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

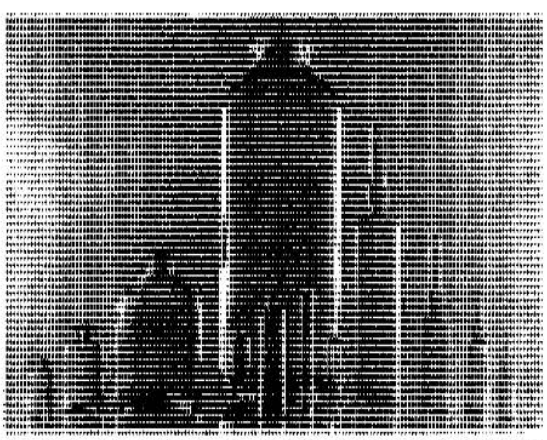


Fig 84-3. Various types of ampuls and multiple-dose vials for parenterals (courtesy, Kimble).

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]

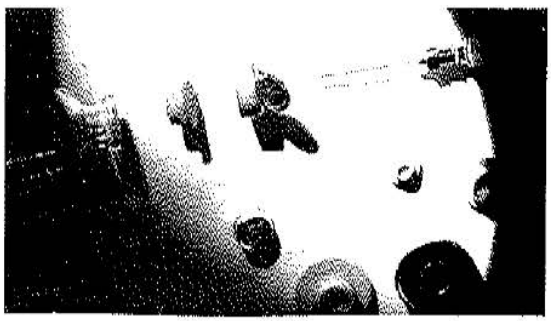


Fig 84-4. Extended view of sealing components for a multiple-dose vial (courtesy, West).

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

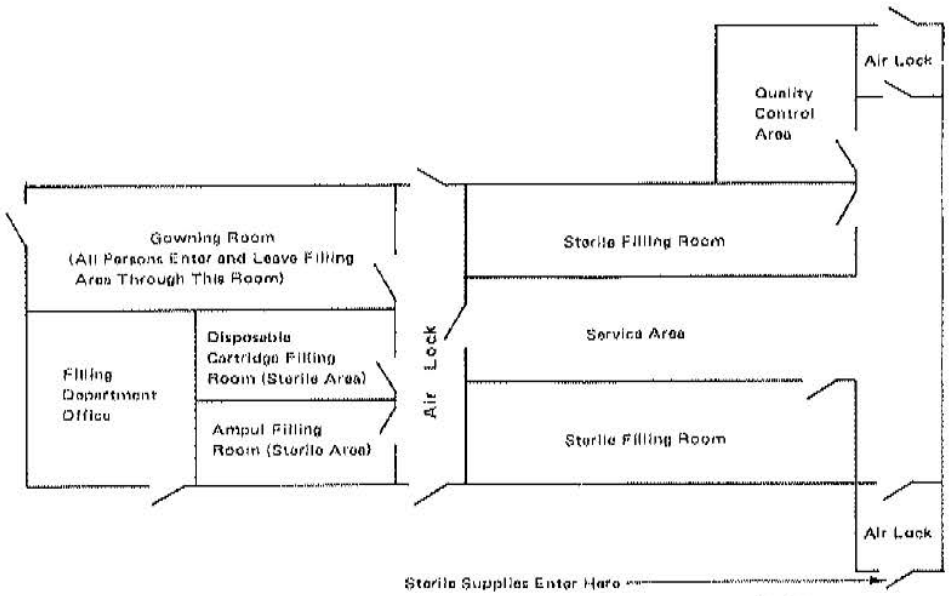


Fig 84-5. Floor plan of an aseptic filling area with its service area (courtesy, Wyeth).

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.

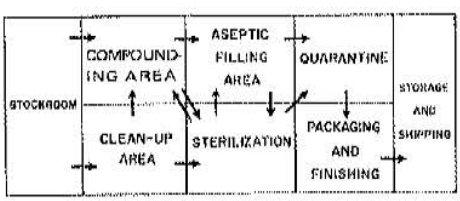


Fig 84-6. Process-flow diagram.

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

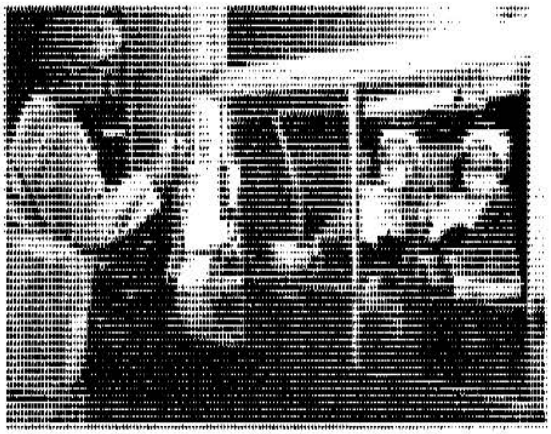


Fig 84-7. View from the service area with pipeting machine and stock-bottle retained outside of the aseptic filling area (courtesy, Wyeth).

