CHAPTER 41

Parenteral Preparations

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Parenteral (Gk, *para enteron,* beside the intestine) dosage forms differ from all other drug dosage forms because they are injected directly into body tissue through the primary protective system of the human body, the skin, and mucous membranes. They must be exceptionally pure and free from physical, chemical, and biological contaminants. These requirements place a heavy responsibility on the pharmaceutical industry to practice current good manufacturing practices (cGMPs) in the manufacture of parenteral dosage forms and upon pharmacists and other health care professionals to practice good aseptic practices (GAPs) in dispensing them for administration to patients.

Certain pharmaceutical agents, particularly peptides, proteins, and many chemotherapeutic agents, can only be given parenterally because they are inactivated in the gastrointestinal tract when given by mouth. Parenterally administered drugs are relatively unstable and generally high potent drugs that require strict control of their administration to the patient. Because of the advent of biotechnology, parenteral products have grown in number and usage around the world.

This chapter will focus on the unique characteristics of parenteral dosage forms and the basic principles for formulating, packaging, manufacturing, and controlling the quality of these unique products. The references and bibliography at the end of this chapter contain the most up-to-date texts, book chapters, and review papers on parenteral product formulation, manufacture, and quality control.

OVERVIEW OF UNIQUE CHARACTERISTICS OF PARENTERAL DOSAGE FORMS

Parenteral products are unique from any other type of pharmaceutical dosage form for the following reasons:

- All products must be sterile.
- All products must be free from pyrogenic (endotoxin) contamination.
- Injectable solutions must be free from visible particulate matter. This includes reconstituted sterile powders.
- Products should be isotonic although strictness of isotonicity depends on the route of administration. Products to be administered into the cerebrospinal fluid must be isotonic. Ophthalmic products, while not parenteral, also must be isotonic. Products to be administered by bolus injection by routes other than intravenous (IV) essentially should be isotonic or at least very close to isotonicity. IV infusions must be isotonic.
- All products must be stable (not only chemically and physically like all other dosage forms, but also "stable" microbiologically, ie, sterility, freedom from pyrogenic and visible particulate contamination must be maintained throughout the shelflife of the product).
- Products must be compatible (if applicable) with IV diluents, delivery systems, and other drug products co-administered.

The author recognizes the long time contributions of Dr. Kenneth Avis. Dr. Avis died in January 1999. Dr. Avis authored this chapter in Remington since 1965. To honor his memory, the author has maintained most of his organization of this chapter with new material and revised information added where appropriate.

FORMULATION PRINCIPLES

Parenteral drugs are formulated as solutions, suspensions, emulsions, liposomes, microspheres, nanosystems, and powders to be reconstituted as solutions. This section will describe the components that are commonly used in parenteral formulations focusing on solutions and freeze-dried products. General guidance also will be provided on appropriate selection of the finished sterile dosage form and initial approaches used to develop the optimal parenteral formulation.

VEHICLES

WATER—Since most liquid injections are quite dilute, the component present in the highest proportion is the vehicle. The vehicle of greatest importance for parenteral products is water. Water of suitable quality for compounding and rinsing product contact surfaces may be prepared either by distillation or by reverse osmosis, to meet United States Pharmacopeia (USP) specifications for Water for Injection (WFI). Only by these two methods is it possible to separate adequately various liquid, gas, and solid contaminating substances from water. These two methods for preparation of WFI and specifications for WFI are discussed later in this chapter. With the possible exception of freeze-drying, there is no unit operation more important and none more costly to install and operate than the one for the preparation of WFI.

WATER-MISCIBLE VEHICLES—A number of solvents that are miscible with water have been used as a portion of the vehicle in the formulation of parenterals. These solvents are used primarily to solubilize certain drugs in an aqueous vehicle and to reduce hydrolysis. The most important solvents in this group are ethyl alcohol, liquid polyethylene glycol, and propylene glycol. Ethyl alcohol is used particularly in the preparation of solutions of cardiac glycosides and the glycols in solutions of barbiturates, certain alkaloids, and certain antibiotics. Such preparations usually are given intramuscularly. There are limitations with the amount of these co-solvents that can be administered because of toxicity concerns, greater potential for hemolysis, and potential for drug precipitation at the site of injection.[1] Formulation scientists needing to use one or more of these solvents must consult the literature (eg, reference [2]) and toxicologists to ascertain the maximum amount of co-solvents

allowed for their particular product. Several references provide information on concentrations of co-solvents used in approved commercial parenteral products.[3–8]

NON-AQUEOUS VEHICLES—The most important group of non-aqueous vehicles are the fixed oils. The USP provides specifications for such vehicles, indicating that the fixed oils must be of vegetable origin so that they will be metabolized, will be liquid at room temperature, and will not become rancid readily. The USP also specifies limits for the free fatty acid content, iodine value, and saponification value (oil heated with alkali to produce soap, ie, alcohol plus acid salt). The oils most commonly used are corn oil, cottonseed oil, peanut oil, and sesame oil. Fixed oils are used particularly as vehicles for certain hormone (eg, progesterone, testosterone, deoxycorticicosterone) and vitamin (eg, vitamin K, vitamin E) preparations. The label must state the name of the vehicle so that the user may beware in case of known sensitivity or other reactions to it.

SOLUTES

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

Reputable chemical manufacturers accept the stringent quality requirements for parenteral products and, accordingly, apply good manufacturing practices to their chemical manufacturing. Examples of critical bulk manufacturing precautions include:

- Using dedicated equipment or properly validated cleaning to prevent cross-contamination and transfer of impurities
- Using WFI for rinsing equipment
- Using closed systems wherever possible for bulk manufacturing steps not followed by further purification
- Adhering to specified endotoxin and bioburden testing limits for the substance.

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

- Increase and maintain drug solubility. Examples include complexing agents and surface active agents. The most commonly used complexing agents are the cyclodextrins, including Captisol®. The most commonly used surface active agents are polyoxyethylene sorbitan monolaurate (Tween 20) and polyoxyethylene sorbitans monooleate (Tween 80).
- Provide patient comfort by reducing pain and tissue irritation, as do substances added to make a solution isotonic or near physiological pH. Common tonicity adjusters are sodium chloride, dextrose, and glycerin.
- Enhance the chemical stability of a solution, as do antioxidants, inert gases, chelating agents, and buffers.
- Enhance the chemical and physical stability of a freeze-dried product, as do cryoprotectants and lyoprotectants.
- Enhance the physical stability of proteins by minimizing self aggregation or interfacial induced aggregation. Surface active agents serve nicely in this capacity.
- Minimize protein interaction with inert surfaces such as glass and rubber and plastic. Competitive binders such as albumin and surface active agents are the best examples.
- Protect a preparation against the growth of microorganisms. The term *preservative* sometimes is applied only to those substances that prevent the growth of microorganisms in a preparation. However, such limited use is inappropriate, being better used for all substances that act to retard or prevent the chemical, physical, or biological degradation of a preparation.
- While not covered in this chapter, other reasons for adding solutes to parenteral formulations include sustaining and/or controlling drug release (polymers), maintaining the drug in a suspension dosage form (suspending agents, usually polymers and surface active agents), establishing emulsified dosage forms (emulsifying agents, usually amphiphilic polymers and surface active agents), and preparation of liposomes (hydrated phospholipids).

Although added substances may prevent a certain reaction from taking place, they may induce others. Not only may visible incompatibilities occur, but hydrolysis, complexation, oxidation, and other invisible reactions may decompose or otherwise inactivate the therapeutic agent or other added substances.[9] Therefore, added substances must be selected with due consideration and investigation of their effect on the total formulation and the container-closure system.

ANTIMICROBIAL AGENTS—The USP states that antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to preparations contained in multiple-dose containers.* They must be present in adequate concentration at the time of use to prevent the multiplication of microorganisms inadvertently introduced into the preparation while withdrawing a portion of the contents with a hypodermic needle and syringe. The USP provides a test for Antimicrobial Preservative Effectiveness to determine that an antimicrobial substance or combination adequately inhibits the growth of microorganisms in a parenteral product.[10] Because antimicrobials may have inherent toxicity for the patient, the USP prescribes maximum volume and concentration limits for those that are used commonly in parenteral products (eg, phenylmercuric nitrate and thimerosal 0.01%, benzethonium chloride and benzalkonium chloride 0.01%, phenol or cresol 0.5%, and chlorobutanol 0.5%).

The above limit rarely is used for phenylmercuric nitrate, most frequently employed in a concentration of 0.002%. Methyl *p*-hydroxybenzoate 0.18% and propyl *p*-hydroxybenzoate 0.02% in combination, and benzyl alcohol 2% also are used frequently. Benzyl alcohol, phenol, and the parabens are the most widely used antimicrobial preservative agents used in injectable products. While the mercurials are still allowed to be used in older products, they are not used for new products because of concerns regarding mercury toxicity. In oleaginous preparations, no antibacterial agent commonly employed appears to be effective. However, it has been reported that hexylresorcinol 0.5% and phenylmercuric benzoate 0.1% are moderately bactericidal. A few therapeutic compounds have been shown to have antibacterial activity, thus obviating the need for added agents.

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

Protein pharmaceuticals, because of their cost and/or frequency of use, are preferred to be available as multiple dose formulations (eg, human insulin, human growth hormone, interferons, vaccines). However, several proteins are reactive with antimicrobial preservative agents (eg, tissue plasminogen activator, sargramostim, interleukins) and, therefore, are only available as single dosage form units.

*The European Pharmacopeia requires multiple-dose products to be bacteriocidal and fungicidal.[10]

Single-dose containers and pharmacy bulk packs that do not contain antimicrobial agents are expected to be used promptly after opening or to be discarded. The ICH/CPMP guidelines† require that products without preservatives must be used immediately (within 3 hours after entering the primary package) or a longer usage period must be justified.

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

BUFFERS are used primarily to stabilize a solution against chemical degradation or, especially for proteins, physical degradation (ie, aggregation and precipitation) that might occur if the pH changes appreciably. Buffer systems employed should normally have as low a buffering capacity as feasible so as not to disturb significantly the body's buffering systems when injected. In addition, the buffer type and concentration on the activity of the active ingredient must be evaluated carefully. Buffer components are known to catalyze degradation of drugs. The acid salts most frequently employed as buffers are citrates, acetates, and phosphates.

ANTIOXIDANTS are required frequently to preserve products because of the ease with which many drugs are oxidized. Sodium bisulfite and other sulfurous acid salts are used most frequently. Ascorbic acid and its salts also are good antioxidants. The sodium salt of ethylenediaminetetraacetic acid (EDTA) has been found to enhance the activity of antioxidants in some cases, apparently by chelating metallic ions that would otherwise catalyze the oxidation reaction.

Displacing the air (oxygen) in and above the solution by purging with an inert gas, such as nitrogen, also can be used as a means to control oxidation of a sensitive drug. Process control is required for assurance that every container is deaerated adequately and uniformly. However, conventional processes for removing oxygen from liquids and containers do not absolutely remove all oxygen. The only approach for completely removing oxygen is to employ isolator technology where the entire atmosphere can be recirculating nitrogen or another non-oxygen gas.

TONICITY AGENTS are used in many parenteral and ophthalmic products to adjust the tonicity of the solution. While it is the goal for every injectable product to be isotonic with physiologic fluids, this is not an essential requirement for small volume injectables that are administered intravenously. However, products administered by all other routes, especially into the eye or spinal fluid, must be isotonic. Injections into the subcutaneous tissue and muscles also should be isotonic to minimize pain and tissue irritation. The agents most commonly used are electrolytes and mono- or disaccharides.

CRYOPROTECTANTS and LYOPROTECTANTS are additives that serve to protect biopharmaceuticals from adverse effects due to freezing and/or drying of the product during freeze-dry processing. *Sugars* (non-reducing) such as sucrose or trehalose, *amino acids* such as glycine or lysine, *polymers* such as liquid polyethylene glycol or dextran, and *polyols* such as mannitol or sorbitol all are possible cryo- or lyoprotectants. Several theories exist to explain why these additives work to protect proteins against freezing and/or drying effects.[11,12] Excipients that are preferentially excluded from the surface of the protein are the best cryoprotectants and excipients that remain amorphous during and after freeze-drying serve best as lyoprotectants.

General Guidance for Developing Formulations of Parenteral Drugs

The final formulation of a parenteral drug product depends on understanding the following factors that dictate the choice of formulation and dosage form:

1. Route of administration—Injections may be administered by routes such as intravenous, subcutaneous, intradermal, intramuscular, intraarticular, and intrathecal. The type of dosage form (solution, suspension, etc.) will determine the particular route of administration that may be employed. Conversely, the desired route of administration will place requirements on the formulation. For example, suspensions would not be administered directly into the bloodstream because of the danger of insoluble particles blocking capillaries. Solutions to be administered subcutaneously require strict attention to tonicity adjustment, otherwise irritation of the plentiful supply of nerve endings in this anatomical area would give rise to pronounced pain. Injections intended for intraocular, intraspinal, intracisternal, and intrathecal administration require stricter standards of such properties as formulation tonicity, component purity, and limit of endotoxins because of the sensitivity of tissues encountered to irritant and toxic substances.

   If the route of administration must be intravenous, then only solutions or microemulsions can be the dosage form. If the route of administration is to be subcutaneous or intramuscular, then the likely type of dosage form is a suspension or other microparticulate delivery system.
2. Pharmacokinetics of the drug—Rates of absorption (for routes of administration other than intravenous or intra-arterial), distribution, metabolism, and excretion for a drug will have some effect on the selected route of administration and, accordingly, the type of formulation. For example, if the pharmacokinetic profile of a drug is very rapid, modified release dosage formulations may need to be developed. The dose of drug and the dosage regimen are affected by pharmacokinetics so the size (ie, concentration) of dose will also influence the type of formulation and amounts of other ingredients in the formulation. If the dosage regimen requires frequent injections, then a multiple dose formulation must be developed, if feasible. If the drug is distributed quickly from the site injection, complexing agents or viscosity inducing agents may be added to the formulation to retard drug dissolution and transport.
3. Drug solubility—If the drug is insufficiently soluble in water at the required dosage, then the formulation must contain a co-solvent or a solute that sufficiently increases and maintains the drug in solution. If relatively simple formulation additives do not result in a solution, then a dispersed system dosage form must be developed. Solubility also dictates the concentration of drug in the dosage form.
4. Drug stability—If the drug has significant degradation problems in solution, then a freeze-dried or other sterile solid dosage form must be developed. Stability is sometimes affected by drug concentration that, in turn, might affect size and type of packaging system used. For example, if concentration must be low due to stability and/or solubility limitations, then the size of primary container must be larger and this might preclude the use of syringes, cartridges, and/or smaller vial sizes. Obviously, stability dictates the expiration date of the product that, in turn, will determine the storage conditions. Storage conditions might dictate choice of container size, formulation components, and type of container. If a product must be refrigerated, then the container cannot be too large and formulation components must be soluble and stable at colder conditions.
5. Compatibility of drug with potential formulation additives—It is well-known that drug-excipient incompatibilities frequently exist.[9] Initial preformulation screening studies are essential to assure that formulation additives, while possibly solving one problem, will not create another. Stabilizers, such as buffers and antioxidants, while chemically stabilizing the drug in one way, may also catalyze other chemical degradation reactions. Excipients and certain drugs can form insoluble complexes. Impurities in excipients can cause drug degradation reactions. Peroxide impurities in polymers may catalyze oxidative degradation reactions with drugs, including proteins, that are oxygen sensitive.
6. Desired type of packaging—Selection of packaging (type, size, shape, color of rubber closure, label, and aluminum cap) often is based on marketing preferences and competition. Knowing the type of final package early in the development process aids the formulation scientist in being sure that the product formulation will be compatible and elegant in that packaging system.

Table 41-1 provides steps involved in the formulation of a new parenteral drug product. This can also be viewed as a list of questions, the answers of which will facilitate decisions on the final formulation that should be developed.

†www.eudra.org/emea/pdfs/CPMP_QWP_159_96.pdf

Table 41-1. Main Steps Involved in the Formulation of a New Parenteral Drug Product

1. Obtain physical properties of active drug substance
   a. Structure, molecular weight
   b. "Practical" solubility in water at room temperature
   c. Effect of pH on solubility
   d. Solubility in certain other solvents
   e. Unusual solubility properties
   f. Isoelectric point for a protein or peptide
   g. Hygroscopicity
   h. Potential for water or other solvent loss
   i. Aggregation potential for protein or peptide
2. Obtain chemical properties of active drug substance
   a. Must have a "validatable" analytical method for potency and purity
   b. Time for 10% degradation at room temperature in aqueous solution in the pH range of anticipated use
   c. Time for 10% degradation at 5°C.
   d. pH stability profile
   e. Sensitivity to oxygen
   f. Sensitivity to light
   g. Major routes of degradation and degradation products
3. Initial formulation approaches
   a. Know timeline(s) for drug product
   b. Know how drug product will be used in the clinic
      i. Single dose vs multiple dose
      ii. If multiple dose, will preservative agent be part of drug solution/powder or part of diluent?
      iii. Shelf life goals
      iv. Combination with other products, diluents
   c. From knowledge of solubility and stability properties, and information from anticipated clinical use formulate drug with components and solution properties that are known to be successful at dealing with these issues. Then perform accelerated stability studies.
      i. High temperature storage
      ii. Temperature cycling
      iii. Light and/or oxygen exposure
      iv. For powders, expose to high humidities
   d. May need to perform several short-term stability studies as excipient types and combinations are eliminated.
   e. Understand need for any special container and closure requirements
   f. Design and implement an initial manufacturing method of the product
   g. Finalize formulation
      i. Need for tonicity adjusting agent
      ii. Need for antimicrobial preservative
   h. Approach to obtain sterile product
      i. Terminal sterilization
      ii. Sterile filtration and aseptic processing

Courtesy of Dr. Eddie Massey and Dr. Alan Fites, Baxter Pharmaceutical Solutions.

ADMINISTRATION

Injections may be classified in six general categories:

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

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

PARENTERAL COMBINATIONS

Most dosage forms, when released to the marketplace by the manufacturer, are consumed by the patient without any significant manipulation of the product. For example, tablets and capsules are ingested in the same form as they were when released by the manufacturer. For many parenteral drug products, this is not the case. For example, products in vials must be withdrawn into a syringe prior to injection and often combined with other products in infusion solutions prior to administration. Freeze-dried products first have to be reconstituted with a specific or nonspecific diluent prior to being withdrawn from the vial. Specifically, it is common practice for a physician to order the addition of a small-volume therapeutic injection (SVI), such as an antibiotic, to large-volume injections (LVIs), such as 1000 mL of 0.9% sodium chloride solution, to avoid the discomfort for the patient of a separate injection. Certain aqueous vehicles are recognized officially because of their valid use in parenterals. Often they are used as isotonic vehicles to which a drug may be added at the time of administration. The additional osmotic effect of the drug may not be enough to produce any discomfort when administered. These vehicles include sodium chloride injection, Ringer's injection, dextrose injection, dextrose and sodium chloride injection, and lactated Ringer's injection.

While the pharmacist is the most qualified health professional to be responsible for preparing such combinations, as is clearly stated in the hospital accreditation manual of the Joint Commission on Accreditation of Healthcare Organizations,[13] interactions among the combined products can be troublesome even for the pharmacist. In fact, incompatibilities can occur and cause inactivation of one or more ingredients or other undesired reactions. Patient deaths have been reported from the precipitate formed by two incompatible ingredients. In some instances incompatibilities are visible as precipitation or color change, but in other instances there may be no visible effect.

The many potential combinations present a complex situation even for the pharmacist. To aid in making decisions concerning potential problems, a valuable compilation of relevant data has been assembled by Trissel[14] and is updated regularly. Further, the advent of computerized data storage and retrieval systems has provided a means to organize and gain rapid access to such information. Further information on this subject may be found in Chapter 42 *(Intravenous Admixtures)*.

