric acid				0.143[c]							3.90			75*	1.7
Tetracaine HCl			0.18	0.109[c]			0.15	0.26	0.12	0.35					
Tetracycline HCl			0.14	0.081[c]			0.10								
Tetrahydrozoline HCl											4.10			60*	6.7
Theophylline				0.02[b]											
Theophylline sodium glycinate											2.94			0	8.9
Thiamine HCl				0.139[c]							4.24			87*	3.0
Thiethylperazine maleate	0.10	0.030	0.09	0.050	0.08	0.089	0.07	0.119	0.05	0.153					
Thiopental sodium				0.155[c]							3.50			74	10.3
Thiopropazate diHCl	0.20	0.053	0.16	0.090	0.12	0.137	0.10	0.170	0.08	0.222					
Thioridazine HCl	0.06	0.015	0.05	0.025	0.04	0.042	0.03	0.055	0.03	0.075					
Thiotepa	0.16	0.045	0.16	0.090	0.16	0.182	0.16	0.278	0.16	0.460	5.67	0.16	0.52	10*	8.2
Tridihexethyl chloride	0.16	0.047	0.16	0.096	0.16	0.191	0.16	0.280	0.16	0.463	5.62	0.16	0.52	97	5.4
Triethanolamine	0.20	0.058	0.21	0.121	0.22	0.252	0.22	0.383			4.05	0.22	0.52	100	10.7
Trifluoperazine 2HCl	0.18	0.052	0.18	0.100	0.13	0.144									
Triflupromazine HCl	0.10	0.031	0.09	0.051	0.05	0.061	0.04	0.073	0.03	0.092					
Trimeprazine tartrate	0.10	0.023	0.06	0.035	0.04	0.045	0.03	0.052	0.02	0.061					
Trimethadione	0.23	0.069	0.23	0.133	0.22	0.257	0.22	0.378			4.22	0.21	0.52	100	6.0
Trimethobenzamide HCl	0.12	0.033	0.10	0.062	0.10	0.108	0.09	0.153	0.08	0.232					
Tripelennamine HCl				0.13[d]							5.50			100	6.3
Tromethamine	0.26	0.074	0.26	0.150	0.26	0.300	0.26	0.450			3.45	0.26	0.52	0	10.2
Tropicamide	0.10	0.030	0.09	0.050											
Trypan blue	0.26	0.075	0.26	0.150											
Tryparsamide				0.11[c]											
Tubocurarine chloride				0.076[c]											
Urea			0.59	0.34							1.63	0.55	0.52	100	6.6
Urethan				0.18[b]							2.93			100	6.3
Uridine	0.12	0.035	0.12	0.069	0.12	0.138	0.12	0.203	0.12	0.333	8.18	0.11	0.52	0*	6.1
Valethamate bromide	0.16	0.044	0.15	0.085	0.15	0.168	0.14	0.238	0.11	0.324					
Vancomycin sulfate	0.06	0.015	0.05	0.028	0.04	0.049	0.04	0.066	0.04	0.098					
Viomycin sulfate			0.08	0.05			0.07	0.12	0.07	0.20					
Xylometazoline HCl	0.22	0.065	0.21	0.121	0.20	0.232	0.20	0.342			4.68	0.19	0.52	88	5.0
Zinc phenolsulfonate											5.40			0*	5.4
Zinc sulfate			0.15	0.086[c]			0.13	0.23	0.12	0.35	7.65	0.12	0.52		

[a] The unmarked values were taken from Hammarlund *et al*,[14,17] and Sapp *et al*.[18]
[b] Adapted from Lund *et al*.[13]
[c] Adapted from BPC.[16]
[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.[18,20] †: pH determined after addition of blood.

Appendix B—Volumes of Water for Isotonicity[2,1,a,b]

Drug (0.3 g)	Water needed for isotonicity, mL	Drug (0.3 g)	Water needed for isotonicity, mL	Drug (0.3 g)	Water needed for isotonicity, mL
Alcohol	21.7	Boric acid	16.7	Ephedrine sulfate	7.7
Ammonium chloride	37.3	Butacaine sulfate	6.7	Epinephrine bitartrate	6.0
Amobarbital sodium	8.3	Caffeine and sodium benzoate	8.7	Epinephrine hydrochloride	9.7
Amphetamine phosphate	11.3	Calcium chloride	17.0	Ethylmorphine hydrochloride	5.3
Amphetamine sulfate	7.3	Calcium chloride (6 H_2O)	11.7	Fluorescein sodium	10.3
Antipyrine	5.7	Chlorobutanol (hydrated)	8.0	Glycerin	11.7
Apomorphine hydrochloride	4.7	Chlortetracycline sulfate	4.3	Holocaine hydrochloride	6.7
Ascorbic acid	6.0	Cocaine hydrochloride	5.3	Homatropine hydrobromide	5.7
Atropine methylbromide	4.7	Cupric sulfate	6.0	Homatropine methylbromide	6.3
Atropine sulfate	4.3	Dextrose, anhydrous	6.0	Hyoscyamine sulfate	4.7
Bacitracin	1.7	Dibucaine hydrochloride	4.3	Neomycin sulfate	3.7
Barbital sodium	10.0	Dihydrostreptomycin sulfate	2.0	Oxytetracycline hydrochloride	4.3
Bismuth potassium tartrate	3.0	Ephedrine hydrochloride	10.0	Penicillin G, potassium	6.0

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.
Penicillin G, sodium	6.0	Scopolamine methylnitrate	5.3	Sodium propionate	20.3
Pentobarbital sodium	8.3	Secobarbital sodium	8.0	Sodium sulfite, exsiccated	21.7
Phenobarbital sodium	8.0	Silver nitrate	11.0	Sodium thiosulfate	10.3
Physostigmine salicylate	5.3	Silver protein, mild	5.7	Streptomycin sulfate	2.3
Pilocarpine hydrochloride	8.0	Sodium acetate	15.3	Sulfacetamide sodium	7.7
Pilocarpine nitrate	7.7	Sodium bicarbonate	21.7	Sulfadiazine sodium	8.0
Piperocaine hydrochloride	7.0	Sodium biphosphate,	15.3	Sulfamerazine sodium	7.7
Polymyxin B sulfate	3.0	anhydrous		Sulfapyridine sodium	7.7
Potassium chloride	25.3	Sodium biphosphate	13.3	Sulfathiazole sodium	7.3
Potassium nitrate	18.7	Sodium bisulfite	20.3	Tetracaine hydrochloride	6.0
Potassium phosphate,	14.7	Sodium borate	14.0	Tetracycline hydrochloride	4.7
monobasic		Sodium iodide	13.0	Viomycin sulfate	2.7
Procainamide hydrochloride	7.3	Sodium metabisulfite	22.3	Zinc chloride	20.3
Procaine hydrochloride	7.0	Sodium nitrate	22.7	Zinc sulfate	5.0
Scopolamine hydrobromide	4.0	Sodium phosphate	9.7		

[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 isosmotic with 0.9% sodium chloride solution but may not be isotonic with blood (see Appendix A for hemolysis data).

[b] To calculate V-values for drugs which do not appear in Appendix B, but are listed in Appendix A, simply take the appropriate sodium chloride equivalent (E) and multiply by 0.3g to convert that quantity of drug to the equivalent weight of sodium chloride and divide by 0.009g (the weight of sodium chloride which will render 1 mL of water isotonic).

Example—Calculate the V-value for amiloridine HCl (Appendix A defines E = 0.18).

$$\frac{0.3 \times 0.18}{0.009} = 6 \text{ mL water for each } 0.3 \text{ g drug}$$

CHAPTER 82

Quality Assurance and Control

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The Pharmaceutical Industry continues as a vital segment of the health-care cycle in conducting research and manufacturing products which are life-maintaining and life-restoring. The last decade has seen an evolution in the concepts relating to the Quality Assurance and Control of these products.

The changes brought about in assuring the safety and therapeutic efficacy of drug products have resulted from a number of factors which are either internal or external to the industry. Internally are the self-designed guidelines the industry has imposed on itself, exemplified by a document prepared in 1967 by the Pharmaceutical Manufacturers Association (PMA) titled "General Principles of Total Quality Control in the Drug Industry." This PMA document became the basis for later regulatory Guidelines prepared by the Food and Drug Administration (FDA) titled "Current Good Manufacturing Practice in Manufacture, Processing, Packing or Holding of Human and Veterinary Drugs." These Current Good Manufacturing Practices (CGMPs) have become the primary external guidelines used by industry and the FDA in the control and inspection of manufacturing facilities.

Quality Control and Assurance Organization

Although the terms Quality Control and Quality Assurance often are used interchangeably, depending on the structure of a specific company, there is a continuing trend to separate and define their functional responsibilities.

Quality Control can be defined broadly as the day-to-day control of quality within a company, a department staffed with scientists and technicians responsible for the acceptance or rejection of incoming raw materials and packaging components, for the myriad of in-process tests and inspections, to assure that systems are being controlled and monitored and, finally, for the approval or rejection of completed dosage forms.

Quality Control, therefore, includes not only the analytical testing of the finished product, but also the assessment of all operations beginning with the receipt of raw materials and continuing throughout the production and packaging operations, finished product testing, documentation, surveillance and distribution.

Quality Assurance may be defined as the responsibility of an organization to determine that systems, facilities and written procedures both are adequate and followed in order to assure that products are controlled and will meet, in the final dosage form, all the applicable specifications. Quality Assurance naturally then becomes an oversight function, often auditing operations to determine that procedures and systems are suitable and, if not, to recommend the required changes. Higher management looks toward the Quality Assurance unit in order to develop some level of "comfort" as to how well they are meeting company standards and applicable government regulations.

Total Quality Control

The high quality of pharmaceutical products results from meticulous adherence to written procedures in carrying out all operations, beginning with research. It is at this early point that the quality begins to be designed into a product. Raw materials must be characterized and purchased from reputable suppliers so that uniform, stable products will result when these materials are incorporated into the finished dosage form. Facilities must be designed, systems installed and the proper equipment selected so that the potential for cross contamination of one product by another is eliminated, that material flow and personnel movements are planned to reduce the potential for product mix-ups and that the air and water, which is being provided to production, is adequate in amount and quality for the particular operations being performed.

Production personnel must be trained properly to perform their jobs, and the directions they follow must be written, approved by responsible individuals and adhered to strictly.

Shipping departments are responsible for seeing that the products are protected from adverse handling and environmental conditions while in transit to distribution points and customers.

Quality Control is ever-present, overseeing each of these operations and giving the final release approval for distribution only after assessing and being satisfied that each step in this process has been completed correctly.

These principles were highlighted in that original PMA document from which the following excerpt is taken:

"The quality of a product is its degree of possession of those characteristics designed and manufactured into it which contribute to the performance of an intended function when the product is used as directed. The quality of medicinal and related products is the sum of all factors which contribute directly or indirectly to the safety, effectiveness and acceptability of the product. Quality must be built into the product during research, development and production.

"Total control of quality as it applies to the drug industry is the organized effort within an entire establishment to design, produce, maintain and assure the specified quality in each unit of product distributed. The effort should not only establish specifications for product acceptance but should provide procedures and methods for achieving conformance with such specifications.

"The large variety of substances used in this industry, the complexity of its products and the various types of company organization make it impossible to design in detail a single universally applicable system for the total control of quality.

"The ultimate objective of a program for the total control of quality in a drug company is the attainment of perfection in meeting specifications for a product of high quality. It is a program designed to assure the professional user or ultimate consumer that every lot of a product conforms to specifications and that each dose distributed will fulfill the representations made in the labeling and will meet all legal requirements and such additional standards as the management of a firm may adopt.

"Total control of quality is a plantwide activity and represents the aggregate responsibility of all segments of a company. The responsibility for auditing the control system and for evaluating product quality is that of a specific group referred to in this statement as Quality Control. The head of Quality Control should have the authority to release satis-

factory lots of products, to reject unsuitable lots and to recommend the recall from distribution of any lots subsequently found to be unsuitable. He should be responsible to a level of management which enables him to exercise independent judgment. His responsibility and authority should be clearly defined by management."

It readily becomes apparent that quality must be built into a product and that it cannot be inspected or tested into a product. Quality results from teamwork, an association which is becoming increasingly important as the industry advances in new technologies which themselves are becoming more complex and demanding.

Quality Control and Assurance Functions

The head of Quality Control, who is ultimately responsible for decisions relating to the acceptability of finished product, should report to someone other than the person directly responsible for producing the product. Often in current organizational structures, the persons in charge of both quality control and production will report to some higher level of authority. This may be the same or different individuals, but it does allow for the independent operation of both functions without direct conflict arising when reaching the ultimate decision on the acceptability of product. The Quality Control function in an organization normally consists of at least two primary units, analytical control and inspection control.

Analytical Control

The Analytical Control Laboratory is responsible for testing and approving raw materials, work in-process and finished product. The laboratory must be staffed with persons who are trained both academically and by experience to perform the often complex analyses required to evaluate the acceptability of a product. Proper personnel is not the only necessity in the laboratory. Equipment also is required which will allow timely and accurate analysis. This equipment continues to become more sophisticated, providing more information about compounds than previously known and has led to a level of accuracy and detectability heretofore unknown.

Detailed specifications also must be available, as well as the test methods against which the products are measured. The specifications include the criteria against which the product will be evaluated and the limits for acceptance or rejection for each critical parameter.

The testing and acceptance of only high-quality raw materials is essential in the preparation of products. Part of this acceptance is to purchase raw materials only from known, reputable suppliers. In order to assure this condition, it is essential that Quality Control be part of a preapproval program of all potential suppliers. This approval always includes testing the material and in many cases necessitates an inspection of the supplier's facility to determine its suitability and degree of compliance with GMP's. At various critical in-process production or intermediate steps it may be necessary to sample and test the materials against criteria previously established for that particular step in the process.

Often, in-process alert or action levels will be identified at the critical operational steps as a means of process control. These alert or action levels are limits or specifications which are more restrictive than the final acceptance limits, but serve as in-process controls by giving early warnings of conditions which could lead to an out-of-control situation and allow timely corrective action to be taken before this occurs. Thus, materials reaching the alert or action-level criteria are acceptable, since they have not exceeded a rejection or unacceptable level.

In-process critical testing will vary depending on the dosage form being manufactured. Sterile parenteral products probably receive the most critical in-process control and testing in order to insure a finished product which is sterile and free of microbial contamination and particulate matter. With sterile products the end product sterility testing cannot be relied upon to insure that each and every container in a lot of an injectable product is sterile and dependence is placed on in-process controls. These in-process controls must have been developed following a prescribed protocol which defines operating conditions and parameters. Only after a series of successful production runs, using the prescribed parameters, can a process be judged to have been validated. Validation of processes is a critical step in the quality assurance of both sterile and nonsterile products. Validation may be defined as "assurance that production processes are controlled in such a manner that they will perform routinely in the manner in which they are purported to."

Testing of the completed lot of a dosage form, in order to measure its conformance with predetermined specifications and appropriate acceptance criteria, always is desirable before releasing the lot for shipment. However, the use of a properly validated manufacturing process is more critical to the quality of a product. End product testing suffers due to the normal variations that arise in the statistical sampling of a lot in assuring that a sample is homogeneous and representative.

Validation of processes and systems gives increased assurance of finished product lot quality and is leading the way toward reducing or eliminating the reliance on end product testing. The parametric release of finished product is beginning, based on control of the critical elements of a validated process.

Tests and specifications may be found in several sources. The *United States Pharmacopeia/National Formulary* (USP) is published on a 5-yr cycle program by the United States Pharmacopeial Convention. The standards established by and published in the USP have been recognized as being official by the Congress of the United States and are recognized in the Federal Food, Drug and Cosmetic Act. These standards are prepared and reviewed so that through regular revision, entirely or in part, they remain current. The reviewing body known as the Committee of Revision represents medical, academe, industrial and other scientific experts. The primary purpose of the Committee is "to provide authoritative standards for materials and substances and their preparations that are used in the healing arts." They establish titles, definitions, descriptions and standards for the identity, quality, strength, purity and, where practical, methods for their examination.

In addition to the procedures defined in the USP, companies will prepare their own test specifications when the products are not "official" (eg, not listed in the USP). These tests and specifications form a necessary part of the Control Sections of New Drug Applications (NDAs) submitted to the Federal Government and which, following careful review by the FDA, may be approved. Finally, there are test procedures for unofficial products and for those not requiring the submission of an NDA. Companies in these cases prepare their own in-house test procedures for controlling the products they produce.

Inspection Control

Many responsibilities assumed by Quality Control are ancillary to the analytical testing. These include the sampling and inspection of incoming raw materials, packaging and labeling components; the physical inspection of product at various intermediate stages; packaging line inspection and the control of shipping inventory within the distribution

cycle. Depending on the organizational structure, additional or different responsibilities will be assigned to this unit.

Documentation

During the course of producing a pharmaceutical product, numerous documents and records are generated. Each batch is assigned a specific code or lot number. All documentation relating to a specific code is referred to as a "batch record," which will include data on each significant phase of production, control and distribution. The batch record provides a historical blueprint of every step, beginning with the receipt of chemical raw materials and packaging components and continuing through each in-process stage. Recording charts or computer printouts of significant operations such as autoclaving, drying, air-particulate monitoring, lyophylizing, etc, all become part of this batch history. After the batch has been completed, including final analytical and physical testing, one additional step should be completed prior to approving the lot for distribution. All documents and records relating to the specific batch are given a final review. Each required document in the batch record must be checked for completeness and accuracy. Any discrepancy must be investigated immediately and answered. Only after this review has been completed satisfactorily may the batch be released for distribution.

When the batch has been released, accurate shipping records must be maintained showing the batch distribution. With these records it is then possible to trace the batch to the market place which will facilitate, if the need arose, recalling the product (batch) from the market place.

Quality Assurance

Total control of quality not only requires the assignments described above, but should include a monitoring or audit function as well. The responsibility for this function is normally separate from both the production and control operations, thus allowing an independent oversight of all operations. Although the function may be separated, the audit responsibilities are often shared by a team representing both the production and control disciplines. It is the duty of this individual (or team) through review and inspection to assure that written procedures and policies are available for each significant production and control operation. Normally, standard operating procedures (SOPs) are developed which, when followed by properly trained operators, will help to assure the quality and integrity of the product. Thus, the QA review function not only determines that the procedures are current and correct, but that they are being followed. Combining a review of SOPs with an audit of facilities and operations following the applicable GMP regulations will give a company an "inside" report on its level of compliance and will allow necessary changes and/or corrections to be made prior to either causing a product failure or being observed during an inspection by an FDA investigator.

Production is responsible for following prescribed procedures to produce acceptable products. The system of total quality management becomes the joint responsibility of quality control and quality assurance.

Quality depends, to a major degree, upon the employees engaged in the production operations. They are responsible for following the prescribed procedures and, along with their training and experience, are able to produce uniformly acceptable products. GMPs properly organized and followed afford a mechanism for preventing human error, the potential for which is especially great in this industry.

New Advances

Statistics and trend analysis are tools already used by the pharmaceutical industry in determining the proper sample size required for testing, for measuring the uniformity of solid dosage forms and for plotting trends of significant factors in order to correct out-of-control situations before unacceptable product results.

New management concepts are being tested, directed toward a reduction of raw material inventories and packaging components. The term "Just-In-Time" refers to ordering and receiving materials when they are required for production rather than to maintaining extensive inventories. This places an additional burden on Quality Control and suppliers to assure the acceptability of materials when received. Certification and qualification of suppliers is an expanding responsibility of control personnel.

Electronic data processing has become another useful tool for assessing process and test parameters and for analyzing the data collected during production. The control of many operations by computers and microprocessors is providing the capability for producing products of further improved uniform quality. These systems have challenged the older ones, resulting in new approaches to in-process controls, collection and analysis of data and the entire system of quality control.

Robotics is finding various applications in pharmaceutical production, packaging and laboratory operations. Filling of product into containers, cartoning, palletizing and other material handling tasks as well as laboratory testing and sample preparation are either in use or being investigated. The uniformity of procedures, costs, nonfatigue factors and flexibility are all advantages. Probably the most practical use of robots is in sterile processing where their nonevasiveness allows aseptic production and testing by removing a primary source of contamination, the human worker. These all present the potential for improved control systems while bringing new challenges to the QC professional.

Environmental Control

Along with the many other advances in the total control of quality is the growing recognition that the environment and the systems used for its control can have a significant effect on the finished product quality. It is well-recognized that parenteral or sterile ophthalmic products must be produced in a manner which will insure their sterility; therefore, control of the areas in which they are manufactured is essential.

Microbiological monitoring of air and water to control the level of particulate and microbial matter in these production areas is necessary. Several levels of "clean" areas are described in Federal Government Standard 209C, "Clean Room and Work Station Requirements, Controlled Environment." The industry commonly uses the specifications described which classify air cleanliness based on the number of particles (of a given size) per cubic foot of air. Generally, conditions listed as "Class 100" are maintained in areas where parenteral products are filled into sterile containers. Class 100 is defined as an area which can be maintained at less than 100 particles per cubic foot of air 0.5 μm and larger.

Another essential control procedure is microbiological monitoring of the environment in which nonsterile products are manufactured. The objective of this monitoring is to first determine particulate and microbial levels within an area to assure that they are reasonable. If found to be excessive, steps must be taken to bring the levels to within acceptable limits. Once this base has been developed, regular monitoring will indicate if operations are continuing under acceptable limits. If not, immediate corrective action should be taken.

The monitoring and control of particulate and microbial matter will further assure the final quality and stability of the product because the environment has been controlled and the product has not been challenged by an unacceptable level of particulate generated by an out-of-control situation.

Good Manufacturing Practice Regulations

In June, 1963, the FDA first issued regulations describing the current good manufacturing practice to be followed in the manufacture, packaging and holding of finished pharmaceuticals. The regulations underwent significant revision and updating in 1978 and became official in March, 1979. These regulations present the minimum requirements to be met by industry when manufacturing, processing, packaging and holding of human and veterinary drugs. Under the Federal Food, Drug and Cosmetic Act, a drug is deemed to be adulterated unless the methods used in its manufacture, processing, packing and holding, as well as the facilities and controls used, conform to current good manufacturing practice so that the drug meets the safety requirements of the Act and has the identity and strength to meet the quality and purity characteristics that it is represented to have. In the preamble to the regulations, the FDA Commissioner answers the comments received from interested persons who responded when the proposed rules were first issued. The preamble provides interesting background information as to why specific sections of the regulations were believed to be necessary and their interpretation.

In July, 1978, the FDA issued regulations establishing similar Good Manufacturing Practices (GMPs) for the Manufacture, Packing, Storage and Installation of Medical Devices. These were published following an amendment to the Food, Drug and Cosmetic Act of 1976, which provided the FDA with the authority to prescribe regulations pertaining to medical devices. In December, 1978, regulations concerning Good Laboratory Practices (GLP) for the control and conducting of clinical studies were issued and for the first time came under FDA inspectional authority.

The FDA proposed, in June 1978, regulations covering the GMPs relating to the manufacture and control of large-volume parenteral products. These regulations, although never officially issued, have become the guideline used by the industry and FDA in the manufacture, control and inspection of large-volume parenteral production. Due to the similarity of the controls required for the production of small-volume parenterals, the guidelines also have been used to assess the adequacy of the manufacture and controls used with these products.

A number of other "guidelines" or "concept" papers have been prepared by various organizations within the industry itself, such as the Pharmaceutical Manufacturers Association and the Parenteral Drug Association. A partial listing is provided at the end of this section.

The current GMP regulations should be read and understood thoroughly by those involved in or interested in pursuing quality control or quality assurance responsibilities. The scope of the present regulations is given in the following outline, along with a brief interpretation of each section.

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PART 211—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURE, PROCESSING, PACKING OR HOLDING—HUMAN AND VETERINARY DRUGS

Subpart A—General Provisions		
211.3	Definitions	*Interpretation* The scope of the regulations are explained for human prescription and OTC drug products including biological products. Reference is made to Part 210.3 of the chapter which gives definitions for all significant terms used in the regulations.
Subpart B—Organization and Personnel		
211.22	Responsibilities of quality control unit	Highlighted here is the assignment to the quality control unit total responsibility for ensuring that adequate systems and procedures exist and are followed to assure product quality.
211.25	Personnel qualifications	Personnel, either supervisory or operational, must be qualified by training and experience to perform their assigned tasks.
211.28	Personnel responsibilities	The obligations of personnel engaged in the manufacture of drug products concerning their personal hygiene, clothing and medical status are defined.
211.34	Consultants	The qualifications of consultants must be approved by Quality Control.
Subpart C—Buildings and Facilities		
211.42	Design and construction features	Buildings and facilities can be considered acceptable only if they are suitable for their intended purpose and can be maintained. Construction concepts, such as air handling systems, lighting, eating facilities and plumbing systems including water, sewage and toilet facilities, are outlined.
211.44	Lighting	
211.46	Ventilation, air filtration, air heating and cooling	
211.48	Plumbing	
211.50	Sewage and refuse	
211.52	Washing and toilet facilities	
211.56	Sanitation	
211.58	Maintenance	

Subpart D—Equipment		
211.63	Equipment design, size and location	Equipment must be designed, constructed, of adequate size, suitably located and able to be maintained in order to be considered suitable for its intended use.
211.65	Equipment construction	
211.67	Equipment cleaning and maintenance	
211.68	Automatic, mechanical and electronic equipment	Reference is made to the use of automatic equipment, data processors and computers highlighting the need to verify output versus input and for proper calibration of recorders, counters and other electrical or mechanical devices.
211.72	Filters	Special note is made that only filters are to be used which do not release fibers into products.
Subpart E—Control of Components and Drug Product Containers and Closures		
211.80	General requirements	Written procedures must be available which describe the receipt, identification, storage, handling, sampling, testing and approval or rejection of components (raw materials) and drug products.
211.82	Receipt and storage of untested components, drug product containers and closures	
211.84	Testing and approval or rejection of components, drug product containers and closures	Once approved or rejected, these materials must be so identified and stored. If approved, they must be inventoried in a manner to assure that the oldest approved stock is used first (FIFO). Materials which are subject to deterioration during storage should be retested at an appropriate time based on stability profiles.
211.86	Use of approved components, drug product containers and closures	
211.87	Retesting of approved components, drug product containers and closures	
211.89	Rejected components, drug product containers and closures	
211.94	Drug product containers and closures	Containers and closures (product contact materials) must be nonreactive with or additive to the product.
Subpart F—Production and Process Controls		
211.100	Written procedures; deviations	Written standard operating procedures (SOP's) for each production process and control procedure are necessary. Any deviation to a SOP must be investigated, recorded and approved prior to final product acceptance.
211.101	Charge-in of components	All products are to be formulated to provide not less than 100% of the required amount of active ingredient. Records are to be maintained of each component and the quantity which is incorporated into a batch.
211.103	Calculation of yield	
211.105	Equipment identification	
211.110	Sampling and testing of in-process materials and drug products	Significant in-process steps are to be identified and appropriate sampling, testing and approvals obtained before proceeding further in the production cycle. If required, time limitations will be placed on in-process steps.
211.111	Time limitations on production	
211.113	Control of microbiological contamination	Appropriate procedures are to be prepared for testing components, products and the environment in order to establish that a product is not microbiologically contaminated.
211.115	Reprocessing	Reprocessing of product is allowed providing there are written procedures covering the methods to be used and approved by quality control. Additional testing of the reprocessed batch may be required to assure conformity with specifications.
Subpart G—Packaging and Labeling Control		
211.122	Materials examination and usage criteria	Labeling & packaging materials are to be received, identified, stored, sampled and tested following detailed written procedures.
211.125	Labeling issuance	Special controls must be exercised over labeling to assure that only the correct labels are issued to packaging for a specific product and that the quantities used are reconciled with the quantity issued.
211.130	Packaging and labeling operations	
211.134	Drug product inspection	
211.137	Expiration dating	Following appropriate stability studies at prescribed temperature conditions, products on the market shall bear an expiration date to assure that they are used within their expected shelf life.
Subpart H—Holding and Distribution		
211.142	Warehousing procedures	Describes the requirements for warehousing and distribution of products and their holding under appropriate conditions of light, temperature and humidity.
211.150	Distribution procedures	
Subpart I—Laboratory Controls		
211.160	General requirements	Concerns written procedures in the form of specifications, standards, sampling plans and test procedures which are used in a laboratory for controlling components and finished drug products. Acceptance criteria for sampling and approval shall be adequate for support release of product to distribution.
211.165	Testing and release for distribution	
211.166	Stability testing	A stability testing program will be followed in order to assess the stability characteristics of drug products. The results of this testing shall be used in assigning appropriate storage conditions and expiration dates.
211.167	Special testing requirements	
211.170	Reserve samples	
211.173	Laboratory animals	Animals used in any testing shall be maintained and controlled in a manner suitable for use.
211.176	Penicillin contamination	Drug products cannot be marketed if, when tested by a prescribed procedure, found to contain any detectable levels of penicillin.
Subpart J—Records and Reports		
211.180	General requirements	Details the various records and documents which should be generated during the manufacture of drug products and which are to be available for review.
211.182	Equipment cleaning and use log	
211.184	Component, drug product container, closure and labeling records	
211.186	Master production and control records	A master production record must be prepared for each drug product, describing all aspects of its manufacture, packaging and control. Individual batch records are derived from this approved master.
211.188	Batch production and control records	
211.192	Production record review	
211.194	Laboratory records	

211.196	Distribution records	Distribution records include warehouse shipping logs, invoices, bills of lading and all documents associated with distribution. These records should provide all the information necessary to trace lot distribution in order to facilitate product retrieval if necessary.
211.198	Complaint files	Records of complaints received from consumers and professionals are to be maintained along with the report of their investigation and response.
Subpart K—Returned and Salvaged Drug Products		
211.204	Returned drug products	Records are to be maintained of drug products returned from distribution channels and the reason for their return. This data can be used as part of the total lot accountability, should the need arise, to trace its distribution and/or for its recall.
211.208	Drug product salvaging	Drug products that have been stored improperly are not to be salvaged.

CHAPTER 83

Solutions, Emulsions, Suspensions and Extracts

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

The preparation of these dosage forms involves several considerations on the part of the pharmacist: purpose of the drug, internal or external use, concentration of the drug, selection of the liquid vehicle, physical and chemical stability of the drug, preservation of the preparation and use of appropriate excipients such as buffers, solubilizers, suspending agents, emulsifying agents, viscosity controlling agents, colors and flavors. The theory of many of these preparations is discussed in earlier chapters in Part 2, *Pharmaceutics*. Because of the complexity of some manufactured products, compounding may be carried out with the aid of linear programming models in order to obtain the optimal product. 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 first have studied the absorption of drugs administered in solution. Since drugs are absorbed in their dissolved state, frequently it is found that the absorption rate of oral dosage forms decreases in the following order: aqueous solution > aqueous suspension > tablet or capsule. The bioavailability of a medicament, for oral ingestion and absorption, should be such that eventually all of the drug is absorbed as it passes through the gastrointestinal tract, regardless of the dosage form. There are a number of reasons for formulating drugs in forms in which the drug is not in the molecular state. These are: improved stability, improved taste, low water solubility, palatability and ease of administration. It becomes apparent, then, that each dosage form will have advantages and disadvantages.

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

The pharmacist, in the first instance, depends on the pharmaceutical manufacturer to produce a product that is effective, elegant and stable when stored under reasonably adverse conditions. Most manufacturers attempt to guarantee efficacy by evaluating their products in a scientifically acceptable manner but, in some instances, such efficacy is relative. For example, cough mixtures marketed by two different manufacturers may contain the same active ingredients and it becomes difficult to assess the relative merits of the two products. In such instances the commercial advantage gained by one over the other may be based on product 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 81.

The more complicated reactions usually involve oxygen. Vitamins, essential oils and almost all fats and oils can be oxidized. Formulators usually use the word *autoxidation* when the ingredient(s) in the product react with oxygen but without drastic external interference. Such reactions first must be initiated by heat, light (including ultraviolet radiant energy), peroxides or other labile compounds or heavy metals such as copper or iron. This initiation step results in the formation of a free radical (R*) which then reacts with oxygen.

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

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

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

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

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

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

The effect of trace metals can be minimized by using citric acid or EDTA (ie, sequestering agents). Antioxidants, 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 66.

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

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

Products may become contaminated for a number of reasons.

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

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

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

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

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 almost is 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 until it is used by the patient.

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

Preservatives may be used alone or in combination 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 normally is used in a 10% concentration.

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 effective mainly 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 it 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-0.25%) are available.

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 used. 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 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 *p*-hydroxybenzoic acid (the parabens) are used widely in the pharmaceutical industry. They are effective over a wide pH range (from about 3 to 9) and are employed up to about the 0.2% concentration level. The two esters often are 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 now should 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, which should be studied in detail. Certain points are self-evident. Stock should be rotated and replaced if expiration dates on the label so indicate. Products should be stored in the manner indicated in the compendium; eg, in a cool place or a tight, light-resistant container. Further, products should be checked for evidence of instability. With respect to solutions, elixirs, and syrups, color change, precipitation and evidence of microbial or chemical gas formation are major signs of instability. Emulsions may cream but if they break (ie, there is a

separation of an oil phase) the product is considered to be unstable. Sedimentation and caking are primary indications of instability in suspensions. The presence of large particles may mean that excessive crystal growth has occurred.

The USP states that 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. If a product is diluted, or where two products are mixed, the pharmacist should use 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 often is unknown, their use should be minimized and every care taken to insure that product characteristics will not change during the time it must be used by the patient.

Because of the number of excipients and additives in these preparations, it is recommended that all the ingredients be listed on the container to reduce the risks which confront hypersensitive patients when these products are administered.

Solutions

Aqueous Solutions

A solution is a homogeneous mixture that is prepared by dissolving a solid, liquid or gas in another liquid and represents a group of preparations in which the molecules of the solute or dissolved substance are dispersed among those of the solvent. Solutions also may be classified on the basis of physical or chemical properties, method of preparation, use, physical state, number of ingredients and particle size. The narrower definition 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 *Water*, *Aromatic Waters*, *Aqueous Acids*, *Solutions*, *Douches*, *Enemas*, *Gargles*, *Mouthwashes*, *Juices*, *Nasal Solutions*, *Otic Solutions* and *Irrigation Solutions*.

Water

The major ingredient in most of the dosage forms described herein is water. It is used both as a vehicle and as a solvent for the desired flavoring or medicinal ingredients. Its tastelessness, freedom from irritating qualities and lack of pharmacological activity make it ideal for such purposes. There is, however, a tendency to assume that its purity is constant and that it can be stored, handled and used with a minimum of care. While it is true that municipal supplies must comply with Environmental Protection Agency (EPA) regulations (or comparable regulations in other countries), drinking water *must* be repurified before it can be used in pharmaceuticals. For further information on water, see Chapter 21.

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 USP tests and assays. It must meet rigid specifications for chemical purity. Such water may be prepared by distillation, by use of ion-exchange resins or by reverse osmosis.

A wide variety of commercially available stills are used to produce distilled water. The end use of the product dictates the size of the still and extent of pretreatment of the drinking water introduced into the system. A description of stills is provided in Chapter 84. Such water may be sterile provided the condenser is sterile, but to be called sterile it must be subjected to a satisfactory sterilization process. However, it has been shown that *P aeruginosa* (and other microorganisms) can grow in the distilled water produced in hospitals. The implications of this are obvious. Sterile water may be sterile at the time of production but may lose this characteristic if it is stored improperly. Hickman *et al*,[5] by regrouping the components of conventional distillation equipment, have described a method for the continuous supply of sterile, ultrapure water. Quality-control procedures for monitoring the microbiological quality of water should be performed in the pharmaceutical manufacturer's production facilities.

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

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

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

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

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

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

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

If the resin contains a hydroxyl 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.

$$H_2SiO_3 + 2AOH \rightarrow A_2SiO_3 + 2H_2O$$

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

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

organisms/mL. Columns can be cleaned partially of pseudomonads by recharging, but a 0.25% solution of formaldehyde will destroy most bacteria. The column must be washed thoroughly and checked for the absence of aldehyde (with a Schiffs Reagent) before it can be used to generate deionized water.

Ultraviolet radiant energy (240–280 nm), heat or filtration can be used to limit the growth, kill or remove microorganisms in water. The latter method employs membrane filters and can be used to remove bacteria from heat-labile materials as described under membrane filters in Chapter 78.

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 77).

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

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

Aromatic Waters

Aromatic waters, known also as medicated waters, are clear, saturated aqueous solutions of volatile oils or other aromatic or volatile substances. Their odors and tastes are similar to those of the drugs or volatile substances from which they are prepared, 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 they 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—Different authorities give different directions for preparing aromatic waters by distillation. For fresh drugs the proportions range from 1 part of drug to 2 of distillate, to 2 parts of drug to 1 of distillate. For dried drugs such as cinnamon, anise, dill, caraway and fennel the proportion is 1 part of drug to 10 of distillate. For dried leaf drugs such as peppermint the proportion is 3 parts of drug to 10 of distillate. The drug should be contused or coarsely ground and combined with a sufficient quantity of *Purified Water*. Most of the water then is distilled; care should be taken to avoid charring or scorching the substances to prevent the formation of empyreumatic odors. On completion of the distillation, any excess oil in the distillate is removed and, if necessary, the clear-water portion is filtered.

Solution—Aromatic waters may be prepared by shaking repeatedly 2 g or (2 mL if a liquid) of the volatile substance with 1000 mL of purified water for 15 min. The mixture is set aside for 12 hr, 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.

Alternately aromatic waters also may be prepared by incorporating thoroughly 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 then is 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 minutes 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 also are unreactive.

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

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

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 preparing pharmaceuticals and cosmetics now is known. Similarly, many synthetic aromatic substances have a characteristic odor; eg, geranyl phenyl acetate has a honey odor. Such substances, either alone or in combination, can be used in nonofficial preparations and, by combining them in definite proportions, it is possible to produce substitutes for the officially recognized oil. Imitation Otto of Rose (which contains phenylethyl alcohol, rhodinol, citronellol and other ingredients) is an example of the types of substitutes which are now available. Additional information regarding the appropriate preparation of aromatic waters is provided in RPS-17, Chapter 84.

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

served than that of a vehicle. 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, 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 usually is 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.

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

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

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

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

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

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

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

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

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

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

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

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

Diluted Hydrochloric Acid USP 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 usually is nonvolatile. Solutions are used for the specific therapeutic effect of the solute, either internally or externally. Although the emphasis here is on the aqueous solution, certain preparations of this type (syrups, infusions and decoctions) have distinctive characteristics and, therefore, are described later in the chapter.

Solvents, solubility and general methods for the incorporation of a solute in a solvent are discussed in Chapter 16. Solutions are usually bottled automatically with equipment of the type shown in Fig 83-1.

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.

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

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

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

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

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

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

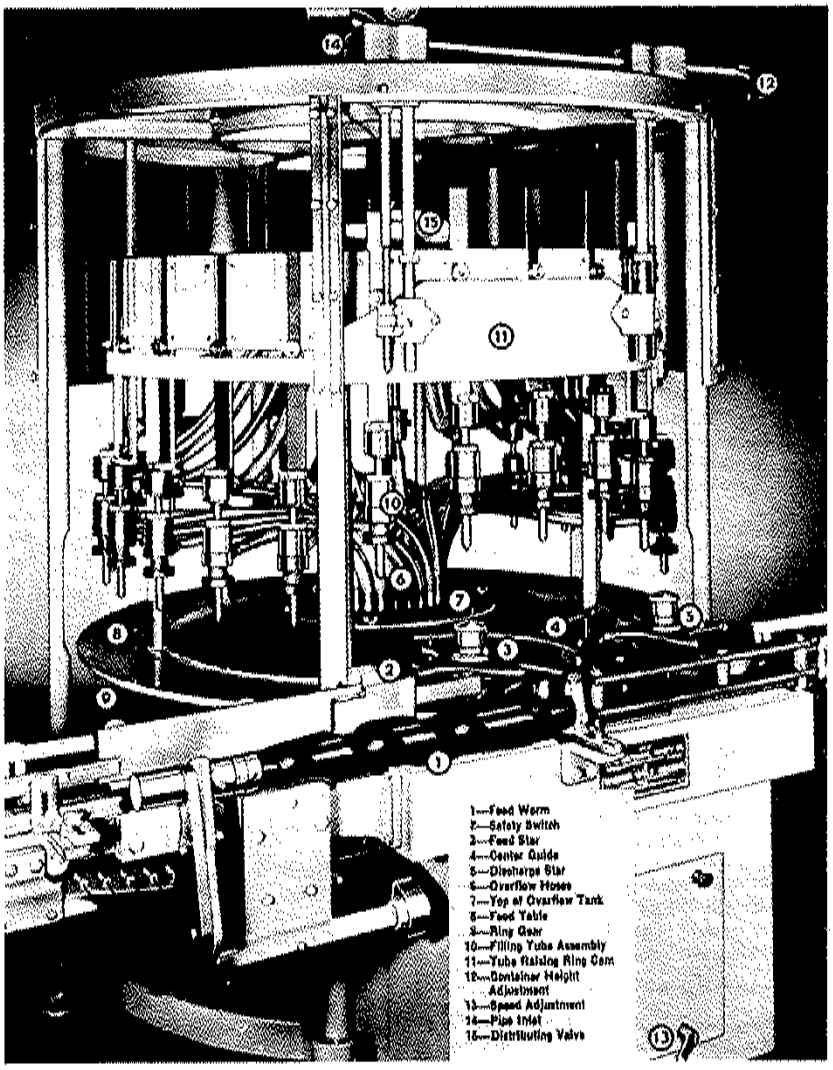


Fig 83-1. A rotary gravity bottle filler (courtesy, US Bottlers).