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-

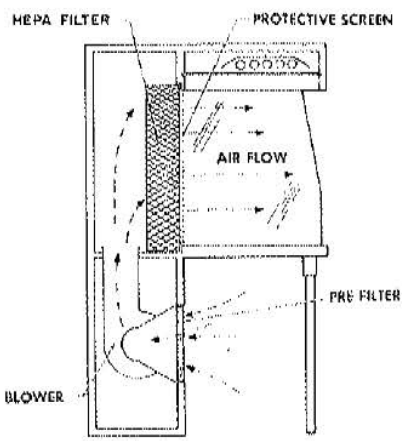


Fig 84-9. Horizontal laminar-flow workbench (courtesy, adaptation, Sandia).

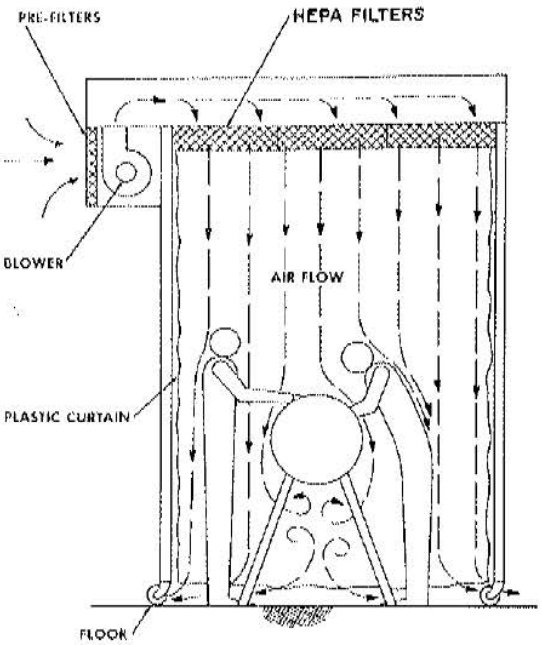


Fig 84-10. Vertical laminar-flow portable room with equipment and operators (courtesy, adaptation, Sandia).

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

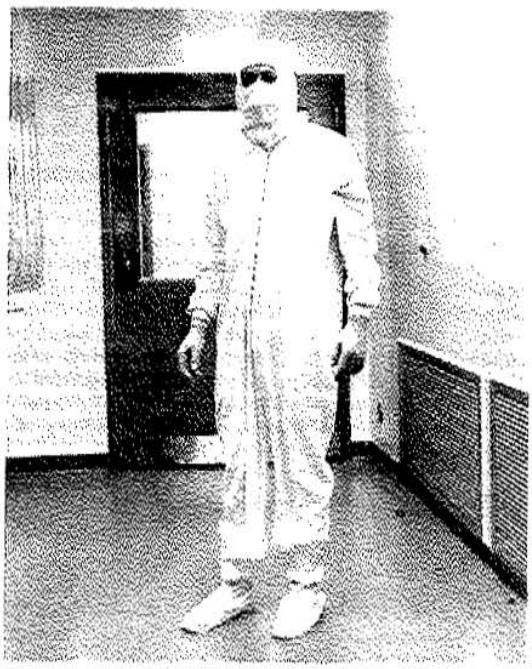


Fig 84-11. Appropriate uniform for operators entering an aseptic filling room (courtesy, Abbott).

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

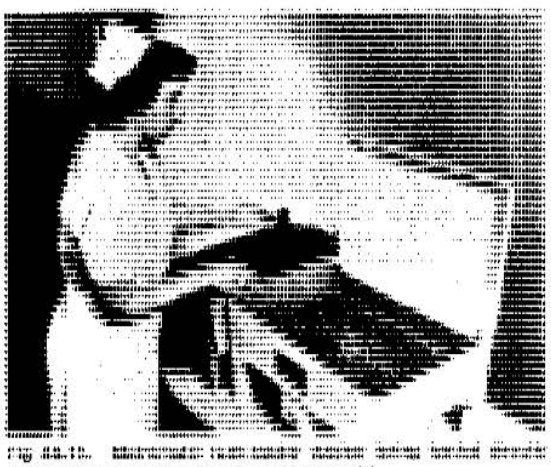
Fig 84-12. Rotary rinser (Cozzoli) in a clean environment provided by vertical laminar airflow within a curtained enclosure (courtesy, Ciba-Geigy).

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 (Better Built) being loaded with ampuls (courtesy, The University of Tennessee College of Pharmacy).

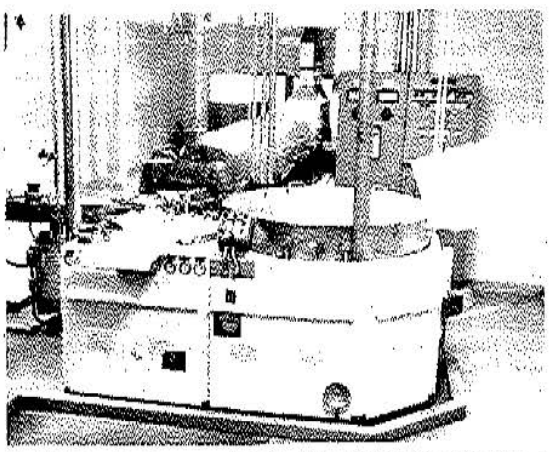


Fig 84-16. Continuous automatic line operation for vials from a rotary rinser through a sterilizing tunnel with vertical laminar-airflow protection of clean vials (courtesy, Abbott).

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.