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

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

GENERAL CONSIDERATIONS

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

Types of Processes

The preparation of parenteral products may be categorized as small-scale dispensing, usually one unit at a time, or large-scale manufacturing, in which hundreds of thousands of units may constitute one lot of product. The former category illustrates the type of processing that is done in early clinical phase manufacturing or in institutions such as hospital pharmacies. The latter category is typical of the processing done in the later clinical phase and commercial manufacturing in the pharmaceutical industry. Wherever they are made, parenteral products must be subjected to the same basic practices of current Good Manufacturing Practices (cGMPs) and good aseptic processing essential for the preparation of a safe and effective sterile product of highest quality, but the methods used must be modified appropriately for the scale of operation.

The small-scale preparation and dispensing of parenteral products might use sterile components in their preparation. Therefore, the overall process focuses on maintaining rather than achieving sterility in the process steps. In the hospital setting, the final product might have a shelf life measured in hours. However, the extensive movement of patients out of the hospital to home care has modified hospital dispensing of parenteral products, wherein multiple units are made for a given patient, and a shelf life of 30 days or more is required. Such products are sometimes made in hospital pharmacies but increasingly in centers set up to provide this service. A discussion of such processing can be found in the USP general chapter <1206>.

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

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

The pursuit of cGMP is an ongoing effort that must flex with new technological developments and new understanding of existing principles. Because of the extreme importance of quality in health care of the public, the US Congress has given the responsibility of regulatory scrutiny over the manufacture and distribution of drug products to the FDA (see Chapter 48 for more detail regarding the new drug approval process). Therefore, the operations of the pharmaceutical industry are subject to the oversight of the FDA and, with respect to manufacturing practices, to the application of the cGMPs. These regulations are discussed more fully in Chapter 51 (*Quality Assurance and Control*).

In concert with the pursuit of cGMPs, the pharmaceutical industry has shown initiative and innovation in the extensive technological development and improvement in quality, safety, and effectiveness of parenteral dosage forms in recent years. Examples include developments in:

- Modular facility design and construction
- Container and closure cleaning, siliconization (if applicable), and sterilization
- Sterilization technologies
- Filling technologies
- Aseptic processing technology including barrier isolator technology
- Freeze-drying technologies including automated loading and unloading
- Control of particulate matter
- Automation in weight checking, inspection technologies, and labeling and finishing operations

GENERAL MANUFACTURING PROCESS

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

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

Procurement encompasses selecting and testing according to specifications of the raw-material ingredients and the containers and closures for the primary and secondary packages. Microbiological purity, in the form of bioburden and endotoxin levels, has become standard requirements for raw materials.

Processing includes cleaning containers and equipment to validated specifications, compounding the solution (or other dosage form), filtering the solution, sanitizing or sterilizing the containers and equipment, filling measured quantities of product into the sterile containers, stoppering (either completely or partially for products to be freeze-dried), freeze-drying, terminal sterilization if possible, and final sealing of the final primary container.

Packaging normally consists of the labeling and cartoning filled and sealed primary containers. The control of quality begins with the incoming supplies, being sure that specifications are met. Careful control of labels is vitally important as errors in labeling can be dangerous for the consumer. Each step of the process involves checks and tests to be sure that the required specifications at the respective step are being met. Labeling and final packaging operations are becoming more automated.

The quality control unit is responsible for reviewing the batch history and performing the release testing required to clear the product for shipment to users. A common FDA citation for potential violation of cGMP is the lack of oversight by the quality control unit in batch testing and review and approval of results.

COMPONENTS

Components of parenteral products include the active ingredient, formulation additives, vehicle(s), and the primary container and closure. Establishing specifications to ensure the quality of each of these components of an injection is essential.

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

Containers and closures are in prolonged, intimate contact with the product and may release substances into, or remove ingredients from, the product. Rubber closures are especially problematic (sorption, leachables, air and moisture transmission properties) if not properly evaluated for its compatibility with the final product. Assessment and selection of containers and closures are essential for final product formulation, to ensure that the product retains its purity, potency, and quality during the intimate contact with the container throughout its shelf life. Administration devices (syringes, tubing, transfer sets) that come in contact with the product should be assessed and selected with the same care as are containers and closures, even though the contact period is usually brief.

WATER FOR INJECTION (WFI)

Preparation

The source water can be expected to be contaminated with natural suspended mineral and organic substances, dissolved mineral salts, colloidal material, viable bacteria, bacterial endotoxins, industrial or agricultural chemicals, and other particulate matter. The degree of contamination will vary with the source and will be markedly different, whether obtained from a well or from surface sources, such as a stream or lake. Hence, the source water usually must be pretreated by one or a combination of the following treatments: chemical softening, filtration, deionization, carbon adsorption, or reverse osmosis purification. A schematic of a typical process used to convert potable water to Water for Injection is showing in Figure 41-1.

Water for Injection can be prepared by distillation or by membrane technologies (reverse osmosis or ultrafiltration).

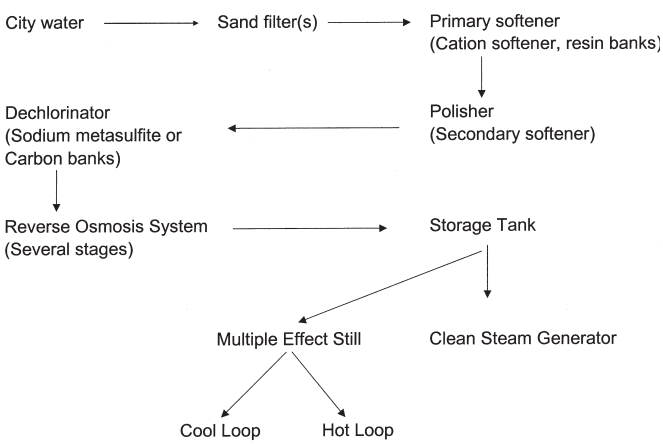


Figure 41-1. Water for injection system. Example of flow from source to end.

The EP (European Pharmacopeia) only permits distillation as the process for producing WFI. The USP and JP (Japanese Pharmacopeia) allow all these technologies to be applied.

Distillation is a process of converting water from a liquid to its gaseous form (steam). Since steam is pure gaseous water, all other contaminants in the feedwater are removed. In general, a conventional still consists of a boiler (evaporator) containing feed water (distilland); a source of heat to vaporize the water in the evaporator; a headspace above the level of distilland, with condensing surfaces for refluxing the vapor, thereby returning nonvolatile impurities to the distilland; a means for eliminating volatile impurities (demister/separation device) before the hot water vapor is condensed; and a condenser for removing the heat of vaporization, thereby converting the water vapor to a liquid distillate.

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

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

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

There are two basic types of WFI distillation units, the vapor compression still and the multiple effect still.

COMPRESSION DISTILLATION—The vapor-compression still, primarily designed for the production of large volumes of high-purity distillate with low consumption of energy and water, is illustrated diagrammatically in Figure 41-2. To start, the feed water is heated from an external source in the evaporator to boiling. The vapor produced in the tubes is separated from the entrained distilland in the separator and conveyed to a compressor that compresses the vapor and raises its temperature to approximately 107°. It then flows to the steam chest where it condenses on the outer surfaces of the tubes containing the distilland; the vapor is thus condensed and drawn off as a distillate, while giving up its heat to bring the distilland in the tubes to the boiling point. Vapor-compression stills are available in capacities from 50 to 2800 gal/hr *(Aqua-Chem, Barnstead, Meco)*.

MULTIPLE-EFFECT STILLS—The multiple-effect still also is designed to conserve energy and water usage. In prin-

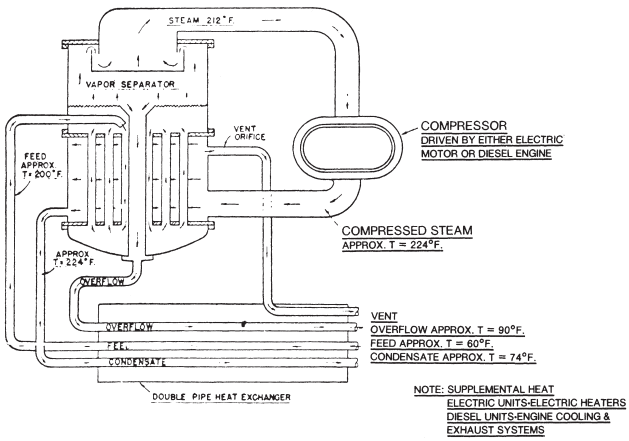


Figure 41-2. Vapor compressor still.

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

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

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

Figure 41-3. Multiple effect still (courtesy, Getinge). See Color Plate 6.

Several WFI installations utilize both RO and distillation systems for generation of the highest quality water. Since feedwater to distillation units can be heavily contaminated, and, thus, affect the operation of the still, water is first run through RO units to eliminate contaminants. For additional information, see Collentro.[15]

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

Whichever system is used for the preparation of WFI, validation is required to be sure that the system, consistently and reliably, will produce the chemical, physical, and microbiological quality of water required. Such validation should start with the determined characteristics of the source water and include the pretreatment, production, storage, and distribution systems. All of these systems together, including their proper operation and maintenance, determine the ultimate quality of the WFI.

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

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

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

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

The chemical and physical standards for WFI have changed in the past few years. The only physical/chemical tests remaining are the new *total organic carbon* (TOC), with a limit of 500 ppb (0.5 mg/L), and *conductivity,* with a limit of 1.3 μS/cm at 25°C or 1.1 μS/cm at 20°C. The former is an instrumental method capable of detecting all organic carbon present, and the latter is a three-tiered instrumental test measuring the conductivity contributed by ionized particles (in microSiemens or micromhos) relative to pH. Since conductivity is integrally related to pH, the pH requirement of 5 to 7 in previous revisions has been eliminated. The TOC and conductivity specifications are now considered to be adequate minimal predictors of the

chemical/physical purity of WFI. However, the *wet chemistry* tests still are used when WFI is packaged for commercial distribution and for SWFI.

Biological requirements continue to be, for WFI, not more than 10 colony-forming units (CFUs)/100 mL and 0.25 USP endotoxin units/mL. The SWFI requirements differ in that since it is a final product, it must pass the USP Sterility Test.

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

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

CONTAINERS AND CLOSURES

Injectable formulations are packaged into containers made of glass or plastic. Container systems include ampoules, vials, syringes, cartridges, bottles, and bags (Fig 41-4).

Ampoules are all glass while bags are all plastic. The other containers can be composed of glass or plastic and must include rubber materials such as rubber stoppers for vials and bottles and rubber plungers and rubber seals for syringes and cartridges. Irrigation solutions are packaged in glass bottles with aluminum screw caps.

Table 41-2 provides a generalized comparison of the three compatibility properties—leaching, permeation, and adsorption—of container materials most likely to be involved in the formulation of aqueous parenterals. Further, the integrity of the container/closure system depends upon several characteristics, including container opening finish, closure modulus, durometer and compression set, and aluminum seal application force. Container-closure integrity testing will be discussed in the Quality Assurance and Control section.

CONTAINER TYPES

Glass

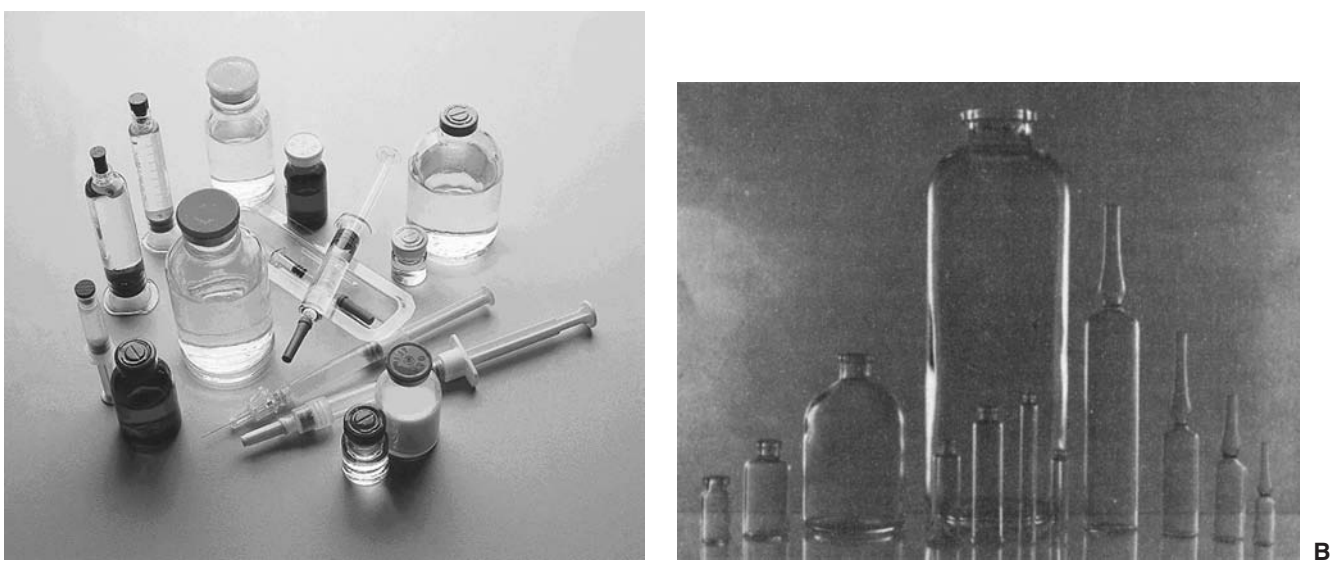
Glass is employed as the container material of choice for most SVIs. It is composed principally of silicon dioxide, with varying amounts of other oxides such as sodium, potassium, calcium, magnesium, aluminum, boron, and iron. The basic structural network of glass is formed by the silicon oxide tetrahedron.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

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

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

Type I glass is composed principally of silicon dioxide (~81%) and boric oxide (~13%), with low levels of the non-network-forming oxides (eg, sodium and aluminum oxides). It is a chemically resistant glass (low leachability) also having a low thermal coefficient of expansion (68×10^{-7} cm/cm-°C).

Types II and III glass compounds are composed of relatively high proportions of sodium oxide (~14%) and calcium oxide (~8%). 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 (eg, 90×10^{-7} cm/cm-°C for Type III). While there is no one standard formulation for glass among manufacturers



A B

Figure 41-4. Various types of packaging for parenterals (courtesy, Kimble, Baxter).

Table 41-2. Comparative Compatibility Properties of Container Materials

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

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

of these USP type categories, Type II glass usually has a lower concentration of the migratory oxides than Type III. In addition, Type II has been treated under controlled temperature and humidity conditions with sulfur dioxide or other dealkalizers to neutralize the interior surface of the container. While it remains intact, this surface will increase substantially the chemical resistance of the glass. However, repeated exposures to sterilization and alkaline detergents will break down this dealkalized surface and expose the underlying soda-lime compound.

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

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

In general, the following rules apply with respect to glass leachables:

- Relatively low levels of leachables at pH 4–8
- Relatively high levels of leachables at pH > 9
- Major extractables are silicon and sodium
- Minor extractables include potassium, barium, calcium, and aluminum.
- Trace extractables include iron, magnesium and zinc.
- Treated glass gives less extractables if pH < 8

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

Schott has developed a technology called Plasma Impulse Chemical Vapor Deposition (PICVD) that coats the inner surface of Type I glass vials with an ultrathin film of silicon dioxide.[16] This film forms a highly efficient diffusion barrier that practically eliminates glass leachables. Such treated glass is especially useful for drug products having high pH values, formulations with complexing agents, or products showing high sensitivity to pH shifts.

PHYSICAL CHARACTERISTICS—Commercially available containers vary in size from 0.5 to 1000 mL. Sizes up to 100 mL may be obtained as ampoules and vials, and larger sizes as bottles. The latter are used mostly for intravenous and irrigating solutions. Smaller sizes also are available as syringes and cartridges. Ampoules, syringes, 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 41-4). Compared to molded glass, tubing glass also has better wall and finish dimensional consistency, no seams, easier to label, weighs less, facilitates inspection, and has lower tooling costs. Tubing glass is preferable to molded glass for freeze-dried products because of more efficient heat transfer from the shelf into the product. Molded containers are uniform in external dimensions, stronger, and heavier.

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

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

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

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

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

Because of concerns for user safety and glass particulate matter occurring when glass is broken, glass sealed ampoules are no longer glass containers of choice for new SVIs in the United States.

RUBBER CLOSURES

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

Rubber closures are composed of multiple ingredients that are plasticized and mixed together at an elevated temperature on milling machines. The elastomer primarily used in rubber closures, plungers, and other rubber items used in parenteral packaging and delivery systems is synthetic butyl or halobutyl rubber. Natural rubber also is used, but if it is natural rubber latex, then the product label must include a warning statement due to the potential for allergic reactions from latex exposure.

The plasticized mixture is placed in molds and vulcanized (cured) under high temperature and pressure. During vulcanization the polymer strands are cross-linked by the vulcanizing agent, assisted by the accelerator and activator, so that motion is restricted and the molded closure acquires the elastic, resilient character required for its use. Ingredients not involved in the cross-linking reactions remain dispersed within the compound and, along with the degree of curing, affect the properties of the finished closure. Examples of rubber- closure ingredients are given in Table 41-3.

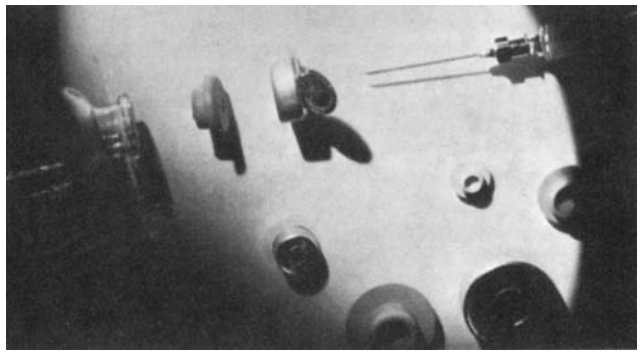


Figure 41-5. Extended view of sealing components for a multiple-dose vial (courtesy, West).

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

The ingredients dispersed throughout the rubber compound may be subject to leaching into the product contacting the closure. These ingredients, examples of which are given in Table 41-2, pose potential compatibility interactions with product ingredients if leached into the product solution, and these effects must be evaluated. Further, some ingredients must be evaluated for potential toxicity. To reduce the problem of leachables, coatings have been applied to the product contact surfaces of

Table 41-3. Examples of Ingredients Found in Rubber Closures

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

closures, with various polymers, the most successful being Teflon. Recently, polymeric coatings have been developed that are claimed to have more integral binding with the rubber matrix, but details of their function are trade secrets.

The physical shape of some typical closures may be seen in Figure 41-5. Most of them have a lip and a protruding flange that extends into the neck of the vial or bottle. Many disk closures are being used now, particularly in the high-speed packaging of antibiotics. Slotted closures are used on freeze-dried products to permit the escape of water vapor, since they are inserted only partway into the neck of the vial until completion of the drying phase of the cycle. Also, the top design of the freeze-dry closure is important to minimize sticking of the closure to the underneath of the dryer shelf after stoppering the vial. Stoppers normally have a small protruding circle at the center of the top of the stopper. Gaps provided within the protruding circle minimize the tendency of the stopper to stick to the freeze-dryer shelf.

The plunger type of rubber is used to seal one end of a syringe or cartridge. At the time of use, the plunger expels the product by a needle inserted through the closure at the distal end of the package. Intravenous solution closures often have permanent holes for adapters of administration sets; irrigating solution closures usually are designed for pouring.

As will be discussed later, rubber closures must be "slippery" in order to move easily through a rubber closure hopper and other stainless steel passages until they are fitted onto the filled vials. Traditionally, rubber materials are "siliconized" (silicone oil or emulsion applied onto the rubber) in order to produce such lubrication. However, advances in rubber closure technologies have introduced closures that do not require siliconization because of a special polymer coating applied to the outer surface of the closure. Examples are the *Daichyo / West* closures (Flurotec) and the *Helvoet* (Omniflex) closures. The *Daichyo* Flurotec coating is a copolymer of tetrafluoroethylene and ethylene.