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

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

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

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

Doubly charged anions may be found also

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

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

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

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

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

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

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

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

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

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

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

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

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

Aluminum Subacetate Topical Solution is used in the preparation of Aluminum Acetate Topical Solution (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 0.0% boric acid.

Solution by Extraction—Drugs or pharmaceutical necessities of vegetable or animal origin often are extracted with water or with water containing other substances. Preparations of this type may be classified 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 or antiseptic agent. An *eye douche*, used to remove foreign particles and discharges from the eyes, is directed gently at an oblique angle and allowed to run from the inner to the outer corner of the eye. *Pharyngeal douches* are used to prepare the interior of the throat for an operation and cleanse it in suppurative conditions. Similarly, there are *nasal douches* and *vaginal douches*. Douches usually are directed to the appropriate body part by using bulb syringes (Chapter 104).

Douches most frequently are dispensed in the form of a powder with directions for dissolving in a specified quantity of water (usually warm). However, tablets for preparing solutions are available (eg, Dobell's Solution Tablets) or the solution may be prepared by the pharmacist. If powders or tablets are supplied, they must be free from insoluble material, in order to produce a clear solution. Tablets are produced by the usual processes (see Chapter 89) but any lubricants or diluents used must be readily soluble in water. Boric acid may be used as a lubricant and sodium chloride normally is used as a diluent. Tablets deteriorate on exposure to moist air and should be stored in airtight containers.

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 (qs 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). Its aqueous solution 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 frequently are 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 douches are used for cleansing the vagina and hygienic purposes. Liquid concentrates or powders, which may be prepared in bulk or as single-use packages, should be diluted or dissolved in the appropriate amount of warm water prior to use. The ingredients used in vaginal douches include antimicrobial agents such as benzalkonium chloride, the parabens or chlorothymol, anesthetics or antipruritics such as phenol or menthol. Astringents such as zinc sulfate or potassium alum, surface-active agents such as sodium lauryl sulfate and chemicals to alter the pH such as sodium bicarbonate or citric acid also are used.

Enemas

These preparations are rectal injections employed to evacuate the bowel (evacuation enemas), influence the general system by absorption (retention enemas) 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 retention enemas are those of aminophylline, hydrocortisone and methylprednisolone acetate. Since they are to be retained in the intestine, they should not be used in larger quantities than 150 mL for an adult. Usually, the volume is considerably smaller, such as a few mL. *Microenema* is a term used to describe these small-volume preparations. Vehicles for retention microenemas have been formulated with small quantities of ethanol and propylene glycol, and no significant difference in irritation, as compared with water, was found. A number of drugs such as valproic acid, indomethacin and metronidazole have been formulated as microenemas for the purpose of absorption. The absorption of large molecular weight drugs, such as insulin, is under current investigation.

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

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

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

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.

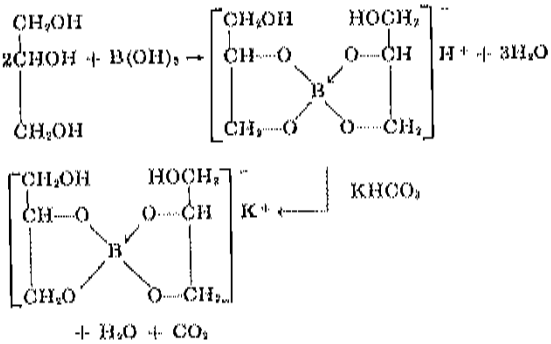
Potassium Chlorate and Phenol Gargle is official in the PC. It contains potassium chlorate, 30 g, patent blue V (Color Index No 42051) commercial food grade (0.01 g), liquified phenol (15 mL) and water for preparations qs to 1000 mL. It should be diluted with 10 volumes of warm water before use. The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

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

Mouthwashes

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

The products of commerce (eg, Cepacol, Listerine, Micrin or Scope) 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.

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

Juices

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

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

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

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

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

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

A formula for Ephedrine Nasal Drops PC is

Ephedrine hydrochloride	0.5 g
Chlorobutanol	0.5 g
Sodium Chloride	0.8 g
Water for preparations	to 100 mL

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

Otic Solutions

These solutions occasionally are referred to as aural preparations. Other otic preparations often include formula-

tions such as suspensions and ointments for topical application in the ear.

The main classes of drugs used for topical administration to the ear include analgesics, eg, benzocaine; antibiotics, eg, neomycin; and anti-inflammatory agents, eg, cortisone. The USP preparations include Antipyrine and Benzocaine Otic Solution. The Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solutions contain appropriate buffers and dispersants usually in an aqueous solution. These 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. Viscous liquids like glycerin or propylene glycol either are used alone or in combination with a surfactant to aid in the removal of cerumen (ear wax).

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

Irrigation Solutions

These solutions are used to wash or bathe surgical incisions, wounds or body tissues. Because they come in contact with exposed tissue, they must meet stringent requirements for Injections of the USP such as sterility, particulate matter and the requirements of the Pyrogen Test. These products are prepared by dissolving the active ingredient in Water for Injection. They are packaged in single-dose containers, preferably Type I or Type II glass, or suitable plastic containers, and then sterilized. See Chapter 78 for sterilization procedures. A number of irrigations are described in the USP: Acetic Acid Irrigation for bladder irrigation, Aminoacetic Acid Irrigation for urethral surgery and Sodium Chloride Irrigation for washing wounds. Other drugs such as amphotericin B also may be formulated as irrigations.

Sweet or Other Viscid Aqueous Solutions

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

Syrups

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

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

Syrups possess remarkable masking properties for bitter or saline drugs. Glycyrrhiza syrup has been recommended for disguising the salty taste of bromides, iodides and chlorides. This has been attributed to its colloidal character and its double sweetness—the immediate sweetness of the sugar and the lingering sweetness of the glycyrrhizin. This syrup is also of value in masking bitterness in preparations containing the B complex vitamins. Acacia Syrup USP, because of its colloidal character, is of particular value as a vehicle for masking the disagreeable taste of many medicaments. Raspberry Syrup PC 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 66 should be consulted for further information on the flavoring of pharmaceuticals and the preparation of a number of official syrups. A series of papers by Schumacher deals with improving the palatability of bulk-compounded products using flavoring and sweetening agents.[8]

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

It is important that the concentration of sucrose approach but not quite reach the saturation point. In dilute solutions sucrose provides an excellent nutrient for molds, yeasts and other microorganisms. In concentrations of 65% by weight or more, the solution will retard the growth of such microorganisms. However, a saturated solution may lead to 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. Sucrose solutions are dextrorotary but, as hydrolysis proceeds, the optical rotation decreases and becomes negative when the reaction is complete. This reaction is termed *inversion* because *invert sugar* (dextrose plus levulose) is formed. The speed of inversion is increased greatly by the presence of acids; the hydrogen ion acts as a catalyst in this hydrolytic reaction. Invert sugar is more readily fermentable than sucrose and tends to be darker in color. Nevertheless, its two reducing sugars are of value in retarding the oxidation of other substances.

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

The levulose formed during inversion is sweeter than su-

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

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

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

The formula and procedure given for Acacia Syrup (page 1301) illustrates this method of preparation.

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

This method and that previously described are used for the preparation of a wide variety of preparations that are 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 USP but no directions are given for their preparation. For example, Guaifenesin Syrup USP (glyceryl guaiacolate syrup) is official but the only known ingredients are guaifenesin (glyceryl guaiacolate) and ethanol (not less than 3% or more than 4%).

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

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

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

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

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

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

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

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

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

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

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

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

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

If pressed in too tightly, the cotton will stop the process effectually; if inserted too loosely, the liquid will pass through the cotton rapidly and the filtrate will be weak and turbid (from imperfect filtration); it should be inserted completely within the neck of the percolator, since a protruding end, inside the percolator, up through the sucrose, will permit the last portions of water to pass out at the lower orifice without dissolving all the sucrose. For specific directions see *Syrups* (page 1301). The process of percolation is applied on a commercial scale for the making of official syrups as well as those for confectionary use.

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

Reconstitution—In order to improve stability and minimize microbial contamination, dry syrup formulations can be prepared and Purified Water USP added just prior to dispensing or use. Powder mixtures, wholly granulated products and partially granulated products have been investigated for this purpose by Ryder.[10]

The powder mixture preparation requires less equipment and energy to prepare. Chemical stability problems are minimal, since no heat or solvents are used in the process and a low moisture content can be obtained in the final product; unfortunately, powder mixtures are prone to homogeneity problems. In the case of the wholly granulated product all the ingredients are included in the granulation stage. The drug may be incorporated into the dry product before granulation or dissolved or suspended in the granulating fluid. After formation, the granules are dried and then screened to break down oversize particles. The advan-

tages of granulated over powder mixtures include better appearance, better flow, fewer segregation problems and less dust during processing. Partially granulated mixtures are used to gain some of the advantages of granulation without the disadvantages. Usually the drug, and other fine particles, are included at the granulation stage, perhaps with some diluents to improve flow and reduce segregation and dust. Materials selected for mixing with the dried granules would include thermolabile excipients, such as flavors, and free flowing materials, such as sugars.

Preservation—Syrups should be made in quantities which can be consumed within a few months, except in those cases where special facilities can be employed for their preservation; a low temperature is the best method. The USP indicates that syrups should not be exposed to excessive heat. Concentration without super-saturation is also a condition favorable to preservation. The USP states that syrups may contain preservatives to prevent bacterial and mold growth such as glycerin, methylparaben, benzoic acid and sodium benzoate, 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. Any attempt to restore syrups 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 4 to 6 weeks and should be filled completely, stoppered carefully and stored in a cool, dark place.

Syrups Prepared from Juices

Blackberry, pineapple and strawberry syrups may be prepared by following the directions in Raspberry Syrup PC. One volume of the concentrated raspberry juice is diluted with 11 volumes of syrup. Black Current Syrup PC is prepared in a similar manner but also can be prepared from black currants, with certain modifications. The pectin in the juice is destroyed with pectinase. The syrup is prepared 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 1301).

Honeys

Honeys are thick liquid preparations somewhat allied to the syrups, differing in that honey, instead of syrup, is used as a base. They are unimportant as a class of preparations today but at one time, before sugar was available and honey was the most common sweetening agent, they were used widely. PC 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. Thick and thin sugar pastes containing Caster sugar (very fine granular sugar), icing sugar (additive-free), polyethylene glycol 400 and hydrogen peroxide (in a final concentration of 0.15%) have been prepared and shown to be beneficial in the process of wound healing.

Mucilages

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

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

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

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

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

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

Several synthetic mucilage-like substances such as *polyvinyl alcohol, methylcellulose, carboxymethylcellulose* and related substances, as described in Chapter 66, are used as mucilage substitutes, emulsifying and suspending agents. Methylcellulose (page 1306) is used widely as a bulk laxative since it absorbs water and swells to a hydrogel in the intestine, in much the same manner as *psyllium* or *karaya gum*. Methylcellulose Oral Solution is a flavored solution of the agent. It may be prepared by adding slowly the methylcellulose to about one-third the amount of boiling water, with stirring, until it is thoroughly wetted. Cold water then should be added and the wetted material allowed to dissolve while stirring. The viscosity of the solution will depend upon the concentration and the specifications of the methylcellulose. The synthetic gums are nonglycogenetic and may be used in the preparation of diabetic syrups. Several formulas for such syrups, based on sodium carboxymethylcellulose, have been proposed.

Uniformly smooth mucilages sometimes are difficult to prepare due to the uneven wetting of the gums. In general, it is best to use fine gum particles and disperse them with good agitation in a little 95% alcohol or in cold water (except for methylcellulose). The appropriate amount of water then can be added with constant stirring. A review of the chemistry and properties of acacia and other gums has been prepared.[11]

Jellies

Jellies are a class of gels in which the structural coherent matrix contains a high portion of liquid, usually water. They are similar to mucilages, in that they may be prepared from similar gums, but they differ from the latter in having a jelly-like consistency. A whole gum of the best quality, rather than a powdered gum, is desirable in order to obtain a clear preparation of uniform consistency. Tragacanth is the gum used in the preparation of Ephedrine Sulfate Jelly NF XII. While the specific thickening agent in the USP jellies is not indicated, reference usually is made in the monograph to a water-soluble viscous base. These preparations also may be formulated with water from acacia, chondrus, gelatin, carboxymethylcellulose and similar substances.

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

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

Nonaqueous Solutions

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

Products of commerce 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 denatured alcohol. This mixture contains 8 parts by volume of acetone, 1.5 parts by volume of methyl isobutyl ketone and 100 parts by volume of ethanol. Besides the alcohol in the Rubbing Alcohol, the final product must contain water, sucrose octaacetate or denatonium benzoate and may contain color additives, perfume oils and a suitable stabilizer. The alcohol content, by volume, is not less than 68.5% and not more than 71.5%. The isopropyl alcohol content in Isopropyl Rubbing Alcohol can vary from 68.0% to 72.0% and the finished product may contain color additives, perfume oils and suitable stabilizers.

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

Although this 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 products produced by the industry. However, the toxicity of many of these solvents is not well-established and, for this reason, careful clinical studies should be carried out on the formulated product before it is released to the marketplace.

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

Collodions

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

Elixirs

Elixirs are clear, pleasantly flavored, sweetened hydroalcoholic liquids intended for oral use. They are used as flavors and vehicles such as Aromatic Elixir (page 1302) 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 elixirs are ethanol and water but glycerin, sorbitol, propylene glycol, flavoring agents, preservatives and syrups often are used in the preparation of the final product.

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 PC contains syrup and 100 mL of ethanol in the same final volume. Definitions are, therefore, inconsistent and, in some in-

stances, 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% of alcohol; Compound Benzaldehyde Elixir, on the other hand, contains 3 to 5%.

Elixirs also may contain glycerin and syrup. These may be added to increase the solubility of the medicinal agent or for sweetening purposes. Some elixirs contain propylene glycol. Claims have been made for this solvent as a satisfactory substitute for both glycerin and alcohol. Sumner,[12] 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. Therefore, the elixir is ineffective for the treatment of bronchitis. However, it 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 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 often is desirable, therefore, to substitute some other solvent that is more effective in masking such tastes for part of the alcohol in the formula. In general, if taste is a consideration, the formulator is more prone to use a syrup rather than a hydroalcoholic vehicle.

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 effected. A high alcoholic content is maintained during preparation by adding the aqueous phase to the alcoholic solution. Elixirs always should be brilliantly clear. They may be strained or filtered and, if necessary, subjected to the clarifying action of purified talc or siliceous earth.

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

The formula for High-Alcoholic Elixir is:

Compound Orange Spirit	4 mL
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 studied 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. Much reserch has been done to find a safe synthetic substitute for sucrose. As a result, aspartame (methyl *N*(-L-α-aspartyl)-L-phenylalaninate), which is about 200 times sweeter than sucrose, is being used now in many commercial preparations as the sweetening agent. It is sparingly soluble in water and is most stable at a pH of 4.3. This compound likely will be used in a number of pharmaceutical formulations in the future.[13]

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

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

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

Glycerins

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

Glycerin is a valuable pharmaceutical solvent forming permanent and concentrated solutions not otherwise obtainable. 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. Antipyrine and Benzocaine Otic Solution USP was discussed previously under *Otic Solutions*. One of the glycerins, Phenol Glycerin PC is diluted with glycerin to form the pharmaceutical preparation, Phenol Ear-Drops PC.

Phenol Glycerin PC

Phenol	160 g
Glycerin	840 g

Dissolve the phenol in the glycerin.

Phenol Ear-Drops PC

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

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. This product no longer is recommended because of the possibility of necrosis and perforation of the tympanic membrane. As noted under *Otic Solutions*, glycerin alone is used to aid in the removal of cerumen.

Sodium Bicarbonate Ear-Drops PC may be used if wax is to be removed from the ear. This preparation contains sodium bicarbonate (5 g), glycerin (30 mL) and purified water (a sufficient quantity to make 100 mL). A glycerin base was chosen as the optimum solvent for an otic preparation in a study involving the stability and antimicrobial activity of kanamycin sulfate otic drops.

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 also may 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 USP, particle size is of major importance in the administration of this type of preparation. The various mechanical devices that are used in conjunction with inhalations are described in some detail in Chapter 104. It has been reported that the optimum particle size for penetration into the pulmonary cavity is of the order of 0.5 to 7 μm. Fine mists are produced by pressurized aerosols and hence possess basic advantages over the older nebulizers; in addition, metered aerosols deliver more uniform doses. See Chapter 92.

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 PC 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 the 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 consist 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 used to relieve nasal congestion. Inhalers which come in contact with the mouth or nasal passages become contaminated by bacteria, thus, they should be restricted to personal use.

Another inhalant is Amyl Nitrite USP which is very flammable and should not be used where it may be ignited. It is packaged in sealed glass vials in a protective gauze. Upon breaking the vial, the gauze absorbs the drug which is then inhaled for the treatment of anginal pain. See page 843.

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

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

White Liniment PC

Ammonium Chloride	12.5 g
Dilute Ammonia Solution	45 mL
Oleic Acid	85 mL

Turpentine Oil	250	mL
Water for Preparations	625	mL

Mix the oleic acid with the turpentine oil. Add the dilute ammonia solution mixed with 40 mL of previously warmed water and shake. Dissolve the ammonium chloride in the remainder of the water, add to the emulsion and mix.

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

Compound Calamine Application PC
(Compound Calamine Liniment)

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

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

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

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

Oleovitamins

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

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

These vitamins are unstable in the presence of rancid oils and, therefore, these preparations and, in particular, 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 medicinally by inhalation and a large number as flavoring agents. The latter group provides a convenient and ready means of obtaining the volatile oil in the proper quantity. For example, a spirit or spirit-like preparation may be used in the formulation of aromatic waters or other pharmaceuticals that require a distinctive flavor.

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 of preparation:

Simple Solution—This is the method by which the majority of spirits are prepared. The formula and procedure given for Aromatic Ammonia Spirit USP illustrate this method of preparation.

Aromatic Ammonia Spirit USP

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, then filter, using a covered funnel.

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

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

Solution with Maceration—In this procedure, the leaves of a drug are macerated in purified water to extract water-soluble matter. They are expressed and the moist, macerated leaves are added to a prescribed quantity of alcohol. The volatile oil is added to the filtered liquid. Peppermint Spirit USP is made by this process. Peppermint Spirit PC 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 had 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 USP (page 798) 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 then is 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 precipi-

tated from their aqueous solutions by the addition of spirits due to their lesser solubility in alcoholic liquids.

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

Toothache Drops

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

These preparations no longer are recognized officially. Furthermore, dentists do not recommend the use of toothache drops if the patient has ready access to adequate dental services. 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, and he should warn the patient of possible hazards associated with their use.

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

Emulsions

An emulsion is a two-phase system prepared by combining two immiscible liquids, one of which is dispersed uniformly throughout the other and consists of globules that have diameters equal to or greater than those of the largest colloidal particles. The globule size is critical, of course, and must be such that the system achieves maximum stability. However, even under the best 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.

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

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 can be diluted easily and uniformly 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 (or emulsifiers) are available, 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 or cholesterol. Acacia, tragacanth, chondrus or pectin are representative of those obtained from vegetable sources. Various cellulose derivatives, eg, methylcellulose and carboxymethylcellulose, are used to increase the viscosity of the aqueous phase and thereby enhance emulsion stability.

Finely Divided Solids—Examples are bentonite, magnesium hydroxide, aluminum hydroxide or magnesium trisilicate.

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

Many of these emulsifying agents are described in greater detail in Chapter 66.

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

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

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

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

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

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

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 particularly is 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, in very fine powder	125 g
Syrup	100 mL
Vanillin	40 mg
Alcohol	60 mL
Purified Water, a sufficient quantity	1000 mL

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

Very few emulsions are included now in the official compendia. The PC suggests that the term "emulsion" be restricted to preparations, usually O/W, intended for internal use and contains 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 reader 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 an oil can be masked partially or wholly, by emulsification. Secondary masking techniques are available to the formulator but these must be used with caution. If flavors and sweetening agents are added to the emulsion, only minimal amounts should be used in order to prevent the nausea or gastric distress that results on ingestion of larger quantities of these.
3. The absorption and penetration of medicaments are controlled more easily if they are incorporated into an emulsion.
4. Emulsion action is prolonged and the emollient effect is greater than that observed with comparable preparations.
5. Water is an inexpensive diluent and a good solvent for the many drugs and flavors that are incorporated into an emulsion.

The effects of viscosity, surface tension, solubility, particle size, complexation and excipients on the bioavailability of oral suspensions and emulsions have been discussed in detail by Rettig.[14]

The aqueous phase of the emulsion favors the growth of microorganisms and, because of this, a preservative usually is added to the product. Some of the preservatives that have been used include chlorocresol, chlorobutanol, mercurial preparations, salicylic acid, the esters of *p*-hydroxybenzoic acid, benzoic acid, sodium benzoate or sorbic acid. The preservative should be selected with regard for the ultimate use of the preparation and possible incompatibilities between the preservative and the ingredients in the emulsion, eg, binding between the surface-active agent and the preservative. Low pH values of 5 to 6 and low concentrations of water are characteristics also likely to inhibit microbiological growth in emulsions.

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

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

An emulsion can be diluted with the liquid that constitutes, or is miscible with, the external phase. The diluting liquid, however, will decrease the viscosity of the preparation and, in certain instances, 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 19. The following procedures are those suggested by Griffin *et al.*[15]

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 also is 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 usually will contain higher concentrations of oils and waxes. The preparation of cream and ointment emulsions for topical use is given in Chapter 87.

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

The technique of emulsification of pharmaceutical preparations has been described by White.[16] 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 O/W emulsion as an example, the addition of the water (external phase) to the oil (internal phase) will promote the formation of a W/O emulsion due to the preponderance of the oil phase. After further addition of the water, phase inversion to an O/W emulsion should take place. This method especially is useful and successful when hydrophilic agents such as acacia, tragacanth or methylcellulose are first mixed with the oil, effecting dispersion without wetting. Water is added and, eventually, an O/W emulsion is formed. This "dry gum" technique is a rapid method for preparing small quantities of emulsion. The ratio 4 parts of oil, 2 parts of water and 1 part of gum provides maximum shearing action on the oil globules in the mortar. The emulsion then can be diluted and triturated with water to the appropriate concentrations. The preparation of Mineral Oil Emulsion described above is an example.

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

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

Multiple Emulsions—A recent innovation in emulsion technology is the development of multiple emulsions. The dispersed phase of these emulsions contains even smaller droplets which are miscible with the continuous phase. Thus, the multiple emulsion may be O/W/O where the aqueous phase is between two oil phases, or W/O/W where the internal and external aqueous phases are separated by an oil phase. In these systems both hydrophobic and hydrophilic emulsifiers are used and both have an effect on the yield and stability, as noted by Florence and Whitehill.[17]

It appears that O/W/O emulsions are formed better by lipophilic, nonionic surfactants using gum acacia-emulsified simple systems, while W/O/W multiple emulsions were formed better by nonionic surfactants in a two-stage emulsification procedure. A specific formulation for a W/O/W emulsion may be prepared by forming the primary (W/O) emulsion from isopropyl myristate (47.5%), sorbitan monooleate (2.5%) and distilled water (100%). This primary emulsion (50%) is added to a polyoxyethylene sorbitan monooleate (2% *w/v*) solution in water. While the technique of preparing these emulsions is more complicated, research indicates potential use of these emulsions for prolonged action, taste-masking, more effective dosage forms, parenteral preparations, protection against the external environment and enzyme entrapment.

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

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

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

If the emulsifier has been selected properly, microemulsification will occur almost spontaneously, leading to a satisfactory and stable preparation. The details of various preparations and the relationship between microemulsions and micellar solutions have been reviewed by Prince *et al.*[18] Microemulsions containing hydrocortisone have been prepared.

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, jet mixers 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, along with journals such as *Pharmaceutical Technology*, should be consulted for further details on the use of such apparatus.

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

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

The mortar and pestle are used widely by the prescription pharmacist in the 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.

Small electric mixers may be used to prepare emulsions at the prescription counter. They will save time and energy and produce satisfactory emulsions when the emulsifying agent is acacia or agar. 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. It transfers large amounts of energy and incorporates air into the emulsion. If an emulsion first is produced by using a blender of this type, the formulator must remember that the emulsion characteristics obtained in the laboratory will not be duplicated necessarily by the production-size agitators.

Production-size agitators include high-powered propeller-shaft stirrers immersed in a tank or self-contained units with

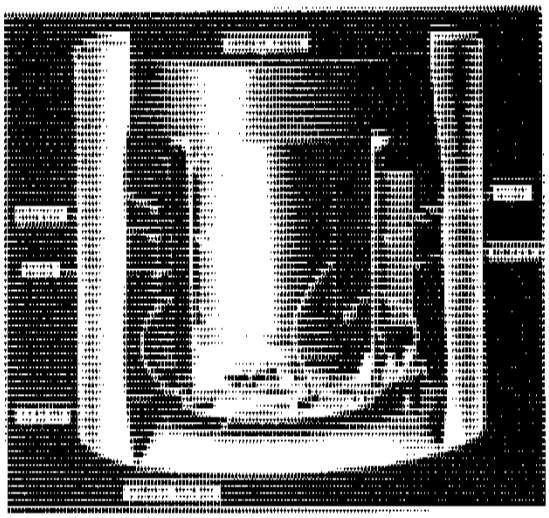
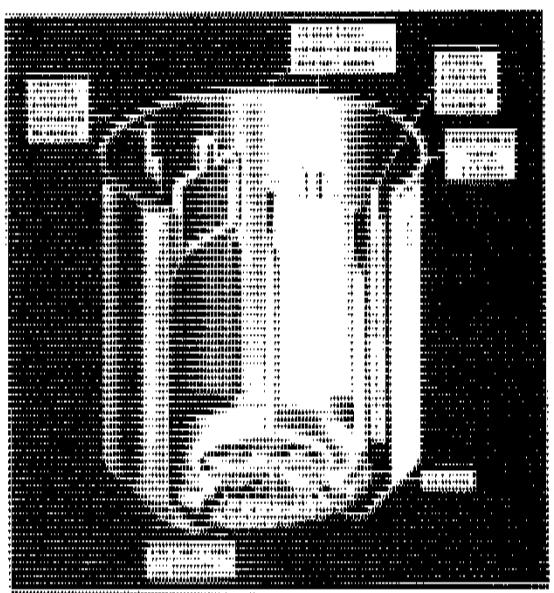


Fig 83-2. Standard slurry-type dispersall mixer with vaned-rotor "mixing" element and slotted draft-tube circulating element (courtesy, Abbe Eng).



(courtesy, Abbe Eng).

propeller and paddle systems. The latter usually are constructed so that the contents of the tank either may be heated or cooled during the production process. Baffles often are built into a tank and these increase the efficiency of agitation. Two mixers manufactured by the same company are shown in Figs 83-2 and 83-3.

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 to 18,000 rpm. The clearance between the rotor and the stator is adjustable, usually from 0.001 in upward. The emulsion mixture, in passing between the rotor and stator, is subjected to a tremendous shearing action which effects a fine dispersion. A colloid mill and various rotors are shown in Figs 83-4 and 83-5. 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.

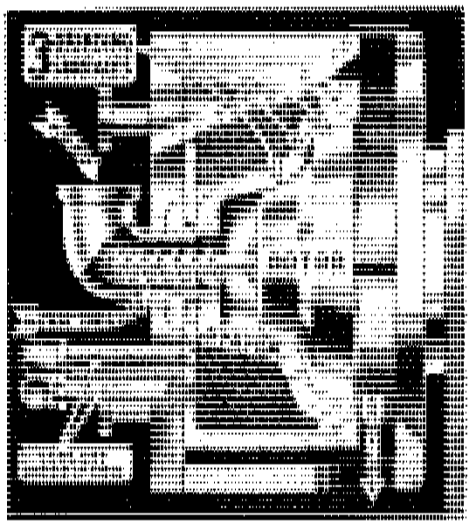


Fig 83-4. A colloid mill shown in cross section (courtesy, Tri-Homo).

Fig 83-5. Types of rotors used in colloid mills. These may be smooth (for most emulsions), serrated (for ointments and very viscous products) or of vitrified stone (for the paints and pigment dispersions) (courtesy, Tri-Homo).

Homogenizers and Viscolizers—In these two types of equipment the mixed phases are passed between a finely ground valve and seat under high pressure. This, in effect, produces an atomization which is enhanced by the impact received by the atomized mixture as it strikes the valve head. They operate at pressures of 1000 to 5000 psi and produce 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.
2. An emulsion is prepared in some other way and then passed through a homogenizer for the purpose of decreasing the particle size and obtaining a greater degree of uniformity and stability.

Two-stage homogenizers are constructed so that the emulsion, after treatment in the first valve system, is conducted directly to another where it receives a second treatment. A single homogenization may produce an emulsion which, although its particle size is small, has a tendency to clump or form clusters. Emulsions of this type exhibit increased creaming tendencies. This is corrected by passing the emulsion through the first stage of homogenization at a high

pressure (eg, 3000 to 5000 psi) and then through the second stage at a greatly reduced pressure (eg, 1000 psi). This breaks down any clusters formed in the first step.

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 adsorbed preferentially at the air/water interface, followed by an irreversible precipitation termed *denaturization*. This is particularly prone to occur with protein emulsifying agents.

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

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

Figure 83-6 shows the flow through the homogenizing valve, the heart of the high-pressure APV Gaulin homogenizer. The product enters the valve seat at high pressure, flows through the region between the valve and the seat at high velocity with a rapid pressure drop and then is discharged as a homogenized product. It is postulated that circulation and turbulence are responsible mainly for the homogenization that takes place. Different valve assemblies, two stage valve assemblies and equipment with a wide range of capacities are available.

The Macro Flow-Master *Kom-bi-nator* employs a number of different actions, each of which takes the ingredients a little further along in the process of subdividing droplets, until complete homogenization results. The machine is equipped with a pump which carries the liquid through the various stages of the process. In the first stage, the ingredients are forced between two specially designed rotors (gears) which shoot the liquid in opposite directions in a small chamber and, in this way, are mixed thoroughly. These rotors also set up a swirling action in the next chamber into

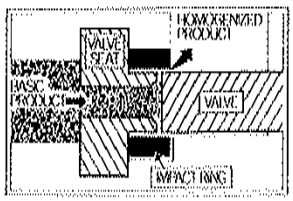


Fig 83-6. Operation of the homogenizer valve assembly (Courtesy APV Gaulin).

which the liquid is forced and swirled back and forth in eddies and crosscurrents. The second stage is a pulsing or vibrating action at rapid frequency. The product then leaves this chamber, goes through a small valve opening and is dashed against the wall of the homogenizing chamber. Pressure is applied, but it is not as great as that used in other types of homogenizers. Pressure is controlled accurately by adjusting devices on the front of the machine, and temperature is controlled by passing coolants through the stators.

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

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

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

Suspensions

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

Certain authors also include liniments, and the newer sustained-release suspensions, in any discussion of this particular subject. The former preparations now usually are considered as solutions although a number of older liniments were, in fact, suspensions. The sustained-release suspensions represent a very specialized class of preparation and, as such, are discussed in more detail in Chapter 91. Some insoluble drugs also are administered in aerosol form; one example is dexamethasone phosphate suspended in a propellant mixture of fluorochlorocarbons. More detail on aerosols is available in Chapter 92.

Suspension formulation and control is based on the prin-

ciples outlined in Chapters 19 and 20. 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 then can be added. Alternatively, the dry suspending agent can be mixed thoroughly 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 19.

The most efficient method of producing fine particles is by dry milling prior to suspension. Suspension equipment such as colloid mills or homogenizers normally are used in wet-milling finished suspensions to reduce particle agglomerates. These machines (Fig 83-4) 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 as described by Nash.[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 storage.

Preparations made extemporaneously for internal use may include, as suspending agents, acacia, methylcellulose or other cellulose derivatives, sodium alginate or tragacanth.

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

Agents suitable for external use include bentonite, methylcellulose or other cellulose derivatives, sodium alginate or 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, therefore, must be administered as a solid, nonsolution dosage form (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 maintaining a consistent dosage regimen. Disagreeable tastes can be covered by using a suspension of the drug or a derivative of the drug, an example of the latter being chloramphenicol palmitate. Suspensions prepared from ion-exchange resins containing an ionic drug can be used not only to minimize the taste of the drug but also to produce a prolonged-action product, since the drug is exchanged slowly for other ions within the gastrointestinal tract.

Suspensions also are chemically more stable than solutions. This particularly is important with certain antibiotics, and the pharmacist often is called on to prepare such a suspension just prior to dispensing the medication. In addition, a suspension is an ideal dosage form for patients who have difficulty swallowing tablets or capsules, which is particularly important in administering drugs to children. An alternate method to enhance compliance includes flavored nystatin "popsicles" which can be prepared by freezing a suspension of the drug so that the taste is improved during the treatment of oral candidiasis.

Suspensions should possess certain basic properties. The dispersed phase should settle slowly and be redispersed readily 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. The suspension must be acceptable to the patient on the basis of its taste, color and cosmetic qualities (elegance), the latter two factors being of particular importance in preparations intended for external use.

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, therefore, are considered in another part of this chapter. The USP definition for Gels is

> 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 sometimes is 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 distributed uniformly throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Single-phase may be made from synthetic macromolecules (eg, Carbomer) or from natural gums (eg, Tragacanth). The latter preparations also are called mucilages. Although these gels are commonly aqueous, 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 usually is prepared by the interaction of a soluble aluminum salt, such as a chloride or sulfate, with ammonia solution, sodium carbonate or bicarbonate. The reactions which occur during the preparation are

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

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

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

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

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

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

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

$$[Al(H_2O)_4(OH)_2]^{+} + H_3O^{+} \rightarrow [Al(H_2O)_5(OH)]^{2+} + H_2O$$
$$[Al(H_2O)_5(OH)]^{2+} + H_3O^{+} \rightarrow [Al(H_2O)_6]^{3+} + H_2O$$

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

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

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 (eg, 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: semisolid state, high degree of clarity, ease of application and ease of removal and use. The gels often provide a faster release of drug substance, independent of the water solubility of the drug, as compared to creams and ointments. Some drugs used in medication gels include urea, hydrogen peroxide, ephedrine sulphate, erythromycin and povidone-iodine.

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

Gels can be prepared from a number of pharmaceutical agents such as tragacanth 2 to 5%, sodium alginate 2 to 10%, gelatin 2 to 15%, methylcellulose 2 to 4%, sodium carboxymethyl-cellulose 2 to 5%, carbomer 0.3 to 5% or polyvinyl alcohols 10 to 20% as noted by Carter.[26] Other gelling agents include methylhydroxyethyl cellulose, polyoxyethylene-polyoxypropylene, hydroxyethyl cellulose and gelatin. Gels prepared from nonpolar materials such as magnesium soap-hydrocarbon and hydrocarbons are being investigated.

The percentages above indicate the concentration ranges of the gelling agent. The lower-percentage preparations may be used as lubricants and the higher-percentage preparations as dermatological bases. Some of the gelling agents are available in different grades indicating the viscosity at a definite concentration. In general, high-viscosity grades result in gels at lower concentrations.

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

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

The preparation of a few gel bases is given below:

Sodium Alginate Gel Base

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

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

Carbomer Jelly

Carbopol 934	2 g
Triethanolamine	1.05 mL
Parabens	0.2 g
Purified Water, to make	100 mL

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

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

Lotions

Lotions usually are 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 adding the remaining liquid phase cautiously. High-speed mixers or homogenizers produce better dispersions and, therefore, are the tools of choice in the preparation of larger quantities of lotion. Calamine Lotion USP is the classic example of this type of preparation and consists of finely powdered, insoluble solids held in more or less permanent suspension by the presence of suspending agents and/or surface-active agents. Many investigators have studied Calamine Lotion and this has led to the publication of many formulations, each possessing certain advantages over the others but none satisfying the collective needs of all dermatologists.

Phenolated Calamine Lotion USP 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*) and carboxymethylcellulose settle less than the official preparations.

Calamine Lotion

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

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

To prepare Phenolated Calamine Lotion add 1 mL of Liquefied Phenol during the mixing stage.

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

White Lotion

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

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

Sulfurated potash is a solid of variable composition but usually is described as K_2S_5·$K_2S_2O_3$. The chemical reaction which occurs when sulfurated potash solution is added to the zinc sulfate is

$$ZnSO_4 \cdot 7H_2O + K_2S_5 \cdot K_2S_2O_3 \rightarrow ZnS + S_2 + K_2SO_4 + K_2S_2O_3 + 7H_2O$$

This lotion must be prepared fresh and does not contain a suspending agent. Bentonite Magma has been used in some formulations. Coffman and Huyck[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. Some lotions are clear solutions and, in fact, the active ingredient of one official lotion, Dimethisoquin Hydrochloride Lotion USP XX 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 PC.

Hydrocortisone Lotion

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

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

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

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

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

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

Magmas and Milks

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

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

Magmas also may 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 is a suspension of magnesium hydroxide containing 7.0–8.5% $Mg(OH)_2$. It has an unpleasant, alkaline taste which can be masked with 0.1% citric acid (to reduce alkalinity) and 0.05% of a volatile oil or a blend of volatile oils.

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

The following reactions occur during the preparation of the magma.

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

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

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

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

If the insoluble substance is precipitated fresh by mixing hot, dilute solutions, there is only slight sedimentation on standing. This characteristic of magmas sometimes is 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 agent for insoluble substances eg, Milk of Magnesia USP and Dihydroxy Aluminum Aminoacetate Magma USP, either for local application or for internal use. All magmas require a "Shake Well" label. Freezing must be avoided.

Several antimicrobial preservatives have been tested in liquid antacid preparations for their stability and effectiveness, such as benzoic acid, chlorhexidine, methylparaben,

propylparaben, sorbic acid, propylene glycol or ethanol. It was found that a combination of methylparaben and sorbic acid was superior to the parabens alone.

Mixtures

The 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 using suitable suspending or thickening agents. This class was introduced originally to secure uniformity in the formulas of certain well-known and largely used preparations. Frequently, the term *mixture* is applied loosely to aqueous preparations of every description. The term *shake mixture* is used often for liquid preparations which contain insoluble ingredients and, therefore, must be shaken before use. The USP does not recognize the term. The term *suspension* now is used to describe a number of similar preparations. The PC uses the term *mixtures* and includes suspensions in this category, for example:

Ammonium Chloride Mixture PC

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

It should be prepared recently.

The term mixture occurs in the expression dry mixture, which may be used to describe many USP products, in particular, antibiotic powders for oral solutions which are described on page 1527.

The pectin and the tragacanth in Kaolin Mixture with Pectin (page 796) act as suspending agents. An alternate formula, based on Veegum (*Vanderbilt*) and sodium carboxymethylcellulose, has been proposed by Kalish.[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, saccharin and glycerin and add to the suspension. A preservative and flavoring agent may be added to the product.

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

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

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

Mixtures, including suspensions, are subject to contamination by microorganisms that remain viable and are a potential health hazard during the period of use of the products. Survival times of organisms depend on the preservative used. A kaolin pediatric mixture that contains benzoic acid kills organisms rapidly, whereas organisms survived for more than a week in a magnesium trisilicate mixture that contained no more than a trace of peppermint oil, as noted by Westwood.[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 (7.2 g)
Glycerin	10 mL
Simple Syrup, to make	120 mL

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

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

A comprehensive checklist of suspension formulations has been reported in the literature by Scheer.[31]

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, 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 PC under *Mixtures*.

A properly prepared suspension has a number of desirable properties:

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

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

Suspensions intended for parenteral or ophthalmic use also are described in the USP. For a discussion of these suspensions, see Chapter 84 and 86.

Extracts

Extraction

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

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

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

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 maceration, percolation, digestion, infusion and decoction. The quality of the finished product can be enhanced by standardizing primary extracts and carrying out analytical assays during production on the raw materials, intermediate products and manufacturing procedures.

The processes of particular importance, insofar as the USP is concerned, are those of maceration and percolation. 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 3 days, with frequent agitation, until soluble matter is dissolved. The mixture then is strained, the marc (the damp solid material) pressed and the combined liquids clarified by filtration or by decantation, after standing.

Percolation—This is the procedure used most frequently to extract the active ingredients in the preparation of tinctures and fluidextracts. Certain specific procedural details are provided in the USP, which should be consulted for such information. In the PC 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 the specified menstruum and allowed to stand for approximately 4 hr 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 dip 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 hr. The outlet of the percolator then is opened and the liquid contained therein 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 clarified by filtration or by allowing it to stand and then decanting.

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

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

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

Extractive Preparations

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

For a discussion of *resins* and *oleoresins* obtained by solvent extraction of plant exudates see Chapter 23, under *Plant Exudates*.

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

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

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

Examples of tinctures prepared by Process M are Compound Benzoin Tincture 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 pharmacopoial fluidextracts are made by percolation, the official compendia previously have described general procedures for three percolation methods used in making fluidextracts.

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

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

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

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

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

Three forms of extracts 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 to be used in pill masses and made into pills, are suited especially for use in ointments and suppositories. Powdered extracts are suited better for incorporation into a dry formulation, as in capsules, powders or tablets. Semiliquid extracts, or extracts of a syrupy consistency, may be used in the manufacture of some pharmaceutical preparations.

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

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

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CHAPTER 84

Parenteral Preparations

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Dosage forms of drugs are designed to make it possible to introduce a drug into the body of a human or animal patient. Since the well-being, or even the life, of the patient may be affected, the dosage form must be designed and prepared in a manner intended to promote the safety of the patient. Concurrently, it is essential that the dosage form compliment or enhance the therapeutic effectiveness of the drug.