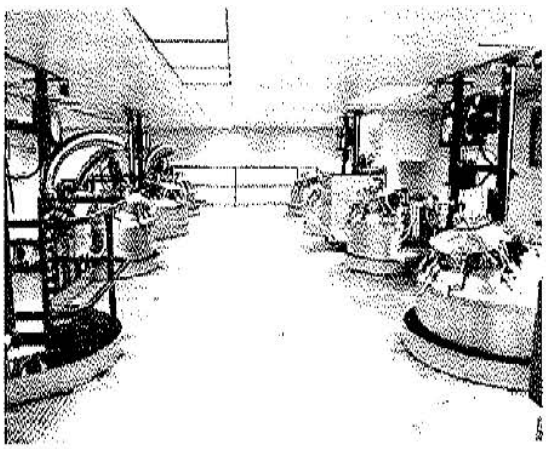


Fig 84-17. Large stainless-steel tanks for product preparation showing mezzanine access level (courtesy, Abbott).

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.

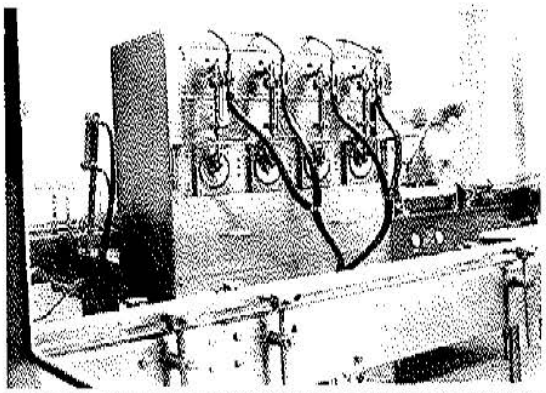


Fig 84-19. Four-pump liquid filler, with a conveyor line for vials protected by a vertical laminar airflow and plastic curtain; note the automatic stoppering machine on the right within the curtain (courtesy, Abbott).

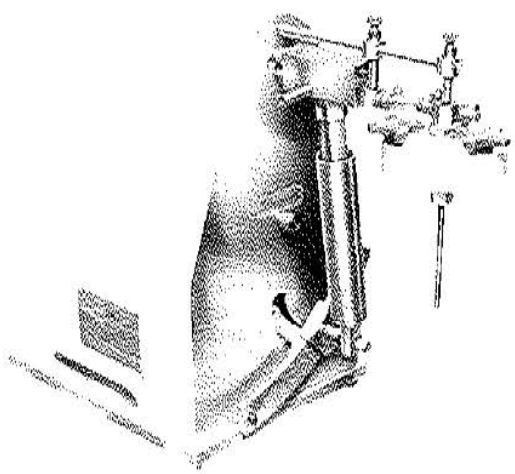


Fig 84-18. Filling machine employing a piston valve and a stainless-steel syringe (courtesy, Cozzoli).

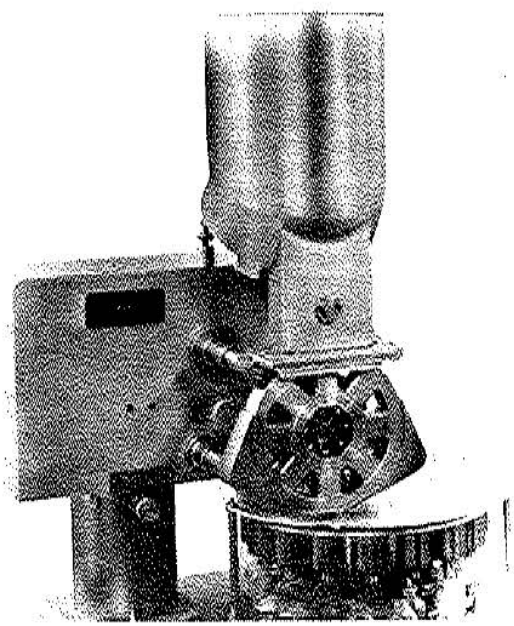


Fig 84-20. Accofil vacuum powder filler (courtesy, Perry).

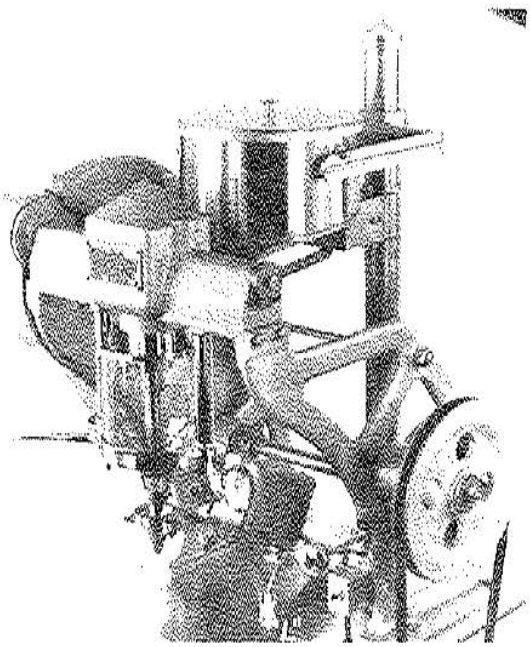


Fig 84-21. Auger-type powder filler (courtesy, Chase-Logeman).

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.