Plastic

Thermoplastic polymers have been established as packaging materials for sterile preparations such as large-volume parenterals, ophthalmic solutions, and, increasingly, small-volume parenterals. For such use to be acceptable, a thorough understanding of the characteristics, potential problems, and advantages for use must be developed. Three principal problem areas exist in using these materials:

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

Permeation, the most extensive problem, may be troublesome by permitting volatile constituents, water, or specific drug molecules to migrate through the wall of the container to the outside and thereby be lost. This problem has been resolved, for example, by the use of an overwrap in the packaging of IV solutions in PVC bags to prevent the loss of water during storage. Reverse permeation also may occur in which oxygen or other molecules may penetrate to the inside of the container and cause oxidative or other degradation of susceptible constituents. *Leaching* may be a problem when certain constituents in the plastic formulation, such as plasticizers or antioxidants, migrate into the product. Thus, plastic polymer formulations should have as few additives as possible, an objective characteristically achievable for most plastics being used for parenteral packaging. *Sorption* is a problem on a selective basis, that is, sorption of a few drug molecules occurs on specific polymers. For example, sorption of insulin and other proteins, vitamin A acetate, and warfarin sodium has been shown to occur on PVC bags and tubing when these drugs were present as additives in IV admixtures. A brief summary of some of these compatibility relationships is given in Table 41-2.

One of the principle advantages of using plastic packaging materials is that they are not breakable as is glass; also, there is a substantial weight reduction. The flexible bags of polyvinyl chloride or select polyolefins, currently in use for large-volume intravenous fluids, have the added advantage that no air interchange is required; the flexible wall simply collapses as the solution flows out of the bag.

Most plastic materials have the disadvantage that they are not as clear as glass and, therefore, inspection of the contents is impeded. However, recent technologies have overcome this limitation, evidenced by plastic resins such as CZ (polycyclopentane, *Daichyo Seiko*) and Topas COC (cyclic olefin copolymer, *Ticona*). In addition, many of these materials will soften or melt under the conditions of thermal sterilization. However, careful selection of the plastic used and control of the autoclave cycle has made thermal sterilization of some products possible, large-volume parenterals in particular. Ethylene oxide or radiation sterilization may be employed for the empty container with subsequent aseptic filling. However, careful evaluation of the residues from ethylene oxide or its degradation products and their potential toxic effect must be undertaken. Investigation is required concerning potential interactions and other problems that may be encountered when a parenteral product is packaged in plastic. For further details see Chapter 54 (*Plastic Packaging Materials*) and the review article by Jenke.[17]

NEEDLES

Historically, stainless steel needles have been used to penetrate the skin and introduce a parenteral product inside the body. The advent of needleless injection systems (eg, Bioject, AdvantaJet, Medi-ject, Medi-Jector Vision) has obviated the need for the use of needles for some injections (eg, vaccines) and are gaining in popularity over the conventional syringe and needle system. However, needleless injections are generally more expensive, can still produce pain on injection, are potentially a greater source of contamination (and cross-contamination from incessant use), and may not be as efficient in dose delivery.

Needles are hollow devices composed of stainless steel or plastic. Needles are available in a wide variety of lengths, sizes, and shapes. *Needle lengths* range from 1/4 inch to 6 inches. *Needle size* is referred to as its gauge (G), or the outside diameter (OD) of the needle shaft. Gauge ranges are 11 to 32 gauge with the largest gauge for injection usually being no greater than 16 G. 16 G needles have an OD of 0.065 inches (1.65 mm) whereas 32 G have an OD of 0.009 inches (0.20 mm). *Needle shape* includes regular, short bevel, intradermal, and winged. Needle shape typically is defined by one end of a needle enlarged to form a hub with a delivery device such as a syringe or other administration device. The other end of the needle is beveled, meaning that it forms a sharp tip to maximize ease of insertion.

The route of administration, type of therapy, and whether the patient is a child or adult dictate the length and size of needle used.[18] Intravenous injections typically use 1–2 inch 15 to 25 G needles. Intramuscular injections use 1–2 inch 19–22 G needles. Subcutaneous injections use 1/4 to 5/8 inch 24 to 25 G needles. Needle gauge for children rarely is larger than 22 G, usually 25–27 G. Winged needles are used for intermittent heparin therapy. Many different types of therapies, (eg, radiology, anesthesia, biopsy, cardiovascular, ophthalmic, transfusions, tracheotomy) have their own peculiar types of needle preferences.

Needles are purchased either alone (eg, Luer-Lok) to be attached to syringes, cartridge, and other delivery systems, or, for syringes, can be part of the syringe set (stake needle).

PYROGENS (ENDOTOXINS)

Since water and packaging materials are the greatest sources of pyrogenic contamination, this subject will now be covered.

Pyrogens are products of metabolism of microorganisms. The most potent pyrogenic substances (endotoxins) are con-

stituents (lipopolysaccharides, LPS) of the cell wall of gram-negative bacteria (eg, *Pseudomonas* sp, *Salmonella* sp, *Escherichia coli)*. Gram-positive bacteria and fungi also produce pyrogens but of lower potency and of different chemical nature. Gram-positive bacteria produce peptidoglycans whereas fungi product β-glucans, both of which can cause non-endotoxin pyrogenic responses. Endotoxins are lipopolysaccharides that typically exist in high molecular weight aggregate forms. However, the monomer unit of LPS is less than 10,000 daltons, enabling endotoxin easily to pass through sterilizing 0.2 micron filters. Studies have shown that the lipid portion of the molecule is responsible for the biological activity. Since endotoxins are the most potent pyrogens and gram-negative bacteria are ubiquitous in the environment, especially water, this discussion focuses on endotoxins and the risk of their presence as contaminants in sterile products.

Pyrogens, when present in parenteral drug products and injected into patients, can cause fever, chills, pain in the back and legs, and malaise. Although pyrogenic reactions are rarely fatal, they can cause serious discomfort and, in the seriously ill patient, shock-like symptoms that can be fatal. The intensity of the pyrogenic response and its degree of hazard will be affected by the medical condition of the patient, the potency of the pyrogen, the amount of the pyrogen, and the route of administration (intrathecal is most hazardous followed by intravenous, intramuscular, and subcutaneous). When bacterial (exogenous) pyrogens are introduced into the body, LPS targets circulating mononuclear cells (monocytes and macrophages) that, in turn, produce pro-inflammatory cytokines such as interleukin-2, interleukin-6, and tissue necrosis factor. Besides LPS, gram-negative bacteria also release many peptides (eg, exotoxin A, peptidoglycan, and muramuyl peptides) that can mimic the activity of LPS and induce cytokine release. The Limulus Amebocyte Lysate (LAL) test, discussed later, can only detect the presence of LPS. It has been suggested that a new test, called Monocyte Activation Test, replace LAL as the official pyrogen test because of its greater sensitivity to all agents that induce the release of cytokines that cause fever and a potential cascade of other adverse physiological effects.[19]

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

Pyrogens may enter a preparation through any means that will introduce living or dead microorganisms. However, current technology generally permits the control of such contamination, and the presence of pyrogens in a finished product indicates processing under inadequately controlled conditions. It also should be noted that time for microbial growth to occur increases the risk for elevated levels of pyrogens. Therefore, compounding and manufacturing processes should be carried out as expeditiously as possible, preferably planning completion of the process, including sterilization, within the maximum allowed time according to process validation studies. Aseptic processing guidelines require establishment of time limitations throughout processing for the primary purpose of preventing the increase of endotoxin (and microbial) contamination that subsequently cannot be destroyed or removed.

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

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

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

Other potential sources of contamination are containers and equipment. Pyrogenic materials adhere strongly to glass and other surfaces, especially rubber closures. Residues of solutions in used equipment often become bacterial cultures, with subsequent pyrogenic contamination. Since drying does not destroy pyrogens, they may remain in equipment for long periods. Adequate washing will reduce contamination and subsequent dry-heat treatment can render contaminated equipment suitable for use. However, all such processes must be validated to ensure their effectiveness. Aseptic processing guidelines require validation of the depyrogenation process by demonstrating at least 3-log reduction in an applied endotoxin challenge.

Solutes may be a source of pyrogens. For example, the manufacturing of bulk chemicals may involve the use of pyrogenic water for process steps such as crystallization, precipitation, or washing. Bulk drug substances derived from cell culture fermentation will almost certainly be heavily pyrogenic. Therefore, all lots of solutes used to prepare parenteral products should be tested to ensure that they will not contribute unacceptable quantities of endotoxin to the finished product. It is standard practice today to establish valid endotoxin limits on active pharmaceutical ingredients and most solute additives.

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

PRODUCTION FACILITIES

The production facility and its associated equipment must be designed, constructed, and operated properly for the manufacture of a sterile product to be achieved at the quality level required for safety and effectiveness. Materials of construction for sterile product production facilities must be "smooth, cleanable, and impervious to moisture and other damage." Further, the processes used must meet cGMP standards. Since the majority of SVIs are aseptically processed (finished product not terminally sterilized), adherence to strict cGMP standards with respect to sterility assurance is essential.

FUNCTIONAL AREAS

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

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

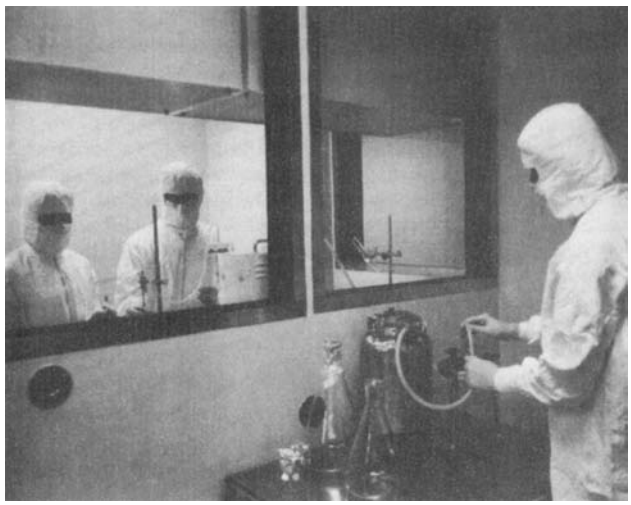


Figure 41-7. Product filtration from the aseptic staging room through a port into the aseptic filling room (courtesy, The University of Tennessee College of Pharmacy).

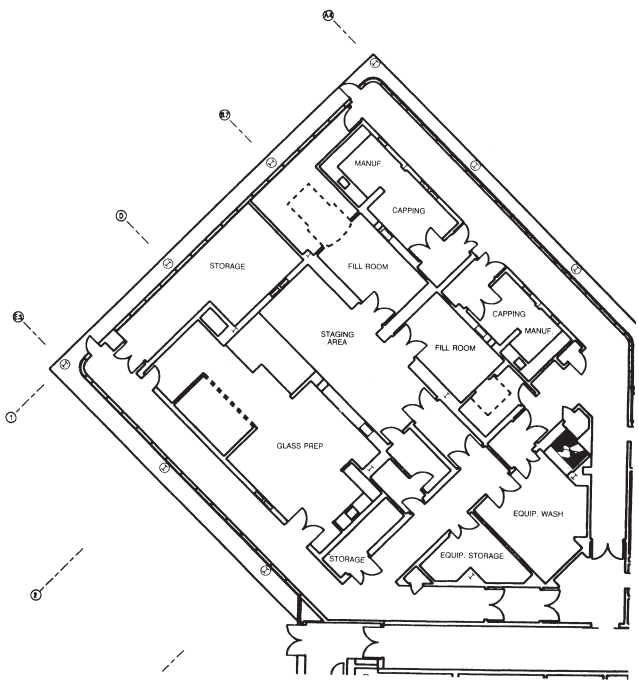


Figure 41-6. Floor plan of aseptic filling rooms and staging room with adjacent support areas (courtesy, Glaxo).

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

Clean Room Classified Areas

Because of the extremely high standards of cleanliness and purity that must be met by parenteral products, it has become standard practice to prescribe specifications for the environments in which these products are manufactured (ie, clean rooms). Clean room specifications are summarized in Table 41-4 that compares United States and European classifications

Table 41-4. Clean Room Classifications

EUROPEAN GRADE	UNITED STATES CLASSIFICATION	INTERNATIONAL SOCIETY OF PHARM. ENG. DESCRIPTION	MAX NO. OF PARTICLES per m^3 >/= 0.5 μm	MAX NO. OF PARTICLES per m^3 >/= 5 μm
A	100	Critical	3,500	0
B	100	Clean	3,500	0
C	10,000	Controlled	350,000	2,000
D	100,000	Pharmaceutical	3,500,000	20,000

and clean room designations assigned by the International Society of Pharmaceutical Engineers. The numbers are based on the maximum allowed number of airborne particles/ft^3 or particles/m^3 of 0.5 μm or larger size and, for Europe, 5.0 μm or larger size. The classifications used in pharmaceutical practice normally range from Class 100,000 (Grade D) for materials support areas to Class 100 (Grade A) for aseptic areas. To achieve Class 100 conditions, HEPA filters are required for the incoming air, with the effluent air sweeping the downstream environment at a uniform velocity, normally 90 to 100 ft/min ± 20%, along parallel lines (laminar air flow). HEPA filters are defined as 99.99% or more efficient in removing from the air 0.3 μm particles generated by vaporization of the hydrocarbon Emory 3004.

Because so many parenteral products are manufactured at one site for global distribution, air quality standards in aseptic processing areas must meet both United States and European requirements. European standards differ from United States standards in the following ways:

- Use Grades A, B, C, and D classifications rather than Class X (eg, 100, 1000, etc)
- Use particle and microbial limits per cubic meter rather than per cubic foot
- Require particle measurements at 5 microns in addition to 0.5 microns in Grade A and B areas
- Differentiate area cleanliness dynamically and "at rest"

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

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

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

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

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

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

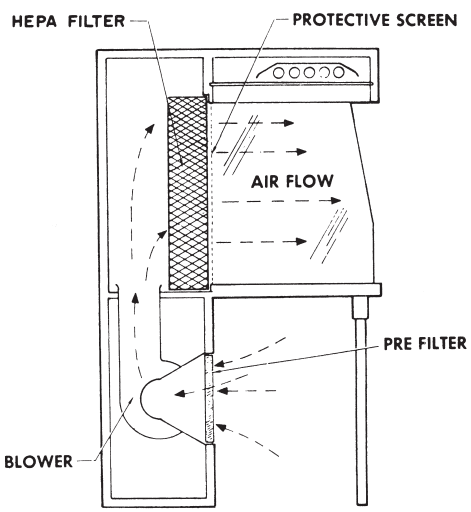


Figure 41-8. Horizontal laminar-flow workbench (courtesy, adaptation, Sandia).

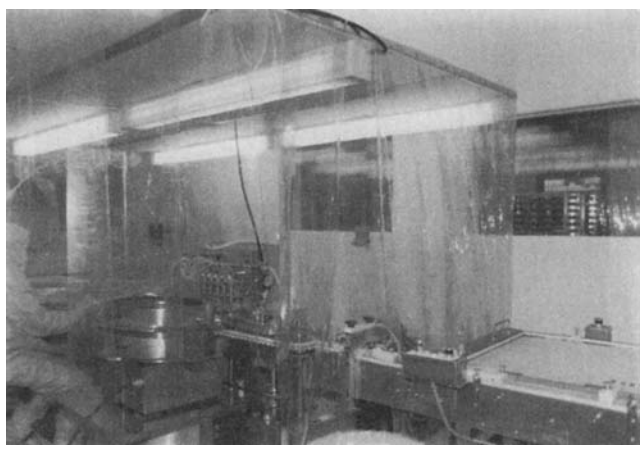


Figure 41-9. Vial filling line under vertical laminar airflow with critical area enclosed within plastic curtains (courtesy, Merck).

Further, great care must be exercised to prevent cross-contamination from one operation to another, especially with horizontal laminar air flow. For most large-scale operations, as shown in Figure 9, a vertical system is much more desirable, with the air flowing through perforations in the countertop or through return louvers at floor level, where it can be directed for decontamination. Laminar-flow environments provide well-controlled work areas only if proper precautions are observed. Any reverse air currents or movements exceeding the velocity of the HEPA-filtered airflow may introduce contamination, as may coughing, reaching, or other manipulations of operators. Therefore, laminar-flow work areas should be protected by being located within controlled environments. Personnel should be attired for aseptic processing, as described below. All movements and processes should be planned carefully to avoid the introduction of contamination upstream of the critical work area. Checks of the air stream should be performed initially and at regular intervals (usually every 6 months) to be sure no leaks have developed through or around the HEPA filters. Workbenches and other types of laminar-flow enclosures are available from several commercial sources (suppliers: *Air Control, Atmos-Tech, Baker, Clean Air, Clestra, Envirco, Flanders, Laminaire, Liberty*).

Clean room design traditionally has Class 100 rooms adjacent to Class 100,000 rooms. Regulatory authorities have raised great concerns about this significant change in air quality from critical to controlled areas. It is now preferable to have an area classified from Class 1000 to Class 10,000 in a buffer area between a Class 100 and Class 100,000 area.

MATERIALS SUPPORT AREA—The area is constructed to withstand moisture, steam, and detergents and is usually a Class 100,000 clean room. The ceiling, walls, and floor should be constructed of impervious materials so that moisture will run off and not be held. One of the finishes with a vinyl or 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 because of the high humidity and heat. In this area preparation for the filling operation, such as cleaning and assembling equipment, is undertaken. Adequate sink and counter space must be provided. This area must be cleanable, and the microbial load must be monitored and controlled. Precautions also must be taken to prevent deposition of particles or other contaminants on clean containers and equipment until they have been properly boxed or wrapped preparatory to sterilization and depyrogenation.

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

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

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

ISOLATION (BARRIER) TECHNOLOGY—This technology is designed to isolate aseptic operations from personnel and the surrounding environment. Considerable experience has been gained in its use for sterility testing, with very positive results, including reports of essentially no false-positive test results.[20] In European circles favorable results also have been reported from use in hospital IV admixture programs. Because of such results, experimental efforts in adapting automated, large-scale, aseptic filling operations to isolators has gained momentum.[21,22]

Figure 41-10 illustrates a configuration of an isolator with transparent plastic sides and gloves for operator access to the enclosure. Figure 41-11 illustrates the adaptation of a large-scale filling line to isolator technology. The operations are performed within windowed, sealed walls with operators working through glove ports. The sealed enclosures are presterilized, usually with peracetic acid, hydrogen peroxide vapor, or steam. Sterile supplies are introduced from sterilizable movable modules through uniquely engineered transfer ports or directly from attached sterilizers, including autoclaves and hot-air sterilizing tunnels. Results have been very promising, giving expectation of significantly enhanced control of the aseptic processing environment.[22]

While isolators have been implemented in the industry, progress has been slower than initially anticipated. There are several reasons for this slow growth and acceptance:

- General regulatory and industry caution because of the relative novelty of isolator technology.

Figure 41-10. Example of an isolator (courtesy, LaCalhene). See Color Plate 7.