Parenteral (Gk, *para enteron* = beside the intestine) is the route of administration of drugs by injection under or through one or more layers of the skin or mucous membranes. Since this route circumvents these highly efficient protective barriers of the human body, exceptional purity of the dosage form must be achieved. The processes used in preparing it must embody good manufacturing practices that will produce and maintain the required quality of the product. New developments in process technology and quality control should be adopted as soon as their value and reliability have been established as a means for further improving the quality of the product.

History[1]

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

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

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

1926—Parenterals were accepted for inclusion in the fifth edition of the *National Formulary*.
1933—The practical application of freeze-drying to clinical materials was accomplished by a team of scientists at the University of Pennsylvania.
1938—The Food, Drug and Cosmetic Act was passed by Congress, establishing the Food and Drug Administration (FDA).
1944—The sterilant ethylene oxide was discovered.
1946—The Parenteral Drug Association was organized.
1961—The concept of laminar airflow was developed by WJ Whitfield.
1962—The FDA was authorized by Congress to establish current good manufacturing practices (CGMP) regulations.
1965—Total parenteral nutrition (TPN) was developed by SJ Dudrick.
1972—The Limulus Amebocyte Lysate test for pyrogens in parenteral products was developed by JF Cooper.

Administration

Injections may be classified in five general categories:

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

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

When compared with other dosage forms, injections possess select advantages. If immediate physiological action is

needed from a drug, it usually can be provided by the intravenous injection of an aqueous solution. Modification of the formulation or another route of injection can be used to slow the onset and prolong the action of the drug. The therapeutic response of a drug is controlled more readily by parenteral administration since the irregularities of intestinal absorption are circumvented. Also, since the drug normally is administered by a professionally trained person, it confidently may be expected that the dose was actually and accurately administered. Drugs can be administered parenterally when they cannot be given orally because of the unconscious or uncooperative state of the patient, or because of inactivation or lack of absorption in the intestinal tract. Among the disadvantages of this dosage form are the requirement of asepsis at administration, the risk of tissue toxicity from local irritation, the real or psychological pain factor and the difficulty in correcting an error, should one be made. In the latter situation, unless a direct pharmacological antagonist is immediately available, correction of an error may be impossible. One other disadvantage is that daily or frequent administration poses difficulties, either for the patient to visit a professionally trained person or to learn to inject oneself.

Parenteral Combinations

Since there is a degree of discomfort for the patient with each injection, a physician frequently will seek to reduce this by combining more than one drug in one injection. This is encountered most commonly when therapeutic agents are added to large-volume solutions of electrolytes or nutrients, commonly called "IV additives," during intravenous administration. Since these are aqueous solutions, there is a high potential for chemical and physical interactions. See Chapter 85. The pharmacist is the professional best qualified to cope with these incompatibilities. However, in the past, these have been handled largely at the patient's bedside by the nurse and physician. Only recently has it been recognized that this professional area is the proper function of a pharmacist and has been so stated by the Joint Commission on Accreditation of Hospitals.[2,3]

As pharmacists have assumed increasing responsibility in this area, awareness has developed gradually of the widespread occurrence of visible, as well as invisible, physical, chemical and therapeutic incompatibilities when certain drugs are combined or added to intravenous fluids.

The development of a precipitate or a color change when preparations are combined is an immediate warning that an alteration has occurred. Such a combination should not be administered to the patient because the solid particles may occlude the blood vessels, the therapeutic agent may not be available for absorption or the drug may have been degraded into toxic substances. Moreover, in other instances, changes not visually apparent may have occurred which could be equally or more dangerous to the welfare of the patient.

The almost innumerable potential combinations present a complex situation even for the pharmacist. To aid him in making rapid decisions concerning potential problems, a number of charts have been compiled based on the visible changes that may be observed when two or more preparations are combined. However, the advent of data storage and retrieval systems using computers has provided a means to organize and gain rapid access readily to such information. The value of such information is limited by such factors as frequent changes in commercial products, variations in order of mixing or the proportions in the mixture, differences in concentration of each ingredient or variations in the period of time that the combination is held before use.

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

Ideally, no parenteral combination should be administered unless it has been studied thoroughly to determine its effect on the therapeutic value and the safety of the combination. However, such an ideal situation does not and may never exist. Therefore, it is the responsibility of the pharmacist to be as familiar as possible with the physical, chemical and therapeutic aspects of parenteral combinations and to exercise the best possible judgment as to whether or not the specific combination extemporaneously prescribed is suitable for use in a patient. A service to pharmacists has been provided through reviews of this subject.[4]

General Requirements

An inherent requirement for parenteral preparations is that they be of the very best quality and provide the maximum safety for the patient. Therefore, the pharmacist, being responsible for their preparation, must use his skills and resourcefulness at the highest level of efficiency to achieve this end. Among the areas requiring dedicated attention are the following:

1. Possession and application of high moral and professional ethics. Even the thought of using inferior techniques or ingredients in a manufacturing process must not be countenanced. The proper attitude of the person responsible for the preparation of the product is its most vital ingredient.
2. The pharmaceutical training received must be used to the fullest measure. The challenges to this knowledge bank will be many and varied.
3. Specialized techniques will be required for the manufacture of sterile preparations, employing them with alertness and sound judgment. These must be subjected to continuous critical review for faults, omissions and improvements.
4. Ingredients of the highest quality obtainable must be used. At times, ingredients may require special purification beyond that of the commercial supply. This normally will require that cost factors be given second place in importance.
5. The stability and effectiveness of the product must be established with substantiating data, either from original or published sources. This must take into account process variations and differences in ingredient specifications from one production site to another.
6. A well-defined and controlled program must be established to assure the quality of the product and the repetition of valid production procedures. This involves the evaluation of all ingredients, vigilant controls of all steps in the production procedures and careful evaluation of the finished product.

Injections or other sterile products rarely are prepared in the community pharmacy because of the lack of adequate facilities and trained personnel necessary to prepare a reliable and safe product.

In some hospital pharmacies injections are prepared from raw materials for research purposes or in the early phases of clinical studies. In most hospital pharmacies aseptic processing often is used for adding commercially available parenteral drug products to IV solutions for an individual patient. Increasingly, hospital pharmacies or independent units are dispensing parenterals for the home care of patients. Since the products dispensed most frequently are to provide the total parenteral nutrition (TPN) requirements of a patient, and these are excellent nutritional preparations for microorganisms as well, strict requirements for sterility must be met in preparation and packaging.

The preparation of the vast majority of injectable products used clinically occurs in the highly technologically advanced plants of the pharmaceutical industry. The operations are subject to the oversite of the Food and Drug Administration (FDA) through the application of the Current Good Manufacturing Practices (CGMPs) Regulations.[6] These regulations are discussed more fully in Chapter 107. While the oversite by the FDA has encouraged strongly the achieving of the essential high quality of parenterals today, the parenteral industry has taken the leadership and initiative in the extensive technological development and improvement in the quality, safety, effectiveness and administrative proficiency of parenteral dosage forms in recent years.

General Process

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

1. Procurement and selection of the components and containers.
2. Production facilities and procedures.
3. Control of quality.
4. Packaging and labeling.

The components of the product to be procured include vehicles, solutes, containers and closures. The steps constituting production include maintaining facilities and equipment, preparing and controlling the environment, cleaning the containers and equipment, preparing the product, filtering the solution, filling containers with the product, sealing the containers and sterilizing the product. The control of quality includes the evaluation of the components, validation of equipment and processes, determination that the production has been executed within prescribed requirements, and performance of necessary evaluative tests on the finished product. The final area of packaging and labeling includes all steps necessary to identify the finished product and enclose it in such manner that it is safely and properly prepared for sale and delivery to the user.

Components and Containers

Establishing specifications to insure the quality of each of the components of an injection is an essential first step. These specifications will be coordinated with the requirements of the specific formulation and necessarily will not be identical for a particular component if used in several different formulations.

The most stringent requirements normally will be encountered with aqueous solutions, particularly if the product is to be sterilized at an elevated temperature where reaction rates will be accelerated greatly. Modification of aqueous vehicles to include a glycol, or replacement with a nonaqueous vehicle, usually will reduce reaction rates. Dry preparations pose relatively few reaction problems but may require definitive physical specifications for ingredients that must have certain solution or dispersion characteristics when a vehicle is added.

Containers and closures are in prolonged, intimate contact with the product and may release substances or remove ingredients from the product. While not usually considered a part of a container, administration devices are a part of a container system and their effect upon the product must be assessed even though the contact period is usually brief.

Vehicles

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

The vehicle of greatest importance for parenteral products is water. Water of suitable quality for parenteral administration must be prepared either by distillation or by reverse osmosis. Only by these means is it possible to separate adequately various liquid, gas and solid contaminating substances from water.

Preparation of Water

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

The specific construction features of a still and the process specifications markedly will affect the quality of distillate obtained from a still. Those required for producing high-purity water, such as Water for Injection USP (WFI), must be considerably more stringent than those required for Purified Water USP. Among the factors that must be considered are:

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

The design features of a still also influence its efficiency of operation, relative freedom from maintenance problems or extent of automatic operation. Stills may be constructed of varying size, rated according to the volume of distillate that can be produced per hour of operation under optimum conditions. Only stills designed to produce high-purity water may be considered for use in the production of WFI.

Conventional commercial stills designed for the production of high-purity water, such as shown in Fig 84-1, are available from several suppliers (*AMSCO, Barnstead, Corning, Finn-Aqua, Vaponics*).

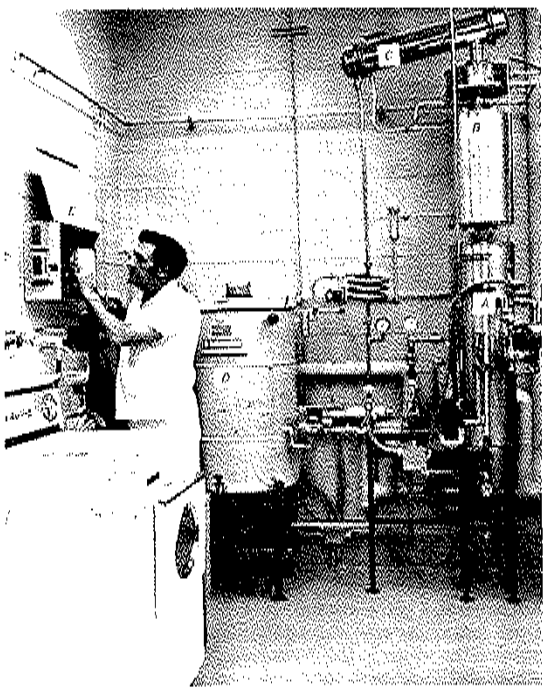


Fig 84-1. High-purity still and sealed water-storage system. *A*: evaporator; *B*: high-purity baffle unit; *C*: condenser; *D*: storage tank with ultraviolet lamp; *E*: control panel (courtesy, Ciba-Geigy).

Compression Distillation—The vapor-compression still, primarily designed for the production of large volumes of high-purity distillate with low consumption of energy and water, is illustrated diagrammatically in Fig 84-2. To start, the feed water is heated in the evaporator to boiling. The vapor produced in the tubes is separated from the entrained distilland in the separator and conveyed to a compressor which compresses the vapor and raises its temperature to approximately 224°F. It then flows to the steam chest where it condenses on the outer surfaces of the tubes containing the distilland; thereby the vapor is condensed and drawn off as a distillate while giving up its heat to bring the distilland in the tubes to the boiling point.

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

Multiple-Effect Stills—The multiple-effect still also is designed to conserve energy and water usage. In principle, it is simply a series of single-effect stills running at differing pressures. A series of up to seven effects may be used, with the first effect operated at the highest pressure and the last effect at atmospheric pressure. Steam from an external source is used in the first effect to generate steam under pressure from raw water; it is used as the power source to drive the second effect. The steam used to drive the second effect condenses as it gives up its heat of vaporization and forms a distillate. This process continues until the last effect when the steam is at atmospheric pressure and must be condensed in a heat exchanger.

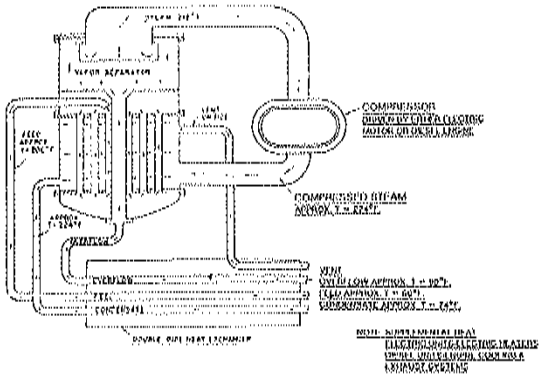


Fig 84-2. Vapor-compression still.

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

Reverse Osmosis—Reverse osmosis has been added by the USP as a method suitable for preparing WFI. As the name suggests, the natural process of selective permeation of molecules through a semipermeable membrane separating two aqueous solutions of different concentrations is reversed. Pressure, usually between 200 and 400 psig, is applied to overcome osmotic pressure and force pure water to permeate through the membrane. Membranes, usually composed of cellulose esters or polyamides, are selected to provide an efficient rejection of contaminant molecules in raw water. The molecules most difficult to remove are small inorganic ones such as sodium chloride. Passage through two membranes in series is sometimes used to increase the efficiency of removal of these small molecules and to decrease the risk of structural failure of a membrane to remove other contaminants, such as bacteria and pyrogens. For additional information, see *Reverse Osmosis* in Chapter 77 (including Fig 77-14) and *Water* in Chapters 66 and 83.

Currently, extensive validation is continuing to determine whether, in fact, this method is capable of consistently producing high-purity water of a quality equal or superior to that producible by distillation. Reverse osmosis systems are available in a range of production sizes. (*AMSCO, Aqua-Chem, Finn-Aqua, Meco, Millipore,* etc).

Water for Injection USP

This is a high-purity water intended to be used as a vehicle for injectable preparations. Sterile Water for Injection USP (SWFI) is described in a separate monograph and differs in that it is intended as a packaged and sterilized product.

Storage—If WFI cannot be used immediately after it is produced, the USP permits storage at room temperature for a period not exceeding 24 hr or for longer periods at a temperature too high or too low for microbial growth to occur. Therefore, WFI usually is collected directly from the reverse-osmosis unit or a still in a closed system designed to prevent recontamination of the water and to hold it at a constant temperature of 60 to 80°C. The system may range from a relatively small single storage tank with a drawoff spout (Fig 84-1) to a very large system holding several thousand gallons of water. The stainless-steel tank in such a system usually is connected to a welded stainless-steel distribution loop supplying the various use sites with a continuously circulating water supply. The tank is provided with a hydrophobic membrane vent filter capable of excluding bacteria and nonviable particulate matter. Such a vent filter is necessary to permit changes in pressure during filling and emptying. The construction material for the tank and connecting lines is usually electropolished 316L stainless steel with heliarc welded pipe. The tanks also may be lined with

glass or a coating of pure tin. Such systems are very carefully designed and constructed and often constitute the most costly installation within the plant.

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

Purity—The USP monographs provide standards of purity for WFI and SWFI. A few of these standards require comment.

SWFI must meet the requirements of the USP Sterility Test, but WFI need not since it is to be used in a product which will be sterilized. Both must meet the requirements of the USP Pyrogen Test (page 492).

The limits for total solids varies in the two monographs. The larger the surface area of the glass container per unit volume of water, the greater the amount of glass constituents that may be leached into the water, particularly during the elevated temperature of steam sterilization.

The WFI monograph stipulates a maximum of 10 ppm of total solids. This is generally considered to be much too high to assure a quality of water that permits the stable formulation of many drugs. A relatively few metallic ions present often can render a formulation unstable. Therefore, it is common practice to set a limit of 0.1 ppm or less of ionic contaminants expressed as sodium chloride.

Ionic contaminant level is not the same as total solids; the former is a measure of only the ionic content, while the latter is a measure of the undissociated constituents as well. The ionic content of water can be measured very easily by means of a conductivity meter which frequently is used as an indicator of the purity. The results are expressed in one of three terms: as sodium chloride ions, as resistance in ohms or megohms or as conductance in micromhos. Ohms and mhos have a reciprocal relationship to each other, but they are related to ppm sodium chloride by an experimentally determined curve. To give one point of comparison, 0.1 ppm sodium chloride is equal to approximately 1.01 megohms and 0.99 micromhos. It should be mentioned that conductivity measurements give no direct indication of pyrogen content since pyrogens are undissociated organic compounds.

WFI may not contain an added substance. SWFI may contain a bacteriostatic agent when in containers of 30-mL capacity or less. This restriction is designed to prevent the administration of a large quantity of a bacteriostatic agent that probably would be toxic in the accumulated amount of a large volume of solution, even though the concentration was low.

Types of Vehicles

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

Water-Miscible Vehicles—A number of solvents that are miscible with water have been used as a portion of the vehicle in the formulation of parenterals. These solvents are used primarily to effect the solubility of certain drugs and to reduce hydrolysis. The most important solvents in this group are ethyl alcohol, polyethylene glycol of the liquid series and propylene glycol. Ethyl alcohol is used particularly in the preparation of solutions of cardiac glycosides and the glycols in solutions of barbiturates, certain alkaloids and certain antibiotics. Such preparations usually are given intramuscularly.

These solvents, as well as nonaqueous vehicles, have been reviewed by Spiegel and Noseworthy.[6]

Nonaqueous Vehicles—The most important group of nonaqueous vehicles are the fixed oils. The USP provides specifications for such vehicles, indicating that the fixed oils must be of vegetable origin so that they will be metabolized, will be liquid at room temperature and will not become rancid readily. The USP also specifies limits for the degree of unsaturation and free fatty acid content. The oils most commonly used are corn oil, cottonseed oil, peanut oil and sesame oil. It should be noted that the official monographs for some of these oils provide for greater latitude than the specifications required for the use of the oil as a vehicle for a parenteral.

Fixed oils are used particularly as vehicles for certain hormone preparations. These and other nonaqueous vehicles, such as ethyl oleate, isopropyl myristate, and benzyl benzoate, may be used provided they are safe in the volume administered and do not interfere with the therapeutic efficacy of the preparation or with its response to prescribed assays and tests. The label also must state the name of the vehicle so that the user may beware in case of known sensitivity or other reactions to it.

Solutes

The requirements for purity of the medicinal compound used in an injection often make it necessary to undertake special purification of the usual chemical grade available. In a few instances, a special parenteral grade of a compound is available, for example, ascorbic acid freed from all traces of copper contamination. As a general rule, the best chemical grade obtainable should be used. It should be obvious that if a few ppm of ionic contaminants in WFI may cause stability problems, a similar level of contamination in the solute itself may, likewise, cause stability problems. Metallic catalysis of chemical reactions is one which is encountered frequently.

Other factors to be considered with respect to the quality of solutes include the level of microbial and pyrogenic contamination, solubility characteristics as determined by the chemical or physical form of the compound and freedom from gross dirt.

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

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

Provide patient comfort, as do substances added to make a solution isotonic.

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

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

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

Antimicrobial Agents—The USP states that antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to preparations contained in multiple-dose containers. They must be present in adequate concentration at the time of use to prevent the multiplication of microorganisms inadvertently introduced into the preparation while withdrawing a portion of the contents with a hypodermic needle and syringe. Among the compounds most frequently employed, with the concentration limit prescribed by the USP, are:

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

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

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

Buffers are used primarily to stabilize a solution against the chemical degradation that might occur if the pH changes appreciably. Buffer systems employed should normally have as low a buffer capacity as feasible in order not to disturb significantly the body buffer systems when injected. In addition, the buffer range and effect on the activity of the product must be evaluated carefully. The acid salts most frequently employed as buffers are citrates, acetates and phosphates.

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

Pyrogens

Pyrogens may be anticipated contaminants in crude drugs, such as antibiotics produced by fermentation, or they may be present as unexpected and unwanted contaminants in a finished product as a result of inadvertent contamination during processing. The former must be eliminated during the purification steps of the drug. The latter can be eliminated best by preventing their introduction or development during the process. In general, the presence of pyrogens in a finished product is indicative of preparation under inadequately controlled clean conditions.

Pyrogens cause a febrile reaction in human beings. Other symptoms include chills, pains in the back and legs and malaise. While pyrogens are rarely fatal, they produce significant discomfort for the patient. On the other hand, pyrogens have been shown to induce a general nonspecific resistance to microorganisms and, on this basis, have been used therapeutically. Recent findings indicate that bacterial pyrogens, when introduced into the body, stimulate the production of an endogenous (leukocytic) pyrogen that causes the familiar physiological responses.

Pyrogens are products of the growth of microorganisms. The most potent pyrogenic substances are produced by Gram-negative bacteria (endotoxins), but Gram-positive bacteria and fungi also produce pyrogenic substances of lesser potency. Chemically endotoxins have been shown to be a phospholipid attached to a polysaccharide carrier.

Pyrogens can be destroyed by heating at high temperatures. The recommended procedure for depyrogenation of glassware and equipment is heating at a temperature of 250° for 45 min. It has been reported that 650° for 1 min or 180° for 4 hr likewise will destroy pyrogens. The usual autoclaving cycle will not do so. Heating with strong alkali or oxidizing solutions will destroy pyrogens. It has been claimed that thorough washing with detergent will render glassware pyrogen-free if protected during manufacture and storage from heavy pyrogenic contamination. Likewise, plastic containers and devices must be protected from pyrogenic contamination during manufacture and storage since known ways to destroy pyrogens will affect the plastic adversely. It has been reported that anion-exchange resins will adsorb pyrogens from water and reverse osmosis will eliminate them. However, the most reliable method for their elimination from water is distillation.

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

Sources of Pyrogens—Pyrogens may enter a preparation by any means that will introduce living or dead microorganisms. Perhaps the greatest potential source of such contamination is the water used in processing. Although proper distillation will provide pyrogen-free water, storage conditions must be such that microorganisms are not introduced and subsequent growth is prevented.

Another potential source of contamination is equipment. Pyrogenic materials adhere strongly to glass and other surfaces. Residues of solutions in used equipment often become bacterial cultures with subsequent pyrogenic contamination. Even washed equipment left wet and exposed to the atmosphere may contain sufficient nutrients for microorganism growth. Since drying does not destroy pyrogens, they may remain in equipment for long periods. Adequate washing greatly will reduce and subsequent dry-heat treatment will render contaminated equipment suitable for use.

The solute may be a source of pyrogens. Solutes may be crystallized or precipitated from aqueous liquids containing pyrogenic contamination. In the process, pyrogens may be trapped within the particle layers. In such cases the solute must be purified by recrystallization, precipitate washing or other means of eliminating pyrogens.

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

Containers

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

Table I provides a generalized comparison of the three compatibility properties—leaching, permeation and adsorption—of container materials most likely to be involved in the formulation of aqueous parenterals. Further, the integrity of the container/closure system depends upon a series of characteristics which determine the effectiveness with which it achieves its role. These considerations have been reviewed by Morton.[8]

Plastic

Thermoplastic polymers have been established as packaging materials for sterile preparations such as large-volume parenterals, ophthalmic solutions and, increasingly, for small-volume parenterals. For such use to be acceptable a thorough understanding of the characteristics, potential problems and advantages for use must be developed. One thorough review of these factors relative to pharmaceuticals has been prepared by Autian.[9] He stated that three principal problem areas exist in using these materials; namely,

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

Permeation, the most extensive problem, may be troublesome by permitting volatile constituents or selected drug molecules to migrate through the wall of the container to the outside and thereby be lost. The reverse of this also may occur by which oxygen or other molecules may permeate to the inside of the container and cause oxidative or other degradation of susceptible constituents. Leaching may be a problem when certain constituents of the plastic material migrate into the product. This potential problem often may be controlled by careful formulation of the polymer mixture with a minimum of additives. Sorption seems to be a limited problem in the packaging of parenterals and is found most commonly in association with polyamides such as nylon.

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

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

Table I—Comparative Compatibility Properties of Container Materials

	Leaching		Permeation		Adsorption (selective)
	Extent[a]	Potential Leachables	Extent[a]	Potential Agents	Extent[a]
Glass					
Borosilicate	1	Alkaline earth and heavy metal oxides	0	N/A	2
Soda-lime	5	Alkaline earth and heavy metal oxides	0	N/A	2
Plastic Polymers					
Polyethylene					
Low density	2	Plasticizers, antioxidants	5	Gases, water vapor, other molecules	2
High density	1	Antioxidants	3	Gases, water vapor, other molecules	2
PVC	4	HCl, especially plasticizers, antioxidants, other stabilizers	5	Gases, especially water vapor and other molecules	2
Polyolefins	2	Antioxidants	2	Gases, water vapor, other molecules	2
Polypropylene	2	Antioxidants, lubricants	4	Gases, water vapor	1
Rubber Polymers					
Natural and related synthetic	5	Heavy metal salts, lubricants, reducing agents	3	Gases, water vapor	3
Butyl	3	Heavy metal salts, lubricants, reducing agents	1	Gases, water vapor	2
Silicone	2	Minimal	5	Gases, water vapor	1

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

ylene oxide or radiation sterilization may be employed for the empty container with subsequent aseptic filling. However, careful evaluation of the residues from ethylene oxide and their potential toxic effect must be undertaken.

Because of the relatively new use of plastic materials for packaging sterile preparations, considerable investigation is still required concerning potential interactions and other problems that may be encountered. For further details see Chapter 80.

Glass

Glass is employed as the container material of choice for most injections. It is composed principally of silicon dioxide with varying amounts of other oxides such as sodium, potassium, calcium, magnesium, aluminum, boron and iron. The basic structural network of glass is formed by the silicon oxide tetrahedron. Boric oxide will enter into this structure, but most of the other oxides do not. The latter are only loosely bound, are present in the network interstices and are relatively free to migrate. These migratory oxides may be leached into a solution in contact with the glass, particularly during the increased reactivity of thermal sterilization. The oxides thus dissolved may hydrolyze to raise the pH of the solution, catalyze reactions or enter into reactions. In a manner as yet uncertain, some glass compounds will be attacked by solutions and, in time, dislodge glass flakes into the solution. Disturbing reactions such as these, however, can be minimized by the proper selection of the glass composition.[10]

Types—The USP has aided in this selection by providing a classification of glass; namely,

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

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

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

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

Care must be used in selecting the glass type to be used for a particular injectable product. In general, Type I glass will be suitable for all products, although sulfur dioxide treatment is sometimes used for a further increase in resistance. Because cost must be considered, one of the other less expensive types may be acceptable. Type II glass may be suitable, for example, for a solution which is buffered, has a pH below 7 or is not reactive with the glass. Type III glass usually will be suitable principally for anhydrous liquids or dry substances.

Physical Characteristics—Examples of the physical shape of glass ampuls and vials are illustrated in Fig 84-3. Commercially available containers vary in size from 0.5 to 1000 mL. Sizes up to 100 mL may be obtained as ampuls and vials, and larger sizes as bottles. The latter are used mostly for intravenous and irrigating solutions. Smaller sizes are also available as cartridges. Ampuls and cartridges are drawn from glass tubing. The smaller vials may be made by molding or from tubing. Larger vials and bottles are made only by molding. Containers made by drawing tubing are generally optically clearer and have a thinner wall than molded containers (see Fig 84-3). Molded containers are uniform in external dimensions, stronger and heavier.

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

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

Preparations which are light-sensitive must be protected by placing them in amber glass containers or by enclosing flint glass containers in opaque cartons labeled to remain on the container during the period of use. Silicone coatings are sometimes applied to containers to produce a hydrophobic surface as a means of reducing adherence of a heavy, costly

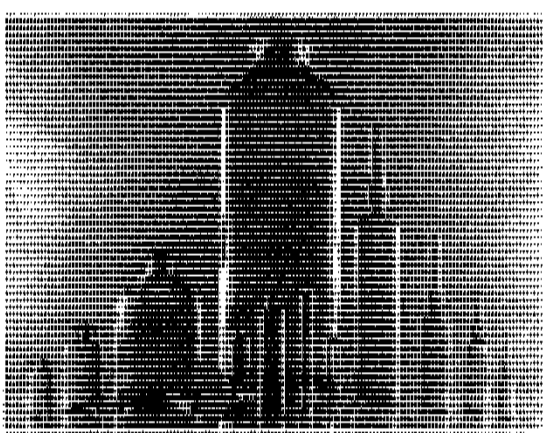


Fig 84-3. Various types of ampuls and multiple-dose vials for parenterals (courtesy, Kimble).

suspension or the friction of a rubber-tip of a syringe plunger.

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

A multiple-dose container is designed so that more than one dose can be withdrawn at different times, the container maintaining a seal between uses. It should be evident that with full aseptic precautions, including sterile syringe and needle for withdrawing the dose and disinfection of the exposed surface of the closure, there is still a substantial risk of introducing contaminating microorganisms and viruses into the contents of the vial. Because of this risk, the USP requires that all multiple-dose vials must contain an antibacterial agent. However, there is no effective antiviral agent available for such use. Therefore, in spite of the advantage of flexibility of dosage provided the physician by a multiple-dose vial, the greater safety of single-dose, disposable administration units has caused their use to increase rapidly during recent years.

Rubber Closures

In order to permit introduction of a needle from a hypodermic syringe into a multiple-dose vial and provide for resealing as soon as the needle is withdrawn, each vial is sealed with a rubber closure held in place by an aluminum band. Figure 84-4 illustrates how this is done. This principle also is followed for single-dose containers of the cartridge type, except that there is only a single introduction of the needle to make possible the withdrawal or expulsion of the contents.

Rubber closures are composed of several ingredients, the primary ones being natural rubber (latex), a synthetic polymer or a combination of these. Other ingredients include a vulcanizing agent, usually sulfur; an accelerator, one of several active organic compounds such as 2-mercaptobenzothiazole; an activator, usually zinc oxide; fillers, such as carbon black or limestone and various other ingredients such as antioxidants and lubricants. These are compounded together and then vulcanized in the desired shape, making use of molds under high pressure and temperature.

Rubber closures must have sufficient elasticity to provide a snug fit between them and the lip and neck of the vial and must spring back to close the hole made by the needle immediately on withdrawal. They must not be so hard that they are highly resistant to the insertion of the needle, and they must not fragment as the hollow needle passes through them. Ideally, they should be completely nonreactive with the solution and its ingredients and should provide a complete barrier to vapor transfer. These qualities are not perfectly met by any rubber compound now available. It is, therefore, essential to determine the compatibility and performance characteristics of each rubber compound to be used.[1]

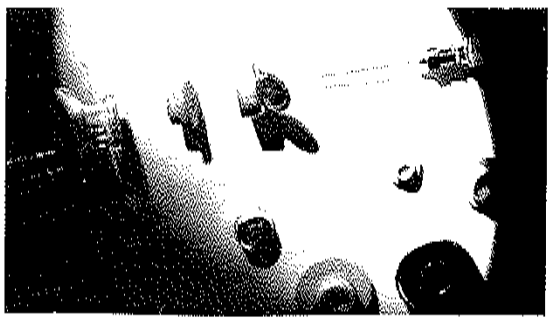


Fig 84-4. Extended view of sealing components for a multiple-dose vial (courtesy, West).

In addition to the physical tests of elasticity, hardness, fragmentation and vapor transfer, closures should be exposed to the product for prescribed periods of time at designated temperature and humidity conditions. The effect on the product of extractives from the rubber compound or loss of ingredients from the product to the closure should be determined analytically. Physicochemical and toxicological tests for evaluating rubber closures are described in the USP.

The physical shape of some typical closures may be seen in Fig 84-4. Most of them have a lip and a protruding flange that extends into the neck of the vial or bottle. Many disk closures are being used now, particularly in the high-speed packaging of antibiotics. Slotted closures are used on freeze-dried products to make it possible to insert the closure part way into the neck of the vial during the drying phase of the cycle. Partial insertion provides some protection from contamination while permitting water vapor to escape from the drying product. The plunger type is used to seal one end of a cartridge. At the time of use, the plunger expels the product by a needle inserted through the closure at the distal end of the cartridge. Intravenous solution closures often have permanent holes for adapters of administration sets; irrigating solution closures usually are designed for pouring.

Production Facilities

A product having components of the best quality quickly may become totally unacceptable if the environment in which it is processed is contaminated or if the manufacturing procedure is not carried out properly. Therefore, the production facilities and the procedure used in processing the product must meet standards adequate for the task. The nearer these standards approach perfection, the better and safer should be the product.

Arrangement of Area

The production area can be considered in terms of five functional areas: the cleanup area, the compounding area, the aseptic area, the quarantine area and the finishing or packaging area. All of these should be designed and constructed for cleaning ease, appropriate environmental control, efficient operation and personnel comfort. The extra requirements for the aseptic area are designed to provide an environment where, for example, an injection may be exposed to the environment for a brief period during subdivision from a bulk container to the individual-dose containers without becoming contaminated. Contaminants such as dust, lint and microorganisms normally are found floating in the air, lying on counters and other surfaces, on clothing and body surfaces of personnel, in the exhaled breath of personnel and deposited on the floor. The design and control of an

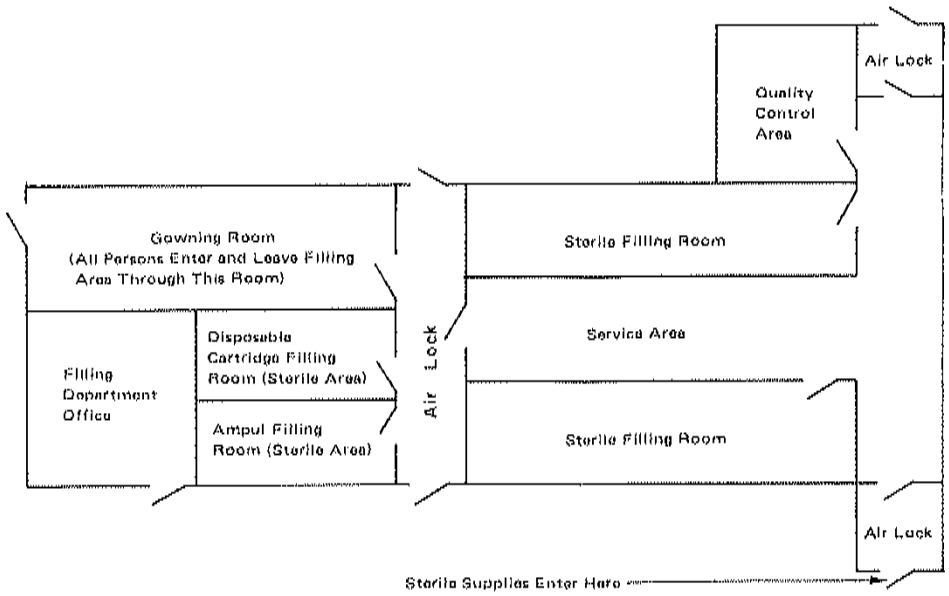


Fig 84-5. Floor plan of an aseptic filling area with its service area (courtesy, Wyeth).

aseptic area is directed toward so reducing the presence of these contaminants that they are no longer a hazard to aseptic filling. Although the aseptic area must be adjacent to support areas so that an efficient flow of components may be achieved, barriers must be provided to minimize ingress of contaminants to the aseptic area. Such a barrier may be a sealed partition, often glass-paneled for greater visibility and light. Another type of barrier is an entranceway through security doors that requires passage through an airlock so designed that both doors cannot be opened at the same time. Figure 84-5 shows an arrangement of aseptic filling rooms with adjacent support areas.

Flow Plan—In general, the components for a parenteral product flow from the stockroom, either to the compounding area, as for ingredients of the formula, or to the cleanup area, as for containers and equipment. See Fig 84-6 for a process-flow diagram. After proper processing in these areas, the components flow into the security of the aseptic area for filling of the product in appropriate containers. From there the product passes into the quarantine area where it is held until all necessary tests have been performed. If the product is to be sterilized in its final container, the passage normally is interrupted after it leaves the aseptic area for subjection to the sterilization process. After the results from all tests are known and the product has been found effective and safe, it passes to the finishing area for final labeling and packaging. There are sometimes variations from this flow plan to meet the specific needs of an individual product or to conform to available facilities. Automated operations convey the components from one area to another with little or no handling by operators.

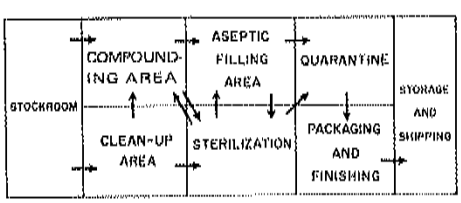


Fig 84-6. Process-flow diagram.

Cleanup Area—The cleanup area is constructed to withstand moisture, steam and detergents. The ceiling, walls, and floor should be constructed of impervious materials so that moisture will run off and not be held. One of the "spray-on-tile" finishes with a vinyl or epoxy sealing coat provides a continuous surface free from all holes or crevices. All such surfaces can be washed at regular intervals to keep them thoroughly clean. These areas should be exhausted adequately so that the heat and humidity will be removed for the comfort of personnel. Precautions must be taken to prevent the accumulation of dirt and the growth of microorganisms, especially in the presence of high humidity and heat. In this area preparation for the filling operation, such as assembling equipment, is undertaken. Adequate sink and counter space must be provided. While this area does not need to be aseptic, it must be cleanable and kept clean and the microbial load must be monitored and controlled. Precautions also must be taken to prevent deposit of particles or other contaminants on clean containers and equipment.

Compounding Area—In this area the formula is compounded. Although it is not essential that this area be aseptic, control over it should be more stringent than in the cleanup area. For example, means may need to be provided to control dust generated from weighing and compounding operations. Cabinets and counters should, preferably, be constructed of stainless steel. They should fit snugly to walls and other furniture so that there are no catch areas for dirt to accumulate. The ceiling, walls and floor should be constructed similar to those for the cleanup area. Figure 84-7 illustrates such an area located adjacent to an aseptic filling area.

Aseptic Area

This area requires construction features designed for maximum security. The ceiling, walls and floor must be sealed so that they may be washed and sanitized with a disinfectant, as needed. All counters should be constructed of stainless steel and hung from the wall so that there are no legs to accumulate dirt where they rest on the floor. All light fixtures, utility service lines and ventilation fixtures should

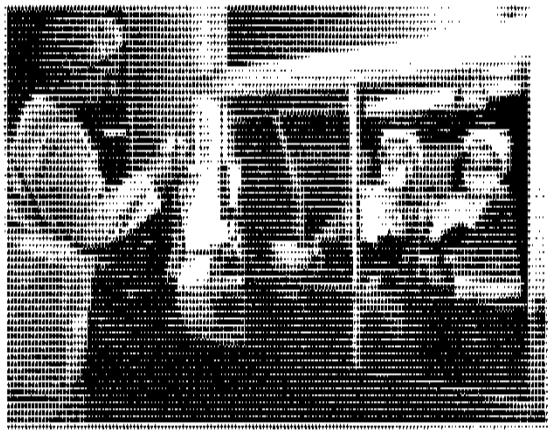


Fig 84-7. View from the service area with pipeting machine and stock-bottle retained outside of the aseptic filling area (courtesy, Wyeth).

be recessed in the walls or ceiling to eliminate ledges, joints and other locations for the accumulation of dust and dirt. As much as possible, tanks containing the compounded product should remain outside the aseptic filling area and the product fed into the area through hose lines. Figure 84-8 shows such an arrangement. Mechanical equipment that must be located in the aseptic area should be housed as completely as possible within a stainless-steel cabinet in order to seal the operating parts and their dirt-producing and accumulating tendencies from the aseptic environment. Mechanical parts that will contact the parenteral product should be demountable so that they can be sterilized.

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

Fig 84-8. Product filtration from the aseptic staging room through a port into the aseptic filling room (courtesy, The University of Tennessee College of Pharmacy).

Air Cleaning

The air in these areas can be one of the greatest sources of contamination. It need not be, however, because several methods are available for providing clean air that is essentially free from dirt particles and microorganisms.

To provide such air, it must be cleaned thoroughly of all contaminants. This may be done by a series of treatments. Air from the outside first is passed through a prefilter, usually of glass wool, cloth or shredded plastic, to remove large particles. Then it is treated by passage through an electrostatic precipitator (Suppliers: *Am Air, Electro-Air, Sturtevant*). Such a unit induces an electrical charge on particles in the air and removes them by attraction to oppositely charged plates. The air then passes through the most efficient cleaning device, a HEPA (high efficiency particulate air) filter having an efficiency of at least 99.97% in removing particles of 0.3 μm and larger, based on the DOP (Dioctyl phthalate) test (Suppliers: *Am Air, Cambridge, Envirco, Flanders*).

For personnel comfort, air conditioning and humidity control should be incorporated into the system. Another system, the Kathabar system (*Surface Combustion*), cleans the air of dirt and microorganisms by washing it in an antiseptic solution and, at the same time, controls the humidity. The clean, aseptic air is introduced into the aseptic area and maintained under positive pressure, which prevents outside air from rushing into the aseptic area through cracks, temporarily open doors or other openings.

Laminar-Flow Environments—The required environmental control of aseptic areas has been made possible by the use of laminar-flow enclosures. Laminar airflow provides a total sweep of a confined area because the entire body of air moves with uniform velocity along parallel lines, originating through a HEPA filter occupying one entire side of the confined area. Therefore, it bathes the total area with very clean air, sweeping away contaminants.

The arrangement for the direction of airflow can be horizontal (see Fig 84-9) or vertical (see Fig 84-10), and may involve a limited area such as a workbench or an entire room. The effective air velocity is considered to be 90 ± 20 ft/min.