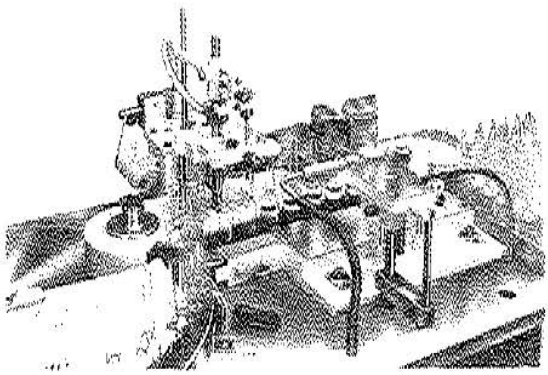


Fig 84-22. Automatic filling and pull-sealing of ampuls (courtesy, Cozzoli).

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

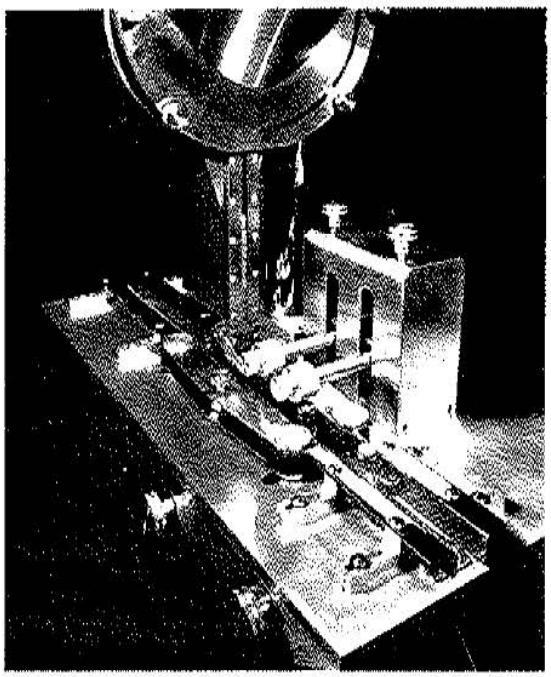


Fig 84-23. Mechanical device for inserting rubber closures in vials (courtesy, Perry).

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*).

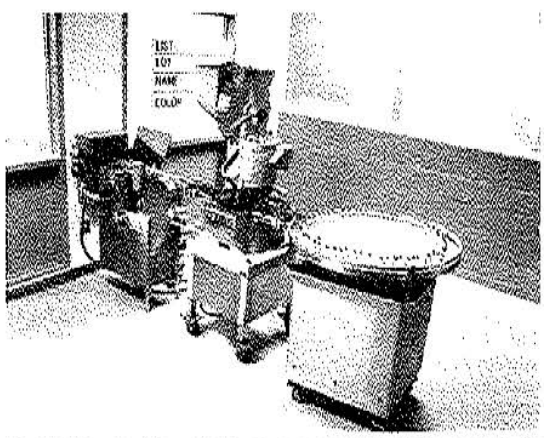


Fig 84-24. Applying aluminum caps to vials at the end of the process line (courtesy, Abbott).

Sterilization

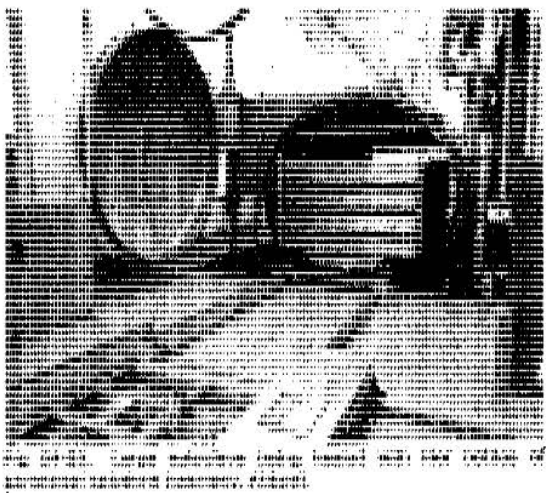
Whenever possible, the parenteral product should be sterilized after being sealed in its final container (terminal sterilization) and within as short a time as possible after the filling and sealing have been completed. Since this usually involves a thermal process, due consideration must be given to 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

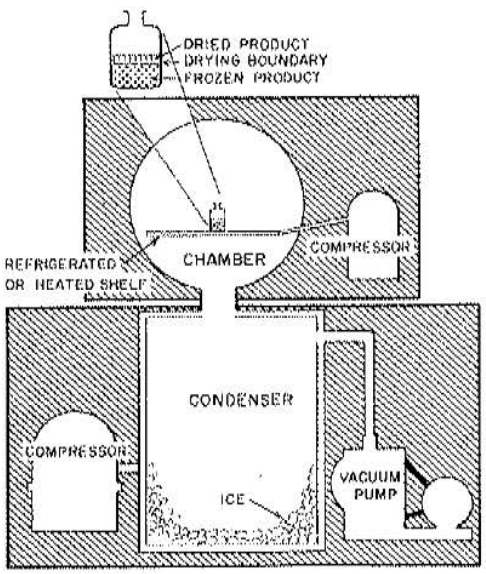


Fig 84-26. Essential components of a freeze-drying system.