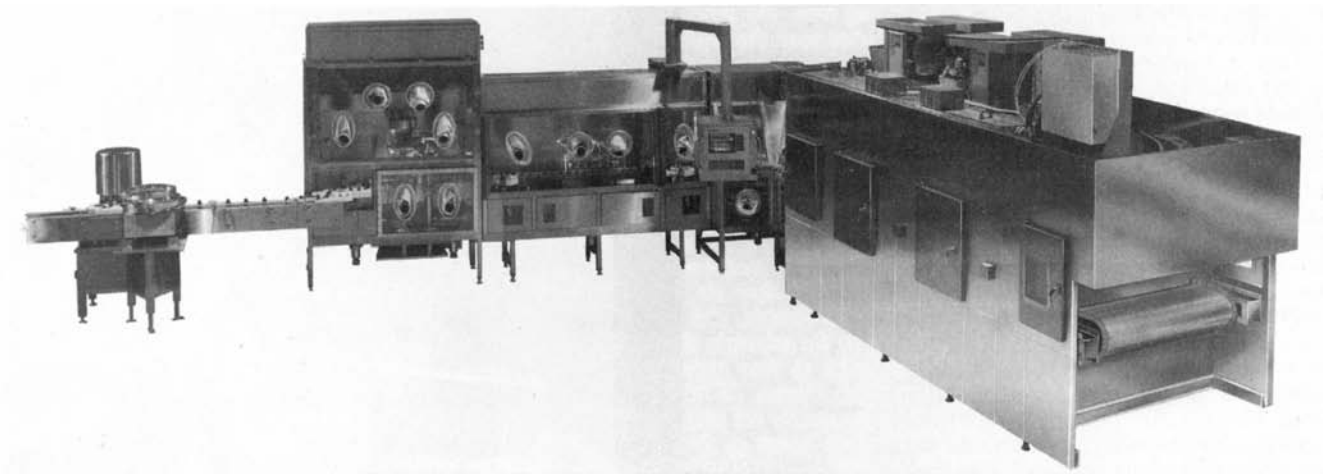


Figure 41-11. Large-scale production line showing, from right to left, container-sterilizing tunnel feeding into isolator enclosing filling and sealing, with access glove ports, and exiting to capper (courtesy, TL Systems).

- Regulatory agencies have insisted so far that isolators be located in classified environments (usually at least Class 100,000). This discouraged investment by some in isolator technology because it was originally thought that classified environments would not be necessary.
- Initial promotion that isolator technology could create a truly sterile environment and, thus, allow a much greater claim for sterility assurance proved not to be true. Isolators tend to have small leaks, particularly at the glove ports and gloves or half suits. The industry has learned the hard way that for aseptic processing, sterility assurance levels for isolators are not much greater than conventional Class 100 filling operations.
- Validation of isolators has been more difficult than expected. For example, it is difficult to convince reviewers that contamination will not occur despite constant movement of materials in and out of the isolator, the occasional need to manipulate equipment, and the problem of pinhole leaks. The significantly increased time and resources required to validate and maintain isolators have discouraged many companies from investing in these systems.

MAINTENANCE OF CLEAN ROOMS

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

Liquid disinfectants (sanitizing agents) should be selected carefully because of data showing their reliable activity against inherent environmental microorganisms. They should be recognized as supplements to good housekeeping, never as substitutes. They should be rotated with sufficient frequency to avoid the development of resistant strains of microorganisms. An example of the "three bucket" system used to sanitize facilities is shown in Figure 41-12. One bucket is to remove as much of the remnant of the "dirty" mop or sponge, the second contains a rinse solution to help clean the mop/sponge, while the third bucket contains the sanitizing solution. The sanitizing solution should be rendered sterile prior to use although, of course, once in use, it will no longer be sterile.

It should be noted that ultraviolet (UV) light rays of 237.5 nm wavelength, as radiated by germicidal lamps, are an effective surface disinfectant. But, it must also be noted that they are only effective if they contact the target microorganisms at a sufficient intensity for a sufficient time. The limitations of their use must be recognized, including no effect in shadow areas, reduction of intensity by the square of the distance from the source, reduction by particulates in the ray path, and the toxic effect on epithelium of human eyes. It generally is stated that

Figure 41-12. Example of a three-bucket assembly used for sanitizing facilities (courtesy, Contec). See Color Plate 8.

an irradiation intensity of 20 $\mu w/cm^2$ is required for effective antibacterial activity.

PERSONNEL

Personnel selected to work on the preparation of a parenteral product must be neat, orderly, and reliable. They should be in good health and free from dermatological conditions that might increase the microbial load. If they show symptoms of a head cold, allergies, or similar illness, they should not be permitted in the aseptic area until their recovery is complete. However, a healthy person with the best personal hygiene still will shed large numbers of viable and nonviable particles from body surfaces.[23] This natural phenomenon creates continuing problems when personnel are present in clean rooms; effective training and proper gowning can reduce, but not eliminate, the problem of particle shedding from personnel.

Aseptic-area operators should be given thorough, formal training in the principles of aseptic processing and the techniques to be employed.[24] Subsequently, the acquired knowledge and skills should be evaluated to assure that training has been effective before they are allowed to participate in the preparation of sterile products. Retraining should be performed on a regular schedule to enhance the maintenance of the required level of expertise. An effort should be made to imbue operators with an awareness of the vital role they play in determining the reliability and safety of the final product. This is especially true of supervisors, since they should be individuals who not only understand the unique requirements of aseptic procedures, but who are able to obtain the full participation of other employees in fulfilling these exacting requirements.

The uniform worn is designed to confine the contaminants discharged from the body of the operator, thereby preventing their entry into the production environment. For use in the aseptic area, uniforms should be sterile. Fresh, sterile uniforms should be used after every break period or whenever the individual returns to the aseptic area. In some plants this is not required if the product is to be sterilized in its final container. The uniform usually consists of coveralls for both men and women, hoods to cover the hair completely, face masks, and Dacron or plastic boots (Fig 41-13). Sterile rubber or latex-free gloves (are also required for aseptic operations, preceded by thorough scrubbing of the hands with a disinfectant soap. Most companies require two pairs of gloves, one pair put on at the beginning of the gowning procedure, the other pair put on after all other apparel have been donned. In addition, goggles are required to complete the coverage of all skin areas.

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

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

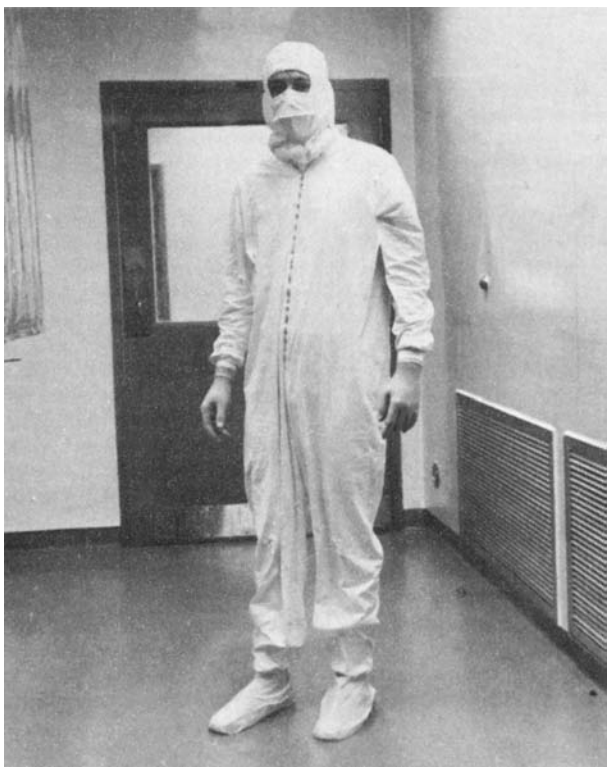


Figure 41-13. Appropriate uniform for operators entering an aseptic filling room (courtesy, Abbott).

ENVIRONMENTAL CONTROL EVALUATION

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

The tests used generally measure either the particles in a volume of sampled air or the particles that are settling or are present on surfaces. To measure the total particle content in an air sample, electronic particle counters are available, operating on the principle of the measurement of light scattered from particles as they pass through the cell of the optical system (Suppliers: *Climet, HIAC Royco, Met One, Particle Measuring Systems*). These instruments not only count particles, but also provide a size distribution based on the magnitude of the light scattered from the particle. While a volume of air measured by an electronic particle counter will detect all particles instantly, these instruments cannot differentiate between viable (eg, bacterial and fungal) and nonviable ones. However, because of the need to control the level of microorganisms in the environment in which sterile products are processed, it also is necessary to detect viable particles. These usually are fewer in number than nonviable ones and are only detectable as colony-forming units (CFUs) after a suitable incubation period at, for example, 30° to 35° for up to 48 hours. Thus, test results will not be known for 48 hours after the samples are taken.

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

of conveyor lines through walls, and sites near the inlet and exit of the air system.

The sample should be large enough to obtain a meaningful particle count. At sites where the count is expected to be low, the size of the sample may need to be increased; for example, in Class 100 areas, Whyte and Niven[25] suggest that the sample should be at least 30 ft^3 and, probably, much more. Many firms employ continuous particle monitoring in Class 100 areas to study trends and/or to identify equipment malfunction.

Several air-sampling devices are used to obtain a count of microorganisms in a measured volume of air. A slit-to-agar (STA) sampler (suppliers: *Mattson-Garvin, New Brunswick, Vai*) draws by vacuum a measured volume of air through an engineered slit, causing the air to impact on the surface of a slowly rotating nutrient agar plate (Fig 41-14). Microorganisms adhere to the surface of the agar and grow into visible colonies that are counted as CFUs, since it is not known whether the colonies arise from a single microorganism or a cluster. A centrifugal sampler (supplier: *Biotest*) pulls air into the sampler by means of a rotating propeller and slings the air by centrifugal action against a peripheral nutrient agar strip. The advantages of this unit are that it can be disinfected easily and is portable, so that it can be hand-carried wherever needed. These two methods are used quite widely.

A widely used method for microbiological sampling consists of the exposure of nutrient agar culture plates to the settling of microorganisms from the air. This method is very simple and inexpensive to perform but will detect only those organisms that have settled on the plate; therefore, it does not measure the number of microorganisms in a measured volume of air (a non-quantitative test). 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.[26]

Whyte and Niven suggested that settling plates should be exposed in Class 100 areas for an entire fill (up to 7 to 8 hours) rather than the more common 1 hour. However, excessive dehydration of the medium must be avoided, particularly in the path of laminar-flow air. The European Union GMP guidelines for sterile manufacture of medicinal products suggest an exposure period of not more than 4 hours.

Figure 41-14. Example of slit-to-air sampler (courtesy, Baxter).

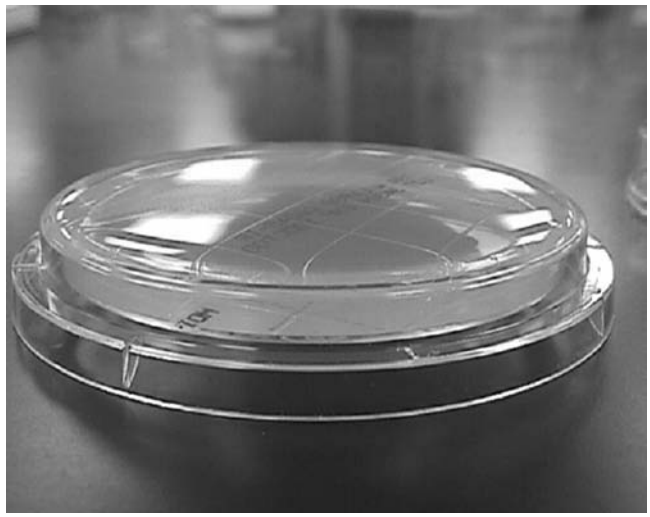


Figure 41-15. Example of a Rodac plate (courtesy, Baxter).

The number of microorganisms on surfaces can be determined with nutrient agar plates having a convex surface *(Rodac Plates)* (Fig 41-15). With these it is possible to roll the raised agar surface over flat or irregular surfaces to be tested. Organisms will be picked up on the agar and will grow during subsequent incubation. This method also can be used to assess the number of microorganisms present on the surface of the uniforms of operators, either as an evaluation of gowning technique immediately after gowning or as a measure of the accumulation of microorganisms during processing. Whenever used, care must be taken to remove any agar residue left on the surface tested.

Further discussion of proposed viable particle test methods and the counts to be accepted will be found in Section <1116> "Microbial Evaluation and Classification of Clean Rooms and Other Controlled Environments" in the USP.

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

Issues regarding environmental monitoring remain among the most controversial aspects of cGMP regulatory inspections of parenteral manufacturing and testing environments. Regulatory trends include requiring an increase in the number and frequency of locations monitored in the clean room and on clean room personnel, enforcing numerical alert and action limits, and linking environmental monitoring data to the decision to release or reject the batch. It has been pointed out that fully gowned personnel will still release a finite number of microorganisms (typically 10 to 100 CFR per hour) so that it is unreasonable to impose the requirement of zero microbial contamination limits at any location in the clean room.[27]

MEDIA FILL (PROCESS SIMULATION TESTING)— FDA inspections have increasingly focused on media fill studies that truly simulate the production process. The *media fill* or *process simulation test* involves preparation and sterilization (often by filtration) of sterile trypticase soy broth and filling this broth into sterile containers under conditions simulating as closely as possible those characteristics of a filling process for

a product. The key is designing these studies that simulate all factors that occur during the normal production of a lot. Table 41-5 lists those factors that are given in the FDA Guidelines for Aseptic Processing.[28] The entire lot, normally at least 4750 units, is incubated at temperatures verified to support microbial growth, usually rotating 20° to 25°C storage and 30° to 35°C storage, for at least 14 days and examined for the appearance of growth of microorganisms. The media used must be verified that it is capable of supporting microbial growth. If growth occurs, contamination has entered the container(s) during the processing. To pass the test at 95% confidence, not more than 0.1% of the challenged units may show growth although the current expectation of regulatory agencies is "approaching zero." This evaluation also has been used as a measure of the proficiency of an individual or team of operators. This test is a very stringent evaluation of the efficiency of an aseptic filling process and, by many, is considered to be the most evaluative test available.

Table 41-5. Considerations When Designing Media Fill Studies

- Longest permitted run on processing line
- "Worst case" environmental conditions
- Number and type of normal interventions, atypical interventions, unexpected results, stoppages, equipment adjustments or transfers
- Include lyophilization steps, if applicable
- Aseptic assembly of equipment at start-up and during processing
- Number of personnel involved and their activities
- Number of aseptic additions
- Shift changes, breaks, and gown changes
- Number and type of aseptic equipment disconnections/connections
- Aseptic sample collections
- Line speed and configurations
- Manual weight checks
- Operator fatigue
- Container-closure systems
- Temperature and humidity extremes
- Specific provisions of aseptic processing standard operating procedures (eg, conditions permitted before line clearance is mandated)

PRODUCTION PROCEDURES

The processes required for preparing sterile products constitute a series of events initiated with the procurement of approved raw materials (eg, drugs, excipients, vehicles) and primary packaging components (eg, containers, closures) and ending with the sterile product sealed in its dispensing package. Each step in the process must be controlled very carefully so that the product will have its required quality. To ensure the latter, each process should be validated to be sure that it is accomplishing what it is intended to do. For example, an autoclave sterilization process must be validated by producing data showing that it effectively kills resistant forms of microorganisms; or, a cleaning process for rubber closures should provide evidence that it is cleaning closures to the required level of cleanliness; or a filling process that repeatedly delivers the correct fill volume per container. The validation of processes requires extensive and intensive effort to be successful and is an integral part of cGMP requirements.

CLEANING CONTAINERS AND EQUIPMENT

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

A variety of machines are available for cleaning new containers for parenteral products. These vary in complexity from a small, hand loaded, rotary rinser to large automatic washers capable of processing several thousand containers per hour (Fig 41-16). The selection of the particular type will be determined largely by the physical type of containers, the type of contamination, and the number to be processed in a given period of time.

Validation of cleaning procedures for equipment is another "hot topic" with respect to cGMP regulatory inspections. Inadequate cleaning processes have been a frequent citing by FDA and other regulatory inspectors when inspecting both active ingredient and final product manufacturing facilities. It is incumbent upon parenteral manufacturers to establish scientifically justified acceptance criteria for cleaning validation. If specific analytical limits for target residues are arbitrarily set, this will cause concern for quality auditors. Validation of cleaning procedures can be relatively complicated because of issues with sample methods (eg, swab, final rinse, testing of subsequent batch), sample locations, sensitivity of analytical methods, and calculations used to establish cleaning limits.

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 con-

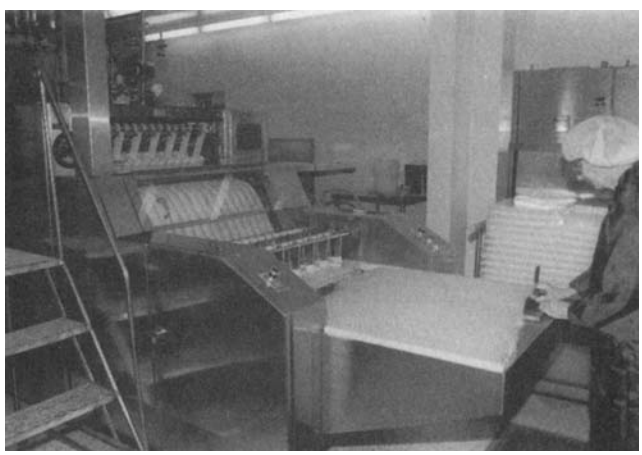


Figure 41-16. Loading end of large conveyor vial washer that subjects inverted vials to a series of cleaning steps before delivery from the far end of the washer. Note the vials in plastic blister packs at right of operator (courtesy, Merck).

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

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

Only new containers are used for parenterals. Improvements have been made in maintaining their cleanliness during shipment from the manufacturer through tight, low-shedding packaging, including plastic blister packs, as can be seen stacked on the right of Figure 41-16.

MACHINERY FOR CONTAINERS—The machinery available for cleaning containers embodies the above principles but varies in the mechanics by which it is accomplished. In one manual loading type, the jet tubes are arranged on arms like the spokes of a wheel, which rotate around a center post through which the treatments are introduced. An operator places the unclean containers on the jet tubes as they pass the loading point and removes the clean containers as they complete one rotation. A washer capable of cleaning hundreds of containers an hour, shown in Figure 41-16, uses a row of jet tubes across a conveyor belt. The belt moves the inverted containers past the programmed series of treatments and discharges the clean containers into a sterilizing oven (not shown), which ultimately discharges them through a wall into a clean room for filling.

A continuous automated line operation, capable of cleaning hundreds of containers an hour, is shown in Figure 41-17. The vials are fed into the rotary rinser in the foreground, transferred automatically to the covered sterilizing tunnel in the center, conveyed through the wall in the background, and discharged into the filling clean room.

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

Increases in process rates have necessitated the development of continuous, automated line processing with a minimum of individual handling, still maintaining adequate control of the cleaning and handling of the containers. In Figure 41-17, 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.

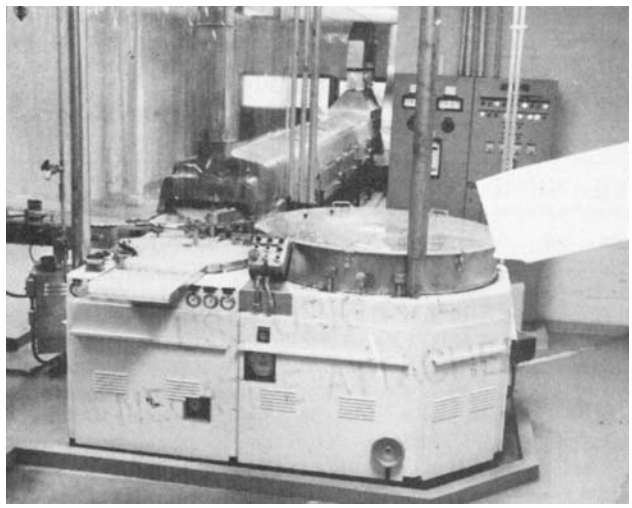


Figure 41-17. Continuous automatic line operation for vials from a rotary rinser through a sterilizing tunnel with vertical laminar-airflow protection of clean vials (courtesy, Abbott).

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

The equipment used for washing large numbers of closures is usually an agitator or horizontal basket-type automatic washing machine. Because of the risk of particulate generation from the abrading action of these machines, some procedures simply call for heating the closures in kettles in detergent solution, followed by prolonged flush rinsing. The final rinse always should be with low-particulate WFI. An example of a modern closure processor that washes, siliconizes, sterilizes, and transports closures directly to the filling line is shown in Figure 41-18.

It is also possible to purchase rubber closures already cleaned and lubricated in sterilizable bags supplied by the rubber closure manufacturer.