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

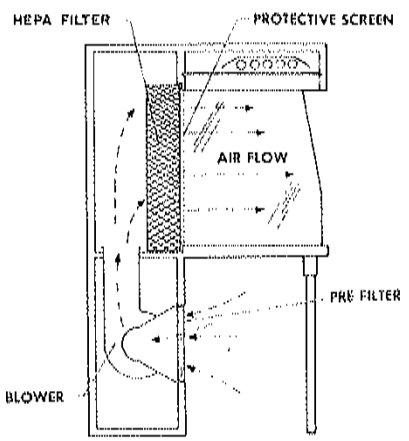


Fig 84-9. Horizontal laminar-flow workbench (courtesy, adaptation, Sandia).

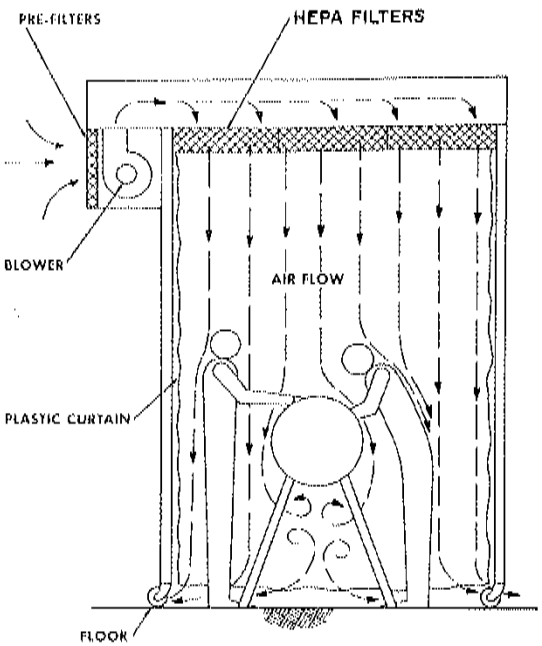


Fig 84-10. Vertical laminar-flow portable room with equipment and operators (courtesy, adaptation, Sandia).

ganisms, the danger is apparent. For operations involving such contaminants a vertical system is much more desirable, with the air flowing through perforations in the countertop or through return louvers at floor level, where it can be directed for decontamination. Vertical flow has been recommended for sterility-testing procedures.

Laminar-flow environments provide well-controlled work areas only if proper precautions are observed. Any air currents or movements exceeding the velocity of the HEPA-filtered airflow may introduce contamination, as may coughing, reaching or other manipulations of operators.

Therefore, laminar-flow work areas should be protected by being located within controlled environments. Personnel preferably should be attired for aseptic processing as described below. All movements and processes should be planned carefully to avoid the introduction of contamination upstream of the critical work area. Checks of the airstream should be performed initially and at regular intervals to be sure no leaks have developed through or around the HEPA filters. This can be done most effectively with electronic particle counters (Suppliers: *Air Techniques, Climet, Met One, Particle Measuring, Royco*).

In the manufacture of parenterals, conventional clean-room facilities frequently are supplemented by vertical laminar-airflow modules suspended above critical sites, such as filling lines. These critical operations thereby are bathed with HEPA-filtered air to provide extra protection for the product.

Laminar flow of HEPA-filtered air should meet the standard for a Class 100 clean room as defined by Federal Standard 209C,[12] which states that such an environment contains no more than 100 particles per cu ft of 0.5 μm and larger size. Conventional clean rooms would be of a lesser degree of cleanliness, such as Class 10,000, defined on the same basis. This standard has brought order into defining clean rooms and provided a common basis for their description.

Workbenches and other types of laminar-flow enclosures are available from several commercial sources (Suppliers: *Air Control, Atmos-Tech, Baker, Controlled Environment, Envirco, Flanders, Germfree, Laminaire, Liberty, Veco, Weber*).

Ultraviolet Radiation

Ultraviolet (UV) light rays have an antibacterial action, thereby producing a disinfectant action on directly irradiated surfaces. Since these rays cannot penetrate most materials, only a surface effect is produced, with the principal exception being limited penetration through air and pure water. UV light rays travel in straight lines only; therefore, objects in the path of the light beam will cast shadows with a resultant lack of irradiation in the shadow area.

UV rays are irritating to the skin and, particularly, the eyes of human beings. Therefore, personnel in the area of irradiation must be protected from direct exposure.

UV lamps may be installed so as to provide either direct or indirect radiation. Direct irradiation of a room when personnel are not present is a valuable means of reducing the bacterial count on working surfaces and floors. Lamps installed above head level, so that personnel present are not irradiated, can irradiate circulating air to reduce the microbial level continuously during processing.

Local irradiation may be useful in hood-type fixtures, over filling and other process operations, within large storage tanks or in any place where additional protection from contamination is needed, provided any product present is not affected adversely by UV rays. UV lamps usually are not employed in conjunction with laminar-flow facilities because the HEPA-filtered air sweeps exposed surfaces clean and the air itself flows too fast for adequate lethal irradiation of microorganisms being carried in the air stream.

The best practical source of UV light rays is the cold-cathode mercury vapor lamp. This lamp emits a high proportion of radiation at the 253.7 nm wavelength. A special glass is used for the tube so that the rays will pass to the outside. This glass gradually will change in crystal structure with use so that passage of the rays is gradually reduced. Such lamps, therefore, rarely burn out as do visible-light lamps but gradually reach an emission level which is ineffective. These lamps also must be kept clean, for dust and grease will lower the effective emission drastically. It generally is stated that an irradiation intensity of 20 $\mu w/cm^2$ is required for effective antibacterial activity.

Maintenance of the Aseptic Area

Important aspects in the control of environmental contamination in the aseptic area are housekeeping and maintenance. These should not be done in a haphazard manner by the general maintenance crews, but rather by crews given special instruction and under the supervision of personnel trained in the care of such areas. In general, cleaning and maintenance should be done after the completion of the day's work with an interval of quietude before the beginning of another aseptic operation. With the advent of laminar flow of HEPA-filtered air the rigors of cleaning have been reduced since the clean airflow continuously "sweeps" the area clean. All maintenance equipment should be selected for its effectiveness and freedom from lint-producing tendencies and should be reserved for use in aseptic areas only.

Personnel

Personnel selected to work on the preparation of a parenteral product must be neat, orderly and reliable. They should be in good health and free from dermatological conditions that might increase the microbial load. If they show symptoms of a head cold or similar illness, they should not

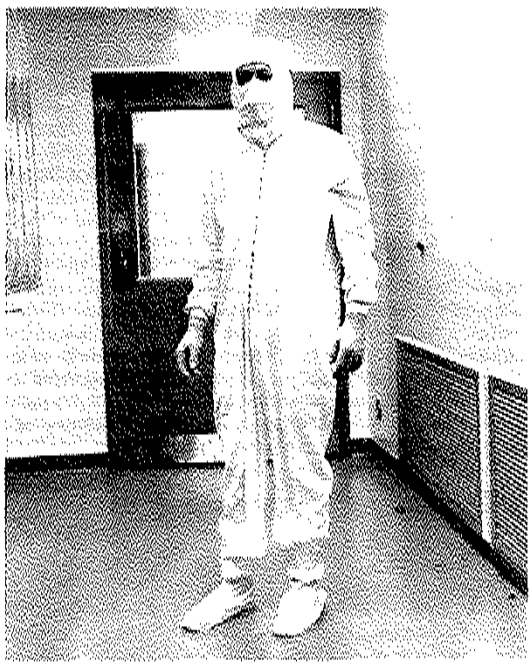


Fig 84-11. Appropriate uniform for operators entering an aseptic filling room (courtesy, Abbott).

be permitted in the aseptic area until their recovery is complete. They must receive intensive instruction in the principles of aseptic processes. They also must be made to appreciate the vital part that every movement they make has in determining the reliability and safety of the final product. Supervisors should be selected with particular care. They must be individuals who understand the unique requirements of aseptic procedures and who are able to obtain the full participation of other employees in fulfilling these exacting requirements.

The attire prescribed for personnel varies from one manufacturing facility to another. However, uniforms should be freshly laundered for each day. For use in the aseptic area, uniforms should be sterile. Usually fresh, sterile uniforms should be used after every break period, or whenever the individual returns to the aseptic area. In some plants this is not required if the product is to be sterilized in its final container. The uniform usually consists of coveralls for both men and women, hoods to completely cover the hair, face masks and Dacron or plastic boots (Fig 84-11). Sterile rubber gloves also may be required for most aseptic operations, preceded by thorough scrubbing of the hands with a disinfectant soap. In addition, goggles may be required to complete the coverage of all skin areas. The uniform is designed to confine the contaminants discharged from the body of the operator, thereby preventing their entry into the product environment.

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

Environmental Control Tests

In spite of the elaborate precautions taken by pharmaceutical manufacturers to provide satisfactory conditions for the proper processing of parenterals, the air may become laden with bacteria or other particles with subsequent contamination of the product. To monitor this condition, suitable environmental control tests should be performed at regular intervals.

Such tests generally are designed to measure either the particles in a volume of sampled air or the particles that are settling or have settled onto surfaces. A volume of air measured by an electronic particle counter will detect all particles and not differentiate between viable and nonviable ones. However, because of the need to control the level of microorganisms in the environment in which sterile products are processed, it also is necessary to detect viable particles, which usually are less in number than nonviable ones.

Locations for sampling should be planned to reveal potential contamination levels which may be critical in the control of the environment. For example, the most critical process step is usually the filling of dispensing containers, a site obviously requiring monitoring. Other examples include the gowning room, high-traffic sites in and out of the filling area, the penetration of conveyor lines through walls and sites near the inlet and exit of the air system.

The size of the sample should be large enough to obtain a meaningful particle count. At sites where the count is expected to be low the size of the sample may need to be increased; for example, in Class 100 areas, Whyte and Niven,[13] suggest that the sample should be at least 30 cu ft and, probably, much more. They also suggest that settling plates should be exposed in Class 100 areas for an entire fill (up to 7 to 8 hr) rather than the more common 1 hr. However, excessive dehydration of the medium must be avoided, particularly in the path of laminar-flow air.

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

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

Another volumetric air sampler is an open-faced filter holder (*Gelman, Millipore, Nuclepore, Sartorius*). The air sample is drawn through the filter membrane in the holder by means of a vacuum, the volume being controlled by means of a limiting orifice. This device can be used for obtaining either a total particle count or a count of CFUs, depending on whether the membrane is subsequently placed on a microscope slide and examined under the microscope for particles or placed on nutrient agar medium and incubated for the growth of CFUs.

It should be noted that most vegetative forms of microorganisms will be dehydrated and killed by the dehydrating effect of the airstream; therefore, the CFUs would arise principally from the growth of spores. Another device is the liquid impinger. An air sample is drawn into the orifice of

the sampler by vacuum through a limiting orifice and bubbled through a dilute nutrient medium or saline. The objective is to wash microorganisms out of the air bubbles and into the liquid medium which then is filtered through a membrane filter, the membrane placed on the nutrient agar medium and incubated. This method is somewhat more complex, but it is used in aerobiology as a reference method. Vegetative microorganisms are likely to survive because of the relatively soft impingement in the liquid.

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

The level of microorganisms on surfaces can be determined with nutrient agar plates having a convex surface (*Rodac Plates*). With these it is possible to roll the raised agar surface over flat or irregular surfaces to be tested. Organisms will be picked up on the agar and will grow during subsequent incubation.

Results from the above tests are very valuable to keep cleaning, production and quality-control personnel apprised of the level of contamination in a given area and, by comparison with baseline counts, will indicate when more extensive cleaning and sanitizing is needed. The results also may serve to detect environmental control defects such as failure in air-cleaning equipment or the presence of personnel who may be disseminating large numbers of bacteria without apparent physical ill effects.

Another test which is much more stringent is the filling and sealing of sterile trypticase soy broth in sterile containers under the same conditions used for an aseptic fill of a product, a "media fill." The entire lot then is incubated and examined subsequently for the appearance of growth of microorganisms which is indicative of contamination from the environment, the process, the operators or the equipment. It also may be used as a measure of the efficiency of a particular operator. Since this is a "total sterility test," it is the best indication of the efficiency of the aseptic filling process.

Production Procedures

Cleaning Containers and Equipment

Containers and equipment coming in contact with parenteral preparations must be cleaned meticulously. It is obvious that if this were not so, all other precautions to prevent contamination of the product would be useless. It also should be obvious that even new, unused containers and equipment will be contaminated with such debris as dust, fibers, chemical films and other materials arising from such sources as the atmosphere, cartons, the manufacturing process and human hands. Much greater contamination must be removed from previously used containers and equipment before they will be suitable for reuse. Equipment should be reserved rigidly for use only with parenteral preparations and, where conditions dictate, only for one type of product in order to reduce the risk of contamination.

A variety of machines are available for cleaning containers for parenteral products. These vary in complexity from a single-jet tube for hand rinsing one inverted container at a time with distilled water, to complex, automatic washers capable of processing several thousand containers an hour. The selection of the particular type will be determined largely by the physical type of containers, their condition with respect to contamination, and the number to be processed in a given period of time.

Characteristics of Machinery—Regardless of the type of cleaning machine selected, certain fundamental characteristics usually are required.

1. The liquid or air treatment must be introduced in such a manner that it will strike the bottom of the inside of the inverted container, spread in all directions and smoothly flow down the walls and out the opening with a sweeping action. The pressure of the jet stream should be such that there is minimal splashing, and the flow should be such that it can leave the container opening without accumulating and producing turbulence inside. Splashing may prevent cleaning all areas, and turbulence may redeposit loosened debris. Therefore, direct introduction of the jet stream within the container with control of its flow is required.
2. The container must receive a concurrent outside rinse.
3. The cycle of treatment should provide for a planned sequence alternating very hot and cool treatments. The final treatment should be an effective rinse with water of a quality equivalent to WFI.
4. All metal parts coming in contact with the containers and with the treatments should be constructed of stainless steel or some other noncorroding and noncontaminating material.

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

Containers previously used cannot be reliably cleaned and the cost of attempting to do so is prohibitive. Therefore, normally, only new containers are used for parenterals. Improvements have been made in maintaining their cleanliness during shipment from the manufacturer through tight, low-shedding packaging, including plastic blister packs.

Machinery for Containers—The machinery available for cleaning large numbers of containers embodies the above principles but varies in the mechanics by which it is accomplished. In one approach, the jet tubes are arranged on arms like the spokes of a wheel, which rotate around a center post

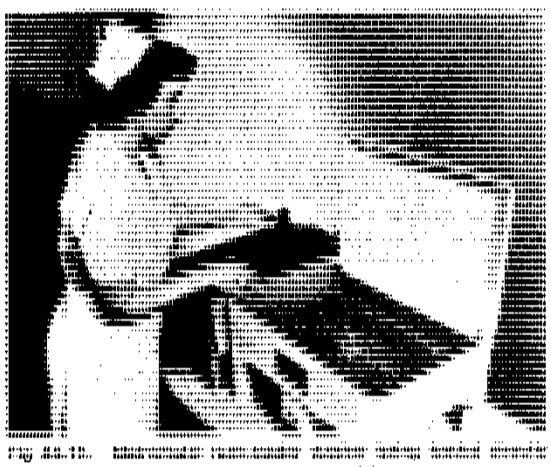
Fig 84-12. Rotary rinser (Cozzoli) in a clean environment provided by vertical laminar airflow within a curtained enclosure (courtesy, Ciba-Geigy).

through which the treatments are introduced. An operator places the unclean containers on the jet tubes as they pass the loading point and removes the clean containers as they complete one rotation. Such a machine is pictured in Fig 84-12. Another machine has a row of jet tubes across a conveyor belt. The belt moves the row of containers past the treatment stations and discharges the clean ones on the opposite end of the machine, preferably through a wall into a clean room. Two operators are required for this machine (Fig 84-13). A cabinet-type washer permits loading the containers on a rack of jet tubes. The rack is pushed inside the cabinet during the cleaning cycle. This type of machine (Fig 84-14) permits handling a variety of sizes and types of containers quite easily, but the number of containers handled in a given period of time is relatively small.

The disadvantage common to all of the above types of machines is that they require the individual handling of each container for loading and unloading. A type which overcomes this disadvantage is the rack-loading washer. Racks are prepared to fit over the open ends of ampuls or vials as they are found in shipping cartons. Inverting the carton permits the containers to be transferred from the carton to the washer without handling them individually. A battery of jet tubes is arranged to enter each container positioned in the rack. The clean containers may be removed in the rack and transferred to a box for dry-heat sterilization and storage (see Fig 84-15). More details of the industrial washing of glassware have been given by Anschel.[14]

Handling after Cleaning—The wet, clean containers must be handled in such a way that contamination will not be reintroduced. A wet surface much more readily will collect contaminants than will a dry surface. For this reason wet, rinsed containers should be protected, such as by a laminar flow of clean air until covered, as within a stainless-steel box (see Figs 84-12 and 84-16). In addition, microorganisms are more likely to grow in the presence of moisture. Therefore, it is preferable, if not required, that containers be dry-heat sterilized in a stainless-steel box that will protect them from contamination during storage after sterilization. Doubling the heating period generally has been considered to be adequate also to destroy pyrogens, but the actual time-temperature conditions required must be validated. If it is

Fig 84-13. Conveyor rinser (Cozzoli) discharging clean vials in a preparation area (courtesy, Schering).



from a container carton (courtesy, Metromatic).

Fig 84-14. Cabinet washer (Getter Built) being loaded with ampuls (courtesy, The University of Tennessee College of Pharmacy).

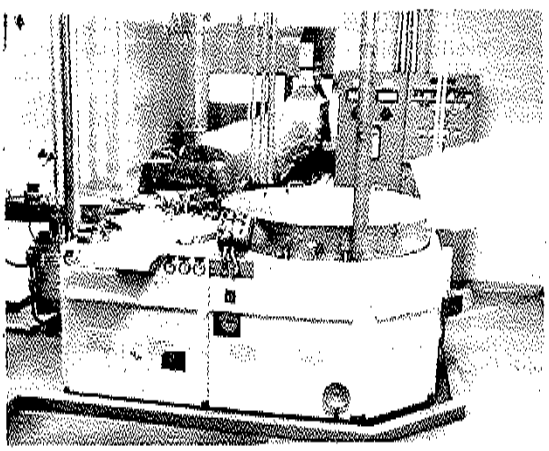


Fig 84-16. Continuous automatic line operation for vials from a rotary rinser through a sterilizing tunnel with vertical laminar-airflow protection of clean vials (courtesy, Abbott).

proved that sterilization is not essential, the containers preferably should be filled immediately with product.

Increases in process rates have necessitated the development of continuous-line processing with a minimum of individual handling, still maintaining adequate control of the cleaning and handling of the containers. Fig 84-16 shows a continuous automatic-line operation from feeding the unwashed container into the rotary rinser to passing it through the drying and sterilizing tunnel. The clean, wet containers are protected by filtered laminar-flow air from the rinser through the tunnel and until they are delivered to the filling line.

Closures—Rubber closures are coated with lubricant from the molding operation. In addition, the rough surface and electrostatic attraction tend to hold debris. Also, the surface "bloom" from migrated inorganic constituents of the compound must be removed. The recommended procedure calls for gentle agitation in a hot solution of a water softener such as 0.5% sodium pyrophosphate. The closures are removed from the solution and rinsed several times, or continuously for a prolonged period, with water and finally with filtered WFI. The rinsing is to be done in a manner which will flush away loosened debris. The wet closures then are sterilized, usually by autoclaving, and stored in closed containers until ready for use. At times this step is carried out in a solution of the bacteriostatic agent to be used in the product, in order to equilibrate the rubber closure with the agent. Subsequent loss of the agent from the solution to the closure is then less likely to occur. If the closures were immersed during autoclaving, the solution is drained off before storage to reduce hydration of the rubber compound. If the closures must be dry for use, they may be subjected to vacuum drying at a temperature in the vicinity of 100°.

The equipment used for washing large numbers of closures is usually an agitator or horizontal basket-type automatic washing machine. Because of particulate generation from the abrading action of these machines, some heat the closures in kettles in detergent solution and follow with prolonged flush rinsing. The final rinse always should be ultraclean WFI.

Equipment—The details of certain prescribed techniques for cleaning and preparing equipment, as well as of containers and closures, have been presented elsewhere.[15] Here, a few points will be emphasized.

All equipment should be disassembled as much as possible to provide access to internal structures. For thorough cleaning, surfaces should be scrubbed thoroughly with a stiff brush using an effective detergent, paying particular attention to joints, crevices, screw threads, and other structures where debris is apt to collect. Exposure to a stream of clean steam will aid in dislodging residues from the walls of stationary tanks, spigots, pipes and similar structures. Thorough rinsing with distilled water should follow the cleaning steps. Large stationary tanks, such as those shown in Fig 84-17, should be protected as much as possible from contamination after cleaning but should be rinsed thoroughly again with distilled water prior to reuse.

A relatively new concept for cleaning tanks, piping and associated attachments is called cleaning in place (CIP). Such an approach involves designing the system, normally of stainless steel, with smooth, rounded internal surfaces and without crevices. That is, for example, with welded rather than threaded connections. The cleaning is accomplished with the scrubbing action of high-pressure spray balls or nozzles delivering hot detergent solution from tanks captive to the system. Thorough rinsing with WFI follows and is accomplished within the same system. Such a process is often automated and may be computer-controlled.[16]

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

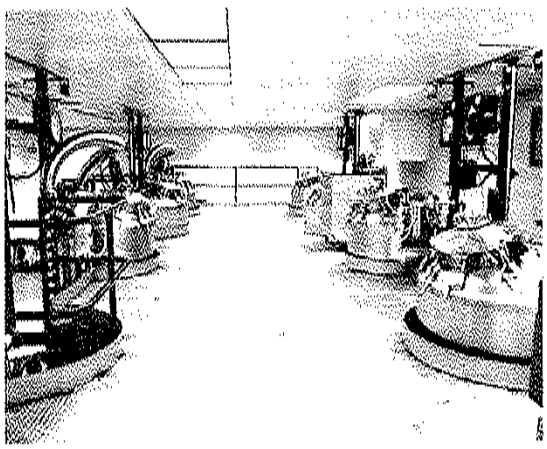


Fig 84-17. Large stainless-steel tanks for product preparation showing mezzanine access level (courtesy, Abbott).

Product Preparation

The basic principles employed in the compounding of the product do not vary from those used routinely by qualified pharmacists. However, selected aspects will be mentioned for emphasis.

All measurements should be made as accurately as possible and should be checked by a second qualified person. Although most liquid preparations are made by volume, where possible they should be made by weight, with the weight experimentally determined from a prescribed volume. This method is more accurate since no consideration need be given to the temperature of the components. In addition, measurements by weight normally can be performed more accurately than those by volume.

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

Parenteral dispersions, including colloids, emulsions and suspensions, provide particular problems. Parenteral emulsions have been reviewed by Singh and Ravin.[17] In addition to the problems of achieving and maintaining proper reduction in particle size under aseptic conditions, the dispersion must be kept in a uniform state of suspension throughout the preparative, transfer and subdividing operations.

The formulation of a stable product is of paramount importance. Certain aspects of this have been mentioned in the discussion of components of the product. Exhaustive coverage of the topic is not possible within the limits of this text, but further coverage is provided in Chapter 76. It should be mentioned here, however, that thermal steriliza-

tion of parenteral products increases the possibility of chemical reactions. Such reactions may progress to completion during the period of elevated temperature in the autoclave, or be initiated at this time but continue during subsequent storage. The assurance of attaining product stability requires a high order of pharmaceutical knowledge and responsibility.

Filtration

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

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

Today, membrane filters are used almost exclusively for parenteral solutions. Their particle retention effectiveness, flow rate, nonreactivity and disposable characteristics have justified their use to the exclusion of most other types. The most common membranes are composed of:

Cellulose ester (Suppliers: *Cuno, Gelman, Millipore, Sartorius, Schleicher*).
Nylon (Supplier: *Pall*).
Polysulfone (Suppliers: *Gelman, Millipore*).
Polycarbonate (Supplier: *Nuclepore*).

but other materials are being used, including Teflon and other plastic polymers. They are available as flat membranes or pleated into cylinders to increase surface area and, thus, flow rate. Each filter in its holder should be tested for integrity before and after use, particularly if it is being used to eliminate microorganisms. While membrane filters are disposable, and thus discarded after use, the holders must be cleaned thoroughly between uses. Increasingly, clean, sterile, pretested, disposable assemblies for small as well as relatively large volumes of solutions are becoming available commercially. Other characteristics of these filters, important for a full understanding of their use, are given in Chapter 78.

Filling

During the filling of containers with a product, the most stringent requirements must be exercised to prevent contamination, particularly if the product has been sterilized by filtration and will not be sterilized in the final container. Under the latter conditions the process usually is called an "aseptic fill." During the filling operation, the product must be transferred from a bulk container and subdivided into dose containers. This operation exposes the product to the environment, equipment and manipulative technique of the operator until it can be sealed in the dose container. Therefore, this operation is carried out in the aseptic filling area where maximum protection is provided. Additional protection may be provided by filling under a blanket of HEPA-filtered laminar-flow air within the aseptic area.

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

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

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

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

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

Liquids—The filling of a small number of containers may be accomplished with a hypodermic syringe and needle, the liquid being drawn into the syringe and forced through the needle into the container. A device for providing greater speed of filling is the Cornwall Pipet (*BD & Co*). This has a

two-way valve between the syringe and the needle and a means for setting the stroke of the syringe so that the same volume will be delivered each time. Clean, sterile, disposable assemblies (Suppliers: *Burron, Pharmaseal*) operating on the same principle have particular usefulness in hospital pharmacy operations.

Mechanically operated instruments substitute a motor for the operator's hand in the previous devices described. Thereby, a much faster filling rate can be achieved. By careful engineering, the stroke of the syringe can be repeated precisely, and so, once a particular setting has been calibrated to the delivery, high delivery precision is possible. However, the speed of delivery, the expansion of the rubber tubing connecting the valve with the delivery tube, and the rapidity of action of the valves can affect the precision of delivery. A filling machine employing a two-way valve assembly is shown in operation in Fig 84-7. One employing a piston valve is shown in Fig 84-18. Stainless-steel syringes are required with viscous liquids because glass syringes are not strong enough to withstand the high pressures developed during delivery.

When high-speed filling rates are desired but accuracy and precision must be maintained, multiple filling units are often joined together in an electronically coordinated machine, such as shown in Fig 84-19.

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

The USP indicates that each container should be filled with a slight excess of volume and gives a table of such suggested excess.

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

Some sterile solids are subdivided into containers by individual weighing. A scoop usually is provided to aid in approximating the quantity required, but the quantity filled into the container finally is weighed on a balance. This is a slow process. When the solid is obtainable in a granular form so that it will flow more freely, other methods of filling may be employed. In general, these involve the measurement and delivery of a volume of the granular material which has been calibrated in terms of the weight desired. In the machine shown in Fig 84-20 an adjustable cavity in the rim of a wheel is filled by vacuum and the contents held by vacuum until the cavity is inverted over the container. The solid material then is discharged into the container by the use of sterile air. Another machine employs an auger in the stem of a funnel at the bottom of a hopper. The granular material is placed in the hopper. By controlling the size of the auger and its rotation, a regulated volume of granular material can be delivered from the funnel stem into the container. Such a machine is shown in Fig 84-21.

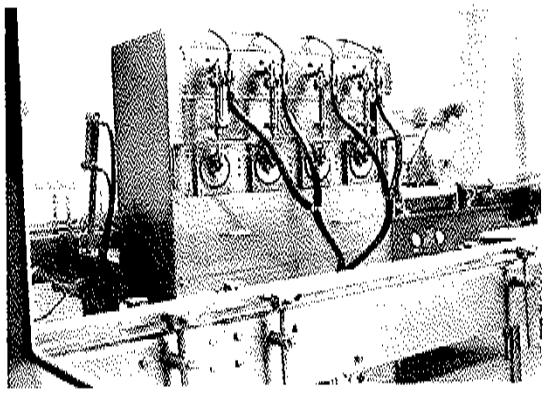


Fig 84-19. Four-pump liquid filler, with a conveyor line for vials protected by a vertical laminar airflow and plastic curtain; note the automatic stoppering machine on the right within the curtain (courtesy, Abbott).

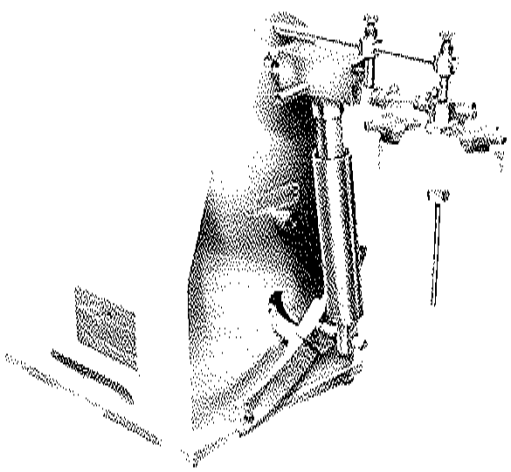


Fig 84-18. Filling machine employing a piston valve and a stainless-steel syringe (courtesy, Cozzoli).

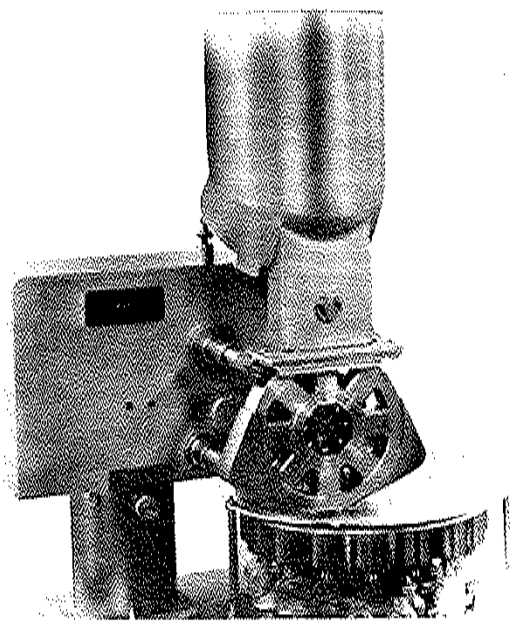


Fig 84-20. Accofil vacuum powder filler (courtesy, Perry).

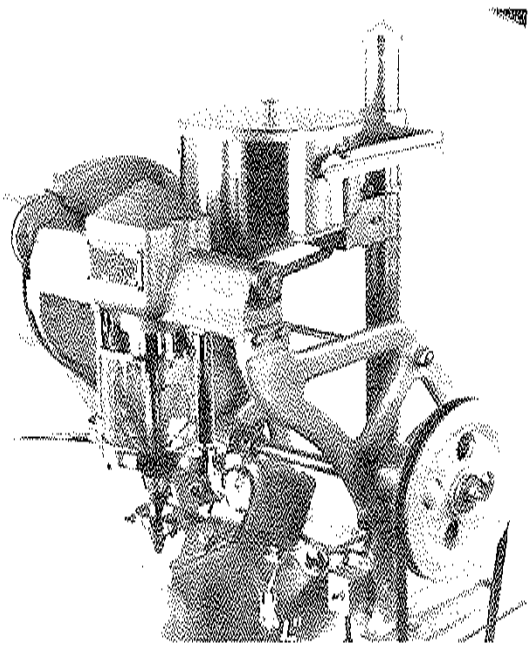


Fig 84-21. Auger-type powder filler (courtesy, Chase-Logeman).

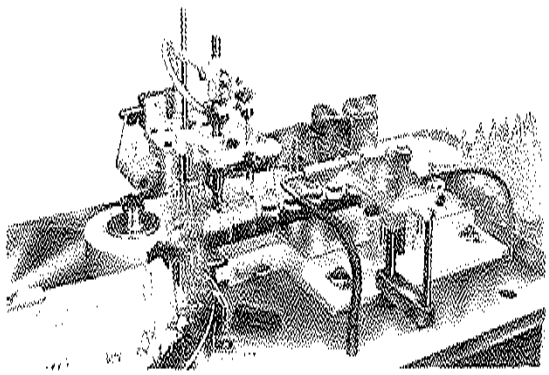


Fig 84-22. Automatic filling and pull-sealing of ampuls (courtesy, Cozzoli).

Sealing

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

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

Pull-seals are made by heating the neck of the ampul below the tip, leaving enough of the tip for grasping with forceps or other mechanical devices. The ampul is rotated in the flame from a single burner. When the glass has softened, the tip is grasped firmly and pulled quickly away from the body of the ampul, which continues to rotate. The small capillary tube thus formed is twisted closed. Pull-sealing is slower, but the seals are more sure than tip-sealing. Fig 84-22 shows a machine combining the steps of filling and pull-sealing ampuls.

Powder ampuls or other types having a wide opening must be sealed by pull-sealing. Were these sealed by tip-sealing, the very large bead produced would induce glass strain with subsequent fracture at the juncture of the bead and neck wall. Fracture of the neck of ampuls during sealing also may occur if wetting of the necks occurred at the time of filling. Also, wet necks increase the frequency of bubble formation. If the product in the ampul is organic in nature, wet necks also will result in unsightly carbon deposits from the heat of sealing.

In order to prevent decomposition of a product, it is sometimes necessary to displace the air in the space above the product in the ampul with an inert gas. This is done by introducing a stream of the gas, such as nitrogen or carbon dioxide, during or after filling with the product. Immediately thereafter the ampul is sealed before the gas can diffuse to the outside.

Vials and Bottles—These are sealed by closing the opening with a rubber closure (stopper). This must be accomplished as rapidly as possible after filling and with reasoned care to prevent contamination of the contents. The large opening makes the introduction of contamination much easier than with ampuls. Therefore, a covering should be provided for such containers except for the minimal time required for filling and for the actual introduction of the rubber closure. During the latter critical time the open containers should be protected from the ingress of contamination, preferably with a blanket of HEPA-filtered laminar airflow. In Fig 84-19 the automatic conveyorized procedure is being performed under vertical laminar airflow within plastic side curtains.

The closure must fit the mouth of the container snugly enough so that its elasticity will permit adjustment to slight irregularities in the lip and neck of the container. However, it must not fit so snugly that it is difficult to introduce into the neck of the container. Closures may be inserted aseptically with sterile forceps or directly with hands encased in sterile rubber gloves. When rubber closures are to be inserted mechanically, their surface is often halogenated or treated with silicone to make them easier to insert. Thus, it is possible to convey the closure through a shute to the place where it is positioned over a vial and then inserted by a plunger or some other pressure device. An example of such a mechanical device is shown in Fig 84-23. Mechanical stoppering has been developed to meet the need for high-speed production.

Rubber closures are held in place by means of aluminum caps. The caps cover the closure and are crimped under the lip of the vial or bottle to hold them in place (see Fig 84-4). The closure cannot be removed without destroying the aluminum cap. Therefore, an intact aluminum cap is proof that the closure has not been removed intentionally or unintentionally. Such confirmation is necessary to assure the integrity of the contents as to sterility and other aspects of quality.

The aluminum caps are so designed that the outer layer of

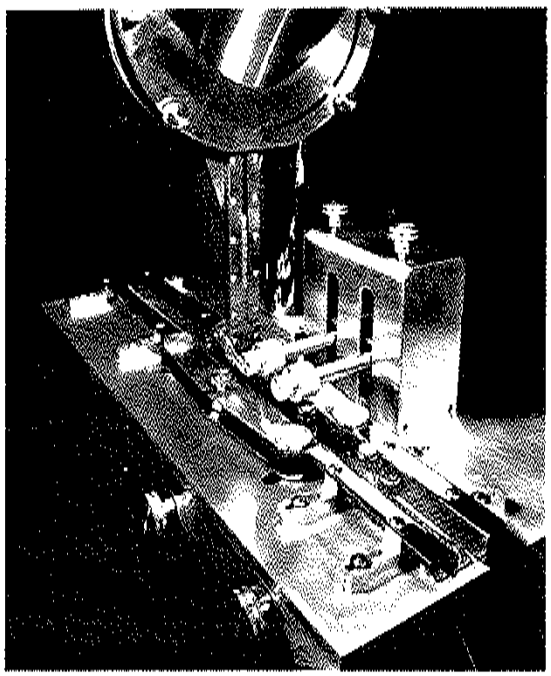


Fig 84-23. Mechanical device for inserting rubber closures in vials (courtesy, Perry).

double-layered caps, or the center of single-layered caps, can be removed to expose the center of the rubber closure without disturbing the band which holds the closure in the container. Rubber closures for use with intravenous administration sets often have a permanent hole through the closure. In such cases, a thin rubber disk overlayed with a solid aluminum disk is placed between an inner and outer aluminum cap, thereby providing a seal of the hole through the closure. These are called triple-layered aluminum caps.

Single-layered aluminum caps may be applied by means of a hand crimper known as the Fermpress (Suppliers: *West, Wheaton*). Double- or triple-layered caps require greater force for crimping; therefore, heavy-duty mechanical crimpers (see Fig 84-24) are required (Suppliers: *Cozzoli, Perry, Seidenader, West, Wheaton*).

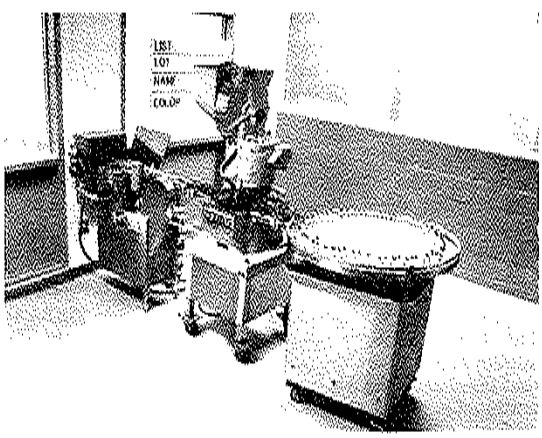


Fig 84-24. Applying aluminum caps to vials at the end of the process line (courtesy, Abbott).

Sterilization

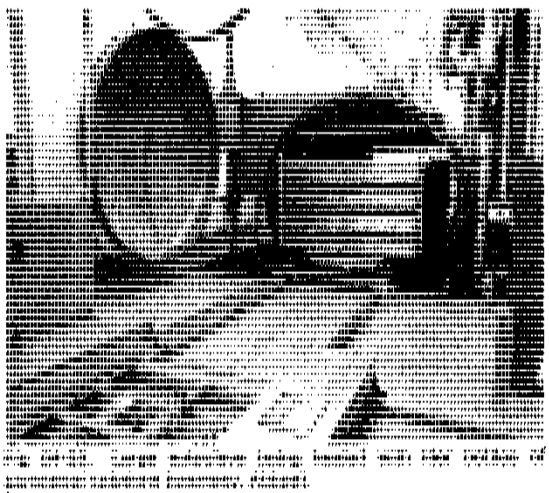
Whenever possible, the parenteral product should be sterilized after being sealed in its final container (terminal sterilization) and within as short a time as possible after the filling and sealing have been completed. Since this usually involves a thermal process, due consideration must be given to the effect of the elevated temperature upon the stability of the product. Many products, both pharmaceutical and biological, will be affected adversely by the elevated temperatures required for thermal sterilization. Such products must, therefore, be sterilized by a nonthermal method. Most thermolabile solutions may be sterilized by filtration through bacteria-retaining filters. Subsequently, all operations must be carried out in an aseptic manner so that contamination will not be introduced into the filtrate. To perform such an aseptic procedure is difficult, and the degree of its accomplishment is always uncertain. Colloids, oleaginous solutions, suspensions and emulsions that are thermolabile may require a process in which each component is sterilized and the product is formulated and processed under aseptic conditions. Because of the ever-present risk of a momentary or prolonged lapse in aseptic control during an aseptic process, and the dangerous condition that could result, sterilization of a product in its final container is preferred, if possible.

Some of the newer nonthermal methods of sterilization are finding important application to components of injections and administration devices. Certain dry solids such as penicillin, streptomycin, polyvitamins and certain hormones are being sterilized effectively by ionized radiations without adverse effects. Catgut sutures now are being sterilized routinely in the final package by this method. Administration sets, disposable needles and syringes and other plastic and stainless-steel equipment and components are being sterilized by ionizing radiations and by gaseous ethylene oxide sterilization. Generally speaking, however, neither of these methods may be used for liquid preparations without adverse effects on the product, and gaseous sterilization cannot be used where a glass container or other impervious barrier prevents the gas from permeating the material.

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

Saturated steam under pressure (autoclaving) is the most commonly used and the most effective method for the sterilization of aqueous liquids or substances that can be reached or penetrated by steam.

Figure 84-25 shows liter containers of solution being loaded into an autoclave for sterilization. It is ineffective in anhydrous conditions, such as within a sealed ampul containing a dry solid or an anhydrous oil. Since the temperature employed in an autoclave is lower than that for dry-heat sterilization, equipment made of materials such as rubber and polypropylene may be sterilized if the time and temperature are controlled carefully. As mentioned previously, some injections will be affected adversely by the elevated temperature required for autoclaving. For some products, such as Dextrose Injection, the use of an autoclave designed to permit a rapid rise to sterilizing temperature and rapid cooling with water spray after the sterilizing hold-period will make it possible to use this method. Other products that will not withstand autoclaving temperatures may withstand marginal thermal methods such as tyndallization or inspissation. These methods may be rendered more effective for



some injections by the inclusion of a bacteriostatic agent in the product.

It should be obvious that all materials subjected to sterilization must be protected from subsequent contamination to maintain their sterile state. Therefore, they must be wrapped or covered so that microorganisms may not gain access when removed from the autoclave. Equipment and supplies are wrapped most frequently with paper and tied or sealed with special autoclave tape. The wrapping must permit penetration of steam during autoclaving but screen out microorganisms when dry. A double wrapping with lint-free parchment paper designed for such use is probably best. Synthetic fiber cloth such as nylon or Dacron also may be used for the inner wrapping. The openings of equipment subjected to dry-heat sterilization are often covered with silver–aluminum foil or with metal or glass covers. Cellulose wrapping materials are affected adversely by the high temperatures of dry-heat sterilization.