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:

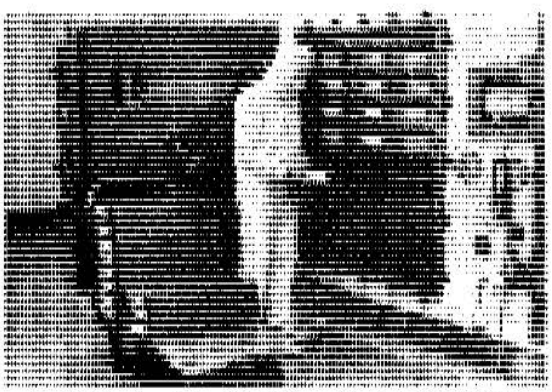


Fig 84-27. Aseptic loading of freeze-drier (courtesy, Upjohn).

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, Rayco*). 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 caloric 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*
Abbott (*Lifecare*)	Plastic	Polyvinyl chloride Flexible Nonvented

* 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,

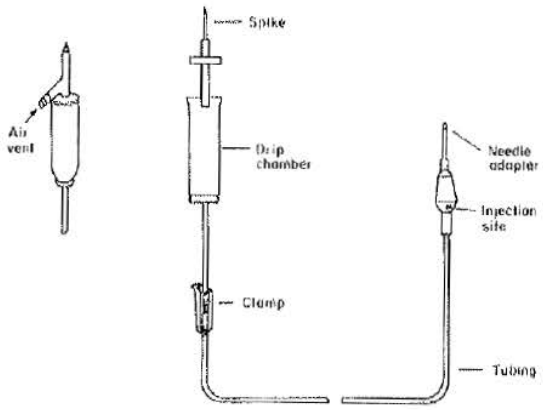

Fig 85-1. Parts of basic administration sets.

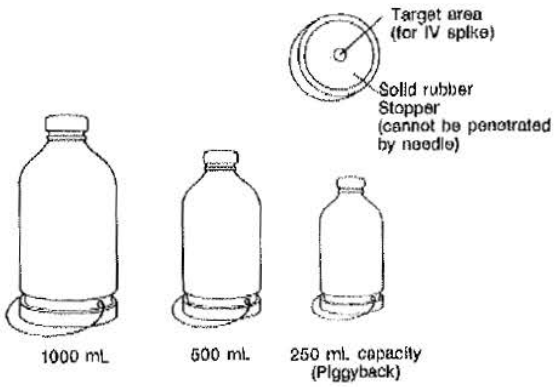

Fig 85-2. Abbott IV glass container. The air venting is provided through the air filter located in the spike of the administration set. See Fig 85-1.

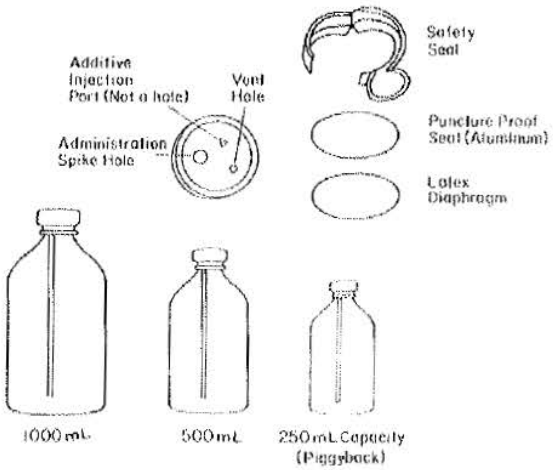

Fig 85-3. Baxter and McGaw glass containers. The plastic air tube allows the air to enter the bottle as the fluid is infused into the patient. The spike of the administration set is not vented. See Fig 85-1.

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.

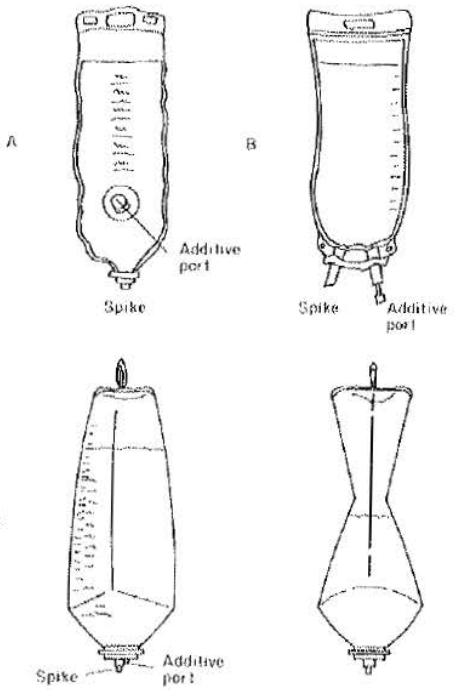

Fig 85-4. (A) Abbott (*Lifecare*) polyvinyl chloride flexible container; (B) Baxter (*Viaflex*) polyvinyl chloride flexible container; McGaw (*Accumed*) polyolefin semirigid container, front and side views. These containers take nonvented administration sets. See Fig 85-1.