EQUIPMENT—The details of certain prescribed techniques for cleaning and preparing equipment, as well as of containers and closures, have been presented elsewhere.[29] Here, a few points will be emphasized.

All equipment should be disassembled as much as possible to provide access to internal structures. Surfaces should be scrubbed thoroughly with a stiff brush, using an effective detergent and paying particular attention to joints, crevices, screw threads, and other structures where debris is apt to

Figure 41-18. Rubber closure processors (courtesy, Getinge USA). See Color Plate 9.

collect. Exposure to a stream of clean steam will aid in dislodging residues from the walls of stationary tanks, spigots, pipes, and similar structures. Thorough rinsing with distilled water should follow the cleaning steps.

Because of the inherent variation in manual cleaning, the difficult accessibility of large stationary tanks and the need to validate the process, computer-controlled systems (usually automated) have been developed and are known as clean-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, followed by thorough rinsing with WFI. The system often is extended to allow sterilizing-in-place (SIP) to accomplish sanitizing or sterilizing as well.

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

PRODUCT PREPARATION

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

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

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

Parenteral dispersions, including colloids, emulsions, and suspensions, provide particular problems. 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.

Proteinaceous solutions are especially "tempermental" when preparing these products. Proteins are usually extremely sensitive to many environmental and processing conditions exposed to during production such as temperature, mixing time and speed, order of addition of formulation components, pH adjustment and control, and contact time with various surfaces such as filters and tubing. Development studies must include evaluation of manufacturing conditions in order to minimize adverse effects of the process on the activity of the protein.

The formulation of a stable product is of paramount importance. Certain aspects of this are mentioned in the discussion of components of the product. Exhaustive coverage of the topic is not possible within the limits of this text, but further coverage is provided in Chapters 39 (*Solutions, Emulsions, Suspensions and Extracts*) and 52 (*Stability of Pharmaceutical Products*). It should be mentioned here, however, that the thermal sterilization of parenteral products increases the possibility of chemical reactions. Such reactions may progress to completion during the period of elevated temperature in the autoclave or be initiated at this time but continue during subsequent storage. The assurance of attaining product stability requires a high order of pharmaceutical knowledge and responsibility.

FILTRATION

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

Filters are thought to function by one or, usually, a combination of the following: (1) sieving or screening, (2) entrapment or impaction, and (3) electrostatic attraction (Fig 41–19). When a filter retains particles by sieving, they are retained on the surface of the filter. Entrapment occurs when a particle smaller than the dimensions of the passageway (pore) becomes lodged in a turn or impacted on the surface of the passageway. Electrostatic attraction causes particles opposite in charge to that of the surface of the filter pore to be held or adsorbed to the surface. It should be noted that increasing, prolonging, or varying the force behind the solution may tend to sweep particles initially held by entrapment or electrostatic charge through the pores and into the filtrate.

Membrane filters are used exclusively for parenteral solutions because of their particle-retention effectiveness, nonshedding property, non-reactivity, and disposable characteristics. However, it should be noted that non-reactivity does not apply in all cases. For example, polypeptide products may show considerable adsorption through some membrane filters, but

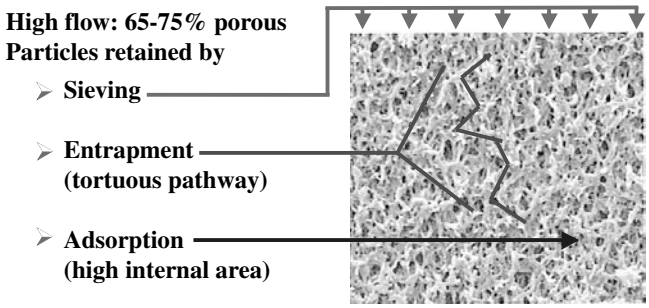


Figure 41-19. Mechanisms of microbial retention on membrane filters (courtesy, Millipore). See Color Plate 10.

those composed of polysulfone and polyvinylidine difluoride (PVDF) have been developed to be essentially non-adsorptive for these products. The most common membranes are composed of Cellulose esters, Nylon, Polysulfone, Polycarbonate, PVDF, or Polytetrafluoroethylene (Teflon).

Filters are available as flat membranes or pleated into cylinders (Fig 41-20) to increase surface area and, thus, flow rate (suppliers: *Cuno, Gelman, Meissner, Millipore, Pall, Sartorius Schleicher*). Each filter in its holder should be tested for integrity before and after use, particularly if it is being used to eliminate microorganisms. This integrity test usually is performed either as the *bubble-point test* or as the *diffusion or forward flow* test. The bubble point test is commonly used on smaller filters. As the surface area of filters becomes large, diffusion of air through the water-filled pores tends to obscure the bubble point. Therefore, the diffusion test has been developed as an integrity test for filters with large surface areas. A *pressure hold test* also can be applied to large surface area filters. The filter manufacturer will recommend the best integrity test for the filter system in question.

These are tests to detect the largest pore or other opening through the membrane. The basic test is performed by gradually raising air pressure on the upstream side of a water-wet filter. The bubble point test keeps raising pressure until a pressure is obtained where air bubbles first appear downstream is the bubble point. The diffusion or forward flow test raises pressure to some point below the known bubble point pressure, then diffusion flow (usually in mL/min) is measured. These pressures are characteristic for each pore size of a filter and are provided by the filter manufacturer. For example, a 0.2-μm cellulose ester filter will bubble at about 50 psig or a diffusive flow rating of no greater than 13 mL/min at a pressure of 40 psig. If the filter is wetted with other liquids, such as a product, the bubble point will differ and must be determined experimentally. If the bubble point is lower than the rated pressure, the filter is defective, probably because of a puncture or tear, and should not be used.

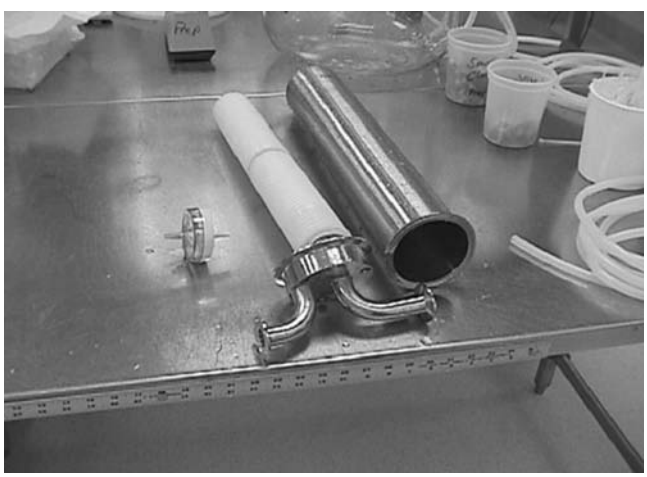


Figure 41-20. Cartridge filter assembly (courtesy, Baxter).

While membrane filters are disposable and thus discarded after use, the holders must be cleaned thoroughly between uses. Today, clean, sterile, pretested, disposable assemblies for small as well as large volumes of solutions are available commercially.

New evidence is being reported that 0.2 μm filters do not remove all possible microbial contamination,[30] necessitating the need to use certain types of 0.1 μm membrane filters.[31] However, most of the parenteral pharmaceutical industry continues to use 0.2 μm filters although now employing redundant (two 0.2 μm filters side-by-side) filtration systems.

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

Most frequently, the compounded product is in the form of a liquid. However, products are also compounded as suspensions or emulsions and as powders. A liquid is more readily subdivided uniformly and introduced into a container having a narrow mouth than is a solid. Mobile liquids are considerably easier to transfer and subdivide than viscous, sticky liquids, which require heavy-duty machinery for rapid production filling.

Although many devices are available for filling containers with liquids, certain characteristics are fundamental to them all. A means is provided for repetitively forcing a measured volume of the liquid through the orifice of a delivery tube that is introduced into the container. The size of the delivery tube will vary from that of about a 20-gauge hypodermic needle to a tube 1/2 in or more in diameter. The size required is determined by the physical characteristics of the liquid, the desired delivery speed, and the inside diameter of the neck of the container. The tube must enter the neck and deliver the liquid well into the neck to eliminate spillage, allowing sufficient clearance to permit air to leave the container as the liquid enters. The delivery tube should be as large in diameter as possible to reduce the resistance and decrease the velocity of flow of the liquid. For smaller volumes of liquids, the delivery usually is obtained from the stroke of the plunger of a syringe, forcing the liquid through a two-way valve providing for alternate filling of the syringe and delivery of mobile liquids. For heavy, viscous liquids, a sliding piston valve, the turn of an auger in the neck of a funnel, or the oscillation of a rubber diaphragm may be used. For large volumes the quantity delivered usually is measured in the container by the level of fill in the container, the force re-

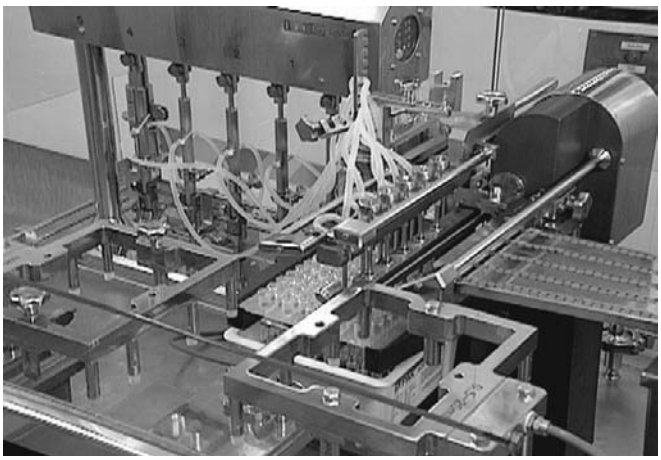


Figure 41-21. Syringe filling machine (courtesy, Baxter). See Color Plate 11.

quired to transfer the liquid being provided by gravity, a pressure pump, or a vacuum pump.

The narrow neck of an ampoule 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 ampoule 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 non-reactive 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 caused by filling pulsations. It should be noted that the insertion of the filter at this point should collect all particulate matter generated during the process. Only that which may be found in inadequately cleaned containers or picked up from exposure to the environment after passage through the final filter potentially remain as contaminants. However, the filter does cushion liquid flow and reduces the efficiency of drop retraction from the end of the delivery tube, sometimes making it difficult to control delivery volume as precisely as would be possible without the filter.

LIQUIDS—There are three main methods for filling liquids into containers with high accuracy: volumetric filling, time/pressure dosing, and net weight filling. Volumetric filling machines employing pistons or peristaltic pumps are most commonly used.

Stainless steel syringes are required with viscous liquids because glass syringes are not strong enough to withstand the high pressures developed during delivery.

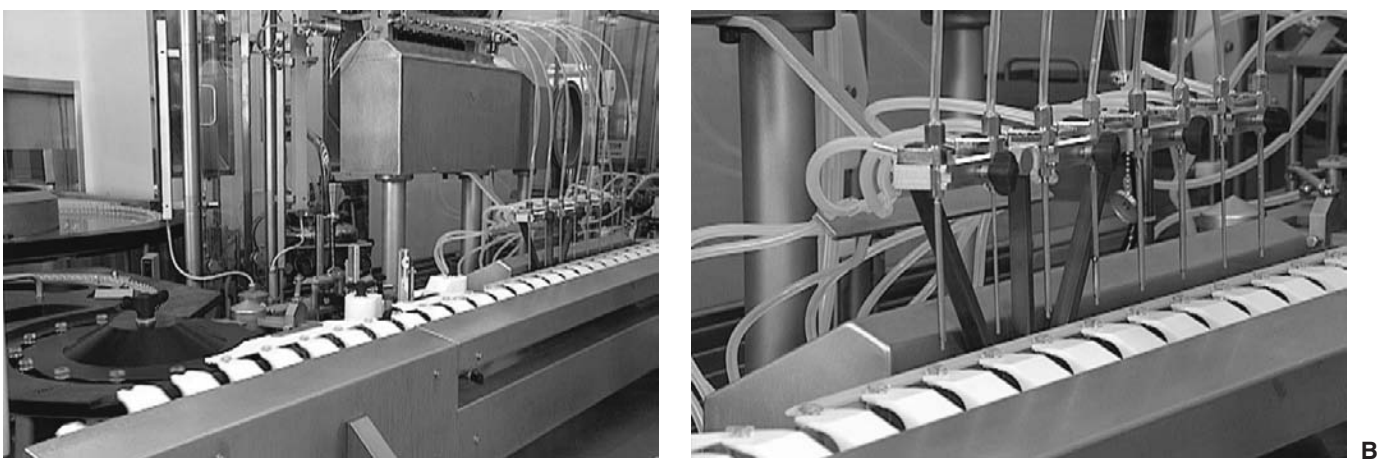
When high-speed filling rates are desired but accuracy and precision must be maintained, multiple filling units often are joined together in an electronically coordinated machine, such as shown in Figures 41-21 and 41-22. When the product is sensitive to metals, a peristaltic-pump filler may be used because the product comes in contact only with silicone rubber tubing. However, there is some sacrifice of filling accuracy.

Time-pressure (or time-gravity) filling machines are gaining in popularity in filling sterile liquids. A product tank is connected to the filling system that is equipped with a pressure sensor. The sensor continuously measures pressure and transmits values to the PLC system that controls the flow of product from tank to filling manifold. Product flow occurs when tubing is mechanically un-pinched and stops when tubing is mechanically pinched. The main advantage of time/pressure filling operations is that these filling apparatuses do not contain mechanical moving parts in the product stream. The product is driven by pressure (usually nitrogen) with no pumping mechanism involved. Thus, especially for proteins that are quite sensitive to shear forces, time/pressure filling is preferable.

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

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

The filling of a small number of containers may be accomplished with a hypodermic syringe and needle, the liquid being drawn into the syringe and forced through the needle into the container. A device for providing greater speed of filling is the Cornwall Pipet *(Becton Dickinson)*. This has a two-way valve



A B

Figure 41-22. Vial filling machine, distant and close-up views (courtesy, Baxter). See Color Plate 12.

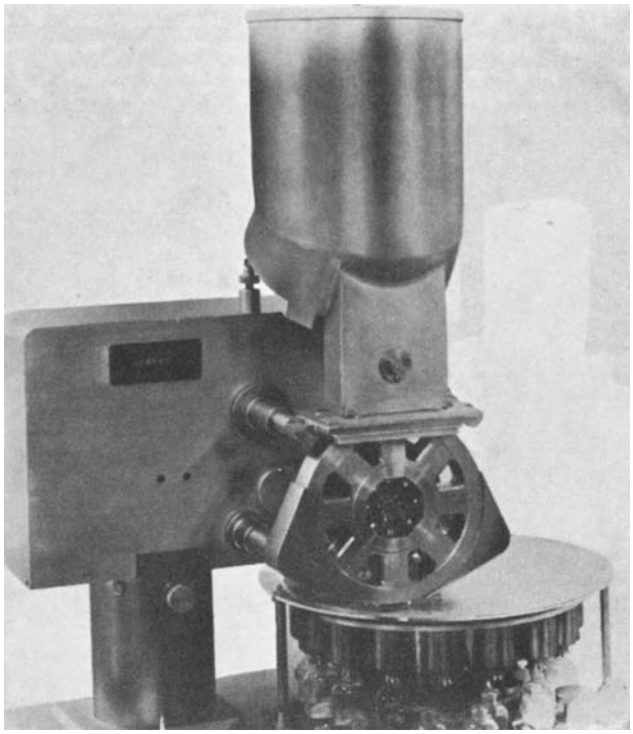


Figure 41-23. Accofil vacuum powder filler (courtesy, Perry).

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

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

Some sterile solids are subdivided into containers by individual weighing. A scoop usually is provided to aid in 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 that has been calibrated in terms of the weight desired. In the machine shown in Figure 41-23 an adjustable cavity in the rim of a wheel is filled by vacuum and the contents held by vacuum until the cavity is inverted over the container. The solid material then is discharged into the container by a puff of sterile air.

SEALING

AMPOULES—Filled containers should be sealed as soon as possible to prevent the contents from being contaminated by the environment. Ampoules 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 ampoule 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 ampoule neck must be heated evenly on all sides, such as by burners on opposite sides of stationary ampoules or by rotating the ampoule in a single flame. Care must be taken to adjust the flame temperature and the interval of heating properly to completely close the opening with a bead of glass. Excessive heating will result in the expansion of the gases within the ampoule against the soft bead seal and cause a bubble to form. If it bursts, the ampoule 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 ampoule is called a *leaker*.

Pull-seals are made by heating the neck of the ampoule below the tip, leaving enough of the tip for grasping with forceps or other mechanical devices. The ampoule 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 ampoule, which continues to rotate. The small capillary tube thus formed is twisted closed. Pull-sealing is slower, but the seals are more sure than tip-sealing. Figure 41-24 shows a machine combining the steps of filling and pull-sealing ampoules.

Powder ampoules or other types having a wide opening must be sealed by pull-sealing. Fracture of the neck of ampoules during sealing may occur if wetting of the necks occurred at the time of filling. Also, wet necks increase the frequency of bubble formation and unsightly carbon deposits if the product is organic.

To prevent decomposition of a product, it is sometimes necessary to displace the air in the space above the product in the ampoule 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 ampoule is sealed before the gas can diffuse to the outside. This process should be validated to ensure adequate displacement of air by the gas in each container.

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

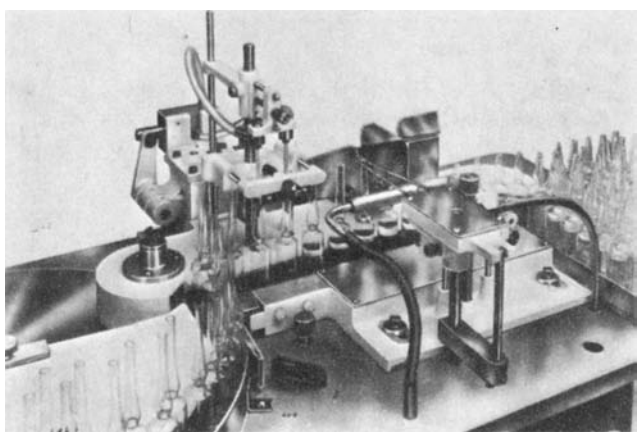


Figure 41-24. Automatic filling and pull-sealing of ampoules (courtesy, Cozzoli).

The closure must fit the mouth of the container snugly enough so that its elasticity will seal rigid to slight irregularities in the lip and neck of the container. However, it must not fit so snugly that it is difficult to introduce into the neck of the container. Closures preferably are inserted mechanically using an automated process, especially with high-speed processing. To reduce friction so that the closure may slide more easily through a chute and into the container opening, the closure surfaces are halogenated or treated with silicone. When the closure is positioned at the insertion site, it is pushed mechanically into the container opening (Fig 41-25). When small lots are encountered, manual stoppering with forceps may be used, but such a process poses greater risk of introducing contamination than automated processes. This is a good test for evaluation aseptic operator aseptic techniques, but not recommended for any product filling and stoppering.

Container-closure integrity testing has become a major focus for the industry because of emphasis by regulatory agencies. Container-closure integrity measures the ability of the seal between the glass or plastic container opening and the rubber closure to remain tight and fit and to resist any ingress of microbial contamination during product shelf life. Container-closure integrity test requirements are covered in USP <1207>, and the various test methods are described by Guazzo.[32]

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. The closure cannot be removed without destroying the aluminum cap; it is tamper-proof. Therefore, an intact aluminum cap is proof that the closure has not been removed intentionally or unintentionally. Such confirmation is necessary to ensure the integrity of the contents as to sterility and other aspects of quality.

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

Single-layered aluminum caps may be applied by means of a hand crimper known as the Fermpress (suppliers: *West, Wheaton*). Double- or triple-layered caps require greater force for crimping; therefore, heavy-duty mechanical crimpers (Fig 41-26) are required (suppliers: *Bosch, Cozzoli, Perry, West, Wheaton*).