The effectiveness of any sterilization technique must be proved (validated) before it is employed; controls then being established to show that subsequent processes repeat the conditions proven to be effective. Since the goal of sterilization is to kill microorganisms, the ideal indicator to prove the effectiveness of the process is a biological one; resistant spores. However, many feel considerable hesitation about using biological indicators (BIs) during the processing of products because of the inherent risk of inadvertent contamination of the product or the environment. Also, it has been found that the resistance of spores may vary from lot to lot, thereby possibly giving false indications of reliability. However, today commercially prepared BIs are established as reliable for use in conjunction with physical-parameter measurement for validating and monitoring sterilization processes. Such physical-parameter monitors include recording thermocouples, color-change indicators and melting indicators. This type of confirmatory evidence is an essential part of the sterilization record for a product.

Further details concerning methods of sterilization and their application will be found in Chapter 78. In addition, the USP provides suggestions concerning the sterilization of injections and related materials.

Freeze-Drying

Freeze-drying (lyophilization) is a process of drying in which water is sublimed from the product after it is frozen.[18] The particular advantages of this process are that biologicals and pharmaceuticals which are relatively unstable in aqueous solution can be processed and filled into dosage containers in the liquid state, taking advantage of the relative ease of processing a liquid. They can be dried without elevated temperatures, thereby eliminating adverse thermal effects, and stored in the dry state in which there are relatively few stability problems.

Further advantages are that these products are often more soluble and/or more rapidly soluble, dispersions are stabilized throughout their shelf life and products subject to degradation by oxidation have enhanced stability because the process is carried out in a vacuum.

However, the increased time and handling required for processing and the cost of the equipment limit the use of this process to those products which significantly have enhanced stability if stored in the dry state.

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

Freeze-drying essentially consists of the following:

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

Figure 84-26 shows such a system. The product may be frozen on the shelf in the chamber by circulating refrigerant (usually Freon, ammonia or ethylene glycol) from the compressor through pipes within the shelf. After freezing is complete, which may require several hours, the chamber and condenser are evacuated by the vacuum pump, the condenser surface having been chilled previously by circulating refrigerant from the large compressor.

Heat then is introduced from the shelf to the product by electric resistance coils or by circulating hot water, silicone or glycol. The process continues until the product is dry (usually 1% or less moisture), leaving a sponge-like matrix of

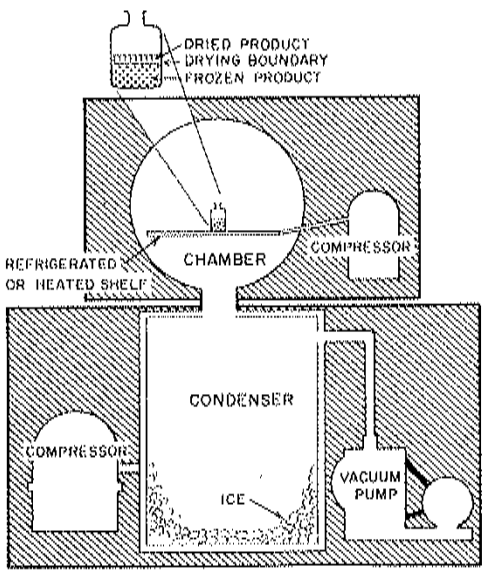


Fig 84-26. Essential components of a freeze-drying system.

the solids originally present in the product, the input of heat being controlled so as not to degrade the product.

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

The chambers may be equipped with hydraulic or rubber diaphragm internal-stoppering devices designed to push slotted rubber closures into the vials to be sealed while the chamber is still evacuated, the closures having been partially inserted immediately after filling so that the slots were open to the outside.

If internal stoppering is not available or containers such as ampuls are used, filtered dry air or nitrogen must be introduced to the chamber at the end of the process to establish atmospheric pressure. Then the containers must be removed and sealed under aseptic conditions. If the product is very sensitive to moisture, the environmental humidity also must be controlled until it is sealed.

Factors Affecting the Process Rate—The greater the depth of the product in the container, the longer will be the drying process. Therefore, a product to be frozen by placing the container on a refrigerated shelf (plug freezing) should be filled to a planned, limited depth. If a large volume of solution must be processed, the surface area may be increased and the depth decreased by freezing the solution on a slant or while rotating the container on an angle (shell freezing) in a liquid refrigerant bath, such as dry ice and alcohol.

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

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

This may be visualized by referring to Fig 84-26.

The passageways between the product surface and the condenser surface must be wide open and direct for effective operation. Therefore, the condensing surfaces in large freeze-driers are usually in the same chamber as the product. Evacuation of the system is necessary to reduce the impeding effect that collisions with air molecules would have on the passage of water molecules. However, the residual pressure in the system must be greater than the vapor pressure of the ice on the condenser or the ice will be vaporized and pulled into the pump, an event detrimental to most pumps.

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

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

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

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

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

Modifications in the Process and Equipment—In some instances a product may be frozen in a bulk container or in trays rather than in the final container and then handled as a dry solid. This may be desirable when large volumes of a product are processed.

Heat may be introduced to all sides of the product by radiation from infrared sources, rather than only from the bottom as with conductive heating. While this generally increases the rate of drying, there are at least two major disadvantages to radiant heating of pharmaceuticals; these are (1) multiple containers produce shadowing with resultant blockage of the radiations and (2) the dried material on the outside of the frozen product may be scorched easily by the heat as drying progresses.

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

Available freeze-driers (Suppliers: *Edwards, FTS, Hull, NRC, Stokes, Virtis*) range in size from small laboratory units to large industrial models such as the one shown in Fig 84-27. Their selection requires consideration of such factors as:

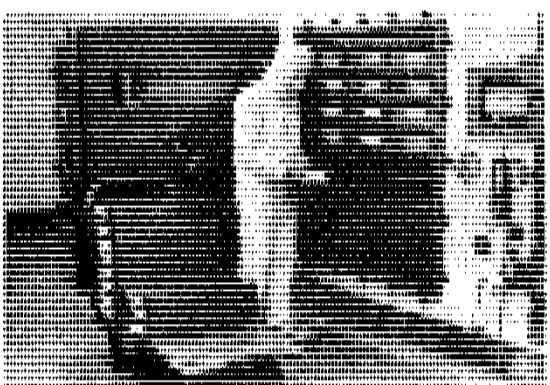


Fig 84-27. Aseptic loading of freeze-drier (courtesy, Upjohn).

The tray area required.
The volume of water to be removed.
Whether or not aseptic processing will be involved.
Is internal stoppering required?
Will separate freezers be used for initial freezing of the product.
The degree of automatic operation desired.

Other factors involved in the selection and use of equipment are considered in the literature.[19]

Freeze-drying is now being used for research in the preservation of human tissue and is finding increasing application in the food industry. Progress on new developments is being made in both the process and the equipment.[20]

Quality Assurance and Control

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

The principles for achieving quality are basically the same for the manufacture of any pharmaceutical. These are discussed in Chapter 82. During the discussion of the preparation of injections, mention was made of numerous quality requirements for components and manufacturing processes. Here, only certain tests characteristically applicable to the finished parenteral products will be discussed.

Sterility Test

All lots of injections in their final containers must be tested for sterility. The USP prescribes the requirements for this test for official injections. The FDA uses these requirements as a guide for testing unofficial sterile products. The official test has acknowledged limitations in the information that it can provide. Therefore, it should be noted that this test is not intended as a thoroughly evaluative test for a product subjected to a sterilization method of unknown effectiveness. It is intended primarily as a check test on the probability that a previously validated sterilization procedure has been repeated, or to give assurance of its continued effectiveness. A discussion of sterility testing is given in Chapter 78.

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

Pyrogen Test

The presence of pyrogens in parenteral preparations is evaluated by a qualitative fever response test in rabbits. The USP tests are described in Chapter 27. Rabbits are used as test animals because they show a physiological response to pyrogenic substances similar to that by man. While a minimum pyrogenic dose (MPD), the amount just sufficient to cause a positive USP Pyrogen Test response, sometimes may produce uncertain test results, a content equal to a few times the MPD will leave no uncertainty. Therefore, the test is valid and has continued in use since introduced by Seibert in 1923. It should be understood that not all injections may be subjected to the rabbit test since the medicinal agent may have a physiological effect on the test animal such that any fever response would be masked.

A new test for pyrogens recently has been accepted, not only for in-process control for pharmaceutical products but also for release testing of such products and for devices. It is an *in vitro* test based on the gelling or color development of a pyrogenic preparation in the presence of the lysate of the amebocytes of the horseshoe crab (*Limulus polyphemus*). The Limulus Test, as it is called, is simpler, more rapid and of greater sensitivity than the rabbit test.[21] Although it detects only the endotoxic pyrogens of Gram-negative bacteria, this probably will not limit its use significantly since most environmental contaminants gaining entrance to sterile products are Gram-negative. The test has gained in stature to the point that automated techniques have been developed.[22]

Particulate Evaluation

Particulate matter in parenteral solutions long has been recognized as unacceptable since the user could be expected to conclude that the presence of visible "dirt" would suggest that the product is of inferior quality. Today, it is recognized that the presence of particles in solution, particularly if injected intravenously, can be harmful. While data defining the extent of risk and the effects produced still are limited, it has been shown that particles of lint, rubber, insoluble chemicals and other foreign matter can produce emboli in the vital organs of animals and man.[23] Further, it has been shown that the development of infusion-phlebitis may be related to the presence of particulate matter in intravenous fluids.[24]

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

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

Since it is recognized that visual inspection will not detect the presence of particles smaller than approximately 50 μm in size, the USP has established a microscopic test method

for identifying particles in large-volume intravenous solutions and has set limits of not more than 50 particles/mL of 10 μm and larger in size and not more than 5 particles/mL of 25 μm and larger in size. This method consists essentially of filtering a measured sample of solution through a membrane filter under ultraclean conditions and then counting the particles on the surface of the filter using oblique light, under a microscope, at both 40× and 100× magnification. These standards are being met readily by the large-volume parenteral solutions currently being manufactured in the US.

More recently the USP established standards for small-volume parenterals to be given intravenously, using an electronic instrument that counts and measures the size of particles by means of a shadow cast by the particle as it passes through a high-intensity light beam (Suppliers: *Climet*, *HIAC*). The limits prescribed are not more than 10,000 particles/mL of ≥ 10 μm in size and not more than 1000 particles/mL ≥ 25 μm in size. These specifications were developed on the premise that as many as five such products may be added to a 1-L bottle of a large-volume parenteral and five products should not contribute more than the overall limits of particles prescribed for a large-volume parenteral. Whether or not these standards are realistic toxicologically has not been established; rather, the objective of the compendium is to establish specification limits that would encourage the preparation of clean parenteral solutions, particularly for those to be given intravenously.

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

The USP methods for counting and sizing particulate matter in intravenous solutions are not the only methods available for such determinations. A number of electronic particle counters are available that use the light-scattering principle to count particles in a liquid sample (Suppliers: *Climet*, *Met One*, *Royco*). There also is an instrument available which counts particles and sizes them by measuring the effect on the resistance between two electrodes as the particles pass between them (Supplier: *Coulter*). It is obvious that only the visual inspection can be used for in-line evaluation of every container produced commercially. All of these methods require very stringent ultraclean preparation techniques to assure reasonable accuracy in counting and sizing only the particles in the solution, rather than those that may have been introduced inadvertently during the sample preparation or the testing procedure. Further, these test procedures are destructive and, therefore, can be performed only on samples of the production lot. Further information may be found in a review article.[25]

Leaker Test

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

This test usually is performed by producing a negative pressure within an incompletely sealed ampul while the ampul is entirely submerged in a deeply colored dye solution. Most often, approximately a 1% methylene blue solution is employed. The test may be performed by subjecting the ampuls to a vacuum in a vacuum chamber, the ampuls being submerged in a dye bath throughout the process. Another procedure frequently employed is to simply autoclave the ampuls in a dye bath. A modification of this is to remove them from the autoclave while hot and quickly submerge them in a cool bath of dye solution. After carefully rinsing the dye solution from the outside, color from the dye will be visible within a leaker. Leakers, of course, are discarded.

Vials and bottles are not subjected to a leaker test because the sealing material (rubber stopper) is not rigid. Therefore, results from such a test would be meaningless. However, evacuated bottles containing a liquid may be checked for a sharp "click" sound produced when struck with an implement such as a rubber mallet.

Safety Test

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

Packaging and Labeling

A full discussion of the packaging of parenteral preparations is beyond the scope of this text. It is essential, of course, that the packaging should provide ample protection for the product against physical damage from shipping, handling and storage as well as protecting light-sensitive materials from ultraviolet radiation. An extensive review of this subject has been published.[26]

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

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

Labeling—The labeling of an injection must provide the physician or other user with all of the information needed to assure the safe and proper use of the therapeutic agent. Since all of this information cannot be placed on the immediate container and be legible, it may be provided on accompanying printed matter. General labeling requirements for drugs are discussed in Chapter 107.

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

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

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

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

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

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

Injections intended for veterinary use are so labeled.

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CHAPTER 85

Intravenous Admixtures

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It has been estimated that 40% of all drugs administered in hospitals are given in the form of injections and their use is increasing. Part of this increase in parenteral therapy is due to the wider use of intravenous fluids (IV fluids). In the last decade the use of IV fluids has doubled, increasing from 150 million units to 300 million units annually. Not only do IV fluids continue to serve as the means for fluid replacement, electrolyte-balance restoration and supplementary nutrition, but they also are playing major roles as vehicles for administration of other drug substances and in total parenteral nutrition (TPN). TPN fluids are finding greater use as the means of administering other drugs because of convenience, the means of reducing the irritation potential of the drugs and the desirability for continuous and intermittent drug therapy. The techniques for providing TPN parenterally have improved steadily in the last decade, and such use is increasing markedly. The use of IV fluids for these purposes requires the compounding of specific intravenous admixtures (parenteral prescriptions) to meet the clinical needs of a given patient. However, the combination of drug substances in an IV fluid can promote parenteral incompatibilities and give rise to conditions not favorable for drug stability. A new area of specialization has been created for hospital pharmacists who can develop the expertise to prepare these solutions—recognizing their compatibility and stability problems and the potential for contamination—and participate in the administration of the solutions. The complex compounding of an order for TPN requires knowledgeable personnel capable of making accurate calculations, compounding and having aseptic technique. The parenteral prescription is becoming increasingly important in hospitals. Centralized admixture programs are now found in 70% of the nation's hospitals having 300 beds or more. Equipment available for administering IV fluids has become more sophisticated, and has made possible increased accuracy of dosage and led to the development of new concepts and methods of nutrition and drug therapy.

Intravenous Fluids

Large-volume injections intended to be administered by intravenous infusion commonly are called IV fluids and are included in the group of sterile products referred to as large-volume parenterals. These consist of single-dose injections having a volume of 100 mL or more and containing no added substances. Intravenous fluids are packaged in containers having a capacity of 100 to 1000 mL. Minitype infusion containers of 250-mL capacity are available with 50- and 100-mL partial fills for solution of drugs when used in the "piggyback" technique (ie, the administration of a second solution through a Y-tube or gum-rubber connection in the administration set of the first intravenous fluid, thus avoiding the need for another injection site). In addition to the IV fluids, this group also includes irrigation solutions and solutions for dialysis.

Intravenous fluids are sterile solutions of simple chemicals such as sugars, amino acids or electrolytes—materials which easily can be carried by the circulatory system and assimilated. Prepared with Water for Injection USP, the solutions are pyrogen-free. Because of the large volumes administered intravenously, the absence of particulate matter assumes a significant role in view of possible biological hazards resulting from insoluble particles. Absence of particulate matter or clarity of IV fluids is as important at the time of administration following their manipulation in the hospital as it is at the time of manufacture of the injection.

Limits for particulate matter occurring in IV fluids, or large-volume injections used for single-dose infusion, are defined in the USP. This represents the first regulatory attempt to define limits for particulate matter in parenterals. Limits also apply to multiple-dose injections, small-volume injections or injections prepared by reconstitution from sterile solids. The USP defines particulate matter as extraneous, mobile, undissolved substances, other than gas bubbles, unintentionally present in parenteral solutions. The total numbers of particles having effective linear dimensions equal to or larger than 10 μm and larger than 25 μm are counted. The IV fluid meets the requirement of the test if it contains not more than 50 particles per mL which are equal to or larger than 10 μm, and not more than 5 particles per mL which are equal to or larger than 25 μm in linear dimension.

Intravenous fluids commonly are used for a number of clinical conditions. These include

Correction of disturbances in electrolyte balance.
Correction of disturbances in body fluids (fluid replacement).
The means of providing basic nutrition.
The basis for the practice of providing TPN.
Use as vehicles for other drug substances.

In both of the latter two cases it has become common practice to add other drugs to certain IV fluids to meet the clinical needs of the patient. Using IV fluids as vehicles offers the advantages of convenience, the means of reducing the irritation potential of the drug and a method for continuous drug therapy. However, the practice requires that careful consideration be given to the stability and compatibility of additives present in the IV fluids serving as the vehicles. This approach also demands strict adherence to aseptic techniques in adding the drugs, as well as in the administration of the IV fluids. These procedures are discussed later in the chapter. The IV fluids commonly used for parenterals are shown in Table I.

Many disease states result in electrolyte depletion and loss. Proper electrolyte concentration and balance in plasma and tissues are critical for proper body function. Electrolyte restoration and balance are achieved most rapidly through administration of IV fluids. Required electrolytes include sodium and chloride ions, which in normal saline more closely approximate the composition of the extracellular fluid than solutions of any other single salt; potassium, the principal intracellular cation of most body tissues and an essential for the functioning of the nervous and muscular

Table I—Fluids Used Commonly for IV Use

Injection	Concentration (%)	pH	Therapeutic Use
Alcohol			
with D5/W[a]	5	4.5	Sedative, analgesic, calories
with D5/W in NSS[b]	5		Sedative, analgesic, calories
Amino Acid (Synthetic)			Fluid and nutrient replenisher
Aminosyn II (*Abbott*)	3.5; 7	5.25	
FreAmine III (*McGaw*)	8.5	6.6	
Travasol (*Baxter*)	3.5; 5.5; 8.5	6.0	
Ammonium Chloride	2.14	4.5–6.0	Metabolic alkaloids
Dextran 40			Priming fluid for extracorporeal circulation
in NSS	10	5	
in D5/W	10	4	Priming fluid for extracorporeal circulation
Dextran 70			
in NSS	6	5	Plasma volume expander
in D5/W	6	4	Plasma volume expander
Dextrose (Glucose, D5/W)	2.5–50	3.5–6.5	Fluid and nutrient replenisher
Dextrose and Sodium Chloride	Varying concn of dextrose from 5–20 with varying concn of sodium chloride from 0.22–0.9	3.5–6.5	Fluid, nutrient and electrolyte replenisher
Invert Sugar (Fructose and Dextrose)	5, 10	4.0	Fluid and nutrient replenisher
Lactated Ringer's (Hartmann's)		6.0–7.5	Systemic alkalizer; fluid and electrolyte replenisher
NaCl	0.6		
KCl	0.03		
$CaCl_2$	0.02		
Lactate	0.3		
Mannitol	5	5.0–7.0	Osmotic diuresis
also in combination with dextrose or sodium chloride	10 15 20		
Multiple electrolyte solutions varying combinations of electrolytes, dextrose, fructose, invert sugar		5.5	Fluid and electrolyte replacement
Ringer's		5.0–7.5	Fluid and electrolyte replenisher
NaCl	0.86		
KCl	0.03		
$CaCl_2$	0.033		
Sodium Bicarbonate	5	8	Metabolic acidosis
Sodium Chloride	0.45; 0.9; 3; 5	4.5–7.0	Fluid and electrolyte replenisher
Sodium Lactate	1/6 *M*	6.3–7.3	Fluid and electrolyte replenisher
Sterile Water for Injection		5.5	Diluent

[a] 5% Dextrose in water.
[b] Normal Saline Solution.

systems as well as the heart; magnesium, as a nutritional supplement especially in TPN solutions and phosphate ion, important in a variety of biochemical reactions. In addition to the number of standard electrolyte fluids shown in Table I, a large number of combinations of electrolytes in varying concentrations are available commercially. Some of these electrolyte fluids also contain dextrose.

Dextrose Injection 5% (D5/W) is the most frequently used IV fluid, either for nutrition or fluid replacement. It is isotonic and administered intravenously into a peripheral vein; 1 g of dextrose provides 3.4 cal and 1 L of D5/W supplies 170 cal. The body utilizes dextrose at a rate of 0.5 g per kg of body weight per hr. More rapid administration can result in glycosuria. Therefore, 1 L of D5/W requires 1½ hours for assimilation. The pH range of D5/W can vary from 3.5 to 6.5. The wide range permitted is due to the free sugar acids present and formed during the sterilization and storage of the injection. To avoid incompatibilities when other drug substances are added to Dextrose Injection, the possible low pH should be considered in using it as a vehicle. More concentrated solutions of dextrose are available and provide increased calorie intake with less fluid volume. Being hypertonic, the more concentrated solutions may be irritating to peripheral veins. Highly concentrated solutions are administered in a larger central vein. Other IV fluids used for intravenous admixtures and providing calories include solutions containing invert sugar. There is some evidence that fructose, unlike dextrose, may be used in diabetic patients; the 10% injection is hypertonic and provides 375 cal per L. Invert sugar consists of equal parts of dextrose and fructose; it is claimed that the presence of fructose promotes more rapid utilization of dextrose.

Intravenous fluids containing crystalline amino acids can provide biologically usable amino acids for protein synthesis (Chapter 51). Protein contributes to tissue growth, wound repair and resistance to infection. The protein requirement for the normal adult is 1 g per kg per day; children and patients under stress require greater amounts. Attempts are made to maintain a positive nitrogen balance, indicating that the protein administered is being utilized properly and

not broken down and eliminated through the urine as creatinine and urea, which are normal waste products. In a positive nitrogen balance patients are taking in more nitrogen than they are eliminating. In a negative nitrogen balance there is more nitrogen being eliminated through the urine regularly than is being administered intravenously. This means that tissues are continuing to be torn down and repair is not necessarily taking place. Amino Acid Injection can afford the total body requirements for proteins by the procedure known as TPN (discussed below) or be used for supplemental nutrition by peripheral administration. In addition to the amino acids, these nutritional injections also may contain dextrose, electrolytes, vitamins and insulin. Fat emulsion (*Intralipid*, Kabi Vitrum AB; *Liposyn II*, Abbott and *Travamulsion*; Travenol) sometimes is used concurrently but usually administered at another site.

Packaging Systems

Containers for intravenous fluids must be designed to maintain solution sterility, clarity (freedom from particulate matter) and nonpyrogenicity from the time of preparation, through storage and during clinical administration. Container closures must be designed to facilitate insertion of administration sets through which the injections are administered, at a regulated flow-rate, into suitable veins. IV fluids are available in glass and plastic containers; the latter may be made from either a flexible or semirigid plastic material. IV fluids are supplied in 1000-mL, 500-mL and 250-mL sizes in addition to 250-mL capacity containers packaged with 50 or 100 mL of D5/W or Sodium Chloride Injection for piggyback use. IV fluids in glass containers are packaged under vacuum, which must be dissipated prior to use. For fluid to leave the IV glass container and flow through the administration set, some mechanism is necessary to permit air to enter the container. Current flexible plastic systems do not require air introduction in order to function. Atmospheric pressure pressing on the container forces the fluid to flow.

All glass and plastic containers are single-dose and should be discarded after opening even if not used. Intravenous fluids are packaged with approximately 3% excess fill to allow for removal of air from the administration set and permit the labeled volume to be delivered from the container. The containers are graduated at 20-mL increments on scales that permit the volume in container to be determined either from an upright or inverted position. Glass containers have aluminum and plastic bands for hanging, while plastic containers have eyelet openings or plastic straps for attachment to IV poles.

Table II—IV Fluid Systems

Source	Container	Characteristics
Baxter	Glass	Vacuum Air tube
Baxter (*Viaflex*)	Plastic	Polyvinyl chloride Flexible Nonvented
McGaw	Glass	Vacuum Air tube
McGaw (*Accumed*)	Plastic	Polyolefin Semirigid
Abbott	Glass	Vacuum Air filter[a]
Abbott (*Lifecare*)	Plastic	Polyvinyl chloride Flexible Nonvented

[a] Part of administration set.

Fluids for IV use are available from three sources; all provide both glass and plastic containers. The glass-container systems of Baxter and McGaw are similar. The characteristics of current packaging systems are summarized in Table II.

Administration Sets

Administration sets used to deliver fluids intravenously are sterile, pyrogen-free and disposable. Although these sets are supplied by different manufacturers, each for its own system, they have certain basic components. These include a plastic spike to pierce the rubber closure or plastic seal on the IV container, a drip (sight) chamber to trap air and permit adjustment of flow rate and a length (150 to 450 cm) of polyvinyl chloride tubing terminating in a gum-rubber injection port. At the tip of the port is a rigid needle or catheter adapter. An adjustable clamp (screw or roller type) on the tubing pinches the tubing to regulate flow. Since the gum-rubber port is self-sealing, additional medication can be added to the IV system at these ports of entry. Glass containers that have no air tubes require air-inlet filters designed as part of the administration set (Abbott). See Figs 85-1 to 85-5.

Administration Procedures

In the administration of IV fluids, the primary IV container provides for fluid replacement, electrolyte replenishment,

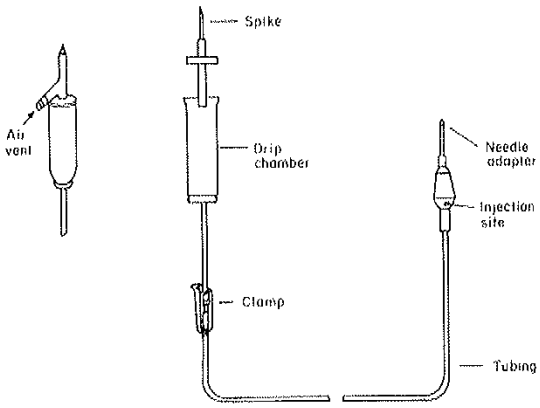

Fig 85-1. Parts of basic administration sets.

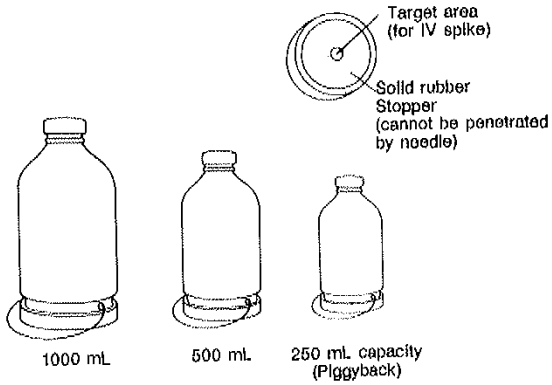

Fig 85-2. Abbott IV glass container. The air venting is provided through the air filter located in the spike of the administration set. See Fig 85-1.

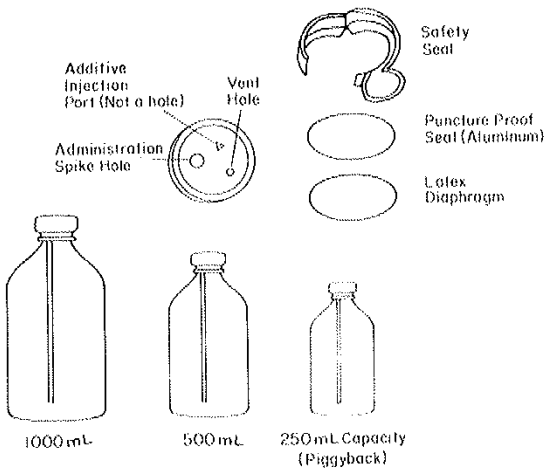

Fig 85-3. Baxter and McGaw glass containers. The plastic air tube allows the air to enter the bottle as the fluid is infused into the patient. The spike of the administration set is not vented. See Fig 85-1.

drug therapy or nutrition; the fluid can be infused over a 4- to 8-hr period. In some cases an IV fluid is infused slowly for the purpose of keeping the vein open (KVO). This will allow additional drugs to be administered when required. The primary IV fluid also can serve as a vehicle for other drugs to be administered, thus becoming an intravenous admixture (IV drip) and results in continuous blood levels of added drugs once the steady state has been reached.

In preparing an IV fluid for administration, the following procedure is used.

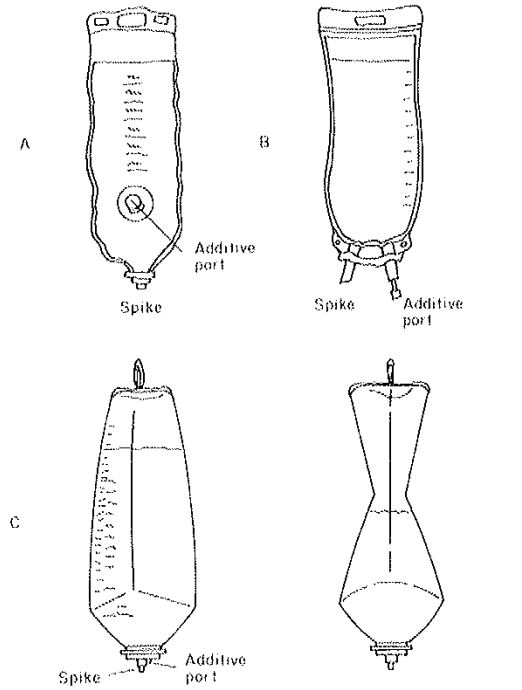

Fig 85-4. (A) Abbott (*Lifecare*) polyvinyl chloride flexible container; (B) Baxter (*Viaflex*) polyvinyl chloride flexible container; McGaw (*Accumed*) polyolefin semirigid container, front and side views. These containers take nonvented administration sets. See Fig 85-1.

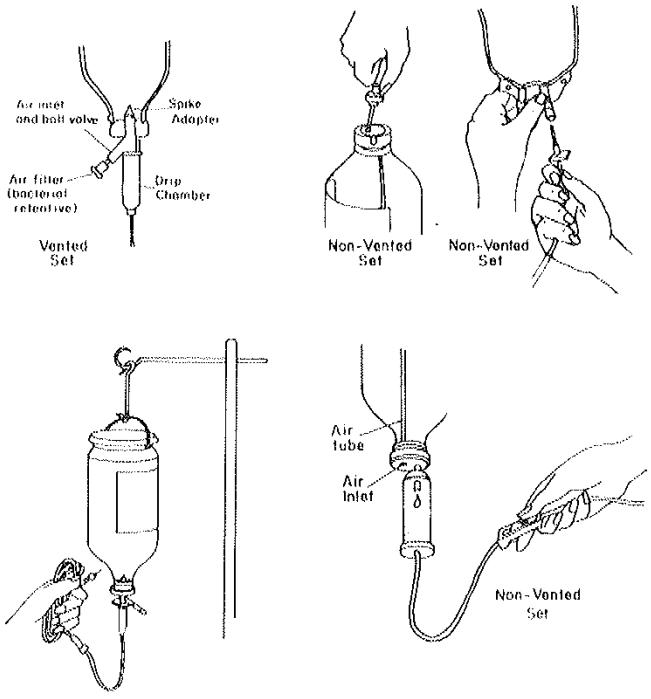

Fig 85-5. Setting up a primary IV fluid for administration.

1. The spike adapter of the administration set is inserted into the stopper or seal of the IV container. See Fig. 85-5.
2. The IV fluid is hung on a stand at bedside and air is purged from the administration set by opening the clamp until fluid comes out of needle. The tubing is then clamped off. See Fig 85-5.
3. The venipuncture is made by member of the IV team, floor nurse or physician.
4. The infusion rate is adjusted by slowly opening and closing the clamp until the desired drop rate, viewed in the drip chamber, is obtained. The usual running time is 4 to 8 hr (usually 125 mL are delivered in 1 hr). Drugs such as heparin, insulin, lidocaine or dopamine may be present in the IV drip. When potent drugs are present, the flow rates will vary depend on the clinical condition of the patient. Sets are calculated to deliver 10, 15, 20, 50 or 60 drops per mL depending on the manufacturer. See Fig 85-5.

Intermittent administration of an antibiotic and other drugs can be achieved by any of three methods: (1) direct intravenous injection (IV bolus or push), (2) addition of the drug to a predetermined volume of fluid in a volume-control device or (3) use of a second container (minibottle, minibag) with an already hanging IV fluid (piggybacking).

Direct Intravenous Injection—Small volumes (1 to 50 mL) of drugs are injected into the vein over a short period of time (1 to 5 min). The injection also can be made through a resealable gum-rubber injection site of an already hanging IV fluid. This method is suitable for a limited number of drugs but too hazardous for most drugs.

Volume-Control Method—Volume-control sets provide a means for intermittent infusion of drug solutions in precise quantities, at controlled rates of flow. These units consist of calibrated, plastic, fluid chambers placed in a direct line under an established primary IV container or more often attached to an independent fluid supply. In either case, the drug to be administered is first reconstituted if it is a sterile solid and injected into the gum-rubber injection port of the volume-control unit. It is then further diluted to 50 to 150 mL with the primary fluid or the separate fluid reservoir. Administration of the total drug-containing solution requires 30 to 60 min and produces a peak concentration in the blood followed by a valley if the dosage is discontinued. The following volume-control sets are available commercially: *Soluset*, Abbott; *Buretrol*, Baxter and *Metriset*, McGaw.

The procedure for setting up an intermittent IV infusion with a volume-control set is as follows:

Fig 85-6. Volume-control set.

1. Using aseptic technique, the spike of the volume-control set is inserted into the primary IV fluid or a separate fluid container. See Fig 85-6.
2. Air is purged from tubing of the volume-control set by opening the clamps until fluid comes through.
3. The clamp is opened above the calibrated chamber and it is filled with 25 to 50 mL fluid from the primary IV container or separate fluid container.
4. The clamp is closed above the chamber.
5. The medication is injected through the gum-rubber port of the volume-control unit.
6. The clamp above the chamber is opened to complete the dilution to the desired volume (50 to 150 mL), then closed.
7. Flow commences when the clamp below the volume-control unit is opened.

Piggyback Method—The piggyback method (Figs 85-7 and 85-8) refers to the intermittent IV drip of a second solution, the reconstituted drug, through the venipuncture site of an established primary IV system. With this setup

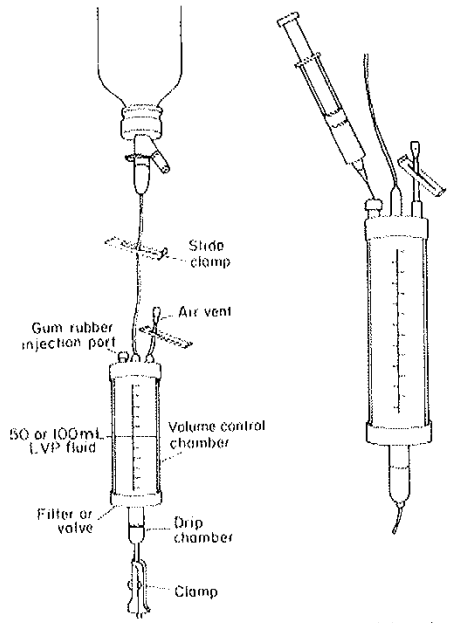

Fig 85-7. Piggyback method: the intermittent administration of a second solution through the venipuncture site of an established primary IV system.

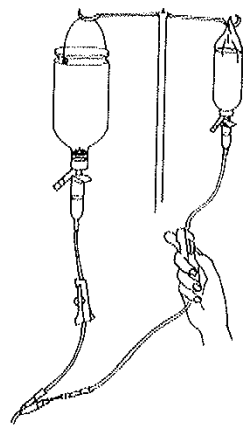

Fig 85-8. Piggyback administration setup.

the drug can be thought of as entering the vein on "top" of the primary IV fluid, hence the designation "piggyback." The piggyback technique not only eliminates the need for another venipuncture, but also achieves drug dilution and peak blood levels within a relatively short time span, usually 30 to 60 min. Drug dilution helps to reduce irritation, and early high serum levels are an important consideration in serious infection requiring aggressive drug therapy. These advantages have popularized the piggyback method of IV therapy, especially for the intermittent administration of antibiotics. In using the piggyback technique, the secondary unit is purged of air and its needle inserted into a Y-injection site of the primary set or into the injection site at the end of the primary set. The piggyback infusion is then started. Once it is completed, the primary fluid infusion will be restarted. See Fig 85-8.

Primary IV administration sets are available that have a built-in check valve for use in piggyback administration. When the piggyback is connected to one of these sets and started, the check valve automatically closes off the primary infusion. When the piggyback runs out, the check valve automatically opens, thereby restarting the primary infusion. The check valve works because of pressure differences. To achieve this difference, the primary container is hung lower than the secondary bottle by means of an extension hanger. See Fig 85-9.

Manufacturers have introduced minibottles prefilled with various antibiotic products; each container is provided with a plastic hanger for direct suspension from an IV pole as the piggyback solution is administered through the resealable gum-rubber injection site or Y-type facility of an existing IV system. Reconstitution of piggyback units requires only the addition of a small volume of compatible diluent. Since reconstitution and administration proceed from the same bottle, no drug transfer is involved, so transfer syringes and additional IV containers are not necessary. Prefilled drug containers offer significant advantages to hospitals. Time-saving, less potential for error and contamination and convenience are outstanding qualities of this type of packaging. The need exists in hospitals for these types of innovative packaging to help alleviate the critical nursing shortage and reduce the error potential. It is a significant event that drug manufacturers and intravenous fluid manufacturers have combined efforts to achieve optimal packaging for hospital use.

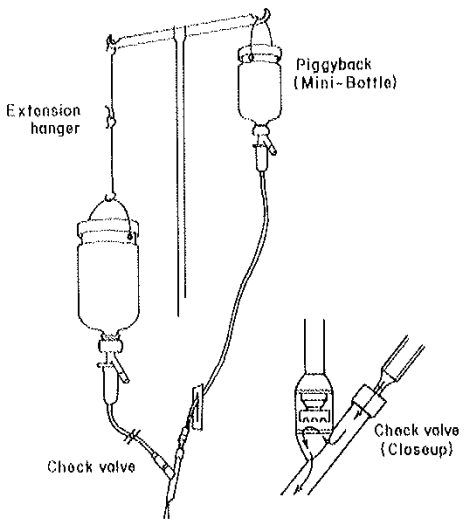

Fig 85-9. Piggyback administration setup with check valve in primary set.

Partial-fill containers available for piggybacking are 250-mL capacity infusion bottles or bags underfilled with 50 or 100 mL D5/W or normal saline. The drug to be administered first is reconstituted in its original parenteral vial and then added by needle and syringe to the partial-fill container. The needle of the piggyback delivery system is inserted into the Y-site or gum-rubber injection port of a hanging primary infusion set. Flow of the primary intravenous fluid is stopped while the drug solution in the partial-fill container is administered (30 to 60 minutes). After the drug solution has been infused totally, the primary fluid flow is reestablished. When the next dose of drug is required, the piggyback procedure is repeated, replacing the prefilled partial-fill container.

Mechanical-Electronic Infusion Devices—Gravity IV administration systems are affected by many variables which tend to alter the accuracy of the system. These include variations in the size of the drip-chamber orifice, the viscosity of the solution being administered, plastic cold flow, clamp slippage, final filters, variations in the patient's blood pressure and body movements, clot formation, pressure changes in IV containers rate of flow, temperature of the IV fluid, changes in the needle, and other factors such as kinked tubing, extravasation and changes in the height of the IV container. Flow in traditional gravity IV systems is controlled by manual clamps (either screw or roller clamps) which can provide considerable discrepancies in volume delivery. These factors have promoted the development and use of mechanical-electronic infusion devices to control more accurately the administration of IV fluids. This group of devices includes infusion controllers and infusion pumps.

Infusion controllers count drops electronically or extrude volumes of fluid mechanically and electronically. Having no moving components, controllers are less complex than pumps, being usually less expensive and having fewer maintenance problems. Infusion controllers are gravity-type systems, but the control is regulated automatically rather than manually. In addition to increasing the accuracy of delivery, electronic equipment may be able to detect infiltration of air, empty containers and excess or deficient flow.

Infusion pumps do not depend on gravity to provide the pressure required to infuse the drug. Pressure is provided by an electric pump that propels a syringe, a peristaltic or roller device or a cassette. Most pumps are volumetric in that the delivery is measured in milliliters rather than drops.

The quality of patient care has improved with the use of infusion devices. Flow rates can be maintained, therefore parenteral and enteral nutrition can be conducted safely. In addition, accurate drug therapy can be accomplished with adults and children and "runaways" of IV fluid administration can be eliminated.

Final-Filter Devices—Particulate matter in IV fluids and IV admixtures can originate from many sources. It can result from the packaging components of the IV fluid, from admixture incompatibilities, from manipulation in preparing the admixture and even from the administration set itself. Concern for particulate matter led to the design of final-filter devices for attaching to the end of the tubing of the administration set. They afford a final filtration of the IV fluid before it passes through the needle into the vein. The device consists of a plastic chamber containing a membrane or stainless-steel filter having porosities varying from 5 to 0.22 μm. Air lock can be a problem with membrane filters. When wet, membranes with a porosity of 0.22 μm and 0.45 μm are impervious to air at normal pressures and air in the system causes blockage. In order to prevent this, the filter housing must be purged completely of air prior to use. Newer designs have air eliminators. Using final-filter de-

vices increases medication cost but reduces the biological hazards associated with particulate matter.