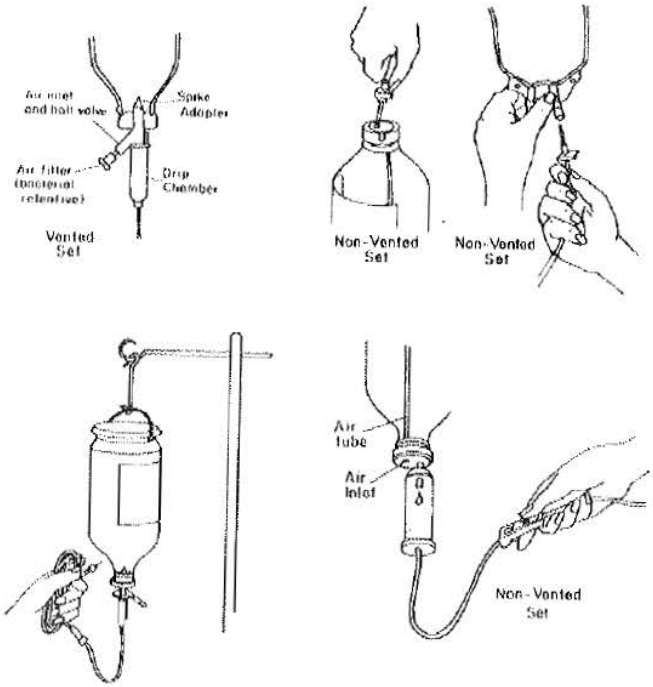

Fig 85-5. Setting up a primary IV fluid for administration.

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

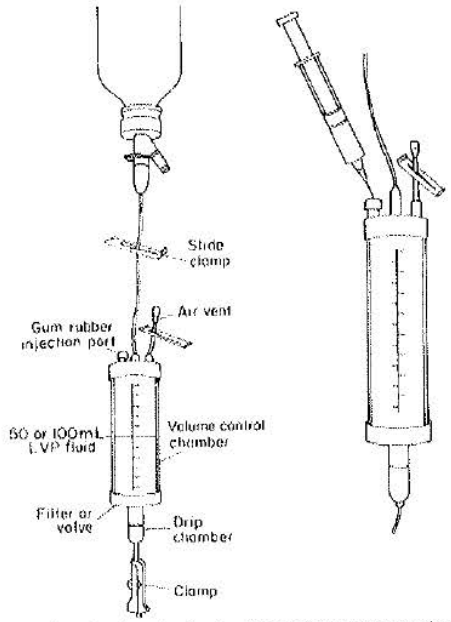

Fig 85-7. Piggyback method: the intermittent administration of a second solution through the venipuncture site of an established primary IV system.

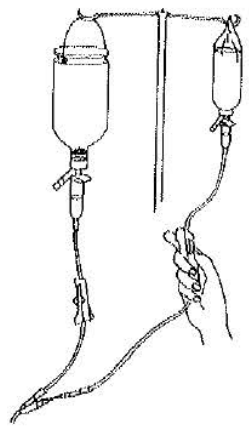

Fig 85-8. Piggyback administration setup.

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.

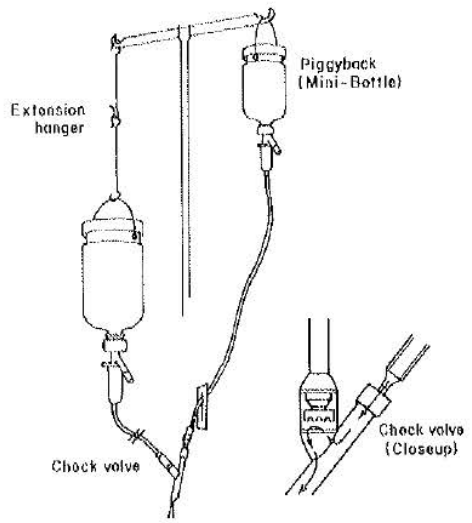

Fig 85-9. Piggyback administration setup with check valve in primary set.

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.

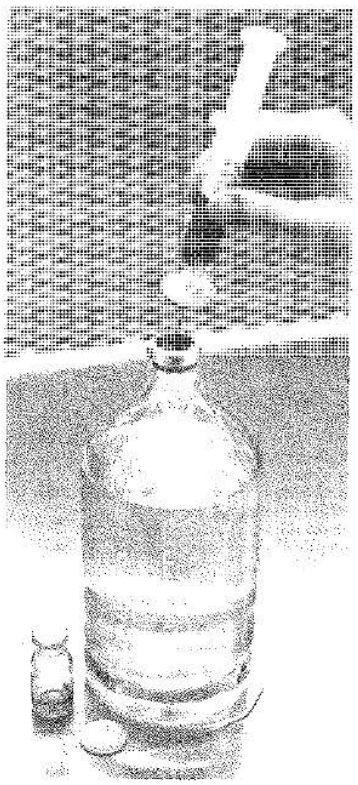

Fig 85-10. Placing an additive into an IV fluid with filtration through a membrane filter (courtesy, Millipore).

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 + 50 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.

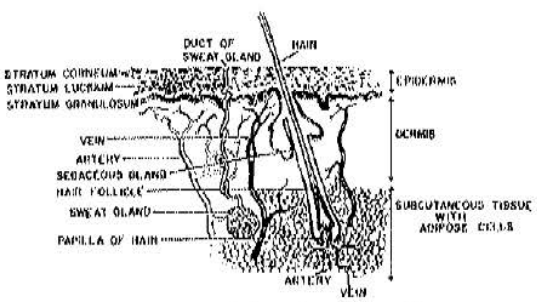

Fig 87-1. Vertical section of human skin.