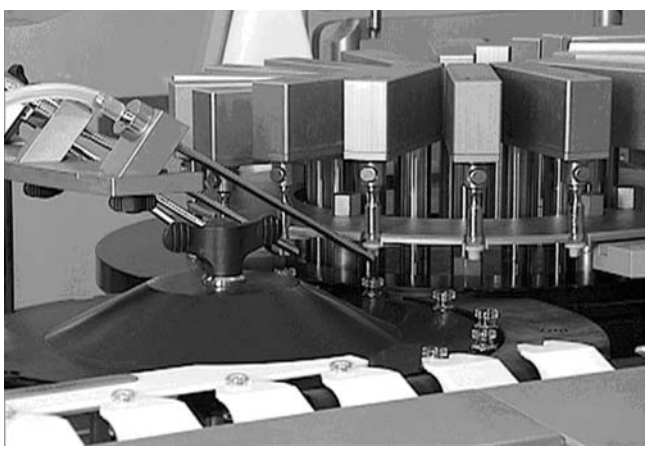


Figure 41-25. Mechanical device for inserting rubber closures in vials (courtesy, Baxter).

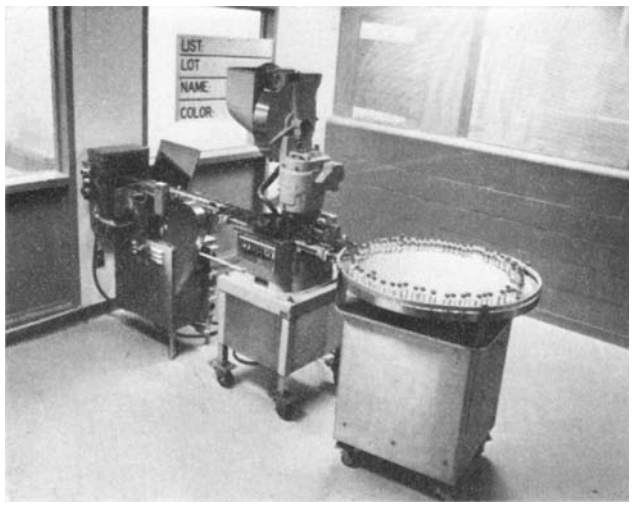


Figure 41-26. Applying aluminum caps to vials at the end of the process line (courtesy, Abbott).

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 (although there is a trend in applying radiation sterilization to finished products), due consideration must be given to the effect of the elevated temperature upon the stability of the product. Many products, both pharmaceutical and biological, will be affected adversely by the elevated temperatures required for thermal sterilization. Heat-labile products must, therefore, be sterilized by a non-thermal method, usually by filtration through bacteria-retaining filters. Subsequently, all operations must be carried out in an aseptic manner so that contamination will not be introduced into the filtrate. Colloids, oleaginous solutions, suspensions, and emulsions that are thermolabile may require a process in which each component is sterilized separately and the product is formulated and processed under aseptic conditions.

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

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

The assessment of aseptic-processing performance is based on the contamination rate resulting from periodic process simulations using media-filling instead of product-filling of containers. A contamination rate no greater than 0.1% at 95% confidence has generally been considered as indicative of satisfactory performance in the industry. However, with current advances in aseptic processing capabilities, lower contamination rates may be achievable.

Radiation sterilization, as mentioned, is gaining some momentum as an alternative terminal sterilization method. There has been limited understanding of the molecular transformations that may occur in drug molecules and excipients under exposure to the high-energy gamma radiation levels of the process. However, lower energy beta particle (electron beam) radiation has seen some success. There is still significant research that must be accomplished before radiation sterilization is used as a terminal sterilization process. The use of radiation for the sterilization of materials such as plastic medical devices is well established.

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

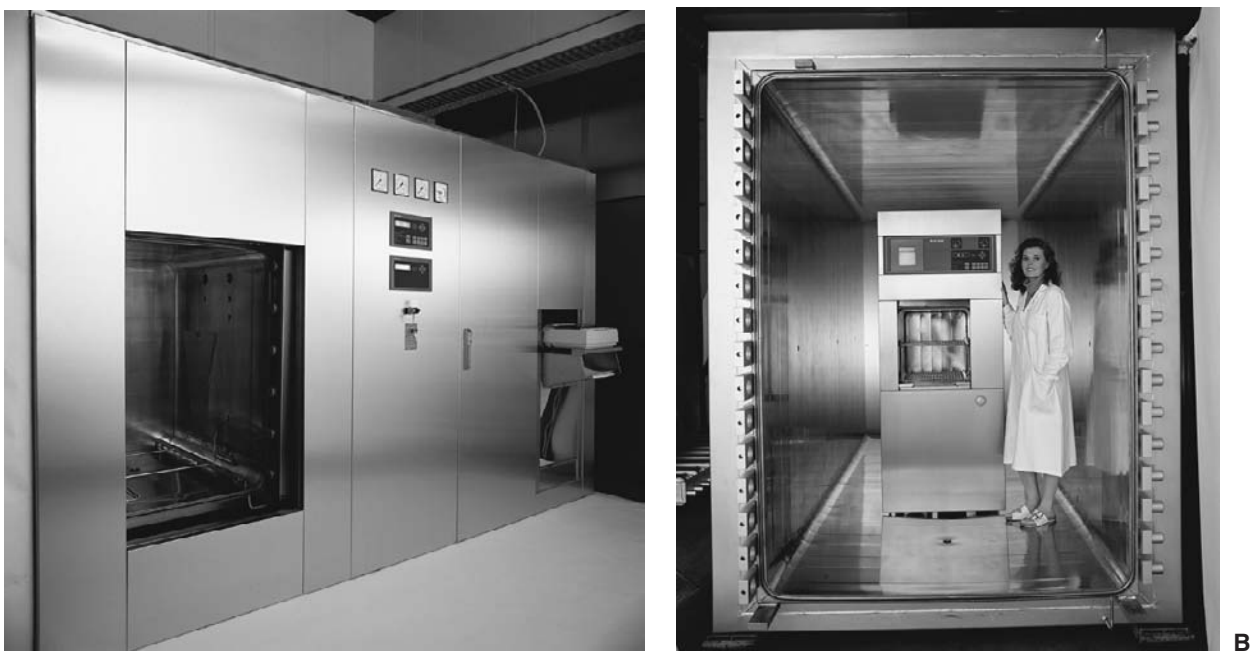
Saturated steam under pressure (autoclaving) is the most commonly used and the most effective method for the sterilization of aqueous liquids or substances that can be reached or penetrated by steam. A survival probability of at least 10^{-6} is readily achievable with terminal autoclaving of a thermally stable product. However, it needs to be noted that for terminal sterilization, the assurance of sterility is based upon an evaluation of the lethality of the process, ie, of the probable number of viable microorganisms remaining in product units. However, for aseptic processing, where the components used have been sterilized separately by validated processes and aseptically put together, the level of sterility assurance is based upon an evaluation of the probable number of product units that were contaminated during the process.

Figure 41-27 shows an example of a modern autoclave for sterilization. Since the temperature employed in an autoclave is lower than that for dry-heat sterilization, equipment made of materials such as rubber and polypropylene may be sterilized if the time and temperature are controlled carefully. As mentioned previously, some injections will be affected adversely by the elevated temperature required for autoclaving. For some products, such as dextrose injection, a shortened cycle using an autoclave designed to permit a rapid temperature rise and rapid cooling with water spray or other cooling methods will make it possible to use this method. It is ineffective in anhydrous conditions, such as within a sealed ampoule containing a dry solid or an anhydrous oil. Other products that will not withstand autoclaving temperatures may withstand marginal thermal methods such as tyndallization or pasteurization, eg, 10 to 12 hours at 60°C. These methods may be rendered more effective for some injections by the inclusion of a bacteriostatic agent in the product.

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

The effectiveness of any sterilization technique must be proved (validated) before it is employed in practice. Since the goal of sterilization is to kill microorganisms, the ideal indicator to prove the effectiveness of the process is a resistant form of an appropriate microorganism, normally resistant spores (a biological indicator, or BI). Therefore, during validation of a sterilization process, BIs of known resistance and numbers are used in association with physical-parameter indicators, such as recording thermocouples. Once the lethality of the process is established in association with the physical measurements, the physical measurements can be used for subsequent monitoring of in-use processes without the BIs. Eliminating the use of BIs in direct association with human-use products is appropriate because of the ever-present risk of an undetected, inadvertent contamination of a product or the environment. The number of spores and their resistance in BIs used for validation studies must be accurately known or determined. Additionally, the manner in which BIs are used in validation is critical and must be controlled carefully.

In addition to the data printout from thermocouples, sometimes other physical indicators are used, such as color-change



A B

Figure 41-27. Steam sterilizers (small and large) (courtesy, Getinge). See Color Plate 13.

and melting indicators, to give visual indication that a package or truckload has been subjected to a sterilization process. Such evidence can become a part of the batch record to confirm that sterilization was accomplished.

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

FREEZE-DRYING (LYOPHILIZATION)

Many parenteral drugs, particularly biopharmaceuticals, are too unstable in solution to be available as ready-to-use liquid dosage forms. Such drugs can still be filled as solutions, placed in a chamber where the combined effects of freezing and drying under low pressure will remove the solvent and residual moisture from the solute components, resulting in a dry powder that has sufficient long term stability. The process of freeze-drying has taken on greater prominence in the parenteral industry because of the advent of recombinant DNA technology. Proteins and peptides generally must be freeze-dried for clinical and commercial use. There are other technologies available to produce sterile dry powder drug products besides freeze-drying, such as sterile crystallization or spray-drying and powder filling. However, freeze-drying is by far the most common unit process for manufacturing drug products too unstable to be marketed as solutions.

The term "lyophilization" describes a process to produce a product that "loves the dry state". However, this term does not include the freezing process. Therefore, although lyophilization and freeze-drying are used interchangeably, freeze-drying is a more descriptive term. Equipment used to freeze-dry products are called freeze-dryers or lyophilizers.

Table 41-6 lists the advantages, features, and disadvantages of freeze-drying.

Freeze-drying essentially consists of:

Freezing stage: Freezing the product solution at a temperature below its eutectic (crystalline) or glass transition temperature

Primary drying stage: Removing the solvent (ice) from the product by evacuating the chamber, usually below 0.1torr (100 μm Hg) and subliming the ice onto a cold, condensing surface at a temperature below that of the product, the condensing surface being within the chamber or in a connecting chamber. During primary drying the temperature of the product must remain slightly below its critical temperature, called "collapse temperature." Collapse temperature is best measured by visual observation using a freeze-dry microscope that simulates the freeze-drying process. Generally, collapse temperature is similar to the eutectic or glass transition temperature of the product.

Secondary drying stage: Removing bound water from solute(s) to a level that assures long term stability of the product. This is accomplished by introducing heat to the product under controlled conditions, thereby providing additional energy to the product to remove adsorbed water. The temperature for secondary drying should be as high as possible without causing any chemical degradation of the active ingredient. Generally, for small molecules, the highest secondary drying temperature used is 40°C while for proteins it is no more than 30°C.

Figure 41-28 shows a photo and diagram of a small-scale lyophilization system and its functional components. The product may be frozen on the shelf in the chamber by circulating refrigerant (usually silicone) from the compressor through pipes within the shelf. After freezing is complete, which may require several hours, the chamber and condenser are evacuated by the vacuum pump, the condenser surface having been chilled previously by circulating refrigerant from the large compressor.

Heat then is introduced from the shelf to the product under graded control by electric resistance coils or by circulating silicone or glycol. Heat transfer proceeds from the shelf into the product vial and mass transfer (ice) proceeds from the product vial by sublimation through the chamber and onto the condenser. The process continues until the product is dry (usually 1% or less moisture except for some proteins that require a minimum amount of water for conformational stability), leaving a sponge-like matrix of the solids originally present in the product, the input of heat being controlled so as not to degrade the product.

For most pharmaceuticals and biologicals the liquid product is sterilized by filtration before being filled into the dosage container aseptically. The containers must remain open during the drying process to allow water vapor to escape; therefore, they must be protected from contamination during transfer from the filling area to the freeze-drying chamber, while in the freeze-drying chamber, and at the end of the drying process until sealed. Automated loading and unloading of product to and from the freeze-dryer shelves is now state-of-the-art where partially open vials are always under the auspices of Class 100 air and human intervention is eliminated.

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

Table 41-7 provides some guidance on a typical formulation approach and initial cycle chosen to freeze-dry a typical product.

FACTORS AFFECTING THE PROCESS RATE—From the diagram in Figure 41-29, it can be seen that the direction of heat and mass transfer causes the top of the product to dry first with drying proceeding downward to the bottom of the vial. Therefore, as drying proceeds, there exists a three component or layer system in each vial—the upper dry product, the middle sublimation front, and the lower frozen liquid product. As the dried layer increases, it becomes a greater barrier or the source of greatest resistance to the transfer of mass out of the vials. This points out the importance of vial dimensions and volume of product per vial on the efficiency of the freeze-drying process. If large volumes of solution must be processed, the surface area relative to the depth may be increased utilizing larger vials or by using such devices as freezing the container in a slanted position to increase the surface area.

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

Table 41-6. Advantages and Disadvantages of Freeze-Drying and Desirable Characteristics of the Finished Freeze-Dried Dosage Form

Advantages of Freeze-dried Products

1. Product is stored in dry state-few stability problems
2. Product is dried without elevated temperatures
3. Good for oxygen and/or air-sensitive drugs
4. Rapid reconstitution time
5. Constituents of the dried material remain homogenously dispersed
6. Product is process in the liquid form
7. Sterility of product can be achieved and maintained

Disadvantages of Freeze-dried Products

1. Volatile compounds may be removed by high vacuum
2. Single most expensive unit operation
3. Stability problems associated with individual drugs
4. Some issues associated with sterilization and sterility assurance of the dryer chamber and aseptic loading of vials into the chamber

Desired Characteristics of Freeze-Dried Products

- Intact cake
- Sufficient strength
- Uniform color
- Sufficiently dry
- Sufficiently porous
- Sterile
- Free of pyrogens
- Free of particulates
- Chemically stable

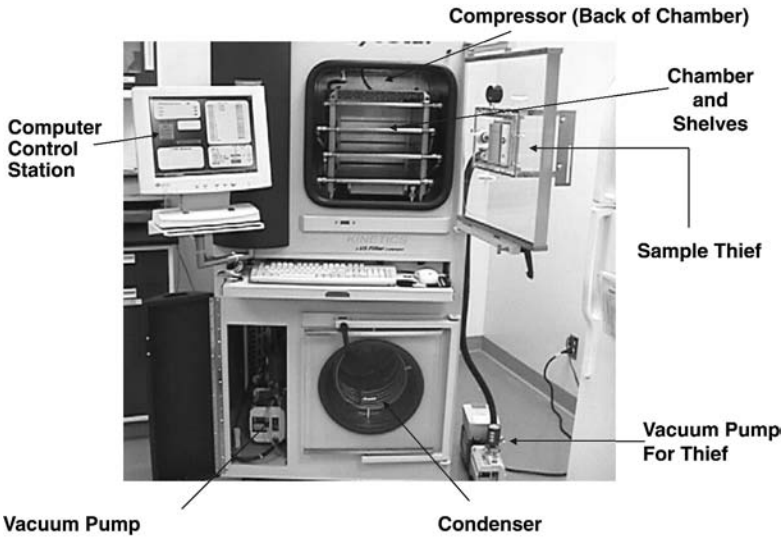


Figure 41-28. Example of a laboratory freeze-dryer (courtesy, Baxter). See Color Plate 14.

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

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

The amount of solids in the product, the ice crystal size, and their thermal conductance will affect the rate of drying. The

Table 41-7. Practical Aspects of Freeze-Drying

- Have appropriate analytical tools and methods in place for formulation characterization and stability studies
- Depend on literature, previous experience (if none, use consultants), and what is known about the active ingredient, design and develop initial formulations, and conduct preliminary stability and compatibility studies
- Initial formulations should use commonly known excipients used in freeze-drying
  - that produce acceptable cakes with rapid reconstitution times
  - that have known minimal collapse temperatures
  - that provide the desired finished product with respect to nature of the final solid (crystalline or amorphous)
- Solids content should be between 5% and 30% with a target of 10% to 15%
- Should have several initial formulations to evaluate and compare. Usually know the qualitative, but not quantitative composition of additives until after initial comparative stability studies have been conducted
- Determine the maximum allowable temperature permitted during freezing and primary drying
  - Know eutectic, glass transition, and/or collapse temperatures, as appropriate
- Select the appropriate size of vial and product fill volume
- Select the appropriate rubber closure
  - Low water vapor transmission
  - No absorption of oil vapor
  - Top design minimizes sticking to shelf during/after stoppering
- Determine appropriate processing parameters
  - Rate of freezing
  - Set point temperatures during all three phases
  - Need for annealing
  - Pressure during primary drying
  - Pressure during secondary drying
  - Stopper seating conditions (eg, vacuum or gas)
- Optimize formulation and process based on stability information during and after freeze-drying and after storage in dry state
- Use a sample thief attachment for laboratory dryers to remove samples during the freeze-dry cycle in order to measure moisture, potency, or other parameters. Provides information for final selection of type and amount of stabilizer(s), if needed, and the cycle parameters necessary to provide an acceptable final moisture level in product
- Typical freeze-dry formulation components
  - Buffers: Phosphate, citrate, acetate
  - Stabilizers: Sucrose, trehalose, glycine
  - Bulking agents: Mannitol, lactose
  - Collapse temperature modifiers: Polymers, sugars
- Typical freeze-dry cycle (without knowing where to start)
  - Freezing phase
    - After loading, cool to 5°C
    - Decrease shelf temperature to −40°C
    - Hold for 2 hours
  - Primary drying phase
    - Must know collapse temperature(Tc)
    - Set shelf temperature approximately 20°C above Tc but making sure product temperature is 5°C below Tc
    - Maintain chamber pressure at 10% to 30% of vapor pressure of ice at the primary drying temperature (usually 100 to 200 microns)
    - Use temperature probes, pressure rise test, or dewpoint measurement to determine end of primary drying
  - Secondary drying
    - Use moderate to high vacuum (typically 100 microns)
    - Adjust shelf temperature to 25°C to 30°C for proteins; 35°C to 40°C for non proteins and hold for at least 4 hours
    - Adjust shelf temperature to 25°C or 5°C prior to stoppering, neutralizing, and unloading

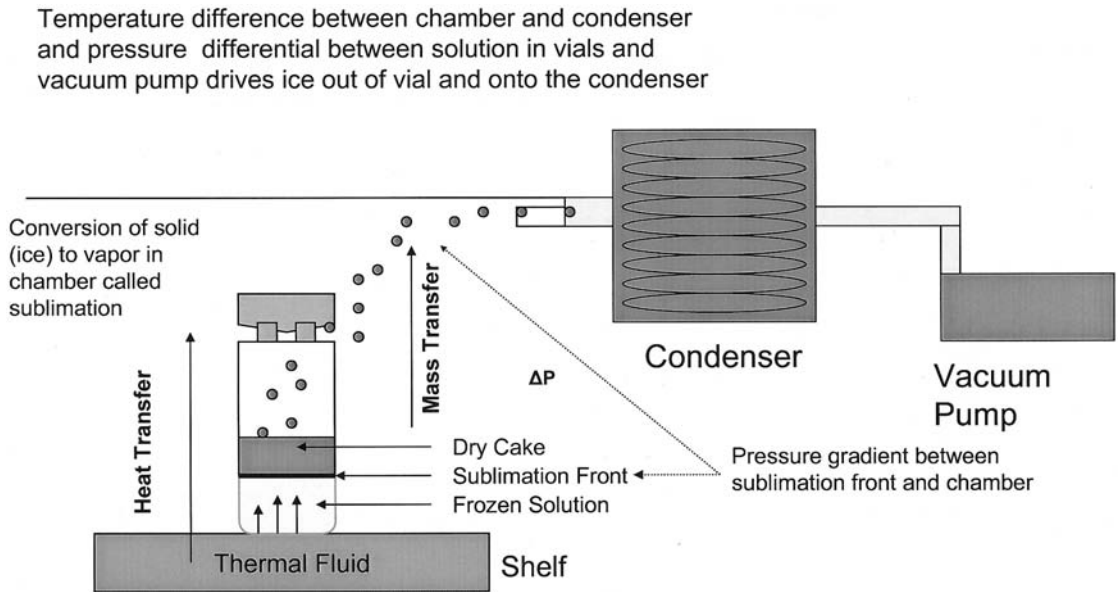


Figure 41-29. Heat and mass transfer in the freeze-dryer. See Color Plate 15.

more solids present, the more impediment will be provided to the escape of the water vapor. The degree of supercooling (how much lower the product temperature goes below its equilibrium freezing point before ice crystals first form) and the rate of ice crystallization define the freezing process and efficiency of primary drying. The larger the size of ice crystals formed, usually as a result of slow freezing, the larger the pore sizes are when the ice sublimes and, consequently, the faster will be the rate of drying. A high degree of supercooling will produce a large number of small ice crystals, a small pore size when the ice sublimes in the dried layer, and a greater resistance to water vapor transport during primary drying. The poorer the thermal conducting properties of the solids in the product, the slower will be the rate of heat transfer through the frozen material to the drying boundary.