Although considerable information is available concerning the clinical use of membrane filters in entrapping particulate matter and microorganisms, little information exists describing drug absorption by the filter. Literature on a limited number of drugs and filter materials indicates that drugs administered in low doses might present a problem with drug bonding to the filter.[1] Solutions containing minute dosages of drugs, 5 mg or less, should not be filtered until sufficient data are available to confirm insignificant absorption. Drugs not recommended to be filtered include all parenteral suspensions, blood and blood products, amphotericin B, digitoxin, insulin, intravenous fat emulsions, mithramycin, nitroglycerin and vincristine.

New IV Delivery Systems—

Frozen Premixes—Underway by Baxter is the delivery to hospitals of frozen drug products packaged in polyvinyl chloride containers. These are stored in a freezer in the hospital's pharmacy, thawed and used when needed.

Faspak/ADS-100 System—Eli Lilly supplies a non-PVC plastic piggyback container, named Faspak, which contains the dry, powdered form of certain drugs (Keflin, Kefzol, Mandol and ampicillin) which, upon reconstitution with the appropriate diluent, allows direct administration of the diluted drug. This avoids a transferring step that normally takes place when reconstituting a powdered drug. To help in the reconstitution step, a specialized dilution pump named the ADS-100 system is supplied. The package design eliminates the need for transferring between containers after reconstitution, and the Faspak acts as a final delivery container.

Abbott/ADD-Vantage System—Introduced in 1985, the Abbott ADD-Vantage system has two parts: a plastic IV bag sold by Abbott that is filled with solution and a separate glass vial of powder or liquid drug sold by a pharmaceutical manufacturer. The vial is encased by a plastic cover that is removed prior to use. The user locks the vial holding the drug into a chamber at the top of the plastic bag and mixes the drug and solution by externally removing the stopper on the vial.

Nutrimix—A Dual-Compartment container is available from Abbott. This container allows for long-term packaging of amino acids and dextrose mixtures.

IVAC-CRIS—The IVAC-Cris (Controlled-Release Infusion System) is a disposable adapter designed to infuse reconstituted injectable drugs directly from the manufacturer's single-dose vial. The CRIS adapter avoids the need to transfer drug doses to piggyback secondary containers and also eliminates the need for a secondary IV set. The adapter has a primary spike that is inserted into the IV fluid container and a secondary spike that receives the drug vial. The vial spike has two fluid paths: one admits IV fluid from the primary container into the vial; the other drains drug solution into the drip chamber of the IV set. A two-position valve allows IV fluid to flow directly from the primary container to the patient or pass through the vial to deliver the drug. A 5 μm in-line filter eliminates particulates.

To operate the CRIS adapter, the drug vial first is reconstituted with an appropriate diluent. With the valve dial in the vertical (primary) position, the spike shield is removed and the vial is attached immediately to the CRIS spike. The valve dial is then turned toward the vial, directing the flow of primary fluid into the vial of drug solution. The incoming fluid dilutes and displaces the drug solution into the drip chamber, through the primary set and into the patient. After the dose has been delivered, the vial remains on the spike until the next dose is required. Flow rate can be adjusted using a roller clamp, electronic pump or controller.

Mini-Infuser Pumps for Intermittent IV Drug Delivery—A novel concept in intermittent drug delivery, introduced several years ago, was the Bard-Harvard Mini-Infuser System. This instrument was designed for the administration of antibiotics and other medications delivered intermittently in 40 min or less. This battery-generated, lightweight instrument uses standard disposable syringes and microbore disposable extension sets. Different models are available, depending on volume-to-be-delivered selection. This instrument provides accuracy, constant flow, convenience and safety for intermittent drug delivery.

Introduced and designed for intermittent IV drug delivery, Becton Dickinson's 360 Infusor allows drug delivery intermittently over 60 min or less in a volume dilution of up to 60 mL.

Implantable Devices—The Infuse-A-Port (*Pharmacia Deltec*) was developed to satisfy the need for repeated access to the peripheral or central venous system or direct placement into an artery for regional therapy. This device may be used to withdraw blood, in addition to its use for bolus injections and short-term infusions. The Infuse-A-Port requires a special needle to allow maximum life of the self-sealing injection port.

The Infusaid Model 400 implantable drug delivery system is designed for long-term therapy in the ambulatory patient. With a 47-mL usable drug volume, it delivers a precise, continuous flow to a selected organ or site via a soft, nontraumatic, nonthrombogenic silicone rubber catheter.

Intravenous Admixtures

When one or more sterile products are added to an IV fluid for administration, the resulting combination is known as an IV admixture. To maintain the characteristics of sterile products, namely sterility, freedom from particulate matter and pyrogens, it is imperative that they be manipulated in a suitable environment using aseptic techniques.

Environment—Proper conditions for aseptic handling can be provided by laminar-flow hoods (see Chapters 78, 84). Within a laminar-flow hood, air filtered through a HEPA (high efficiency particulate air) filter moves in a parallel flow configuration at a velocity of 90 fpm. HEPA filters remove 99.97% of all particles larger than 0.3 μm. Since microbial contaminants present in air usually are found on other particulates, removal of the latter results in a flow of air free of both microbial contaminants and particulate matter. The movement of the filtered air in a laminar-flow configuration at a velocity of 90 fpm can maintain the area free of contamination. The flow of air may be in either a horizontal or vertical pattern. In the former case the HEPA filter is located at the back of the hood and the air flows to the front. In vertical flow the air passes through the HEPA filter located in the top of the cabinet and is exhausted through a grated area around the working surface of the hood. Regardless of the type of laminar air flow, the hood must be operated and maintained properly in order to achieve a satisfactory environment for the preparation of parenteral admixtures.

The hood is situated best in a clean area in which there is little traffic flow past the front of the hood. The inside of the hood is wiped down thoroughly with a suitable disinfectant and allowed to run for at least 30 min before starting manipulations. It is important to remember that the laminar-flow hood is not a means of sterilization. It only maintains an area free of microbial contaminants and particulate matter when it has been prepared, maintained and utilized properly by operators having proper aseptic techniques.

Before working in a laminar-flow hood the operator washes his hands thoroughly and scrubs them with a suitable disinfectant. Some laboratories may require gowning and

using sterile gloves. Sterile gloves can be an asset but there is always the problem that they can give the operator a false sense of security. Gloved hands can become contaminated as easily as ungloved hands. Additives and IV fluids to be used in the preparation of the admixture, along with suitable syringes, are lined up in the hood in the order they are to be used. The containers must be clean and dust-free. They are inspected for clarity and freedom from cracks. Operators are encouraged to use a lighting device for inspecting IV fluids for particulate matter and cracks. The lighting device should permit the container to be viewed against both a light and a dark background during inspection. If the IV fluid is packaged in plastic containers, pressure is applied to assure that they are sealed properly and do not leak. Some laboratories disinfect the containers prior to placing them in the hood.

In working within the hood the operator works in the center of the hood, with the space between the point of operation and the filter unobstructed. If the flow of air is blocked, the validity of the laminar flow is destroyed. Articles are arranged within the hood in a manner to prevent clean air from washing over dirty objects and contaminating other objects that must remain sterile. The working area must be at least 6 inches from the front edge of the hood. As the operator stands in front of the hood, his body acts as a barrier to the laminar air flow causing it to pass around him and create backflow patterns which can carry room air into the front of the hood.

Laminar-flow hoods must be maintained and evaluated periodically to insure that they are functioning properly. The velocity of air flow can be determined routinely using a velometer. A decrease in the air flow usually indicates a clogged HEPA filter. Some laminar-flow hoods are equipped with pressure gauges indicating pressure in the plenum behind the filter; in these hoods pressure increase also can indicate a clogged filter. Settling plates can be exposed within the hood for given periods of time to determine the presence of microbial contaminants.

The best way to determine the proper functioning of a HEPA filter is to use the dioctyl phthalate (DOP) test using the vapor at room temperature. DOP vapor (particles of ~0.3 μm) is allowed to be taken up by the hood through its intake filter. If the HEPA filter is intact and properly installed, no DOP can be detected in the filtered air stream using a smoke photometer. Certification services are available through commercial laboratories; the HEPA filters within laminar-flow hoods should be evaluated every 6 months.

Additives—The additives are injections packaged in ampuls or vials, or sterile solids; the latter are reconstituted with a suitable diluent before addition to the IV fluid. A fresh, sterile, disposable syringe is used for each additive. Before removing a measured volume from an ampul, the container is wiped with a disinfectant solution. If the ampul is scored, the top can be snapped off; if not scored, an ampul file must be used. A sterile syringe is removed from its protective wrapping. The syringe needle with its cover is separated from the syringe aseptically and may be replaced with a sterile aspirating needle. Aspirating needles usually are made from clear plastic and contain a stainless-steel or nylon filter having a porosity of 5 μm. The filter will remove glass particles and other particulates from the injection as it is drawn up from the ampul into the syringe. The aspirating needle is replaced with the regular needle. The exact volume is calibrated and the injection is ready to be added to the IV fluid (see Fig 85-10). In the case of additives packaged in multiple-dose vials, the protective cover is removed and the exposed target area of the rubber closure disinfected. A volume of air, equal to the volume of solution to be removed, is drawn up into the syringe and injected into the air space above the injection within the vial. This facilitates withdrawal of the injection. The solution is drawn into the syringe, the exact dose is measured and the injection is ready to be added to the IV fluid.

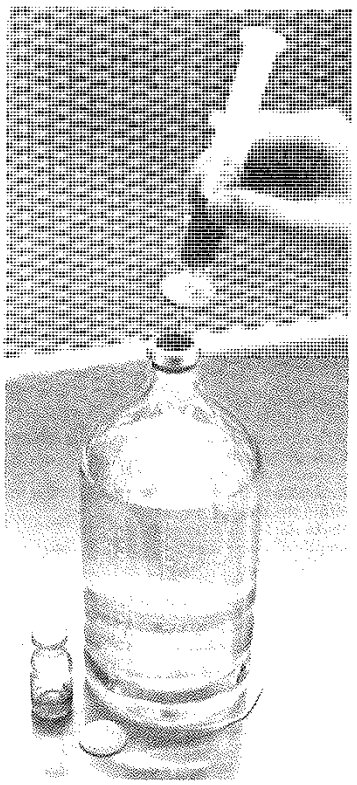

Fig 85-10. Placing an additive into an IV fluid with filtration through a membrane filter (courtesy, Millipore).

Certain injections are light-sensitive and protected against photolysis by the container packaging. The manufacturer may use amber glass, individual container wrapping or an amber plastic cover. Many hospital pharmacists use aluminum foil as a protective wrap for light-sensitive drugs during their administration.

In the case of drug substances having poor stability in aqueous solution, the drug is packaged as a sterile solid, either dry-filled or lyophilized. The diluent recommended on the labeling is used to reconstitute the powder; the proper quantity of solution then is removed for addition to the IV fluid. When large volumes of diluent are required for reconstitution, as for Keflin 4 g, a sterile needle is placed through the closure to vent the container and facilitate addition of the diluent. In order to increase the efficiency of IV admixture programs, a limited number of hospital pharmacists have found it convenient to freeze reconstituted drugs, particularly antibiotics. The stability of reconstituted drugs is somewhat limited. In some cases stability is limited to only a few hours; in many cases, however, reconstituted solutions can be frozen and thawed at the time of use. In the frozen form the stability of the antibiotic solution can be increased. In a number of instances the stability in the frozen form is known and supplied by the manufacturer. Reports have been published on the frozen stability of certain drugs. However, it is unwise to freeze drug solutions without adequate stability studies for guidance. In those cases where published information is available, close adherence must be

observed as to freezing temperature, storage conditions and packaging.

There is an increasing awareness of the potential hazard to pharmacists handling antineoplastic drugs.[2] Although the evidence is not conclusive, it appears that measures should be taken to minimize unnecessary exposure.[3] These precautions include the use of vertical laminar-flow hoods for the preparation and reconstitution of these agents, the wearing of gloves and masks by the personnel, special labeling of the containers to insure their proper handling and disposal and periodic blood studies of personnel involved in preparing admixtures of antineoplastic agents.

The procedure for placing an additive in an IV fluid will vary depending on the type of IV fluid packaging system being used by the hospital. The packaging systems have been described in Table II.

Abbott Glass Containers (Fig 85-2)

1. Remove the aluminum tear seal exposing the solid-rubber closure with a target circle in the center.
2. Wipe the closure with suitable disinfectant.
3. Insert the needle of the additive syringe through the target area. The vacuum within the bottle draws in the solution.
4. Gently shake the bottle after each addition.
5. When completed, cover the closure with a plastic protective cap if it is not to be used immediately.

Baxter and McGaw Rigid Glass Containers (Fig 85-3)

1. Remove the aluminum tear seal and the aluminum disc covering the latex diaphragm.
2. Upon exposing the latex diaphragm, note that the latex cover is drawn in over the openings in the rubber closure.
3. The larger of the two holes receives the administration set, the other is the air vent. The triangle-shaped indentation can serve as the site for injecting the additives as well as the opening for the administration set.
4. Wipe the diaphragm with a suitable disinfectant and pierce the latex cover to place additive into bottle. The vacuum within the bottle will draw additive from the syringe. Do not remove the diaphragm or the vacuum will dissipate. It will be removed at the time of administration prior to the insertion of the administration set.
5. Gently shake the bottle after each additive.
6. When completed, cover the bottle with a plastic additive cap if the administration set is not to be inserted immediately.

Baxter and Abbott Plastic Container (Fig 85-4)

1. Remove the additive port protective sleeve and rub the gum-rubber plug with a suitable disinfectant.
2. Additives are placed in container by piercing the gum-rubber cover over the additive port.
3. After each addition, milk the container to insure adequate mixing.
4. Containers do not contain a vacuum, but vacuum chambers are available for use in conjunction with the flexible plastic container.
5. Protective additive caps are available if the administration set is not inserted immediately.

McGaw Semirigid Plastic Container (Fig 85-4)

1. Remove the additive port protective covering and rub the gum-rubber plug with a suitable disinfectant.
2. Additives are placed in containers by piercing the gum-rubber over the additive port.
3. After each addition, shake the container gently to insure adequate mixing.
4. Containers do not contain a vacuum.

Parenteral Incompatibility—When one or more additives are combined with an IV fluid, their presence together may modify the inherent characteristics of the drug substances present, resulting in a parenteral incompatibility. Parenteral incompatibilities have been divided arbitrarily into three groups: physical, chemical and therapeutic. The latter is the most difficult to observe because the combination results in undesirable antagonistic or synergistic pharmacologic activity. For example, the report that penicillin or cortisone antagonizes the effect of heparin and produces a misleading picture of the anticoagulant effect of heparin represents a therapeutic incompatibility. Physical incompatibilities are observed most easily and can be detected by changes in the appearance of the admixture, such as a change in color, formation of a precipitate or evolution of a gas. Physical incompatibilities frequently can be predicted by knowing the chemical characteristics of the drugs involved. For example, the sodium salts of weak acids, such as phenytoin sodium or phenobarbital sodium, precipitate as free acids when added to intravenous fluids having an acidic pH. Calcium salts precipitate when added to an alkaline medium. Injections that require a special diluent for solubilization, such as diazepam, precipitate when added to aqueous solutions because of their low water solubility.

Decomposition of drug substances resulting from combination of parenteral dosage forms is called a chemical incompatibility, an arbitrary classification since physical incompatibilities also result from chemical changes. Most chemical incompatibilities result from hydrolysis, oxidation, reduction or complexation and can be detected only with a suitable analytic method.

An important factor in causing a parenteral incompatibility is a change in the acid-base environment.[4] The solubility and stability of a drug may vary as the pH of the solution changes. A change in the pH of the solution may be an indication in predicting an incompatibility, especially one involving drug stability, since this is not necessarily apparent physically. The effect of pH on stability is illustrated in the case of penicillin. The antibiotic remains active for 24 hr at pH 6.5, but at pH 3.5 it is destroyed in a short time. Potassium penicillin G contains a citrate buffer and is buffered at pH 6.0 to 6.5 when reconstituted with Sterile Water for Injection, Dextrose Injection or Sodium Chloride Injection. When this reconstituted solution is added to an intravenous fluid such as Dextrose Injection or Sodium Chloride Injection, the normal acid pH of the solution is buffered at pH 6.0 to 6.5, thus assuring the activity of the antibiotic.

While it may be impossible to predict and prevent all parenteral incompatibilities, their occurrence can be minimized. The IV admixture pharmacist should be cognizant of the increasing body of literature concerning parenteral incompatibilities. This includes compatibility guides published by large-volume parenteral manufacturers,[5-7] compatibility studies on individual parenteral products by the manufacturer and published with the product as part of the labeling, the study of the National Coordinating Committee on Large-Volume Parenterals,[8] reference books[9,10] and literature reports of studies with specific parenteral drugs.[11] The pharmacist should encourage the use of as few additives as possible in IV fluids since the number of potential problems increases as the number of additives increases. Physicians should be made aware of possible incompatibilities and the pharmacist can suggest alternate approaches to avoid the difficulties. In some instances, incompatibilities can be avoided by selecting another route of administration for one or more of the drugs involved.

Quality Control—Each hospital should have written procedures covering the handling and storage, use in preparing admixtures, labeling and transportation of IV fluids to the floors. In-use clarity and sterility tests should be devised to assure that IV admixtures retain the characteristics of sterility and freedom from particulate matter. Training and monitoring personnel involved in preparation of IV admixtures should be done on a regular basis.[12] The efforts of the hospital pharmacy should be no less than those of the industry in following Current Good Manufacturing Practice to assure the safety and efficacy of these compounded medications.

Total Parenteral Nutrition

Intravenous administration of calories, nitrogen and other nutrients in sufficient quantities to achieve tissue synthesis and anabolism is called total parenteral nutrition (TPN).[13]

Originally, the term hyperalimentation was used to describe the procedure, but it is being replaced by TPN, the latter being more descriptive for the technique.

The normal caloric requirement for an adult is approximately 2500 per day. If these were to be provided totally by D5/W, approximately 15 L would be required. Each liter contains 50 g dextrose, equivalent to 170 calories. However, it is only possible to administer 3 or 4 L per day without causing fluid overload. To reduce this fluid volume the concentration of dextrose would have to be increased. By increasing the dextrose to 25%, it is possible to administer five times the calories in one-fifth the volume. D25/W is hypertonic and cannot be administered in large amounts into a peripheral vein without sclerosing the vein.

Dudrick developed the technique for administering fluids for TPN by way of the subclavian vein into the superior vena cava where the solution is rapidly diluted by the large volume of blood available, thus minimizing the hypertonicity of the solution. For administration of the TPN fluids, a catheter is inserted and retained in place in the subclavian vein. TPN is indicated in patients who are unable to ingest food due to carcinoma or extensive burns; patients who refuse to eat, as in the case of depressed geriatrics or young patients suffering from anorexia nervosa and surgical patients who should not be fed orally.

The preferred source for calories in TPN fluids is the carbohydrate dextrose. Both fat emulsions and alcohol are caloric sources, but they are not used in TPN fluids. In IV fluid kits commercially available for the preparation of TPN solutions, D50/W is provided. On dilution with amino acid injection, the resulting dextrose concentration is approximately 25%. It is this concentration that is administered.

The source of nitrogen in TPN fluids is crystalline amino acids (*Aminosyn*, Abbott; *FreAmine III*, McGaw; *Travasol*, Travenol). The crystalline amino acid injections contain all the essential and nonessential amino acids in the L-form. For optimum utilization of amino acids and for promoting tissue regeneration, the nitrogen-to-calorie ratio should be 1:150. Calories are needed to provide energy for the metabolism of nitrogen.

Electrolyte requirements vary with the individual patient. The electrolytes present in Amino Acid Injection are given

Table III—Typical IV Orders (Parenteral Prescriptions)

Prescription	Comment
1. ℞ NSS 1000 mL 125 mL/hr	Sodium Chloride Injection (Normal Saline Solution) 1000 mL, is to be administered at a flow rate of 125 mL per hr. It will require approximately 8 hr.
2. ℞ 1000 D5 + NSS + Vits 12 hr	Dextrose Injection 5%, 1000 mL, containing 0.9% sodium chloride and container of vitamin B complex with vitamin C is to be administered over a 12-hr period.
3. ℞ 500 D5 + ½NSS KVO	Dextrose Injection 5%, 500 mL, containing 0.45% sodium chloride is to be administered at a flow rate to keep the vein open (KVO). The flow rate will be approximately 10 mL per 1 hr.
4. ℞ 1000 cc D5 + ½NSS Add 1 amp Vits to each + 100 mg Thiamine Each to run 6 hr	Dextrose Injection 5%, 1000 mL, containing 0.45% sodium chloride, the contents of one ampul vitamin B complex with vitamin C and sufficient volume of Thiamine Hydrochloride Injection to give 100 mg thiamine, is to be administered over a 6-hr period (approximately 170 mL per hr). Additional orders of the same can be anticipated.
5. ℞ 1000 cc D5 + ½NSS + 20 mEq KCl	Dextrose Injection 5%, 1000 mL, is to be provided containing 0.45% sodium chloride and 20 mEq potassium chloride.
6. ℞ 1000 Hyperal + 10 NaCl + 10 KCl + 5 $MgSO_4$ + 10 Insulin	One L of the hospital's basic TPN solution is to be provided with the addition of 10 mEq sodium chloride, 10 mEq potassium chloride, 5 mEq magnesium sulfate and 10 units regular zinc insulin.
7. ℞ 1000 cc Hyperal (FreAmine) + 40 mEq $NaHCO_3$ + 30 mEq KCl + Vits + 5U Reg Insulin to run 80 cc/hr	One L of the basic TPN solution, FreAmine II, is to be provided with the addition of 40 mEq $NaHCO_3$, 30 mEq potassium chloride, the contents of one container vitamin B complex with vitamin C plus 5 units of regular zinc insulin. It is to be administered at the flow rate of 80 mL per hr (approximately 12 hr).
8. ℞ 1000 Hyperal + 40 mEq NaCl + 10 KCl + 10 Insulin + 10 Cal Gluconate	One L of the hospital's basic TPN solution is to be provided with the addition of 40 mEq sodium chloride, 10 mEq potassium chloride, 10 units regular zinc insulin and 10 mL Calcium Gluconate Injection.
9. ℞ Keflin 2 g + 100 mL D_5W q 6 hr	Cephalothin, 2 g, is reconstituted with Sterile Water for Injection and added to a minibottle containing 100 mL Dextrose Injection 5%. This dose is given every 6 hr using a piggyback technique with a flow rate requiring 30 to 60 min for delivery.
10. ℞ Gentamicin 80 mg IVPB q 8 hr	Gentamicin, 80 mg, is added to a minibottle containing 100 mL Dextrose Injection 5%. This dose is given every 8 hr using the piggyback technique (IVPB) with a flow rate requiring at least 80 min (not less than 1 mg per min).

on the label and must be taken into consideration in determining the quantities to be added. Usual electrolyte concentrations are required to fall within the following ranges: sodium, 100–120 mEq; potassium, 80–120 mEq; magnesium, 8–16 mEq; calcium, 5–10 mEq; chloride, 100–120 mEq and phosphate, 40–60 mEq. It is better to keep a 1:1 ratio between sodium and chloride ions. In adding potassium, the acetate salt is preferred to the chloride. If the combination of calcium and phosphate ions exceeds 20 mEq, precipitation occurs.

In addition to the electrolytes, the daily requirement for both water-soluble and fat-soluble vitamins may be added, usually in the form of a multivitamin infusion concentrate. Iron, should be administered separately from the TPN fluids. Trace elements such as zinc, copper, manganese and iodide are a concern only in long-term cases and can be added when required.

The Parenteral Prescription

The physician writes an admixture order or parenteral prescription on a physician's order-form located on the patient's chart. A copy of the order is sent to the pharmacy for compounding. It includes the patient's name, room number, the intravenous fluid wanted, additives and their concentrations, rate of flow, starting time and length of therapy. The order is taken by the technician, nurse or pharmacist to the pharmacy. Orders may be telephoned to the pharmacy; verification with the original order is made on delivery of the admixture. IV orders usually are written for a 24-hour therapy period; the patient's chart is reviewed and new orders are written on a daily basis. The order may be for multiple containers, in which case the containers are numbered consecutively. Unlike the extemporaneously compounded prescription, additives are added without regard to final volume of IV fluid. The prescription is checked for proper dose, compatibility, drug allergies and stability. Additives usually are given an expiration period of 24 hours from the time of preparation. Drugs such as ampicillin may require shorter expiration periods.

The clerical work for the admixture is prepared. This includes typing of the label and the preparation of the profile worksheet. The profile sheet is filed so that the pharmacist will be alerted when subsequent containers are due for preparation. Charging the patient's account can be done from the profile worksheet. The label includes the patient's name, room number, bottle number, preparation date, expiration time and date, intravenous fluid and quantity, additives and quantities, total time for infusion, the milliliters per hour or drops per minute and space for the name of the nurse who hangs the container. The label will be affixed to the container upside down in order that it can be read when hung.

The admixture is prepared by the pharmacist or a supervised technician. In handling sterile products, aseptic techniques as discussed previously must be observed. When completed, a plastic additive cap is affixed before delivery to the floor. The label is applied and checked with the original order. The empty additive containers are checked to confirm the additives present. The admixture is inspected for any color change or particulate matter.

The completed admixture is delivered to the floor. If it is not to be infused immediately (within 1 hour), it is stored under refrigeration; if refrigerated, it must be used within 24 hours. The nurse checks for accuracy of patient's name, drug and concentration, IV fluid, expiration date, time started and clarity. The infusion of admixtures may run ahead or behind schedule, necessitating that the pharmacist modify the preparation of continued orders. Examples of IV orders are shown in Table III.

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CHAPTER 87

Medicated Applications

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The application of medicinal substances to the skin or various body orifices is a concept doubtless as old as humanity. The papyrus records of ancient Egypt describe a variety of such medications for external use. Galen described the use in Roman times of a forerunner to today's vanishing creams.

Medications are applied in a variety of forms reflecting the ingenuity and scientific imagination of pharmacists through the centuries. New modes of drug delivery have been developed to remedy the shortcomings of earlier vehicles or, more recently, to optimize drug delivery. Conversely, some external medications have fallen into disuse because of changes in the practice of medicine.

Medications are applied to the skin or inserted into body orifices in liquid, semisolid or solid form. Ophthalmic ointments and topical aerosol products will not be discussed in this chapter. Ophthalmic use imposes unusual particle size, viscosity and sterility specifications that require separate, detailed discussion (see Chapter 86). The complexity of pharmaceutical aerosol systems necessitates their inclusion elsewhere (see Chapter 92).

Epidermal and Transdermal Drug Delivery

The Skin

The skin often has been referred to as the largest of the body organs: an average adult's skin has a surface area of about 2 m^2. It is probably the heaviest organ of the body. Its accessibility and the opportunity it affords to maintain applied preparations intact for a prolonged time have resulted in its increasing use as a route of drug administration, whether for local, regional or systemic effects.

Anatomically, human skin may be described as a stratified organ with three distinct tissue layers: the epidermis, the dermis and the subcutaneous fat layer (Fig 87-1).

Epidermis, the outermost skin layer, comprises stratified squamous epithelial cells. Keratinized, flattened remnants of these actively dividing epidermal cells accumulate at the skin surface as a relatively thin region (about 10 μm thick) termed the stratum corneum, or horny layer. The horny layer is itself lamellar with the keratinized cells overlapping one another and compressed into about 15 layers. The region behaves as a tough but flexible coherent membrane. The stratum corneum also is markedly hygroscopic—far more so than other keratinous materials such as hair or nails. Immersed in water the isolated stratum corneum swells to about three times its original thickness, absorbing about four to five times its weight in water in the process. The stratum corneum functions as a protective physical and chemical barrier and is only slightly permeable to water. It retards water loss from underlying tissues, minimizes ultraviolet light penetration and limits the entrance of microorganisms, medications and toxic substances from without. The stratum corneum is abraded continuously. Thus, it tends to be thicker in regions more subject to abrasion or the bearing of weight. Its regeneration is provided by rapid cell division in the basal cell layer of the epidermis. Migration or displacement of dividing cells towards the skin surface is accompanied by differentiation of the epidermal cells into layers of flat, laminated plates, as noted above. An acidic film (pH ranging between 4.0 and 6.5, depending on the area tested) made up of emulsified lipids covers the surface of the stratum corneum.

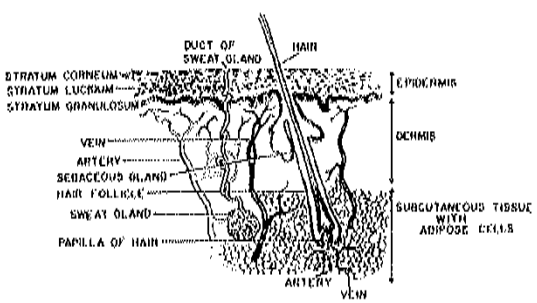

Fig 87-1. Vertical section of human skin.

The dermis apparently is a gel structure involving a fibrous protein matrix embedded in an amorphous, colloidal, ground substance. Protein, including collagen and elastin fibers, is oriented approximately parallel to the epidermis. The dermis supports and interacts with the epidermis facilitating its conformation to underlying muscles and bones. Blood vessels, lymphatics and nerves are found within the dermis, though only nerve fibers reach beyond the dermal ridges or papillae into the germinative region of the epidermis. Sweat glands and hair follicles extending from the dermis through the epidermis provide discontinuities in an otherwise uniform integument.

The subcutaneous fat layer serves as a cushion for the dermis and epidermis. Collagenous fibers from the dermis thread between the accumulations of fat cells providing a connection between the superficial skin layers and the subcutaneous layer.

Hair Follicles and Sweat Glands—Human skin is sprinkled liberally with surface openings extending well into the dermis. Hair follicles, together with the sebaceous glands that empty into the follicles, make up the pilosebaceous unit. Apocrine and eccrine sweat glands add to the total.

Pilosebaceous Unit—Human hair consists of compacted keratinized cells formed by follicles. Sebaceous glands empty into the follicle sites to form the pilosebaceous unit. The hair follicles are surrounded by sensory nerves; thus, an important function of human hair is sensory. Human hair varies enormously within the same individual, even within the same specific body area. Individual hairs can vary in microscopic appearance, diameter, cuticle appearance and even presence or absence of medulla.

Sebaceous glands are similar anatomically and functionally but vary in size and activity according to location. Popu-

Table I—Composition of Sebum

Constituents	Percent w/w
Triglycerides	57.5
Wax Esters	26.0
Squalene	12.0
Cholesterol Esters	3.0
Cholesterol	1.5

lation in the scalp, face and anogenital areas may vary from 400 to 900/cm^2. Fewer than 100/cm^2 are found in other areas. Sebaceous glands are richly supplied with blood vessels.

Sebaceous cells synthesize and accumulate lipid droplets. This accumulation results in enlarged cells which fragment to form sebum. Sebum is made up of a mixture of lipids, approximately as shown in Table I.

The sebaceous gland, containing sebum, cell debris and microorganisms such as *Propionibacterium acnes*, is connected to the pilosebaceous canal by a duct of squamous epithelium. When access to the surface is blocked and bacteria multiply, the result is the comedo of acne.

Sebum presumably functions as an emollient, although Kligman once stated it was useless. Montagna suggests that sebum functions as a pheromone to provide the human with a distinctive aroma.

Sweat Glands—Sweat glands are classified as apocrine and eccrine. Apocrine glands are secretory but are not necessarily responsive to thermal stimulation. Such glands do not produce sweat in the normal sense of the word. Apocrine glands, however, often are associated with eccrine sweat glands particularly in the axilla.

Eccrine sweat glands are coiled secretory glands, equipped with a blood supply, extending from the dermis to the epidermal surface. Eccrine sweat glands function to regulate heat exchange in man. As such, they are indispensable to survival.

About 3 million eccrine glands are thought to be distributed over the human body. Distribution varies from less than 100 to more than 300/cm^2. Gland counts after thermal stimulation do not always agree with anatomical counts.

Drug Effects and the Extent of Percutaneous Drug Delivery

Drugs are applied to the skin to elicit one or more of four general effects: an effect on the skin surface, an effect within the stratum corneum, a more deep-seated effect requiring penetration into the epidermis and dermis or a systemic effect resulting from delivery of sufficient drug through the epidermis and the dermis to the vasculature to produce therapeutic systemic concentrations.

Surface Effects—An activity on the skin surface may be in the form of a film, an action against surface microorganisms or a cleansing effect. Film formation on the skin surface may be protective, eg, a zinc oxide cream or a sunscreen. Films may be somewhat occlusive and provide a moisturizing effect by diminishing loss of moisture from the skin surface. In such instances the film or film formation *per se* fulfils the objective of product design. The action of antimicrobials against surface flora requires more than simple delivery to the site. The vehicle must facilitate contact between the surface organisms and the active ingredient. Skin cleansers employ soaps or surfactants to facilitate the removal of superficial soil.

Stratum Corneum Effects—Drug effects within the stratum corneum are seen with certain sunscreens; *p*-aminobenzoic acid is an example of a sunscreening agent which both penetrates and is substantive to stratum corneum cells. Skin moisturization takes place within the stratum corneum. The dry outer cells are hydrated by surface films. The increased moisture results in an apparent softening of the skin. Keratolytic agents, such as salicylic acid, act within the stratum corneum to cause a breakup or sloughing of stratum corneum cell aggregates. This is particularly important in conditions of abnormal stratum corneum such as psoriasis, a disease characterized by thickened scaly plaques.

The stratum corneum also may serve as a *reservoir phase* or depot wherein topically applied drug accumulates due to partitioning into or binding with skin components. This interaction can limit the subsequent migration of the penetrant unless the interaction capacity of the stratum corneum is surpassed by providing excess drug. Examples of drugs which exhibit significant skin interaction include benzocaine, scopolamine and corticosteroids.

Epidermal, Dermal, Local and Systemic Effects—The penetration of a drug into the viable epidermis and dermis may be difficult to achieve, as noted above. But, once transepidermal permeation has occurred, the continued diffusion of drug into the dermis is likely to result in drug transfer into the microcirculation of the dermis and then into general circulation. Nonetheless, it is possible to formulate drug delivery systems which provide substantial localized delivery without achieving correspondingly high systemic concentrations. Limited studies in man of topical triethanolamine salicylate, minoxidil and retinoids demonstrate the potential of this approach.

Unwanted systemic effects stemming from the inadvertent transdermal penetration of drugs have been reported for a wide variety of compounds (eg, hexachlorophene, lindane, corticosteroids) over the years. With the commercial introduction of transdermal drug delivery systems for scopolamine, nitroglycerin, clonidine and 17β-estradiol, transdermal penetration is being regarded increasingly as an opportunity rather than a nuisance.

Percutaneous Absorption

Percutaneous absorption involves the transfer of drug from the skin surface into the stratum corneum, under the aegis of a concentration gradient, and its subsequent diffusion through the stratum corneum and underlying epidermis, through the dermis and into the microcirculation. The skin behaves as a passive barrier to diffusing molecules. Evidence for this includes the fact that the impermeability of the skin persists long after the skin has been excised. Furthermore, Fick's Law is obeyed in the vast majority of instances.

Molecular penetration through the various regions of the skin is limited by the diffusional resistances encountered. The total diffusional resistance (R_{skin}) to permeation through the skin has been described by Chien as

$$R_{skin} \approx R_{sc} + R_e + R_{pd}$$

where R is the diffusional resistance and the subscripts *sc*, *e* and *pd* refer to the stratum corneum, epidermis and papillary layer of the dermis, respectively. In addition, resistance to transfer into the microvasculature limits the systemic delivery of drug.

By and large, the greatest resistance to penetration is met in the stratum corneum, ie, diffusion through the stratum corneum tends to be the rate-limiting step in percutaneous absorption.

The role of hair follicles and sweat glands must be considered; however, as a general rule their effect is minimized by the relatively small fractional areas occupied by these appendages. In the very early stages of absorption, transit through the appendages may be comparatively large, partic-

ularly for lipid-soluble molecules and those whose permeation through the stratum corneum is relatively low.

The stratum corneum can be regarded as a passive diffusion membrane but not an inert system; it often has an affinity for the applied substance. The adsorption isotherm is frequently linear in dilute concentration ranges. The correlation between external and surface concentrations is given in terms of the solvent membrane distribution coefficient K_m. The integrated form of Fick's Law is given as

$$J_s = \frac{K_m D C_s}{\delta}$$

and

$$K_p = \frac{K_m D}{\delta}$$

where K_p is the permeability coefficient, J_s is the steady state flux of solute, C_s is the concentration difference of solute across membrane, δ is the membrane thickness,

$$K_m \text{ is the } \frac{\text{solute sorbed per cc of tissue}}{\text{solute in solution per cc solvent}} = \frac{C_m}{C_s}, \text{ and}$$

D is the average membrane diffusion coefficient for solute.

Permeability experiments have shown that the hydrated stratum corneum has an affinity for both lipophilic and hydrophilic compounds. The bifunctional solubility arises from the filament-matrix ultrastructure of the keratin, which allows aqueous and lipid regions to coexist. Thus, attempts to predict permeability constants from oil:water or solvent:water partition coefficients have had limited success.

The effect of regional variation on skin permeability can be marked. Kligman suggests that two species of horny layer be recognized: the palms and soles, adapted for weight-bearing and friction; and the body horny layer, adapted for flexibility, impermeability and sensory discrimination.

Overall, data suggest the following order for diffusion of simple molecules through the skin: plantar > palmar > dorsum of hand > scrotal and postauricular > axillary > scalp > arms, legs, trunk. Electrolytes in solution penetrate the skin poorly. Ionization of a weak electrolyte substantially reduces its permeability, eg, sodium salicylate permeates poorly compared with salicylic acid. Nonetheless, the development of iontophoretic devices in recent years may minimize this problem with ionic penetrants.

In Vitro and In Vivo Studies

Classically, percutaneous absorption has been studied *in vivo* using radioactively labeled compounds or by *in vitro* techniques using excised human skin. A diffusion cell frequently used for *in vitro* experiments is shown in Fig 87-2.[1] In this system the intact skin or the epidermis is treated as a semipermeable membrane separating two fluid media. The transport rate of a particular drug is evaluated by introducing the drug in solution on the stratum corneum side of the "membrane," then measuring penetration by periodic sampling and analysis of the fluid across the skin membrane.

More recently investigators have recognized that transport across an immersed, fully hydrated stratum corneum may not represent the absorption system or rate observed in *in vivo* studies. Percutaneous absorption across a fully hydrated stratum corneum may be an exaggeration. It may be more representative of enhanced absorption that is seen after *in vivo* skin is hydrated by occlusive wrapping.

Using separated epidermal skin mounted in diffusion cells, Scheuplein and Ross[2] varied the atmosphere above the skin strip by use of Drierite to simulate dry conditions and wetted paper strips to simulate the effect of occlusion and observed marked reduction in penetration of cortisone under dry conditions but greatly enhanced penetration on humidifying the stratum corneum (see Fig 87-3).[2]

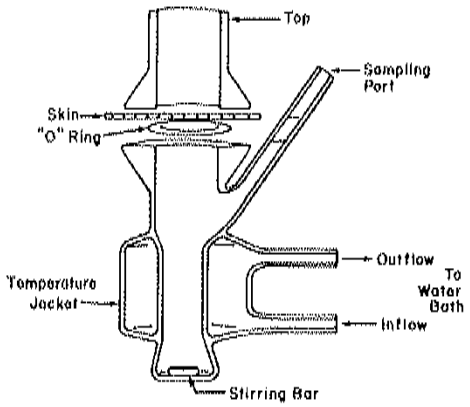

Fig 87-2. Schematic representation of diffusion cell. Top is open to ambient laboratory environment.[1]

The studies of Scheuplein and Ross,[2] and of Franz,[1] demonstrate that *in vitro* studies of percutaneous absorption under controlled conditions are relevant to *in vivo* drug penetration. As stated by Franz, "whenever a question is asked requiring only a qualitative or directional answer, the *in vitro* technique appears perfectly adequate."

Relevance of Animal Studies

Any evaluation of a study of percutaneous absorption in animals must take cognizance of species variation. Just as percutaneous absorption in man will vary considerably with skin site, so will absorption in various animal species. Bartek *et al*[3] investigated percutaneous absorption and found a decreasing order of permeability, thus, rabbit > rat > swine > man. They studied the *in vivo* absorption of radioactively labeled haloprogin, *N*-acetylcysteine, testosterone, caffeine and butter yellow; their results with testosterone, shown in Fig 87-4, illustrate the penetration differences observed with different animal skins.

Subsequently, using a similar *in vivo* technique, Wester

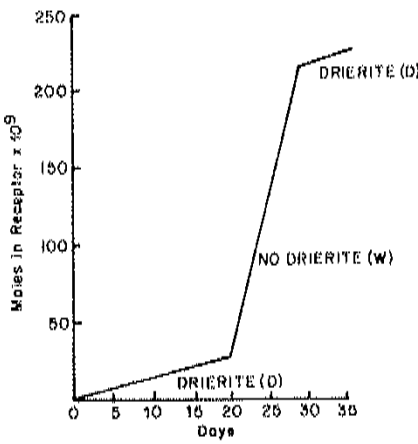

Fig 87-3. Change in cortisone penetration by alternately drying (D) and humidifying (W) the stratum corneum.[2]

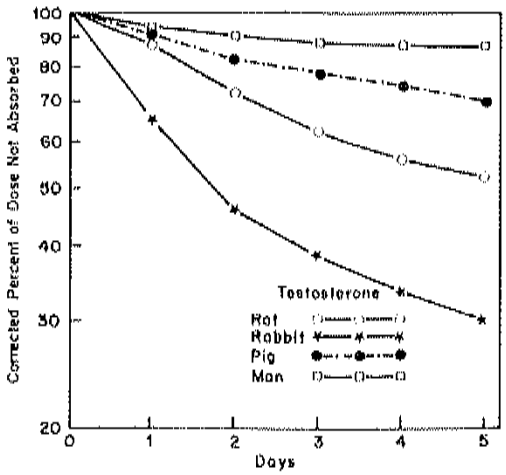

Fig 07-4. Percutaneous absorption of testosterone in rats, rabbits, swine and man for 5 days after application.[4]

and Maibach[5] investigated the percutaneous absorption of benzoic acid, hydrocortisone and testosterone in the rhesus monkey. Radioactively tagged compounds were applied to the ventral surface of the forearm, and absorption was quantified on the basis of radioactivity excreted in the urine for five days following application. The investigators concluded that the percutaneous penetration of these compounds in the rhesus monkey is similar to that in man, and regarded the data as encouraging because of the similarity.