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/cm². Fewer than 100/cm² 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/cm². 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

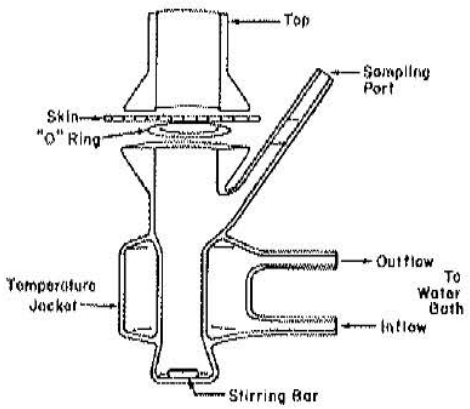

Fig 87-2. Schematic representation of diffusion cell. Top is open to ambient laboratory environment.[1]

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]

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

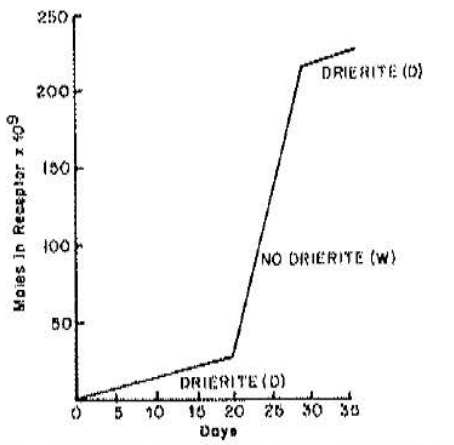

Fig 87-3. Change in cortisone penetration by alternately drying (D) and humidifying (W) the stratum corneum.[2]

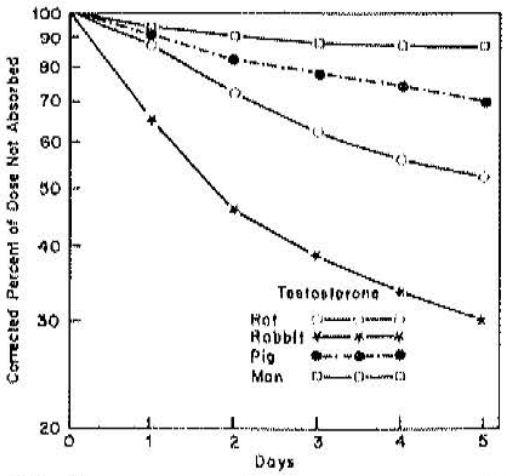

Fig 07-4. Percutaneous absorption of testosterone in rats, rabbits, swine and man for 5 days after application.[4]

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[9]

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 (85.9–106)	10–20
Prednisolone	2.44 (1.54–7.76)	1–2
Prednisolone 21-acetate	5.43 (4.06–7.70)	3
Betamethasone	97.3 (16.7–141)	3–5
Betamethasone 21-acetate	1072.0 (876–1179)	18–33
Fluorometholone	136.3 (67.9–333)	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.

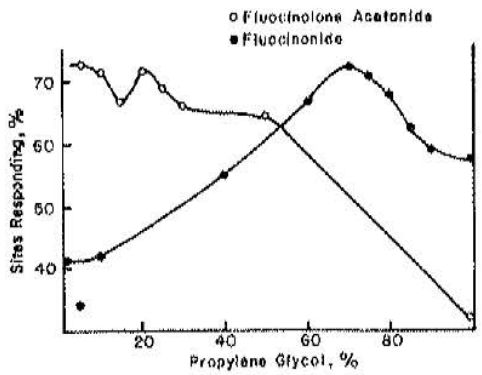

Fig 87-5. *In vivo* response as a function of vehicle composition (24-hour vasoconstriction).[10]

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]

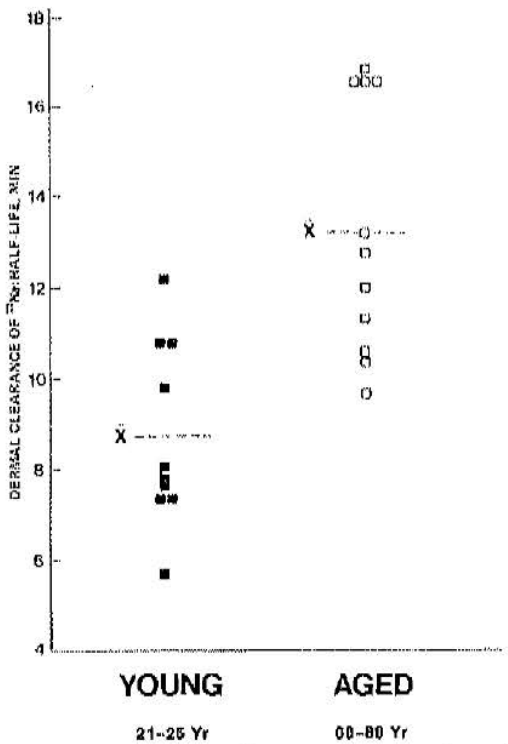

Fig 87-6. Dermal clearance of ^{22}Na in young and aged subjects after intradermal injection (data from Ref 13).