The rate of drying is slow, most often requiring 24 hours 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. In fact, the solids content of the original product ideally should be between 5% and 30%. Therefore, excipients often are added to increase the amount of solids. Such excipients are called "bulking agents"; the most commonly used bulking agent in freeze-dried formulations is mannitol. However, most freeze-dried formulations must contain other excipients because of the need to buffer the product and/or to protect the active ingredient from the adverse effects of freezing and/or drying. Thus, buffering agents such as sodium or potassium phosphate, sodium acetate and sodium citrate are commonly used in freeze-dried formulations. Sucrose, trehalose, dextran, and amino acids such as glycine are commonly used lyoprotectants.

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

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

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-dryers (suppliers: *BOC Edwards, FTS, Hull, Serail, Stokes, Usifroid, Virtis*) range in size from small laboratory units to large industrial models such as the one shown in Figures 41-30 and 41-31. Their selection requires consideration of such factors as

- The tray area required
- The volume of water to be removed
- How the chamber will be sterilized

Figure 41-30. Example of a production freeze-dryer (courtesy, Edwards). See Color Plate 16.

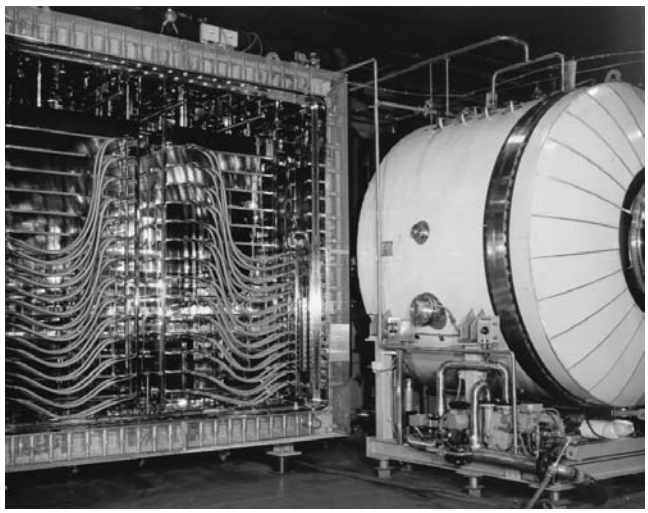


Figure 41-31. Inside view of a production freeze-dryer (courtesy, Edwards). See Color Plate 17.

- Whether internal stoppering is required
- Whether separate freezers will be used for initial freezing and condensation of the product
- The degree of automatic operation desired

Other factors involved in the selection and use of equipment are considered in the literature.[33]

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

QUALITY ASSURANCE AND CONTROL

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

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

STERILITY TEST

All lots of injectables in their final containers must be tested for sterility, except for products that are allowed to apply parametric release.‡ The USP prescribes the requirements for this test for official injections. The FDA uses these requirements as a guide for testing official sterile products. The primary official test is performed by means of filtration, but direct transfer is used if membrane filtration is unsuitable. To give greater assurance that viable microorganisms will grow, if present, the USP requires that all lots of culture media be tested for their growth-promotion capabilities. However it must be recognized that the reliability of both test methods has the inherent limitations typical of microbial recovery tests. Therefore, it should be noted that this test is not intended as a thoroughly evaluative test for a product subjected to a sterilization method of unknown effectiveness. It is intended primarily as a check test on the probability that a previously validated sterilization procedure has been repeated or to give assurance of its continued effectiveness. A discussion of sterility testing is given in Chapter 40 (*Sterilization*).

In the event of a sterility-test failure, the immediate issue concerns whether the growth observed came from viable microorganisms in the product (true contamination) or from adventitious contamination during the testing (a false positive). The USP does not permit a retest, unless specific evidence is discovered to suggest contamination occurred during the test. Therefore, a thorough investigation must be launched to support the justification for performing the retest and assessing the validity of the retest results relative to release of the lot of product.

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

As stated previously, isolator technology has been applied to significantly reduced the incidence of false positives in the conductance of the sterility test. An example of a sterility testing isolator is shown in Figure 41-32. Validation of isolator systems for sterility testing is described in USP <1208>.

‡Parametric release means that a lot of product, if terminally sterilized by a well-defined, fully validated sterilization process, has a sterility assurance level sufficient to omit the sterility test for release. [34]

Figure 41-32. Example of an isolator used for sterility testing (courtesy, Baxter). See Color Plate 18.

PYROGEN TEST

The USP evaluates the presence of pyrogens in parenteral preparations by a qualitative fever response test in rabbits, the Pyrogen Test (Section <151>), and by the Bacterial Endotoxins Test (Section <85>). These two USP tests are described in Chapter 40 (*Sterilization*). Rabbits are used as test animals in Section <151> because they show a physiological response to pyrogenic substances similar to that of man. While a minimum pyrogenic dose (MPD), the amount just sufficient to cause a positive USP Pyrogen Test response, sometimes may produce uncertain test results, a content equal to a few times the MPD will leave no uncertainty. Therefore, the test is valid and has continued in use since introduced by Seibert in 1923. It should be understood that not all injections may be subjected to the rabbit test, since the medicinal agent may have a physiological effect on the test animal such that any fever response would be masked.

The *Bacterial Endotoxins Test* (BET) is an *in vitro* test based on the formation of a gel or the development of color in the presence of bacterial endotoxins and the lysate of the amebocytes of the horseshoe crab *(Limulus polyphemus)*. The *Limulus Amebocyte Lysate* (LAL) test, as it also is called, is a biochemical test performed in a test tube and is simpler, more rapid, and of greater sensitivity than the rabbit test. An example of a positive endotoxin test result in a test tube is shown in Figure 41-33. Although it detects only the endotoxic pyrogens of gram-negative bacteria, these are the most prominent environmental microbial contaminants likely to invade sterile products. The test has been automated and can determine the quantitative amount of endotoxin in a sample. This test has enabled endotoxin limits to be established on finished products and bulk drug substances and excipients.

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

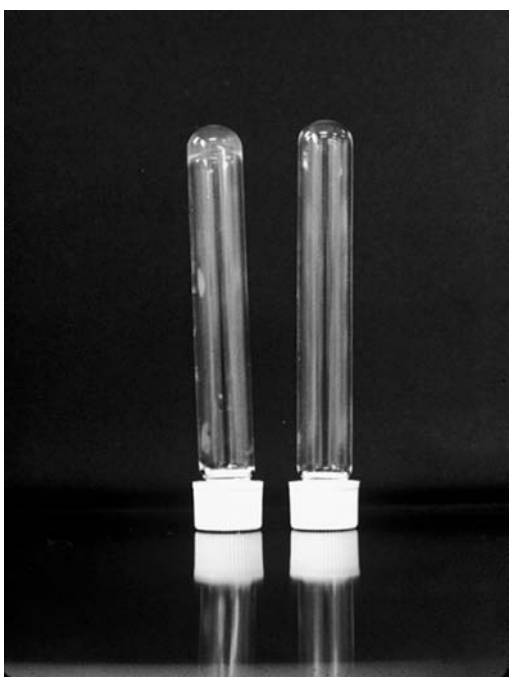


Figure 41-33. Example of positive (left tube) endotoxin test.

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. Further, it has been shown that the development of infusion phlebitis may be related to the presence of particulate matter in intravenous fluids.

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

The assessment of the level of particulate matter below the visible size of about 50 μm has become an increasingly used QC indicator of process cleanliness in the manufacture of injections. The tests used, however, are destructive of container units. Therefore, they are performed on appropriately selected samples of products. Further, all of these methods require very

Table 41-8. Subvisible Particulate Matter Limits in Injectable Products

COMPENDIA	LVI/SVI	METHOD	≥10μm	≥25μm
USP	LVI	Light Blockage	25 part/mL	3 part/mL
		Microscope	12 part/mL	2 part/mL
USP	SVI	Light Blockage	6000 part/contain.	600 part/contain.
		Microscope	3000 part/contain.	300 part/contain.
EP	LVI	Light Blockage	25 part/mL	3 part/mL
	SVI Soln	Light Blockage	6000 part/contain.	600 part/contain.
	SVI Powder	Light Blockage	10000 part/contain.	1000 part/contain.
BP	LVP	Coulter Counter	1000 part/mL ≥ 2μm	100 part/mL ≥ 5μm
		Light Blockage	500 part/mL ≥ 2μm	80 part/mL ≥ 5μm
JP	LVP	Microscope	20 part/mL	2 part/mL

stringent, ultraclean preparation techniques to ensure accuracy in the counting and sizing of particles only in the product, rather than those that may have been introduced inadvertently during the sample preparation or the testing procedure.

The USP has identified two test methods in <788>, *Particulate Matter in Injections*. All LVIs for single-dose infusion and those SVIs for which the monograph specifies a limit (primarily those commonly added to infusion solutions) are subject to the specified limits given in Table 41–8. The first test to be used is the light obscuration test, which uses an electronic instrument designed to count and measure the size of particles by means of a shadow cast by the particle as it passes through a high-intensity light beam (suppliers: *Climet, HIAC/Royco*). If the injection formulation is not a clear, colorless solution (eg, an emulsion) or it exceeds the limits specified for the light obscuration test, it is to be subjected to the microscopic count test. The latter method consists of filtering a measured sample of solution through a membrane filter under ultraclean conditions and then counting the particles on the surface of the filter, using a microscope and oblique light at 100× magnification. The time requirements for performing the latter test are very long. These standards are being met readily in the US today by the manufacturers of LVIs and the specified SVIs.

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

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

CONTAINER/CLOSURE INTEGRITY TEST

Ampoules 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 ampoule 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 ampoule while the ampoule is submerged entirely in a deeply colored dye solution. Most often, approximately 1% methylene blue solution is employed. After carefully rinsing the dye solution from the outside, color from the dye will be visible within a leaker. Leakers, of course, are discarded.

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

Container-closure integrity tests are summarized in Table 41-9.[32]

SAFETY TEST

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

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.

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

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

LABELING—The labeling of an injection must provide the physician or other user with all of the information needed to ensure the safe and proper use of the product. Since all of this in-

Table 41-9. Container-Closure Integrity Tests

TEST	BASIC PRINCIPLE	ADVANTAGES	DISADVANTAGES
Acoustic Imaging *(Sonoscan.com)*	Ultrasonic energy focused onto sample submerged in water or other solvent. Echo patterns produce images of package material interior	Visualize delamination, channels Mostly applies to microchip technology	Expensive Sample must be immersed Slow, requires expertise Not for porous materials
Bubble Test	Submerge package in liquid, pressurize and/or temperature cycling to accelerate leakage, improvement sensitivity	Simple Inexpensive Location of leaks can be observed Good troubleshooting technique	Relatively insensitive Operator dependent Wets package seal Qualitative
Gas Tracer Detection *(Mocon.com)*	Test tracer gas is placed on one side of container seal. Inert carrier gas passed along opposite seal side. Tracer gas is detected either by a coulombic detector (Oxygen) or by photoelectric sensor (Water or Carbon Dioxide). Instruments designed to pierce containers and test package headspace for oxygen or carbon dioxide are another type of gas detection method	Directly relates to package performance Does not pick up false leaks as helium detection can Used on screw-cap bottles, blister packs, polymer and foi pouches	Slow Often fixture dependent
Helium Mass Spectrometry *(alcatelvacuum.com)* *(inficon.com)* *(varian.com)*	Helium is place either inside or outside of the container. Vacuum is applied to seal interface and migrating helium is detected by mass spectrometry	Inert gas Extremely sensitive test Rapid test time Quantitative	May confuse helium diffusion with leakage Expensive and expertise Helium bombing takes time May be destructive
High-Voltage Leak Detection (HVLD) *(nikkadensok.com)*	High frequency, high voltage is applied to seal container. Increase in conductivity correlated to presence of liquid along the seal	100% automatic inspection Clean, non-destructive Rapid Used for ampoules, vials, syringes, blow/fill/seal containers	Difficult to validate with st'd defects Requires liquid-fill product
Liquid Tracer Tests	Package immersed in solution of tracer chemical or dye. Pressure/vacuum or temperature cycling used to improve sensitivity. Leakage detected visually (dye) or instrumentally (dye or chemical)	Correlates to liquid leakage and microbial ingress Operator independent (instrum method) Inexpensive Simple to perform	Destructive Human variability (dye) Large sample numbers needed Slow
Microbial Challenge	Containers are media filled and the seal is either challenged directly with microorganisms or is allowed to sit in ambient storage environment. Presence of microbial growth is visually confirmed	May provide direct correlation to microbial integrity No special equipment required Airbone challenge best approach for tortuous seal tests Widely used in the industry	Insensitive Expensive in time, storage and resources Slow
Noninvasive Moisture and Oxygen Analysis *(foss-nirsystems.com)*	Method 1: Moisture by NIR spectroscopy Measures powder moisture inside unopened glass package Method 2: oxygen and moisture Tunable diode laser light passed through package headspace. Frequency of light matched to oxygen or water. Absorbed light proportional to headspace contents	Nondestructive Rapid Sensitive to trace moisure Simple Used for lyophilized and powder filled pdts	Calibration unique for each type of product
Residual Gas Ionization Test *(Electro-Technic Pdts)*	High voltage, high frequency field is applied to vials sealed under vacuum. The field causes residual gas to glow. Glow intensity is function of vacuum level.	On-line, non-destructive test Rapid Used for lyophilized products	Unknown sensitivity Inconsistencies in results

(continues)

Table 41-9. ***Continued***

TEST	BASIC PRINCIPLE	ADVANTAGES	DISADVANTAGES
Residual Seal Force *(dynatup.com) (genmap.com)*	Vials sealed with closures are compressed at a constant rate of strain. Stress-strain deformation curves generated. Second derivative of the curve = residual seal force	Measures closure forces post compression Non-destructive (plastic cap removed) No human error Qualitative measure; simple	Residual seal force variable Very dependent on rubber material and history
Vacuum/Pressure Decay *(packagingtechnologies.com) (wilco.com) (tmelectronics.com)*	Change in pressure or vacuum measured inside package (destructive) or outside in a sealed package chamber (nondestructive). Pressure/vacuum change significantly greater than non-leaking package indicative of a reject	Clean Non-destructive (test chamber method) Relevant to shipping/distribution Sensitivity good for leaks >5 microns Rapid test	Difficult to detect leaks <5 mic Some package headspace needed
Visual Inspection *(seidenader.de)*	Look for leaks	Simple Inexpensive	Insensitive Operator Dependent Qualitative
Weight Change	Container is filled with liquid or dessicant, sealed, stored at various stress conditions, and reweighed over time	Easy Directly relates to closure performance Quantitative Inexpensive	Time consuming Leak location not detected

From Akers MJ, Larrimore DS, Guazzo DM. *Parenteral Quality Control.* New York: Dekker, 2002, pp 310–319.

formation cannot be placed on the immediate container and be legible, it may be provided on accompanying printed matter.

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. 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.

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.

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 42

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 320 million units annually. Not only do IV fluids continue to serve as the means for fluid replacement, electrolyte-balance restoration, and supplementary nutrition, they also are playing major roles as vehicles for administration of other drug substances and in total parenteral nutrition (PN). Intravenous 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 PN parenterally have improved steadily in the last decade, and such use is increasing. 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 PN 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 90% of the nation's hospitals with 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.

Electronic mechanical equipment is now commonplace in hospitals. Its use, as well as its sophistication, continues to increase. Newly designed electronic pumps have been developed for hospital ambulatory use. Multichannel pumps have become available for multiple-drug infusion. Over 500,000 implantable infusion ports have been inserted into patients and 100,000 new patients receive these implantable ports each year to accomplish drug therapy. New methods of IV drug delivery systems have been introduced and are constantly evolving. The introduction of patient-controlled analgesia (PCA) is commonplace in hospitals. This technology allows the patient with pain to control the degree of analgesia.

The growth of PN in hospitals has been paralleled by home PN programs. Large numbers of patients conduct parenteral nutrition in the home environment, including those with infectious and neoplastic diseases. More-stringent and more-complete guidelines for the preparation of parenterals in hospitals by pharmacists have been published. These guidelines, promoting sophisticated methods of preparation by the pharmacist, have become recommendations. They are a testament to the importance of parenteral preparation in the institutional setting. Packaging of parenterals in the past 5 years also has undergone dramatic changes. Prefilled, premixed, prefrozen parenterals are now supplied by the manufacturers. Plastic minibags (ADD-Vantage, *Abbott*) have been introduced. Premixed liquids (eg, antibiotics, theophylline, heparin, lidocaine, dopamine) are available from parenteral manufacturers. Multiple-dose containers have been developed to accommodate new methods of preparation of parenterals by the pharmacist. The pharmaceutical industry has responded to the needs of pharmacists by addressing the packaging, labeling, and design requirements necessary to facilitate patient care. The parenteral drug industry continues its efforts to meet higher standards of quality and to ensure the availability of sterile and particulate-free products.

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 used in the *piggyback* technique (ie, the administration of a second solution through a Y-tube 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 that 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 that are equal to or larger than 10 μm and not more than 5 particles per mL that 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 PN.
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 vehicle. 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 42-1.

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 essential for the functioning of the nervous and muscular systems as well as the heart; magnesium, as a nutritional supplement especially in PN solutions; and phosphate ion, important in a variety of biochemical reactions. In addition to the number of standard electrolyte fluids shown in Table 42-1, 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 for fluid replacement. It is slightly hypotonic and administered intravenously into a peripheral vein; 1 g of dextrose provides 3.4 cal, and 1 L of D5/W supplies 170 Kcal. The body uses dextrose at a rate of 0.5 g per kg of body weight per hour. More-rapid administration can result in glycosuria. Therefore, 1 L of D5/W requires 1 1/2 hr 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

Table 42-1. 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, 8.5, 10, 15	5.25	
FreAmine III (*B.Braun*)	8.5, 10	6.6	
Travasol (*Baxter*)	3.5, 5.5, 8.5. 10	6.0	
Ammonium chloride	2.14	4.5–6.0	Metabolic alkalosis
Dextran 40			
in NSS	10	5	Priming fluid for plasma volume expander
in D5/W	10	4	Priming fluid for plasma volume expander
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, 5–20, with varying concn of sodium chloride 0.22–0.9	3.5–6.5	Fluid, nutrient, and electrolyte 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, also in combination	5	5.0–7.0	Osmotic diuresis
with dextrose or sodium chloride	15		
	20		
Multiple electrolyte solutions, varying combinations of electrolytes, dextrose,		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.

Table 42-2. IV Fluid Systems

SOURCE	CONTAINER	CHARACTERISTICS
Baxter	Glass	Vacuum Air tube
Baxter (*Viaflex*)	Plastic	Polyvinyl chloride Flexible Nonvented
B.Braun	Glass	Vacuum Air tube
B.Braun (*Excel*)	Plastic	Flexible
Abbott	Glass	Vacuum Air filter[a]
Abbott (*Lifecare*)	Plastic	Polyvinyl chloride Flexible Nonvented

[a] Part of administration set.