Stoughton[6] performed *in vitro* studies using animal skins. Using a variety of compounds and a diffusion-cell apparatus he concluded that the skin of the hairless mouse or the baby rat is useful for screening for absorption or epidermal response.

It should be stressed again that percutaneous absorption studies in animals, either *in vivo* or *in vitro*, only can be useful approximations of activity in man. The effect of species variation, site variability (about which little is known in animals), skin condition, experimental variables and, of major importance, the vehicle, must be kept in mind.

Drug Testing in Animals

Drug testing in animals is a characteristic of new-drug development, and the testing of dermatological products or drugs in animals is no exception. Such testing typically may take three forms: Animals may be used to estimate the safety of a drug product or substance; animal skin may be substituted for human skin for a specific measurement, eg, percutaneous absorption; animal skin may be used as a disease model to simulate an equivalent human condition.

Animals have been used to detect contact sensitization, measure antimitotic drug activity, measure phototoxicity and evaluate the comedogenic and comedolytic potential of substances. In each of these test procedures, be it a safety test or assay model, the animal is considered a substitute for man. It is, therefore, important to realize that the animal is not man, even though man is the ultimate test animal. Animal-testing presents the investigator with unique advantages; lack of appreciation of the variables involved can destroy these advantages.

Mershon and Callahan[7] recorded and illustrated the considerations involved in selecting an animal test model. They interpreted the rabbit irritancy data of several investigators, and impressively visualized different possible interpretations of the differing response between rabbit and man.

Table II—Relative Potency of Anti-Inflammatory Agents[8]

Compound	Topical anti-inflammatory potency: Rat-ear edema assay	Topical anti-inflammatory potency: Human vasoconstrictor assay
Dexamethasone	73.2 (49.4–110)	10–20
Dexamethasone 21-acetate	117.3 (85.9–160)	10–20
Prednisolone	2.44 (1.54–7.76)	1–2
Prednisolone 21-acetate	5.43 (4.05–7.70)	3
Betamethasone	97.3 (16.7–141)	3–5
Betamethasone 21-acetate	1072.0 (876–1179)	18–33
Fluorometholone	136.3 (57.9–333)	30–40
Fluorometholone acetate	219.5 (9.15–536)	
Fluprednisolone	31.8 (13.3–76.1)	4–6
Fluprednisolone acetate	61.3 (25.6–147)	
Hydrocortisone	1	1

( ) = 95% confidence limits

While the ultimate system for establishing therapeutic efficacy is man, there are specific animal test models that are recognized to be valuable as prehuman-use screens predictive of drug activity in humans. For example, the rat-ear assay and the granuloma-pouch procedure in rats are recognized procedures for the estimation of steroid anti-inflammatory activity.

Lorenzetti[8] tabulated the potency of various topical steroids, comparing the rat-ear-edema assay with potency measured in humans using the vasoconstrictor procedure of Stoughton and McKenzie; the results are given in Table II.[9] Animal assay models of this kind, particularly the steroid anti-inflammatory assays, are most useful as preliminary activity screens. The simplicity, safety and reproducibility of the vasoconstrictor assay in humans recommend it over any corresponding animal procedure.

In Numero Models

In recent years, *in numero* modeling or computer simulation of percutaneous absorption has been advocated as a link between *in vitro* and *in vivo* studies. A number of relatively simplistic dermatopharmacokinetic models have been developed that do provide the formulator with some insight into transdermal drug delivery, in spite of the biological and physicochemical complexity of drug transport into and through the skin. By and large, these models are analogous to the classical pharmacokinetic models which have been employed to assess *in vivo* drug uptake and disposition. Some of the dermatopharmacokinetic models proposed differ from more classically oriented models in that drug transport in the vehicle and in the epidermis, particularly the stratum corneum, is modeled in accordance with Fickian diffusion. Thus, the formulator can anticipate the effect of variables such as the thickness of the applied (vehicle) phase, alterations in drug partitioning between the vehicle and the stratum corneum and the frequency of reapplication on the overall appearance of drug systemically as a function of time following topical application.

Dosage-Form Design

More than 35 years ago Lane and Blank pointed out that sufficient thought rarely is given to the function which the vehicle performs and to the physicochemical characteristics of the base. These investigators were not discussing optimization of drug activity in today's meaning of the term. They emphasized that the type of skin, application site, lesion type and physicochemical action of the base are important considerations.

In many (if not most) clinical situations the rate-limiting step is penetration of the drug across the skin barrier, ie,

percutaneous penetration through the skin alone. Diffusion of the drug from its vehicle, although dependent on the same diffusion parameters, should not be unknowingly the rate-limiting step in percutaneous absorption. Such a rate limitation or control may, of course, be an objective and the end point of specific drug optimization, but inappropriate formulation can reduce substantially the effectiveness of a topical drug substance.

In the formulation of a vehicle for topical drug application many factors must be considered. Drug stability, specific product use, site of application and product type must be combined in a dosage form which will readily release the drug when placed in contact with the skin. Further, the release characteristics of the vehicle are dependent on the physical-chemical properties of the specific drug substance to be delivered to the skin. A vehicle optimized for delivery of hydrocortisone may be quite inappropriate for delivery of a different steroid.

T Higuchi discussed (1960 to 1961) equations describing the rate of release of solid drugs suspended in ointment bases. Ostrenga *et al*, in a series of publications, discussed the significance of vehicle composition on the percutaneous absorption of fluocinolone acetonide and fluocinolone acetonide 21-acetate (fluocinonide) (see Fig 87-5).[10] These investigators used propylene glycol/isopropyl myristate partition coefficients, *in vitro* (human) skin penetration and finally *in vivo* vasoconstrictor studies to evaluate formulation variables. They concluded that

> "In general, an efficacious topical gel preparation is one in which (a) the concentration of diffusible drug in the vehicle for a given labeled strength is optimized by ensuring that all of the drug is in solution, (b) the minimum amount of solvent is used to dissolve the drug completely and yet maintain a favorable partition coefficient and (c) the vehicle components affect the permeability of the stratum corneum in a favorable manner."

The effect of propylene glycol concentration on *in vivo* vasoconstrictor activity is illustrated strikingly in Fig 87-5, taken from Ostrenga *et al*.[10]

Experimental work of the kind described by Ostrenga *et al*[10] provides a means of optimizing drug release from a vehicle and penetration of the drug into the skin. This is a beginning. The formulator must proceed to develop a total composition in which the drug is stable and causes no irritation to sensitive skin areas. Safety, stability and effective preservative efficacy must be combined with optimum drug delivery in the total formulation.

Optimization of drugs other than steroids may be approached by direct *in vivo* assays. Layers of the stratum corneum can be removed or stripped successively away by the repeated application and removal of cellulose adhesive tape strips. The penetration into the skin, as well as the effect of additives on *p*-aminobenzoic acid, were studied by Lorenzetti through analysis of individual skin strips. The results provided a profile of skin penetration and visualized the effect of additives. Similar experiments have been carried out using benzoyl peroxide. Penetration *per se*, as well as the effect of additives, can be measured by chemical analysis of individual tape strips following application of a specific quantity of drug or drug product.

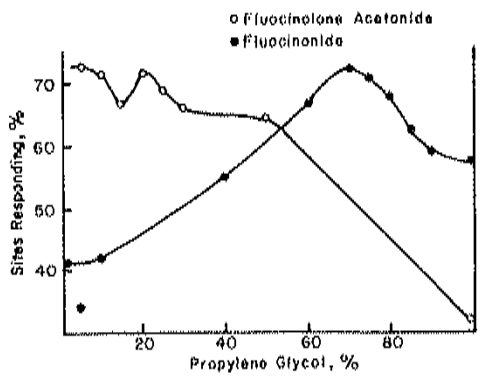

Fig 87-5. *In vivo* response as a function of vehicle composition (24-hour vasoconstriction).[10]

Factors Affecting Drug Absorption

In the foregoing it has been seen that drug-release from its vehicle is a function of concentration, solubility in the vehicle and partition coefficient between the vehicle and the receptor site. Percutaneous absorption of a drug also can be enhanced by the use of occlusive techniques or by the use of so-called penetration enhancers.

Skin Hydration and Temperature—Occluding the skin with wraps or impermeable plastic film such as Saran Wrap prevents the loss of surface water from the skin. Since water is absorbed readily by the protein components of the skin the occlusive wrap causes greatly increased levels of hydration in the stratum corneum. The concomitant swelling of the horny layer ostensibly decreases protein network density and the diffusional path length. Occlusion of the skin surface also increases skin temperature (~2 to 3°) resulting in increased molecular motion and skin permeation.

Hydrocarbon bases which occlude the skin to a degree will bring about an increase in drug penetration. However, this effect is trivial compared with the effects seen with a true occlusive skin wrap. Occlusive techniques are useful in some clinical situations requiring anti-inflammatory activity and occlusive wrappings are used most commonly with steroids. Since steroid activity can be enhanced so enormously by skin occlusion it is possible to depress adrenal function unknowingly. Early in the 1960s McKenzie demonstrated that penetration of steroid could be increased 100-fold by use of occlusion. The FDA requires the following label statement:

> If extensive areas are treated or if the occlusive technique is used, the possibility exists of increased systemic absorption of the corticosteroid and suitable precautions should be taken.

Transdermal delivery systems, with their occlusive backing, can effect increased percutaneous absorption as a result of increased skin temperature and hydration.

Penetration Enhancers—This term has been used to describe substances that facilitate absorption through the skin. While most materials have a direct effect on the permeability of the skin, other so-called enhancers (eg polyols, such as glycerin and propylene glycol) appear to augment percutaneous absorption by increasing the thermodynamic activity of the penetrant, thereby increasing the effective escaping tendency and concentration gradient of the diffusing species. Penetration enhancers with a direct effect on skin permeability include solvents, surfactants and miscellaneous chemicals such as urea and *N,N*-diethyl-*m*-toluamide (Table III).[11] The mechanism of action of these enhancers is complex since these substances also may increase penetrant solubility. Nonetheless, the predominant effect of these enhancers on the stratum corneum is either to increase its degree of hydration or disrupt its lipoprotein matrix. In either case, the net result is a decrease in resistance to penetrant diffusion. (The formulator should note that the inclusion of a penetration enhancer in a topical formulation mandates additional testing and evaluation to ensure the absence of enhancer-related adverse effects.)

Foremost among the solvents which affect skin permeability is water. As noted above, water is a factor even for

Table III—Penetration Enhancers[a]

Solvents	
	Water
	Alcohols
	Methanol
	Ethanol
	2-propanol
	Alkyl methyl sulfoxides
	Dimethyl sulfoxide
	Decylmethyl sulfoxide
	Tetradecylmethyl sulfoxide
	Pyrrolidones
	2-Pyrrolidone
	N-Methyl-2-pyrrolidone
	N-(2-Hydroxyethyl)pyrrolidone
	Laurocapram
	Miscellaneous solvents
	Acetone
	Dimethyl acetamide
	Dimethyl formamide
	Tetrahydrofurfuryl alcohol
Amphiphiles	
	Anionic surfactants
	Cationic surfactants
	Amphoteric surfactants
	Nonionic surfactants
	Fatty acids and alcohols
Miscellaneous	
	Urea
	N,N-Diethyl-*m*-toluamide

[a] Adapted from Ref 11.

anhydrous transdermal delivery systems due to their occlusive nature. Due to its safety and efficacy, water has been described as the ultimate penetration enhancer. Other solvents include the classic enhancer, dimethyl sulfoxide (DMSO), which is of limited utility because of its potential ocular and dermal toxicity, its objectionable taste and odor (a consequence of its absorption and subsequent biotransformation) and the need for concentrations in excess of 70% to promote absorption. Analogs of DMSO such as decylmethyl sulfoxide are used currently in some topical formulations. In contrast with other solvents, laurocapram (1-dodecylazacycloheptan-2-one; Azone) has been shown to function effectively at low concentrations (≤5%). Furthermore, Azone's effect on skin permeability persists long after a single application due apparently to its prolonged retention within the stratum corneum.

Surfactants, long recognized for their ability to alter membrane structure and function, can have a substantial effect on skin permeability.[12] However, given the irritation potential of surfactants applied chronically, their utility as penetration enhancers is limited. Their effect on permeability may be complicated further by surfactant-monomer aggregation to form micelles and the concomitant solubilization of the permeant. As the impact of surfactants on skin permeability of a penetrant is problematic, the effect of their inclusion in a formulation should be evaluated using appropriate *in vitro* and *in vivo* studies.

Stratum Corneum Barrier Efficacy and Dermal Clearance—Even though *in vitro* studies of percutaneous transport may reflect the resistance of the skin to drug diffusion, there is no way such studies can characterize adequately the transfer of diffusing drug into the microvasculature of the dermis and its subsequent transfer into general circulation.

Christophers and Kligman[13] evaluated the dermal "clearance" of ^{22}Na from the midback skin of volunteers following the intradermal injection of ^{22}Na as normal saline solution. The dermal "clearances," expressed in terms of the half-life for disappearance of radioactivity, are plotted in Fig. 87-6.[13]

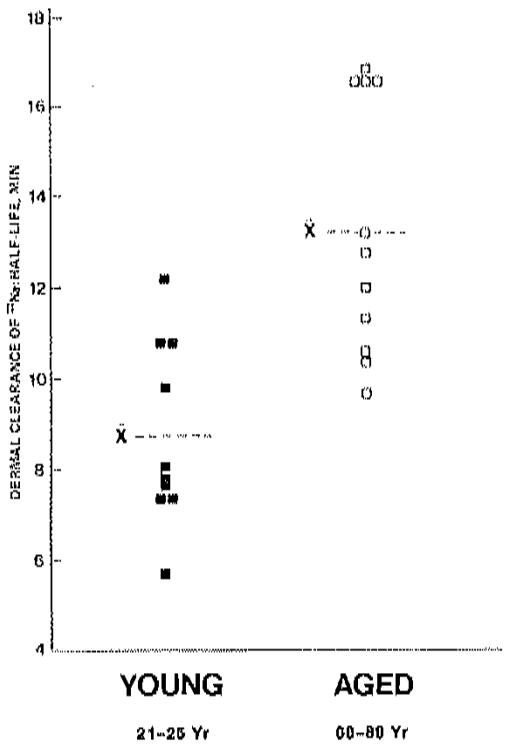

Fig 87-6. Dermal clearance of ^{22}Na in young and aged subjects after intradermal injection (data from Ref 13).

Similar results were obtained with disappearance of skin fluorescence after intradermal injection of sodium fluorescein. The data are indicative of markedly delayed dermal clearance in the aged. This may reflect, in part, a decrease in older subjects in dermal capillary loop density, a decrease in the rate and/or extent of dermal blood perfusion or an increase in resistance to transfer into the capillaries.

On the other hand, Christophers and Kligman[13] demonstrated increased *in vitro* skin permeation by sodium fluorescein in the stratum corneum excised from young and old subjects (Fig. 87-7[13]). Thus, the stratum corneum of older subjects may offer less resistance to the penetration of topically applied drugs.

Given the substantial intersubject variations that occur in diffusional resistance and in dermal clearance, it is not surprising that *in vivo* studies of percutaneous absorption often demonstrate marked differences in systemic availability of drugs. Furthermore, the tendency to employ normal, healthy, *young* adults in such studies may not provide data that is indicative of drug permeation through the skin of older subjects or patients. It would seem that more comprehensive studies of percutaneous absorption as a function of age are warranted.

Cutaneous Biotransformation—Catabolic enzyme activity in the viable epidermis is substantial. In fact, the viable epidermis is metabolically more active than the dermis. If the topically applied drug is subject to biotransformation during skin permeation, local and systemic bioavailability can be affected markedly. Enzymatic activity in the skin, or for that matter in systemic fluids and tissues, can be taken advantage of to facilitate percutaneous absorption. Sloan and Bodor,[14] for example, synthesized 7-acyloxymethyl derivatives of theophylline which diffuse through

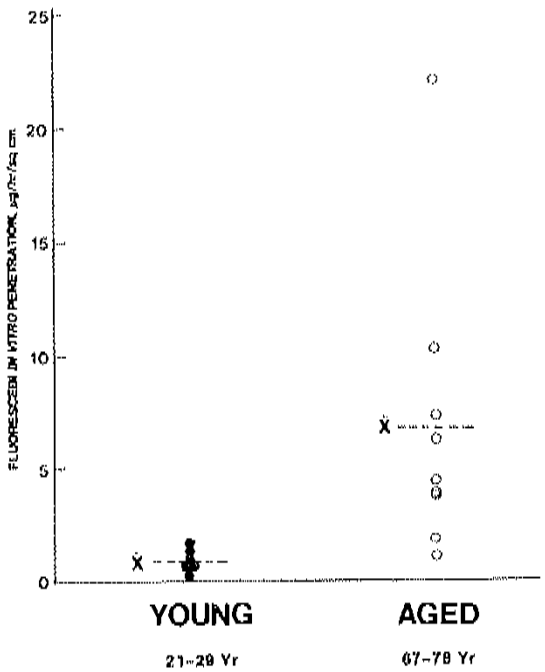

Fig 87-7. Flux of fluorescein through stratum corneum excised from young and aged subjects (data from Ref 13).

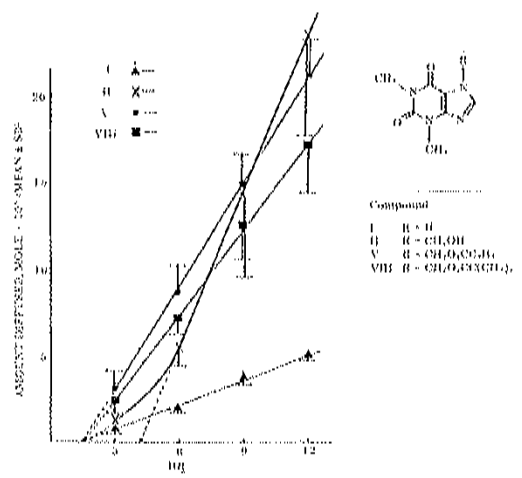

Fig 87-8. Diffusion of theophylline (I) and its derivatives through hairless mouse skin.[14]

the skin far more efficiently than theophylline itself (Fig 87-8[14]) but which are biotransformed rapidly to theophylline. Thus, theophylline delivery to systemic circulation can be enhanced substantially.

Further Considerations for Transdermal Drug Delivery

In order for a drug to qualify as a candidate for systemic delivery after topical application, it must satisfy requirements in addition to exhibiting good skin permeation. Successful candidates for transdermal drug delivery should be nonirritating and nonsensitizing to the skin. Since relatively little drug may reach systemic circulation over a relatively long time, drug candidates should be relatively potent drugs. In addition, the limitation to relatively potent drugs can ease problems of formulation since the amount of drug that can be incorporated in the formulation may be limited by physicochemical considerations such as solubility.

Iontophoretic Drug Delivery through the Skin[15,16]—For some poorly absorbed (ionic) compounds, parenteral administration appears to be the only viable option for regional or systemic delivery as chemical penetration enhancers (see Table III) often do not function well for these compounds. Given the increased risk of adverse reactions associated with the use of such enhancers, the increased evaluation of iontophoretic devices for the enhancement of topical drug delivery has been of great interest. Iontophoretic drug delivery implies the delivery of ionic drugs into the body by means of an electric current. While the stratum corneum forms the principal barrier to electrical conductivity—due, in part, to its lower water content—the skin also acts as a capacitor. Thus, biological tissues such as the skin provide for a reactive electrical circuit. Ionic transport through the skin in the presence of a uniform electric field can be described, in part, in accordance with the Nernst-Planck equation

$$J_i = -D\frac{dC}{dx} + \frac{DzeEC}{kT}$$

where J_i is the flux of ions across the membrane, C is the concentration of ions with valence, z, and electron charge, e, dC/dx is the concentration gradient, E is the electric field, k is Boltzmann's constant and T is the absolute temperature. Thus, the ionic flux is the sum of the fluxes that arise from the concentration gradient and the electric field. Given the complexity of the skin's composition, the thickness of the stratum corneum and the occurrence of electroosmotic effects, the Nernst-Planck equation is only a first approximation of the overall transdermal flux of a solute. Faraday's Law

$$\frac{Q}{t} = \frac{t_j i}{|z|F}$$

further characterizes the iontophoretic flux Q/t in terms of the current i (in amperes) and its duration t (in sec), the transference number parameter t_j and the Faraday constant F. Additional factors that influence the rate and extent of iontophoretic delivery through the skin include pH and ionic strength of the drug solution.

Although iontophoretic techniques have been shown to increase percutaneous absorption of ionizable or ionic drugs (including lidocaine, salicylates and peptides and proteins such as insulin) markedly, the clinical safety and efficacy of drug delivery systems employing iontophoretic technology have yet to be evaluated fully.

Ointments

Ointments are semisolid preparations intended for external application to the skin or mucous membranes; usually, but not always, they contain medicinal substances. The types of ointment bases used as vehicles for drugs are selected or designed for optimum delivery of the drugs and also to contribute emolliency or other quasi-medicinal qualities. Ointment properties vary, since they are designed for specific uses, ease of application or extent of application.

The official definition of ointment in its present form was introduced in the USP XV in 1955. The definition is broad and encompasses petrolatum, ie, oleaginous bases, emulsion bases—either water-in-oil (W/O) or oil-in-water (O/W)—and the so-called water-soluble bases.

In unofficial terms, oleaginous bases are described as ointments, but emulsion bases may be termed creams or lotions. Either of these containing large amounts of solids is termed a paste. All of these subclasses are defined officially as ointments.

Pharmaceutical authors have a penchant for defining "ideal" preparations eg, the ideal base, the ideal vehicle and so on. In practice, of course, there is no such thing. An individual cannot be all things to all people; neither can an ointment base be ideal for all drugs, all situations or all skins, for that matter. An ointment base functioning as a drug vehicle should be optimized for a specific drug and, insofar as possible, for specific disease states or skin conditions.

It is, of course, possible to define certain specific requirements for an ointment base to be used for extemporaneous compounding. Such a base should be nonirritating, easily removable, nonstaining, stable, non-pH-dependent and widely compatible with a variety of medicaments. When one adds the stipulation that the base must release the same variety of medicaments, the implausibility of such definitions becomes evident.

Classification and Properties of Ointment Bases

The USP recognizes four general classes of ointment bases, hereunder categorized into five classes for the purpose of indicating more definitively some differences in the principal properties of the bases.

Hydrocarbon Bases (Oleaginous)
Example: White Petrolatum
1. Emollient
2. Occlusive
3. Nonwater-washable
4. Hydrophobic
5. Greasy

Absorption Bases (Anhydrous)
Examples: Hydrophilic Petrolatum; Anhydrous Lanolin
1. Emollient
2. Occlusive
3. Absorb water
4. Anhydrous
5. Greasy

Emulsion Bases (W/O Type)
Examples: Lanolin, Cold Cream
1. Emollient
2. Occlusive
3. Contain water
4. Some absorb additional water
5. Greasy

Emulsion Bases (O/W Type)
Example: Hydrophilic Ointment
1. Water-washable
2. Nongreasy
3. Can be diluted with water
4. Nonocclusive

Water-Soluble Bases
Example: Polyethylene Glycol Ointment
1. Usually anhydrous
2. Water-soluble and washable
3. Nongreasy
4. Nonocclusive
5. Lipid-free

The selection of the optimum vehicle from the classification above may require compromises so often encountered in drug formulation. For example, stability or drug activity might be superior in a hydrocarbon base, however, acceptability is diminished because of the greasy nature of the base. The water-solubility of the polyethylene glycol bases may be attractive, but the glycol(s) may be irritating to traumatized tissue. Drug activity and percutaneous absorption may be superior when using a hydrocarbon base; however, it may be prudent to minimize percutaneous absorption by the use of a less occlusive base.

Ointment Bases

Hydrocarbon Bases

Hydrocarbon bases are usually petrolatum *per se* or petrolatum modified by waxes or liquid petrolatum to change viscosity characteristics. Liquid petrolatum gelled by the addition of a polyethylene resin also is considered a hydrocarbon ointment base, albeit one with unusual viscosity characteristics.

Hydrocarbon ointment bases are classified as oleaginous bases along with bases prepared from vegetable fixed oils or animal fats. Bases of this type include lard, benzoinated lard, olive oil, cottonseed oil and other oils. Such bases are emollient but generally require addition of antioxidants and other preservatives. They are now largely of historic interest.

Petrolatum USP is a tasteless, odorless, unctuous material with a melting range of 38 to 60°; its color ranges from amber to white (when decolorized). Petrolatum often is used externally, without modification or added medication, for its emollient qualities.

Petrolatum used as an ointment base has a high degree of compatibility with a variety of medicaments. Bases of this type are occlusive and nearly anhydrous and thus provide optimum stability for medicaments such as antibiotics. The wide melting range permits some latitude in vehicle selection and the USP permits addition of waxy materials as an aid in minimizing temperature effects.

Hydrocarbon bases, being occlusive, increase skin hydration by reducing the rate of loss of surface water. Bases of this kind may be used solely for such a skin-moisturizing effect, eg, white petroleum jelly as noted above. Skin hydration on the other hand may increase drug activity. Studies have indicated that steroids have increased activity, as measured by vasoconstrictor effects, when applied to the skin in a hydrocarbon vehicle. Stoughton consistently found the same steroid more active when applied in a petrolatum vehicle than when applied in a cream (ie, O/W emulsion) vehicle.

A gelled mineral oil vehicle represents a unique addition to this class of bases comprised of refined natural products. Liquid petrolatum may be gelled by addition of a polyethylene. When approximately 5% of low-density polyethylene is added, the mixture heated and then shock-cooled, a soft unctuous, colorless material resembling white petrolatum is produced. The mass maintains unchanged consistency over a wide temperature range. It neither hardens at low temperatures nor melts at reasonably high temperatures. Its useful working range is between −15° and 60°. Excessive heat, ie, above 90°, will destroy the gel structure.

On the basis of *in vitro* studies, drugs may be released faster from the gelled mineral oil vehicle than from conventional petrolatum. This quicker release has been attributed to easier migration of drug particulates through a vehicle which is essentially a liquid, compared with petrolatum.

Despite the advantages hydrocarbon or oleaginous vehicles provide in terms of stability and emolliency such bases have the considerable disadvantage of greasiness. The greasy or oily material may stain clothing and is difficult to remove. In terms of patient acceptance, hydrocarbon bases, ie, ointments, rank well below emulsion bases such as creams and lotions.

Absorption Bases

Absorption bases are hydrophilic, anhydrous materials or hydrous bases that have the ability to absorb additional

water. The former are anhydrous bases which absorb water to become W/O emulsions; the latter are W/O emulsions which have the ability to absorb additional water. The word absorption in this connotation refers only to the ability of the base to absorb water. Both types of base are exemplified by Anhydrous Lanolin and Lanolin. The former is converted to the latter by the addition of 30% water. The latter in turn will absorb additional amounts of water.

Hydrophilic Petrolatum USP is an anhydrous absorption base. The W/O emulsifying property is conferred by the inclusion of cholesterol. This composition is a modification of the original formulation which contained anhydrous lanolin. The lanolin was deleted because of reports of allergy; cholesterol was added. Inclusion of stearyl alcohol and wax add to the physical characteristics, particularly firmness and heat stability.

Hydrophilic Petrolatum USP

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

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

Lanolin is a complex mixture of substances. Its ability to absorb water is probably a characteristic of the material rather than a single component. The chemistry of lanolin has been studied in detail. Such studies have resulted in the introduction of a large variety of lanolin derivatives and separated fractions. Available now are lanolin alcohols, dewaxed lanolins, acetylated lanolins, ethoxylated lanolins, hydrogenated lanolins, lanolin esters and other products. Most of these derivatives have been produced for specific purposes, such as improved emulsification characteristics or to reduce allergic reactivity.

The specific compounds responsible for lanolin allergy remain unknown; however, the greater portion of lanolin allergens reside in the wool wax alcohols fraction. Thus, fractional separation to obtain, for example, the so-called liquid lanolins substantially reduces the incidence of allergic reactions. Given the plethora of lanolin fractions, derivatives, modifications and levels of purity, it is quite possible, even likely, that lanolin-sensitive individuals can tolerate specific lanolin products.

Absorption bases, particularly the emulsion bases, impart excellent emolliency and a degree of occlusiveness on application. The anhydrous types can be used when the presence of water would cause stability problems with specific drug substances, eg, antibiotics. Absorption bases also are greasy when applied and are difficult to remove. Both of these properties are, however, less obvious than with hydrocarbon bases.

Commercially available absorption bases include Aquaphor (*Beiersdorf*) and Polysorb (*Fougera*). Nivea Cream (*Beiersdorf*) is a hydrated emollient base. Absorption bases, either hydrous or anhydrous, are seldom used as vehicles for commercial drug products. The W/O emulsion system is more difficult to deal with than the more conventional O/W systems and there is, of course, reduced patient acceptance because of greasiness.

Water-Removable Bases

Water-washable bases or emulsion bases, commonly referred to as creams, represent the most commonly used type of ointment base. By far the majority of commercial dermatologic drug products are formulated in an emulsion or cream base. Emulsion bases are washable and removed easily from skin or clothing. Emulsion bases can be diluted with water, although such additions are uncommon.

As a result of advances in synthetic cosmetic chemistry the formulator of an emulsion base can be faced with a bewildering variety of selections. Fortunately, the emulsion base can be subdivided into three component parts, designated as the oil phase, the emulsifier and the aqueous phase. The medicinal agent may be included in one of these phases or added to the formed emulsion.

The oil phase, sometimes called the internal phase, is typically made up of petrolatum and/or liquid petrolatum together with one or more of the higher-molecular-weight alcohols, such as cetyl or stearyl alcohol. Stearic acid may be included if the emulsion is to be based on a soap formed *in situ*, eg, triethanolamine stearate. A calculated excess of stearic acid in such a formulation will produce a pearlescent appearance in the finished product.

For drug-delivery vehicles, simplified systems are in order to minimize component interactions, either physical or chemical, and, of course, to minimize cost. Hydrophilic Ointment USP is a typical emulsion base. The composition is as follows:

Hydrophilic Ointment USP

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

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

Stearyl alcohol and petrolatum comprise an oil phase with the proper smoothness and comfort for the skin. Stearyl alcohol also serves as an adjuvant emulsifier. Petrolatum in the oil phase also contributes to the water-holding ability of the overall formulation.

A glance at the cosmetic literature and such volumes as the Cosmetic, Toiletry and Fragrance Association's *Cosmetic Ingredient Dictionary* impresses one with the enormous number and variety of emulsion-base components, particularly oil-phase components. Many of these substances impart subtle but distinct characteristics to cosmetic emulsion systems. While desirable, many of these characteristics are not really necessary in drug dosage forms and delivery systems.

The aqueous phase of an emulsion base usually, but not always, exceeds the oil phase in volume. The aqueous phase contains the preservative materials, the emulsifier or a part of the emulsifier system and humectant. The last is usually glycerin, propylene glycol or a polyethylene glycol. The humectant normally is included to minimize water loss in the finished composition. Humectants also add to overall physical product acceptability.

The aqueous phase contains the preservative(s) which are included to control microbial growth. Preservatives in emulsion bases usually include one or more of the following: methylparaben and propylparaben, benzyl alcohol, sorbic acid or quaternary ammonium compounds. Propylene glycol in sufficient concentration also can function as a preservative. The general subject of preservatives and preservation is discussed elsewhere in this chapter.

The aqueous phase also contains the water-soluble components of the emulsion system, together with any additional stabilizers, antioxidants, buffers, etc that may be neces-

sary for stability, pH control or other considerations associated with aqueous systems.

The emulsifier or emulsifier system in a cream formulation is a major consideration. The emulsifier may be nonionic, anionic, cationic or amphoteric.

Anionic Emulsifiers—Sodium lauryl sulfate, the emulsifier in Hydrophilic Ointment USP, is typical of this class. The active portion of the emulsifier is the anion (lauryl sulfate ion). Similar anionic emulsifiers include soaps such as triethanolamine stearate. Soaps, of course, are alkaline and, hence, incompatible with acids.

Sodium lauryl sulfate and other anionic surfactants of its type are more acid-stable and permit adjustment of the emulsion pH to the desirable acid range of 4.5 to 6.5. As anionic emulsifiers are incompatible with cations, the overall product composition must be kept in mind.

Depending on the chemical type and concentration, anionic surfactants may be irritating in certain situations. It has been reported that percutaneous absorption of certain drugs, notably steroids, may be enhanced by the use of anionic compounds such as sodium lauryl sulfate.

Cationic Emulsifiers—Cationic compounds are highly surface-active but are used infrequently as emulsifiers. The cation portion of the molecule is generally a quaternary ammonium salt including (usually) a fatty acid derivative, eg, dilauryldimethylammonium chloride. Cationics may be irritating to the skin and eyes, and they have a considerable range of incompatibilities, including anionic materials.

Nonionic Emulsifiers—Nonionic emulsifiers show no tendency to ionize in solution. This advantage results in excellent pH and electrolyte compatibility in such emulsions. Nonionic emulsifiers range from lipophilic to hydrophilic. The usual emulsifier system may include both a lipophilic and hydrophilic member to produce a so-called hydrophilic-lipophilic balance (or HLB).

Many nonionic surfactants are the result of condensation of ethylene oxide groups with a long chain hydrophobic compound. The hydrophilic characteristics of the condensation product are controlled by the number of (usually) oxyethylene groups (OCH_2CH_2). Examples of nonionic surfactants are given in Table IV.[17]

Emulsions containing nonionic emulsifiers usually are prepared by dissolving or dispersing the lipophilic component in the oil phase and the hydrophilic component in the aqueous phase. The two phases then are heated separately and combined as described on page 1534. The nonionic emulsifier content of an emulsion may total as much as 10% of the total weight or volume. Emulsions based on nonionic emulsifiers are generally low in irritation potential, stable and have excellent compatibility characteristics.

Soaps and detergents, ie, emulsifiers, have, overall, a damaging effect on the skin. Both anionic and cationic surfactants can cause damage to the stratum corneum in direct proportion to concentration and duration of contact. Nonionic surfactants appear to have much less effect on the stratum corneum.

After the proper selection of ingredients the emulsion base is formed by heat and agitation. The oil phase is melted and heated to 75° in a container equipped with a variable-speed agitator. The aqueous phase with the emulsifier added is placed in a second container, components are dissolved and the whole heated to 75° or slightly in excess. The aqueous phase then is added slowly with continuous stirring to the oil phase. The first addition should be carried out slowly but continuously with thorough but careful agitation, ie, the emulsion should not be agitated at a rate that incorporates excess air. Progressively slower stirring should be continued during addition of the aqueous phase and until the temperature reaches about 30°. Medicinal agents usually are added after the emulsion has formed and much of the aqueous phase has been added. Drug substances frequently are added as dispersed concentrates in aqueous suspension. Colors and dyes are similarly added as concentrates. Colors sometimes are employed to distinguish different concentrations of the same drug product. Fragrances, if any, are added after the formed emulsion has cooled to about 35°.

Table IV—Nonionic Emulsifiers[17]

Type	Examples
Polyoxyethylene fatty alcohol ethers	Polyoxyethylene lauryl alcohol
Polyoxypropylene fatty alcohol ethers	Propoxylated oleyl alcohol
Polyoxyethylene fatty acid esters	Polyoxyethylene stearate
Polyoxyethylene sorbitan fatty acid esters	Polyoxyethylene sorbitan monostearate
Sorbitan fatty acid esters	Sorbitan monostearate
Polyoxyethylene glycol fatty acid esters	Polyoxyethylene glycol monostearate
Polyol fatty acid esters	Glyceryl monostearate Propylene glycol monostearate
Ethoxylated lanolin derivatives	Ethoxylated lanolins Ethoxylated cholesterol

Water-Soluble Bases

Soluble ointment bases, as the name implies, are made up of soluble components, or may include gelled aqueous solutions. The latter often are referred to as gels, and in recent years have been formulated specifically to maximize drug availability.

Major components, and in some instances the only components, of water-soluble bases are the polyethylene glycols. These are liquids or waxy solids identified by numbers which are an approximate indication of molecular weight. Polyethylene glycol 400 is a liquid superficially similar to propylene glycol, while polyethylene glycol 4000 is a waxy solid.

Polyethylene glycols have the general chemical formula

$$HOCH_2(CH_2OCH_2)_nCH_2OH$$

They are nonvolatile, water-soluble or water-miscible compounds and chemically inert, varying in molecular weight from several hundred to several thousand. Patch tests have shown that these compounds are innocuous and continuous use has confirmed their lack of irritation.

Polyethylene glycols of interest as vehicles include the 1500, 1600, 4000 and 6000 products, ranging from soft, waxy solids (polyethylene glycol 1500 is similar to petrolatum) to hard waxes. Polyethylene glycol 6000 is a hard wax-like material melting at 58 to 62°; it is nonhygroscopic.

Polyethylene glycols, particularly 1500, can be used as a vehicle *per se;* however, better results often are obtained by using blends of high- and low-molecular-weight glycols, as in Polyethylene Glycol Ointment NF.

Polyethylene Glycol Ointment NF

Polyethylene Glycol 3350	400 g
Polyethylene Glycol 400	600 g

Heat the two ingredients on a water bath to 65°. Allow to cool and stir until congealed. If a firmer preparation is desired, replace up to 100 g of the polyethylene glycol 400 with an equal amount of polyethylene glycol 3350.

Note—If 6–25% of an aqueous solution is to be incorporated in polyethylene glycol ointment, replace 50 g of the polyethylene glycol 3350 with an equal amount of stearyl alcohol.

The water-solubility of polyethylene glycol vehicles does not insure availability of drugs contained in the vehicle. As hydrated stratum corneum is an important factor in drug penetration, the use of polyethylene glycol vehicles which

are anhydrous and nonocclusive actually may hinder percutaneous absorption due to dehydration of the stratum corneum.

Aqueous gel vehicles containing water, propylene and/or polyethylene glycol, and gelled with a carbomer or a cellulose derivative, also are classed as water-soluble bases. Bases of this kind, sometimes referred to as gels, may be formulated to optimize delivery of a drug, particularly steroids. In such a preparation propylene glycol is used as a steroid solvent as well as an antimicrobial or preservative.

Gelling agents used in these preparations may be nonionic or anionic. Nonionics include cellulose derivatives, such as methylcellulose or hydroxypropyl methylcellulose. These derivatives form gels when dissolved in water but also exhibit the characteristic of reverse solubility. The celluloses are wetted, ie, dispersed in hot water, and then cooled to effect solution. Sodium carboxymethylcellulose is an ionic form of cellulose gelling agent. It is conventionally soluble, and not heat-insoluble.

Carbopol 934 is a white, fluffy, powdered polymeric acid, dispersible but insoluble in water. When the acid dispersion is neutralized with a base a clear, stable gel is formed. Carbopol 934 is physiologically inert and is not a primary irritant or sensitizer.

Another gelling agent is colloidal magnesium aluminum silicate (*Veegum*). It is an inorganic emulsifier and suspending agent, as well as a gelling agent. Veegum dispersions are compatible with alcohols (20 to 30%), acetone and glycols. It frequently is employed as a gel stabilizer, rather than as the sole gelling agent.

Sodium alginate and the propylene glycol ester of alginic acid (*Kelcoloid*) also are satisfactory gelling agents. Sodium alginate is a hydrophilic colloid that functions satisfactorily between pH 4.5 and 10; addition of calcium ions will gel fluid solutions of sodium alginate.

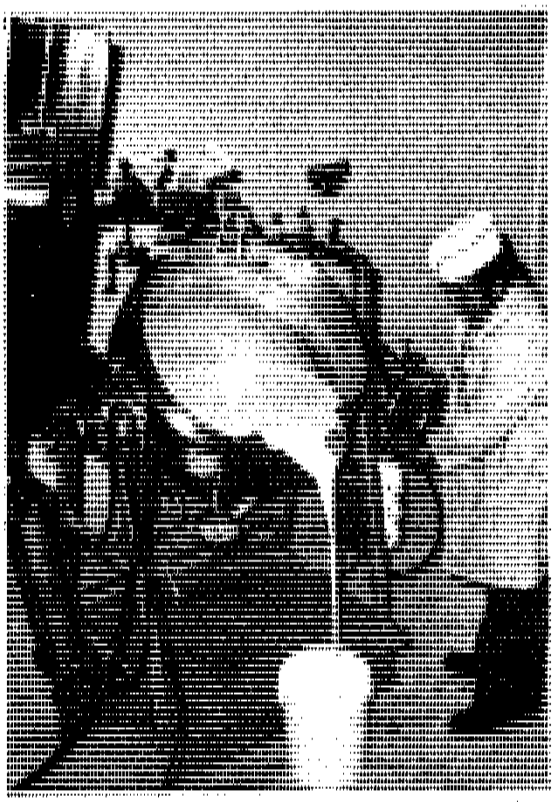

Fig 87-9. Pilot scale ointment manufacture (courtesy, Alcon).