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

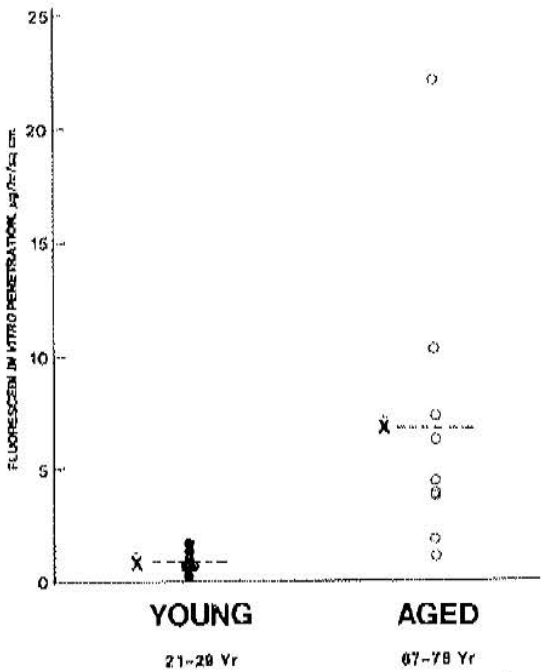

Fig 87-7. Flux of fluorescein through stratum corneum excised from young and aged subjects (data from Ref 13).

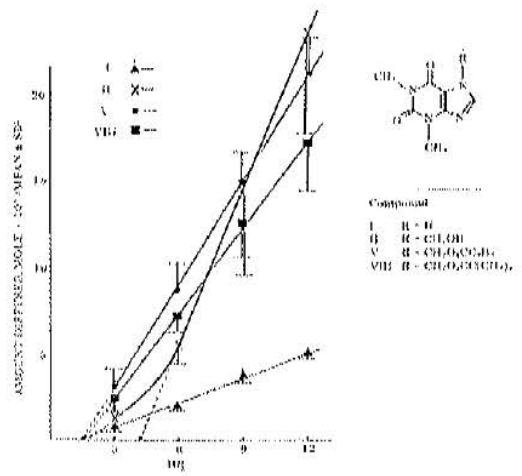

Fig 87-8. Diffusion of theophylline (I) and its derivatives through hairless mouse skin.[14]

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 nonoccclusive 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.

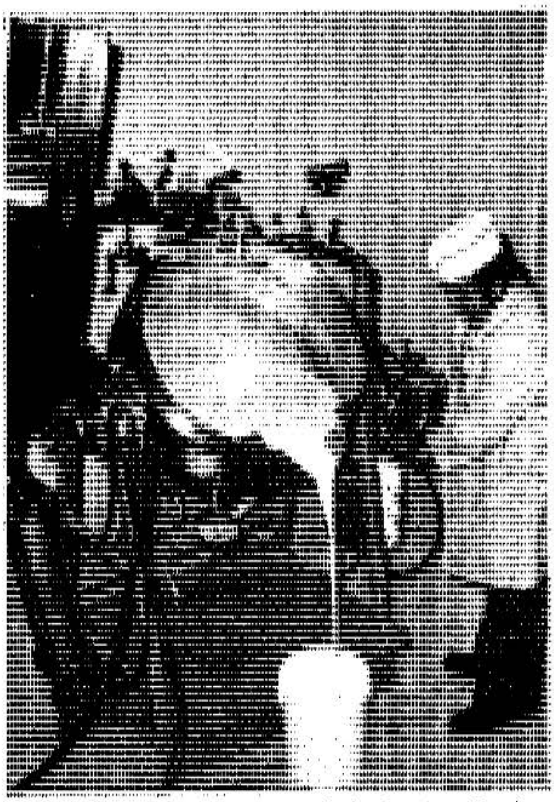

Fig 87-9. Pilot scale ointment manufacture (courtesy, Alcon).

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

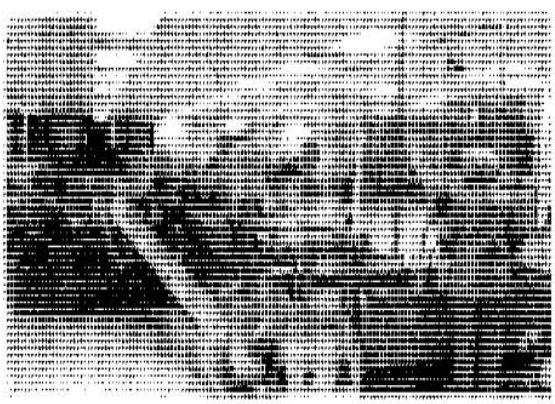

Fig 87-10. Ointment manufacture and packaging (courtesy, Owen Laboratories).

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 "pips" 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.

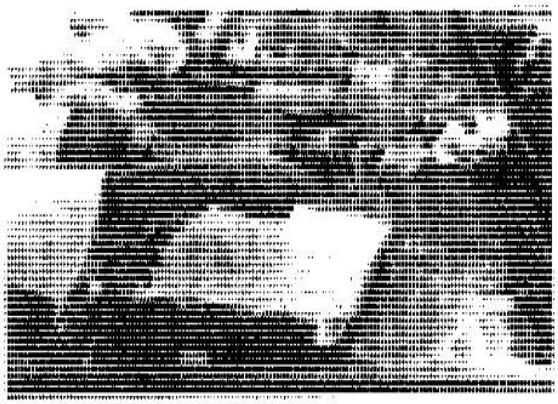

Fig 67-11. Removing cocoa butter suppositories from mold (courtesy, Webcon Div, Alcon).

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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