Preparation

Ointment preparation or manufacture depends on the type of vehicle and the quantity to be prepared. The objective is the same, ie, to disperse uniformly throughout the vehicle a finely subdivided or dissolved drug substance(s). Normally, the drug materials are in finely powdered form before being dispersed in the vehicle.

Incorporation by Levigation

The preparation of small quantities of ointment by the pharmacist, ie, one to several ounces, can be accomplished by using a spatula and an ointment tile (either porcelain or glass). The finely powdered drug material is levigated thoroughly with a small quantity of the base to form a concentrate. The concentrate then is diluted geometrically with the remainder of the base. Such a procedure is useful particularly with petrolatum or oleaginous bases.

If the drug substance is water-soluble it can be dissolved in water and the resulting solution incorporated into the vehicle using a small quantity of lanolin if the base is oleaginous. Generally speaking, an amount of anhydrous lanolin equal in volume to the amount of water used will suffice.

When ointments are made by incorporation in quantities too large to be handled with a tile and spatula, mechanical mixers are used. Hobart mixers, pony mixers and others of the type usually are used for this purpose. The drug substance in finely divided form usually is added slowly or sifted into the vehicle contained in the rotating mixer. When the ointment is uniform, the finished product may be processed through a roller mill to assure complete dispersion and reduce any aggregates.

This procedure may be modified by preparing and milling

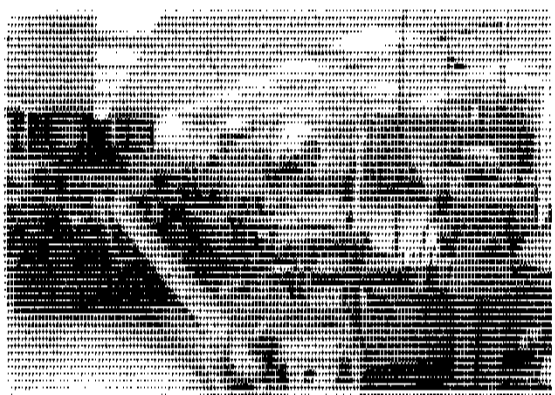

Fig 87-10. Ointment manufacture and packaging (courtesy, Owen Laboratories).

a concentrate of the drug in a portion of the base. The concentrate then is dispersed in the balance of the vehicle, using a mixer of appropriate size. Occasionally, the base may be melted for easier handling and dispersing. In such cases the drug is dispersed and the base slowly cooled using continuous agitation to maintain dispersion.

Emulsion Products

Medicated creams and lotions are prepared by means of a two-phase heat system. The oil-phase ingredients are combined in a jacketed tank and heated to about 75°. At this

temperature the oil-phase ingredients are liquefied and uniform. In a separate tank the aqueous-phase ingredients, including the emulsifier, are heated together to slightly above 75°. The aqueous phase then is added to the oil phase, slowly and with constant agitation. When the emulsion is formed the mixture is allowed to cool, maintaining slow agitation.

At this stage in the process the medicinal ingredients usually are added as a concentrated slurry, which usually has been milled to reduce any particle aggregates. Volatile or aromatic materials generally are added when the finished emulsion has cooled to about 35°. At this point additional water may be added to compensate for any evaporative losses occurring during exposure and transfer at the higher temperatures of emulsion formation.

While the product remains in the tank in bulk, quality-control procedures are performed, ie, for pH, active ingredients, etc. If control results are satisfactory the product is filled into the appropriate containers.

Preservatives in Ointment Bases

Antimicrobial preservative substances are included in ointment formulations to maintain the potency and integrity of product forms and to protect the health and safety of the consumer. The USP addresses this subject in its monograph on Microbiological Attributes of Non-Sterile Pharmaceutical Products. The significance of microorganisms in nonsterile products should be evaluated in terms of the use of the product, the nature of the product and the potential hazard to the user. The USP suggests that products applied topically should be free from *P aeruginosa* and *S aureus*.

The attributes of an ideal preservative system have been defined by various authors as

1. Effective at relatively low concentrations against a broad spectrum or variety of microorganisms which could cause disease or product deterioration.
2. Soluble in the required concentration.
3. Nontoxic and nonsensitizing at in-use concentrations.
4. Compatible with ingredients of the formulation and package components.
5. Free from objectionable odors and colors.
6. Stable over a wide spectrum of conditions.
7. Inexpensive.

No preservative or preservative system meets these ideal criteria. In fact, preservative substances once considered most acceptable, if not ideal, now have been questioned. Methylparaben and propylparaben, second and third only to water in frequency of use in cosmetic formulations, have been associated with allergic reactions.

Use of parabens as preservatives in topical products began nearly a half-century ago. Animal testing indicated that they virtually are nontoxic and the compounds, usually in combination, became nearly ubiquitous as preservatives in dermatologic and cosmetic products. In 1968 Schorr was among the first in this country to express concern about contact sensitization to parabens. Other investigators have voiced similar concerns.

Topical parabens do not appear to constitute a significant hazard to the public based on their low index of sensitization and low overall toxicity.

Alternative preservation substances available for use in ointment bases, together with comments on possible limitations, are given in Table V.[18] It is probably sensible to note that, with few exceptions, most of these compounds—in contrast to the parabens—do not have a half-century history of use nor have had extensive patch-testing experiments carried out.

Following selection of preservative candidates and preparation of product prototypes, the efficacy of the preservative system must be evaluated. A variety of methods to accomplish this have been proposed. The organism challenge procedure is currently the most acceptable. In this procedure the test-product formulation is inoculated with specific levels and types of microorganisms. Preservative efficacy is evaluated on the basis of the number of organisms killed or whose growth is inhibited as determined during a specific sampling schedule. Critical to the organism challenge procedure are the selection of challenge microorganisms, the level of organisms in the inoculum, the sampling schedule and data interpretation.

Variations of the organism challenge procedure have usually centered around the selection of organisms, the challenge schedule, use of a rechallenge and standards of effectiveness, ie, cidal activity required rather than static or inhibitory activity.

Table VI gives the challenge organisms and other criteria used in several preservative challenge procedures.

In addition to efficacy in terms of antimicrobial effects, the preservative system must be assessed in terms of chemical and physical stability as a function of time. This often is done using antimicrobial measurements in addition to chemical analysis.

Table V—Topical Preservatives: Benefits and Risks[18]

Preservatives	Limitations relative to use in cosmetic/dermatological formulations
Quaternary ammonium compounds	a) inactivated by numerous ingredients including anionics, nonionics and proteins
Organic mercurial compounds	a) potentially toxic and may sensitize the skin b) limited use in formulations used near or in the eye
Formaldehyde	a) volatile compound with an objectionable odor b) irritating to the skin c) high chemical reactivity
Halogenated phenols hexachlorophene, *p*-chloro-*m*-cresol (PCMC) *p*-chloro-*m*-xylenol (PCMX) dichloro-*m*-xylenol (DCMX)	a) objectionable odor b) often inactivated by nonionics, anionics or proteins c) limited gram-negative antibacterial activity
Sorbic acid potassium sorbate	a) pH-dependent (can be used only in formulations below the pH of 6.5 to 7.0) b) higher concentrations are oxidized by sunlight resulting in product discoloration c) limited antibacterial activity
Benzoic acid sodium benzoate	a) pH-dependent (limited to use in formulations with pH of 5.5 or less) b) replaced by newer antimicrobials because of its limited antimicrobial activity

Table VI—Preservative Effectiveness Test Procedures

	USP XX	CTFA	FDA
Challenge microorganisms	*S aureus* *E coli* *P aeruginosa* *C albicans* *A niger*	*S aureus* *E coli* *P aeruginosa* *C albicans* *A niger* *P luteum* *B subtilis*	*S aureus* *E coli* *P aeruginosa* *P putida* *P multivorans* *Klebsiella* *S marcescens* *C albicans* *A niger*
Inoculum level	1×10^5–1×10^6 Cells/mL or gm	1×10^6 Cells/mL or gm	0.8–1.2×10^6 Cells/mL or gm rechallenge 1–2.0×10^5 vegetative cells
Sampling schedule	0, 7, 14, 21, 28 days	0, 1–2, 7, 14, 28 days	weekly intervals
Standards	Bacteria < 0.1% survival by 14th day. Yeast & molds at or below initial concentration during first 14 days. No increase in organism counts for remainder of 28-day survival	Based on intended use	Vegetative cells < 0.01% survival in 28 days *C albicans* < 1% survival *A niger* < 1% survival Rechallenge 0.1% survival in 28 days

Safety, Safety Testing and Toxicity

Safety is defined as the condition of being safe from undergoing (or causing) injury. Safety is not absolute but must be taken in the context of conditions of use. Toxicity refers to a specific substance or product and the adverse effect on a system caused by such a substance or product acting for a given period of time at a specific dose level.

Ointment bases may cause irritant or allergic reactions. Allergic reactions are usually to a specific base component. Irritant reactions are more frequent and more important, hence a number of test procedures have been devised to test for irritancy levels, both in the animal and in man. The consequences of species differences and specificity must be included in the evaluation of animal-test results.

Probably the most common irritancy measure is the Draize dermal irritation test in rabbits. In this procedure the test material is applied repeatedly to the clipped skin on the rabbit's back. The test material may be compared with one or more control materials.

End-points are dermal erythema and/or edema. By assigning numerical scores for erythema and edema, mathematical and statistical treatment of results is possible.

In the human, a variety of test procedures are used to measure irritancy, sensitization potential and phototoxicity. Among the most common are the following:

21-Day Cumulative Irritation Study

In this test the test compound is applied daily to the same site on the back or volar forearm. Test materials are applied under occlusive tape and scores are read daily. The test application and scoring is repeated daily for 21 days or until irritation produces a predetermined maximum score. Typical erythema scores are

0 = no visible reaction
1 = mild erythema
2 = intense erythema
3 = intense erythema with edema
4 = intense erythema with edema and vesicular erosion.

Usually, 24 subjects are used in this test. Fewer subjects and a shorter application time in days are variants of the test.

Draize-Shelanski Repeat-Insult Patch Test

This test is designed to measure the potential to cause sensitization. The test also provides a measure of irritancy potential. In the usual procedure the test material or a suitable dilution is applied under occlusion to the same site, for 10 alternate-day 24-hr periods. Following a 7-day rest period the test material is applied again to a fresh site for 24 hr. The challenge sites are read on removal of the patch and again 24 hr later. The 0–4 erythema scale is used. A test panel of 100 individuals is common.

Kligman Maximization Test

This test is used to detect the contact sensitizing potential of a product or material. The test material is applied under occlusion to the same site for 48-hr periods. Prior to each exposure the site may be pretreated with a solution of sodium lauryl sulfate under occlusion. Following a 10-day interval the test material again is applied to a different site for 48 hr under occlusion. The challenge site may be treated briefly with a sodium lauryl sulfate solution.

The Maximization test is of shorter duration and makes use of fewer test subjects than the Draize Shelanski test. The use of sodium lauryl sulfate as a pretreatment increases the ability to detect weaker allergens.

These test methods are adequate to detect even weak irritants and weak contact sensitizers. Positive results, however, automatically do not disqualify the use of a substance as unsafe. The actual risk of use depends on concentration, period of use and skin condition. Benzoyl peroxide in tests such as the Draize Shelanski and Maximization is a potent sensitizer, yet the incidence of sensitization among acne patients is low.

Packaging and Labeling

Ointments usually are packaged in ointment jars or in metal or plastic tubes of a convenient size. Ointment jars are available in one-half to 16-oz sizes; tubes from 3.5-g capacity (often ophthalmic) to 4-oz and on occasion greater capacities.

Ointment Jars—Straight-sided screw cap jars of glass or plastic are available. Clear, amber or opaque glass containers are used, as well as white, opaque, plastic, usually high-density polyethylene, jars. Metal or composition plastic tops are available, with a variety of inner liners to assure a dust- and airtight closure. Liners are usually paper or plastic laminates or discs glued or otherwise fitted to the closure.

Ointment jars are filled mechanically to somewhat less than capacity to minimize contact between the ointment and the cap or cap-liner. Ointment jars hand-filled by the pharmacist also should be finished to avoid contact between the

ointment and cap. This can be accomplished quite readily by skillful use of a flexible spatula. The spatula is forced across the ointment jar while depressed slightly into the ointment. The result is a conical depression that is esthetically acceptable. Much of the same result can be accomplished by depressing the spatula into the center of the filled jar and gradually rotating the jar against the stationary spatula. Small points perhaps, but time well spent to avoid having part of the ointment-jar contents removed inadvertently by the cap when the patient opens the jar.

Ointment Tubes—Ointment tubes made of tin or aluminum, or of an increasing variety of plastic materials, are available. The latter are normally polyethylene, polypropylene or other flexible, heat-sealable plastics. Ointment tubes have obvious advantages over jars; the use of fingers is minimized, as is dust and air contact, and light exposure.

Depending on the expected shelf-life, a number of factors should be considered in selecting an ointment tube. Metal contact and the possibility of metal-ion catalyzed instability must be considered. Conversely, plastic tubes may become stained or discolored by migration of colored materials into the plastic sidewalls of the tube; coal tar in ointment form may cause such discoloration. Tube interactions involving either metal or plastic can be minimized by internal coatings. Such coatings usually are epoxy films that become the primary product contact.

The suitability of ointment containers, either jars or tubes, should be verified by adequate testing prior to use. Compatibility and physical and chemical stability should be established by proper tests before final selection of a jar or tube.

Ointments prepared on prescription can be conveniently filled into a metal ointment tube using the following procedure.

Select an ointment tube of the proper size and remove any lint or dust. Transfer the ointment to a piece of paper of suitable size (use glassine or strong paper). Roll the paper and ointment into a cylinder shape of a diameter slightly less than that of the ointment tube. Insert the rolled paper-ointment cylinder into the ointment tube. The length of the paper cylinder should exceed the tube length. Remove the ointment tube cap and, using a spatula, compress the paper cylinder and tube. Continue compressing the ointment and tube until the ointment appears in the neck-orifice of the open tube. Replace the cap. Using the spatula side as a knife-edge, compress the ointment tube and paper cylinder a reasonable distance from the end of the tube. Holding the spatula firmly in place, draw out the paper cylinder, leaving the ointment within the tube.

The ointment tube selected should be of adequate capacity. After compressing the ointment and paper cylinder into the tube, constrict the tube for cylinder removal at a distance from the end of the tube that will allow at least a double foldover to seal the tube. The fold dimensions are inexact, however, the individual folds on a 1-oz tube are approximately $\frac{1}{8}$ to $\frac{3}{16}$ in. Ointment tube sealing folds easily can be made by folding the tube over on itself using a spatula blade to flatten the tube and serve as a folding point. Ointment tube clips can be fixed over the tube ends and clamped in place using pliers or a small vise. The sole purpose of folding and clamping is to prevent leakage when routine use pressure is applied to the tube.

On a larger scale, ointment-tube filling is accomplished using automatic equipment which air-cleans the tubes, fills, folds and crimps the end in one continuous operation. Some equipment will stamp an expiration date onto the crimped surface. In larger-scale manufacturing operations plastic tubes are used with increasing frequency. From a filling standpoint plastic tubes are handled much like metal tubes. The final step, however, is a heat seal with no end foldover.

Labeling Ointment Tubes—Attaching labels to ointment tubes is a minor difficulty compounded by the increasing unsightliness characteristic of many ointment tubes during use. The label increasingly can become obliterated, difficult to read and, frequently, lost. As a general rule the label should be attached to itself, ie, it should completely encircle the tube. It should be attached to the tube, affixed close to the neck end.

Given the usual handling of ointment tubes by the patient, it is good practice to dispense the tube in a vial or hinged pasteboard box of convenient size. The outer container serves to hold and protect the ointment tube as well as to carry the label. The ointment tube is marked with a container prescription number so that both tube and container are identified.

On a manufacturing scale tubes are labeled in a variety of ways. Paper labels may be used, labeling may be silk-screened onto plastic surfaces; expiration dates and code lot numbers may be stamped on as a part of the tube-crimping procedure.

Suppositories

Suppositories are solid dosage forms of various weights and shapes, usually medicated, for insertion into the rectum, vagina or the urethra. After insertion, suppositories soften, melt or dissolve in the cavity fluids.

The use of suppositories dates from the distant past, this dosage form being referred to in writings of the early Egyptians, Greeks and Romans. Suppositories are suited particularly for administration of drugs to the very young and the very old, a notion first recorded by Hippocrates. Despite the antiquity of this dosage form, little was known about drug absorption or drug activity via suppository administration until recent years.

Types

Rectal Suppositories—The USP describes rectal suppositories for adults as tapered at one or both ends and usually weighing about 2 g each. Infant rectal suppositories usually weigh about one-half that of adult suppositories. Drugs having systemic effects, such as sedatives, tranquilizers and analgesics, are administered by rectal suppository; however, the largest single-use category is probably that of hemorrhoid remedies dispensed over-the-counter. The 2-g weight for adult rectal suppositories is based on use of cocoa butter as the base; when other bases are used the weights may be greater or less than 2 grams.

Vaginal Suppositories—The USP describes vaginal suppositories as usually globular or oviform and weighing about 5 g each. Vaginal medications are available in a variety of physical forms, eg, creams, gels or liquids, which depart from the classical concept of suppositories. Vaginal tablets, however, do meet the definition, and represent convenience both of administration and manufacture.

Urethral Suppositories—Urethral suppositories—sometimes referred to as bougies—are not described specifically in the USP, either by weight or dimension. Traditional values, based on use of cocoa butter as base, are as follows for these cylindrical dosage forms: diameter, 5 mm; length, 50 mm female, 125 mm male; weight, 2 g female, 4 g male. Urethral suppositories are an unusual dosage form and seldom are encountered.

Rectal Absorption

Drug absorption for systemic activity generally is limited to rectal administration. As noted previously, the bioavailability of rectally administered drugs is a relatively recent concern. Rectally instilled preparations, whether supposi-

tories, foams or solutions (enemas), tend to be confined to the rectum and sigmoid colon if the volume is less than about 50 mL. Foams tend to dissipate or spread to a lesser extent than solutions, particularly large-volume solutions (~100 to 200 mL). Though large-volume fluid formulations—solutions or enemas—may allow drug to reach the ascending colon, substantial intra- and intersubject variation is evident.[19] Literature information indicates that rectal drug absorption from suppositories can be erratic and may be substantially different from absorption following oral administration. With only a few recent exceptions, suppository studies are based on either *in vivo* or *in vitro* data with few attempts to correlate *in vitro* results with *in vivo* studies.

Major factors affecting the absorption of drugs from suppositories administered rectally are the following: anorectal physiology, suppository vehicle, absorption site pH, drug pK_a, degree of ionization and lipid solubility.

Anorectal Physiology—The rectum is about 150 mm in length, terminating in the anal opening. In the absence of fecal matter the rectum contains a small amount of fluid of low buffering capacity. Fluid pH is said to be about 7.2; because of the low buffer capacity pH will vary with the pH of the drug product or drug dissolved in it. The rectal epithelium is lipoidal in character. The lower, middle and upper hemorrhoidal veins surround the rectum. Only the upper vein conveys blood into the portal system, thus drugs absorbed into the lower and middle hemorrhoidal veins will bypass the liver. Absorption and distribution of a drug therefore is modified by its position in the rectum, in the sense that at least a portion of the drug absorbed from the rectum may pass directly into the inferior vena cava, bypassing the liver.

Spreading characteristics of rectal formulations may be affected considerably by intraluminal rectal pressure—due, in part, to the weight of abdominal organs and to respiratory activity—and by periodic contractile activity of the rectal wall.[20]

Suppository Vehicle—The ideal suppository base should meet the following general specifications:

1. The base is nontoxic and nonirritating to mucous membranes.
2. The base is compatible with a variety of drugs.
3. The base melts or dissolves in rectal fluids.
4. The base should be stable on storage; it should not bind or otherwise interfere with release and absorption of drug substances.

Absorption Factors—Prior to absorption the administered drug must be in solution. Solution, therefore, must be preceded by dissolution or melting of the vehicle. Dissolution is followed by partitioning or diffusion of the drug into the rectal fluid.

Rectal suppository bases can be classified broadly into two types. The traditional cocoa butter vehicle is immiscible with aqueous tissue fluids but melts at body temperature. Water-soluble vehicles also have been used. Typical of this class is the polyethylene glycol vehicle. Drug absorption from such dissimilar bases can differ substantially. Lowenthal and Borzelleca[21] investigated the absorption of salicylic acid and sodium salicylate administered to dogs. The drugs were formulated in a cocoa butter base and in a base comprised of polyethylene glycol, synthetic glycerides and a surfactant. Absorption of salicylic acid and sodium salicylate was about equal from the cocoa butter base; however, salicylic acid gave higher plasma levels than sodium salicylate when the glycol base was used.

Parrott[22] compared the absorption of salicylates after rectal and oral administration. Using urinary excretion data both aspirin and sodium salicylate were found to be equally bioavailable orally or rectally. Aspirin was released more rapidly from water-miscible suppositories than from the oily type. Conversely, sodium salicylate was released more rapidly from a cocoa butter vehicle.

Based on available data the bioavailability of a drug from a suppository dosage form is dependent on the physicochemical properties of the drug as well as the composition of the base. The drug-dissolution rate and, where appropriate, the partition coefficient between lipid and aqueous phase should be known.

For suppository formulation the relative solubility of the drug in the vehicle is a convenient comparison measure. Lipid-soluble drugs present in low concentration in a cocoa butter base will have little tendency to diffuse into rectal fluids. Drugs that are only slightly soluble in the lipid base will partition readily into the rectal fluid. The partition coefficient between suppository base and rectal fluid thus becomes a useful measure. In water-soluble bases and assuming rapid dissolution, the rate-limiting step in absorption would be transport of the drug through the rectal mucosa.

A wide variety of substances have been investigated for their ability to enhance rectal permeability to drugs. Agents such as EDTA have been used to chelate Ca^{2+} and Mg^{2+} in the vicinity of paracellular tight junctions and, thus, alter epithelial permeability. Other promoters of rectal absorption (eg, bile salts and nonsteroidal anti-inflammatory agents, including aspirin, salicylic acid and diclofenac) appear to exert their influence by affecting water influx and efflux rates across the rectal mucosa. Surfactants not only may modify membrane permeability but also enhance wetting or spreading of the base and dissolution of the drug. In any event, it should be evident that, whatever the mechanism, enhancing the *rectal* absorption of drugs—especially those which undergo presystemic elimination—could result in substantially reduced dosage requirements and decreased risk of adverse reactions.

Clearly, the bioavailability of a drug administered rectally depends on the nature of the drug and the composition of the vehicle or base. The physical properties of the drug can be modified to a degree, as can the characteristics of the base selected as the delivery system. Preformulation evaluations of physicochemical properties must then be confirmed by *in vivo* studies in animals and ultimately in the primary primate, man.

***In Vivo* Rectal Absorption Studies**—Dogs are probably the animal of choice in evaluating rectal drug availability. (The pig is a closer physiological match, but size and manageability argue in favor of the dog.) Blood and urine samples can be obtained from the dog and rectal retention can be accomplished with facility. Smaller animals have been used; rabbits, rats and even mice have been employed, but dosing and sampling become progressively more difficult.

Human subjects provide the ultimate measure of drug bioavailability. Subjects are selected on the basis of age, weight and medical history. Subjects usually are required to fast overnight and evacuate the bowel prior to initiation of the study. Fluid volume and food intake usually are standardized in studies of this kind.

Given the difficulty of standardizing pharmacological end-points the usual measure of rectal drug bioavailability is the concentration of the drug in blood and or urine as a function of time. A control group using oral drug administration provides a convenient means of comparing oral and rectal drug availability. Such a comparison is meaningful particularly in view of uncertainties and conflicts encountered in the literature. While there is general agreement about drug absorption from the rectum there is less agreement on dosage adequacy and the relationship between oral and rectal dosage. This state of affairs argues in favor of adequate studies to establish proper dosage and verify bioavailability.

Vaginal Absorption

Passive drug absorption via the vaginal mucosa, as with other mucosal tissues, is influenced by absorption site physiology, absorption site pH and the solubility and partitioning characteristics of the drug. The vaginal epithelial surface usually is covered with an aqueous film—emanating from cervical secretions—whose volume, pH and composition vary with age, stage of the menstrual cycle and location. Postmenarche, a vaginal pH gradient is evident with the lowest values (pH ~4.0) near the anterior fornix and the highest (pH ~5.0) near the cervix.[23] Following intravaginal administration, some drug absorption from the intact vaginal mucosa is likely, even when the drug is employed for a local effect. In fact, extensive drug absorption can occur from the vagina. For example, Patel *et al*[24] reported that plasma propranolol concentrations following vaginal dosing were significantly higher than those after peroral administration of an equivalent dose; a reflection, in part, of decreased first-pass biotransformation following vaginal absorption. Nonetheless, the notion persists that the vaginal epithelium is relatively impermeable to drugs. The widespread extemporaneous compounding of progesterone vaginal suppositories,[25,26] as well as the marketing of an intrauterine progesterone drug delivery system [Progestasert, *Alza*] have focused interest on systemic drug absorption following intravaginal administration. However, only limited reports of research on *in vitro* and *in vivo* aspects of vaginal absorption have appeared in the literature to date.

Bases

The USP lists the following as usual suppository bases: cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

Cocoa Butter—Theobroma oil, or cocoa butter, is a naturally occurring triglyceride. About 40% of the fatty acid content is unsaturated. As a natural material there is considerable batch-to-batch variability. A major characteristic of theobroma oil is its polymorphism, ie, its ability to exist in more than one crystal form. While cocoa butter melts quickly at body temperature, it is immiscible with body fluids; this may inhibit the diffusion of fat-soluble drugs to the affected sites.

If, in the preparation of suppositories, the theobroma oil is overheated, ie, heated to about 60°, molded and chilled, the suppositories formed will melt below 30°. The fusion treatment of theobroma oil requires maximum temperatures of 40 to 50° to avoid a change in crystal form and melting point. Theobroma oil, heated to about 60° and cooled rapidly will crystallize in an alpha configuration characterized by a melting point below 30°. The alpha form is metastable and will slowly revert to the beta form with the characteristic melting point approaching 35°. The transition from alpha to beta is slow, taking several days. The use of low heat and slow cooling allows direct crystallization of the more stable beta crystal form.

Certain drugs will depress the melting point of theobroma oil. This involves no polymorphic change although the net effect is similar. Chloral hydrate is the most important of those substances because its rectal hypnotic dose of 0.5 to 1.0 g will cause a substantial melting-point depression. This effect can be countered by addition of a higher melting wax, such as white wax or synthetic spermaceti. The amount to be added must be determined by temperature measurements. The effect of such additives on bioavailability also must be considered.

Water-Soluble or Dispersible Bases—Water-miscible suppository bases are of comparatively recent origin. The majority are comprised of polyethylene glycols or glycol-surfactant combinations. Water-miscible suppository bases have the substantial advantage of lack of dependence on a melting point approximating body temperature. Problems of handling, storage and shipping are simplified considerably.

Polymers of ethylene glycol are available as polyethylene glycol polymers (Carbowax, polyglycols) of assorted molecular weights. Suppositories of varying melting points and solubility characteristics can be prepared by blending polyethylene glycols of 1000, 4000 or 6000 molecular weight.

Polyethylene glycol suppositories are prepared rather easily by molding. The drug-glycol mixture is prepared by melting and then is cooled to just above the melting point before pouring into dry unlubricated molds. Cooling to near the melting point prevents fissuring caused by crystallization and contraction. Polyethylene glycol suppositories cannot be prepared satisfactorily by hand-rolling.

Water-miscible or water-dispersible suppositories also can be prepared using selected nonionic surfactant materials. Polyoxyl 40 stearate is a white, water-soluble solid melting slightly above body temperature. A polyoxyethylene derivative of sorbitan monostearate is water-insoluble but dispersible. In using surfactant materials the possibility of drug–base interactions must be borne in mind. Interactions caused by macromolecular adsorption may have a significant effect on bioavailability.

Examples of water-miscible suppository bases, devised by Zopf *et al*, are

Base 1

Polyethylene glycol 1000	95%
Polyethylene glycol 4000	5%

Base 2

Polyethylene glycol 1000	75%
Polyethylene glycol 4000	25%

Base 1 is low-melting and may require refrigeration; Base 2 is more heat-stable. Each is prepared conveniently by molding techniques.

Water-dispersible bases may include polyoxyethylene sorbitan fatty acid esters. These are either soluble (Tween, Myrj) or water-dispersible (Arlacel), used alone or in combination with other wax or fatty materials. Surfactants in suppositories should be used only with recognition of reports that such materials may either increase or decrease drug absorption.

Glycerinated Gelatin—Glycerinated gelatin usually is used as a vehicle for vaginal suppositories. For rectal use a firmer suppository can be obtained by increasing the gelatin content. Glycerinated gelatin suppositories are prepared by dissolving or dispersing the drug substance in enough water to equal 10% of the final suppository weight. Glycerin (70%) is then added and Pharmagel A or B (20%), depending on the drug compatibility requirements. Pharmagel A is acid in reaction, Pharmagel B is alkaline. Glycerinated gelatin suppositories must be formed by molding. The mass cannot be processed by hand-rolling. These suppositories, if not for immediate use, should contain a preservative such as methylparaben and propylparaben.

Preparation

Suppositories are prepared by rolling (hand-shaping), molding (fusion) and cold compression.

Rolled (Hand-Shaped) Suppositories—Hand-shaping suppositories is the oldest and the simplest method of pre-

paring this dosage form. The manipulation requires considerable skill, yet avoids the complications of heat and mold preparation.

The general process can be described as follows:

General Process

Take the prescribed quantity of the medicinal substances and a sufficient quantity of grated theobroma oil. In a mortar reduce the medicating ingredients to a fine powder or, if composed of extracts, soften with diluted alcohol and rub until a smooth paste is formed. The correct amount of grated theobroma oil then is added, and a mass resembling a pill mass is made by thoroughly incorporating the ingredients with a pestle, sometimes with the aid of a small amount of wool fat. When the mass has become plastic under the vigorous kneading of the pestle, it quickly is loosened from the mortar with a spatula, pressed into a roughly shaped mass in the center of the mortar and then transferred with the spatula to a piece of filter paper which is kept between the mass and the hands during the kneading and rolling procedure. By quick, rotary movements of the hands, the mass is rolled to a ball which immediately is placed on a pill tile. A suppository cylinder is formed by rolling the mass on the tile with a flat board, partially aided by the palm of the other hand, if weather conditions permit. The suppository "pipe" frequently will show a tendency to crack in the center, developing a hollow core. This occurs when the mass has not been kneaded and softened sufficiently, with the result that the pressure of the roller board is not carried uniformly throughout the mass but is exerted primarily on the surface. The length of the cylinder usually corresponds to about four spaces on the pill tile for each suppository, thus making the piece, when cut, practically a finished suppository except for the shaping of the point. When the cylinder has been cut into the proper number of pieces with a spatula, the conical shape is given it by rolling one end on the tile with a spatula, or in some cases even by shaping it with the fingers to produce a rounded point.

Compression-Molded (Fused) Suppositories—This method of suppository preparation also avoids heat. The suppository mass, such as a mixture of grated theobroma oil and drug, is forced into a mold under pressure, using a wheel-operated press. The mass is forced into mold openings, pressure is released, the mold removed, opened and replaced. On a large scale cold-compression machines are hydraulically operated, water-jacketed for cooling and screw-fed. Pressure is applied via a piston to compress the mass into mold openings.

Fusion or Melt Molding—In this method the drug is dispersed or dissolved in the melted suppository base. The mixture then is poured into a suppository mold, allowed to cool and the finished suppositories removed by opening the mold. Using this procedure, one to hundreds of suppositories can be made at one time.

Suppository molds are available for the preparation of various types and sizes of suppositories. Molds are made of aluminum alloy, brass or plastic and are available with from six to several hundred cavities.

Suppositories usually are formulated on a weight basis so that the medication replaces a portion of the vehicle as a function of specific gravity. If the medicinal substance has a density approximately the same as theobroma oil, it will replace an equal weight of oil. If the medication is heavier, it will replace a proportionally smaller amount of theobroma oil.

For instance, tannic acid has a density of 1.6 as compared with cocoa butter (see Table VII[27]). If a suppository is to contain 0.1 g tannic acid, then 0.1 g ÷ 1.6 or 0.062 g cocoa butter should be replaced by 0.1 g of drug. If the blank weight of the suppository is 2.0 g, then 2.0 − 0.062 g or 1.938 g cocoa butter is required per suppository. The suppository will actually weigh 1.938 g + 0.1 g or 2.038 g. Table VII indicates the density factor, or the density as compared with cocoa butter, of many substances used in suppositories.

It always is possible to determine the density of a medicinal substance relative to cocoa butter, if the density factor is not available, by mixing the amount of drug for one or more suppositories with a small quantity of cocoa butter, pouring the mixture into a suppository mold and carefully filling the mold with additional melted cocoa butter. The cooled suppositories are weighed providing data from which a working formula can be calculated as well as the density factor itself.

When using suppository bases other than cocoa butter, such as a polyethylene glycol base, it is necessary to know either the density of the drug relative to the new base or both the densities of the drug and the new base relative to cocoa butter. The density factor for a base other than cocoa butter is simply the ratio of the blank weight of the base and cocoa butter.

For instance, if a suppository is to contain 0.1 g tannic acid in a polyethylene glycol base, then 0.1 g ÷ 1.6 × 1.25 or 0.078 g polyethylene glycol base should be replaced by 0.1 g drug (the polyethylene glycol base is assumed to have a density factor of 1.25). If the blank weight is 1.75 g for the polyethylene glycol base, then 1.75 g − 0.078 g or 1.672 g of base is required per suppository. The final weight will be 1.672 g base + 0.1 g drug or 1.772 g.

When the dosage and mold calibration are complete the drug–base mass should be prepared using minimum heat. A water bath or water jacketing usually is used. The melted mass should be stirred constantly but slowly to avoid air entrapment. The mass should be poured into the mold openings slowly. Prelubrication of the mold will depend on the vehicle. Mineral oil is a good lubricant for cocoa butter

Table VII—Density Factors for Cocoa Butter Suppositories[27,28]

Medication	Factor
Acid, boric	1.5
Acid, benzoic	1.5
Acid, gallic	2.0
Acid, salicylic	1.3
Acid, tannic	1.6
Alum	1.7
Aminophylline	1.1
Aminopyrine	1.3
Aspirin	1.3
Barbital	1.2
Belladonna extract	1.3
Bismuth carbonate	4.5
Bismuth salicylate	4.5
Bismuth subgallate	2.7
Bismuth subnitrate	6.0
Castor oil	1.0
Chloral hydrate	1.3
Cocaine hydrochloride	1.3
Digitalis leaf	1.6
Glycerin	1.6
Ichthammol	1.1
Iodoform	4.6
Menthol	0.7
Morphine hydrochloride	1.6
Opium	1.4
Paraffin	1.0
Peruvian Balsam[a]	1.1
Phenobarbital	1.2
Phenol[a]	0.9
Potassium bromide	2.2
Potassium iodide	4.5
Procaine	1.2
Quinine hydrochloride	1.2
Resorcinol	1.4
Sodium bromide	2.3
Spermaceti	1.0
Sulfathiazole	1.6
Tannic acid	1.6
White wax	1.0
Witch hazel fluidextract	1.1
Zinc oxide	4.0
Zinc sulfate	2.8

[a] Density adjusted taking into account white wax in mass.

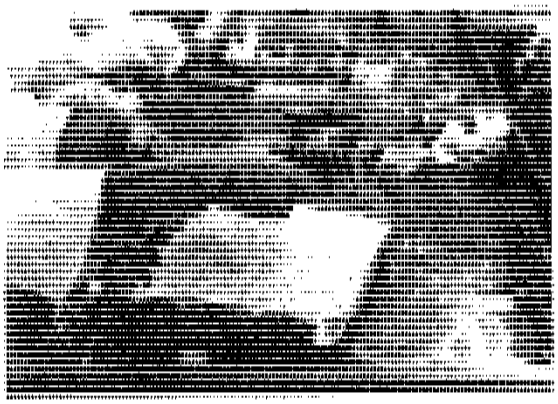

Fig 87-11. Removing cocoa butter suppositories from mold (courtesy, Webcon Div, Alcon).

suppositories. Molds should be dry for polyethylene glycol suppositories.

After pouring into tightly clamped molds the suppositories and mold are allowed to cool thoroughly using refrigeration on a small scale or refrigerated air on a larger scale. After thorough chilling any excess suppository mass should be removed from the mold by scraping, the mold opened and the suppositories removed. It is important to allow cooling time adequate for suppository contraction. This aids in removal and minimizes splitting of the finished suppository.

Packaging and Storage—Suppositories often are packaged in partitioned boxes which hold the suppositories upright. Glycerin and glycerinated gelatin suppositories often are packaged in tightly closed screw-capped glass containers. Though many commercial suppositories are wrapped individually in aluminum foil, or PVC-polyethylene strip-packaging is commonplace.

The most recent innovation in suppository manufacture is the procedure for molding the suppository directly into its primary packaging. In this operation the form into which the suppository mass flows consists of a series of individual molds formed from plastic or foil. After the suppository is poured and cooled the excess is trimmed off and the units are sealed and cut into 3s or 6s as desired. Cooling and final cartoning then can be carried out.

Suppositories with low-melting ingredients are best stored in a cool place. Theobroma oil suppositories, in particular, should be refrigerated.

Other Medicated Applications

Cataplasms (Poultices)

Poultices represent one of the most ancient classes of pharmaceutical preparations. A poultice, or cataplasm, is a soft, moist mass of meal, herbs, seed, etc, usually applied hot in cloth. The consistency is gruel-like, which is probably the origin of the word poultice.

Cataplasms were intended to localize infectious material in the body or to act as counterirritants. The materials tended to be absorptive, which, together with heat accounts for their popular use. None is now official in the USP. The last official product was Kaolin Poultice NF IX.

Pastes

Pastes are concentrates of absorptive powders dispersed (usually) in petrolatum or hydrophilic petrolatum. They are stiff to the point of dryness and reasonably absorptive in view of the petrolatum base. Pastes often are used in the treatment of oozing lesions where they act to absorb serous secretions. Pastes also are used to restrict the area of treatment by acting as an absorbent and physical dam.

Pastes adhere reasonably well to the skin, and are poorly occlusive. For this reason they are suited for application on and around moist lesions. The heavy consistency of pastes imparts a degree of protection and may, in some instances, make the use of bandages unnecessary. Pastes are less macerating than ointments.

Because of their physical properties pastes easily may be removed from the skin by the use of mineral oil or a vegetable oil. This is particularly true when the underlying or surrounding skin is traumatized easily.

An official paste is the conventional Zinc Oxide Paste; another is Triamcinolone Acetonide Dental Paste, for the specialized use the name implies.

Powders

Powders for external use usually are described as dusting powders. Such powders should have a particle size of not more than 150 μm, ie, less than 100-mesh, to avoid any sensation of grittiness which could irritate traumatized skin. Dusting powders usually contain starch, talc and zinc stearate. Absorbable Dusting Powder USP is comprised of starch treated with epichlorohydrin, with not more than 2.0% magnesium oxide added to maintain the modified starch in impalpable powder form; as it is intended for use as a lubricant for surgical gloves it should be sterilized (by autoclaving) and packaged in sealed paper packets.

The fineness of powders often is expressed in terms of mesh size, with impalpable powders generally in the range of 100- to 200-mesh (149–125 mm). Determination of size by mesh analysis becomes increasingly difficult as particle size decreases below 200-mesh.

Dressings

Dressings are external applications resembling ointments usually used as a covering or protection. Petrolatum Gauze is a sterile dressing prepared by adding sterile, molten, white petrolatum to precut sterile gauze in a ratio of 60 g of petrolatum to 20 g of gauze. Topical antibacterials are available in the form of dressings.

Creams

Creams are viscous liquid or semisolid emulsions of either the o/w or w/o type. Pharmaceutical creams are classified as water-removable bases and are described under *Ointments*. In addition to ointment bases, creams include a variety of cosmetic-type preparations. Creams of the o/w type include shaving creams, hand creams and foundation creams; w/o creams include cold creams and emollient creams.

Plasters

Plasters are substances intended for external application made of such materials and of such consistency as to adhere to the skin and attach to a dressing. Plasters are intended to afford protection and support and/or to furnish an occlusive and macerating action and to bring medication into close contact with the skin. Medicated plasters, long used for local or regional drug delivery, are the prototypical transdermal delivery system.

Plasters usually adhere to the skin by means of an adhesive material. The adhesive must bond to the plastic backing and to the skin (or dressing) with proper balance of cohesive strengths. Such a proper balance provides for re-

moval, ie, adhesive breakage at the surface of application thus leaving a clean (skin) surface when the plaster is removed.

Contraceptives

In the context of this chapter contraceptives are considered in the form of creams, jellies or aerosol foams intended for vaginal use to protect against pregnancy. Contraceptive creams and jellies are designed to melt or spread, following insertion, over the vaginal surfaces. These agents act to immobilize spermatozoa.

Creams and jellies for contraceptive use may contain spermicidal agents such as nonoxynol 9 or they may function by a specific pH effect. A pH of 3.5 or less has an appreciable spermicidal effect. It is important to note that a final *in situ* pH of 3.5 or less is required; thus, the dilution effect and pH change brought about by vaginal fluids must be considered. To achieve the proper pH effect and control, buffer systems composed of acid and acid salts such as lactates, acetates and citrates are used frequently. The user must, of course, be assured of the safety, lack of irritancy, acceptability and effectiveness of such products; also, detailed and specific information and instructions should be available to physicians.

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