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.

Intravenous fluids containing crystalline amino acids can provide biologically usable amino acids for protein synthesis (Chapter 106). 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 used 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 PN (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, *Baxter*; Liposyn II, *Abbott*) sometimes is used concurrently but usually administered at Y-site. However, new systems such as three-in-one packaging permit mixing of amino acids, carbohydrates, and fat in one container for PN.

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 are made from a flexible 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 0.9% for piggyback use in addition to 0.45% sodium chloride and 2.5% dextrose injections. 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 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 a container to be determined from either 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.

Fluids for IV use are available from three sources (*Abbott, Baxter,* and *B.Braun*); all provide both glass and plastic containers. The glass-container systems of *Baxter* and *B.Braun* are similar. The characteristics of current packaging systems are summarized in Table 42-2.

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 usually 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 (PVC) tubing terminating in a gum-rubber injection port. Non–PVC sets are available for special uses. 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 Y-site 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 Figures 42-1 to 42-6.

Administration Procedures

In the administration of IV fluids, the primary IV container provides for fluid replacement, electrolyte replenishment, drug therapy, or nutrition; the fluid can be infused usually over a 4- to 12-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

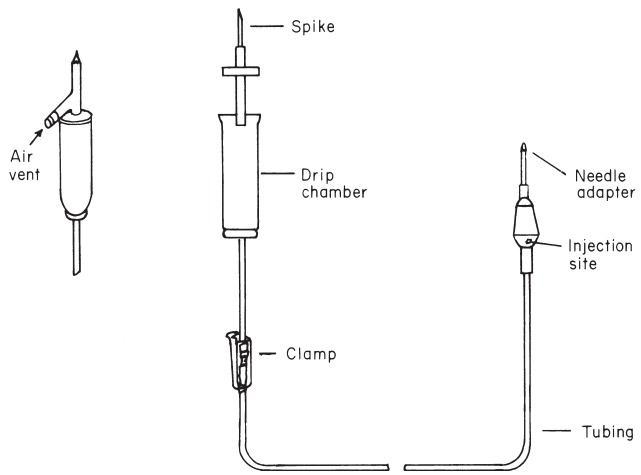

Figure 42-1. Parts of basic administration sets.

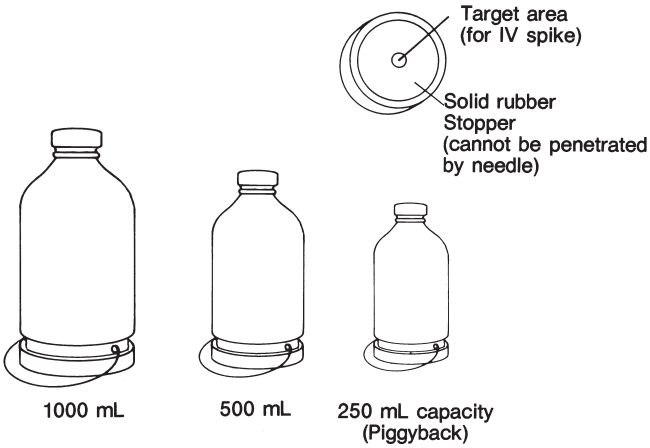

Figure 42-2. Abbott IV glass container. The air venting is provided through the air filter located in the spike of the administration set. See Figure 42-1.

results in continuous blood levels of added drugs once the steady state has been reached.

Incinerated PVC products produce hydrogen chloride gas as a toxic pollutant. Diethylhexylphthalate (DEHP), a component of PVC containers, may leach into the soil in landfills. A number of drugs adsorb on PVC containers, notably nitroglycerin. Some drugs (fat emulsions, blood, Paclitaxel) are known to leach DEHP.

The Excel container is claimed to eliminate or minimize these problems. The plastic film contains no plasticizers and exhibits no leachability. The solution-contact layer of the container is composed of a rubberized copolymer of ethylene and propylene, which is claimed to be clear, nontoxic, and biologically inert. The container is available in 250-mL, 500-mL, and 1-L sizes. Smaller sizes are available in 25, 50, and 100 mL known as PAB containers.

In preparing an IV fluid for administration, the following procedure is used.

The spike adapter of the administration set is inserted into the stopper or seal of the IV container.

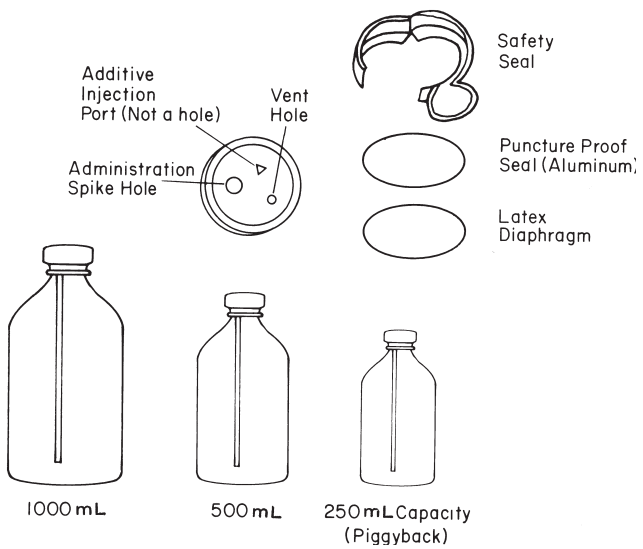

Figure 42-3. B.Braun glass containers. The plastic air tube allows the air to enter the bottle as the fluid is infused into the patient. The spike of the administration set is not vented. See Figure 42-1.

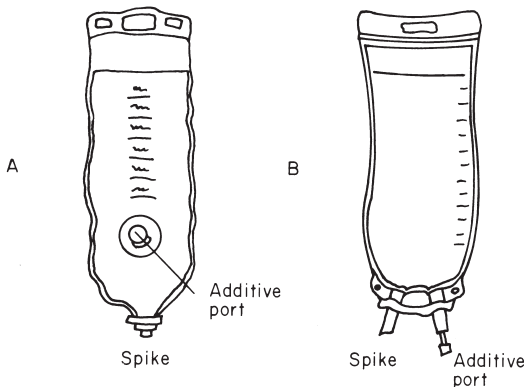

Figure 42-4. *A,* Abbott *(*Lifecare*)* polyvinyl chloride flexible container; *B,* Baxter *(*Viaflex*)* polyvinyl chloride flexible container. These containers take nonvented administration sets. See Figure 42-1.

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.

The venipuncture is made by a member of the IV team, floor nurse, or physician.

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 is 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, depending 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. Critical drugs are usually administered by electronic pumps.

Intermittent administration of an antibiotic and other drugs can be achieved by any of three methods:

1. Direct IV injection (IV bolus or push)
2. Addition of the drug to a predetermined volume of fluid in a volume-control device
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 Y 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.

To set up an intermittent IV infusion with a volume-control set, the spike of the volume-control set is inserted into the primary IV fluid or a separate fluid container using aseptic technique. See Figure 42-6.

Air is purged from tubing of the volume-control set by opening the clamps until fluid comes through.

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.

The clamp is closed above the chamber.

The medication is injected through the gum-rubber port of the volume-control unit.

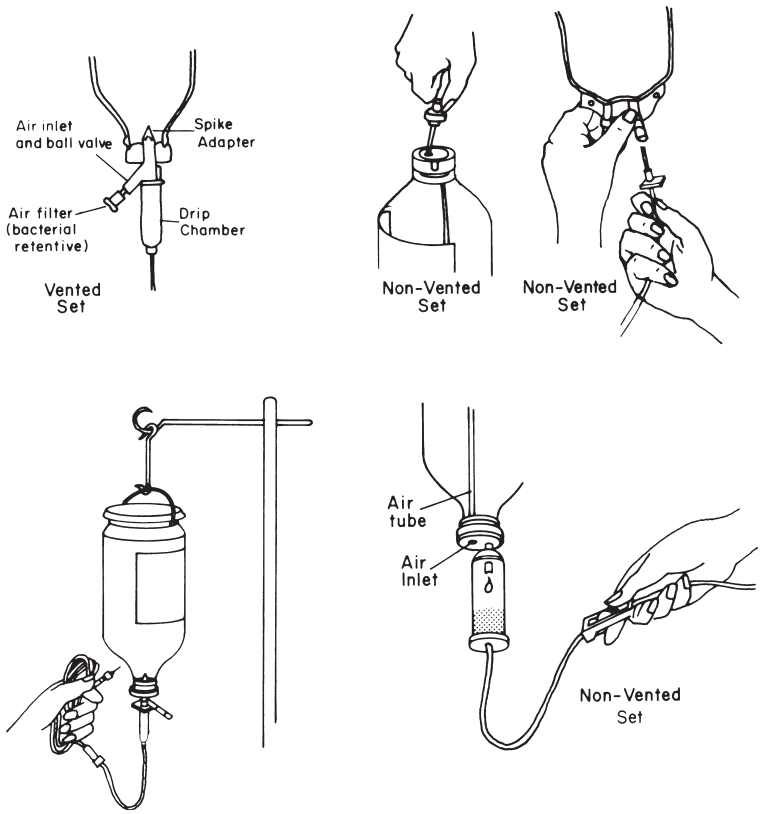

Figure 42-5. Setting up a primary IV fluid for administration.

The clamp above the chamber is opened to complete the dilution to the desired volume (50 to 150 mL), then closed.

Flow commences when the clamp below the volume-control unit is opened.

PIGGYBACK METHOD—The piggyback method (Fig 42-7) refers to the intermittent IV drip of a second admixture drug, through the venipuncture site of an established primary IV system. With this 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 timespan, 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 or blunt cannula inserted into a Y-injection site of the primary set or into the injection site at the end of the primary set.

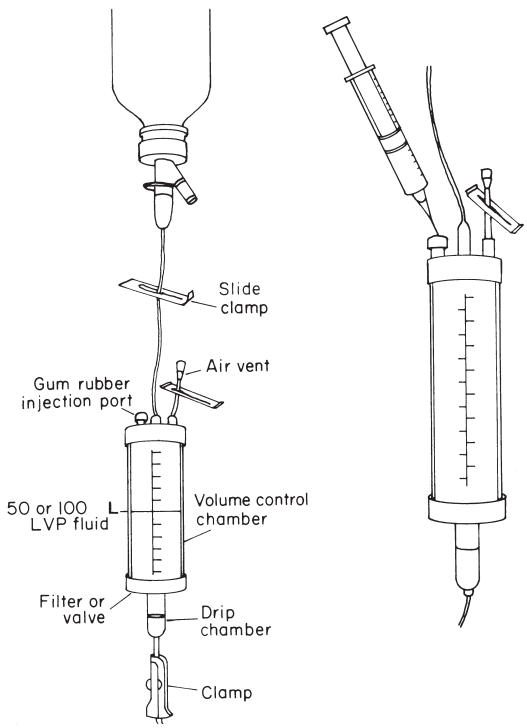

Figure 42-6. Volume control unit for intermittent administration.

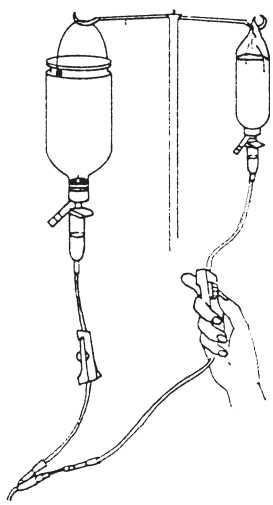

Figure 42-7. Piggyback administration setup.

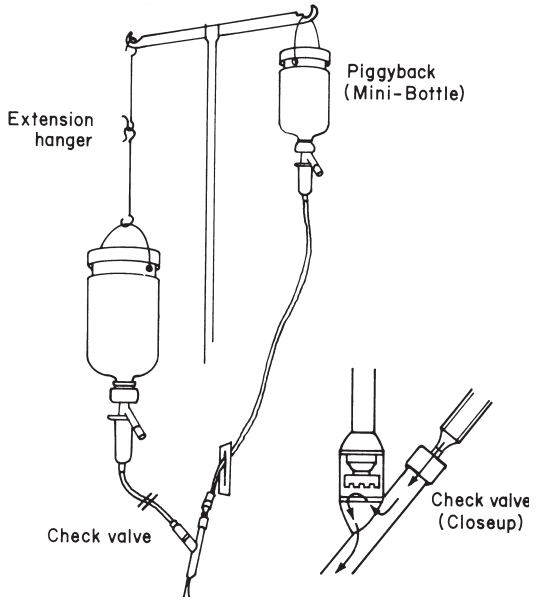

Figure 42-8. Piggyback administration setup with check valve in primary set.

The piggyback infusion is then started. Once it is completed, the primary fluid infusion will be restarted. See Figure 42-7.

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 Figure 42-8.

Manufacturers have introduced minibottles and minibags 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.

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 min). 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 that 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, are usually less expensive, and have 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. Controllers are used less frequently in favor of pumps.

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.

PATIENT-CONTROLLED ANALGESIA (PCA)—Usually and traditionally the acute or chronic pain experienced by patients in selected diseases is treated initially by oral narcotics and analgesics. However, many clinical situations preclude oral administration. Typically, the unsatisfied pain from disease has been treated by parenteral analgesics given by the IM or SC route.

This medication cycle from patient complaint to pain relief often can be lengthy. Frequently, the dose administered may be too large or too small, resulting in either sedation or poor pain relief. See Figure 42-9.

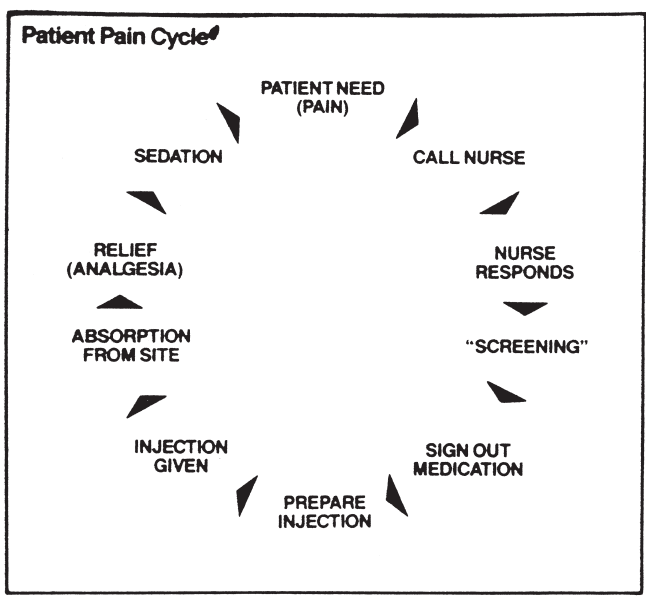

Figure 42-9. Patient pain cycle—sequence of events.[3]

Parenteral drugs given intravenously offer rapid distribution in the body and fast onset of action. The drug undergoes no biotransformation or inactivation and, therefore, allows more precise dose management.

PCA is a system for delivery of IV or SC narcotics by direct patient intervention. This therapy uses a mechanical, electronic, infusion-control device that permits self-administration of analgesics in proportion to the degree of relief desired.

A number of these devices have been developed and are undergoing development at *Bard, Abbott, Deltec, Baxter,* and *Becton Dickinson.* The early devices allowed for patient- triggered IV doses, and later refinement in the microprocessors allowed tailoring of infusions so that additional bolus doses could be given to a baseline infusion. Additional developments have led to ambulatory PCA devices that are small enough to be worn on a belt. An additional design being used is a balloon-powered disposable device (*Baxter*) that operates mechanically from an inflated balloon.

In its simplest terms, PCA allows a patient to initiate an IV infusion of a prescribed narcotic analgesic and maintain a self-regulated small amount of incremental doses needed for controlling a variety of pain-associated medical problems.

The success and popularity of PCA is based upon the inadequacy of conventional IM and IV dosing, such as variables that affect absorption and distribution[1] such as conventional nursing practices, inherent procedural delays in securing medication, and the ultimate administration to the patient.[2] The perception and sensation of pain in any one patient depends upon individual levels of endorphins and other biochemicals in cerebrospinal fluid.[3]

The last several years have seen the increasing use of infusion devices for epidural or intrathecal administration.

PCA eliminates the peak and valley effects of traditional drug therapy (Fig 42-10). Epidural or intrathecal therapy of PCA allows a longer duration of drug action. Kwan[4] reviewed the use of infusion devices for epidural or intrathecal administration.

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 about 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

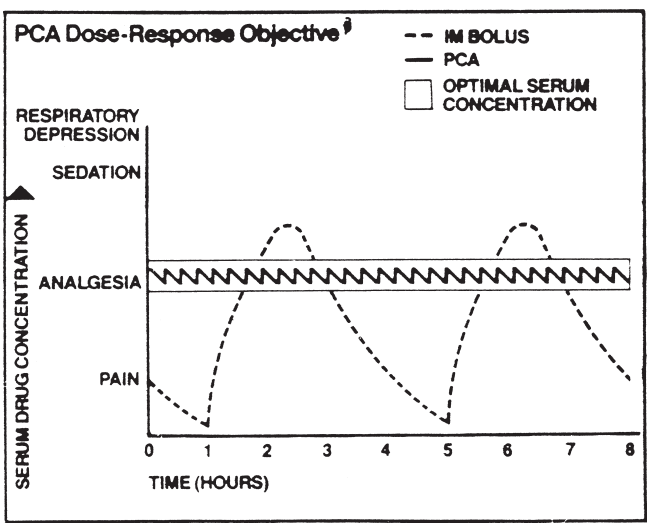

Figure 42-10. Characteristic pattern comparison of IM bolus serum concentration versus PCA.[3]

with porosities varying from 5 to 0.22 μm. Air lock can be a problem with membrane filters. When wet, membranes with porosities of 0.22 μm and 0.45 μm are impervious to air at normal pressures, and air in the system causes blockage. To prevent this, the filter housing must be purged completely of air prior to use. Newer designs have air eliminators. Using final-filter devices 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.[5] 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.

Blood is filtered by utilizing blood filters of larger porosity (210 microns).

2 in 1 TPN solutions usually require a 0.22 micron filter.

3 in 1 TPN solutions usually require a 1.2 micron filter.

IV DELIVERY SYSTEMS—*Frozen Premixes*—Baxter provides delivery to hospitals of frozen drug products packaged in PVC containers. These are stored in a freezer in the hospital's pharmacy, thawed, and used when needed. See Figure 42-11*A*.

Abbott/ADD-Vantage System—Introduced in 1985, the *Abbott* ADD-Vantage system (Fig 42-11*B*) has two parts: a plastic IV bag (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 in 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 which allows drugs to fall into the diluent.

Nutrimix—A dual-compartment container is available from Abbott that allows long-term packaging of amino acids and dextrose mixtures.

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 the volume to be delivered. This instrument provides accuracy, constant flow, convenience, and safety for intermittent drug delivery. See Figure 42-11*C*.

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.

INTERNAL METHODS USED TO ACHIEVE INTRAVASCULAR ACCESS—*Implantable Ports* (Infuse-A-Port, *Infusaid;* Port-A-Cath, *Pharmacia*)—Broviac and Hickman catheters have been used to achieve long-term venous access in a variety of diseases. Although these catheters are widely used, they are associated with some morbidity, which includes fracture of catheters, entrance-site infection, and catheter sepsis. Implantable catheters have been developed to overcome catheter complications and are designed to permit repeated access to the infusion site. The catheters consist of implantable-grade silicone tubing connected to a stainless steel port with a self-sealing septum that allows needle access. The delivery catheter can be placed in a vein, cavity, artery, or the central nervous system (CNS). The system is accessed with a Huber-point needle through the skin into the self-sealing silicone plug positioned in the center of the portal.

The specialized Huber-point needle is designed with an angle bevel that reduces coring and permits easy entry. These

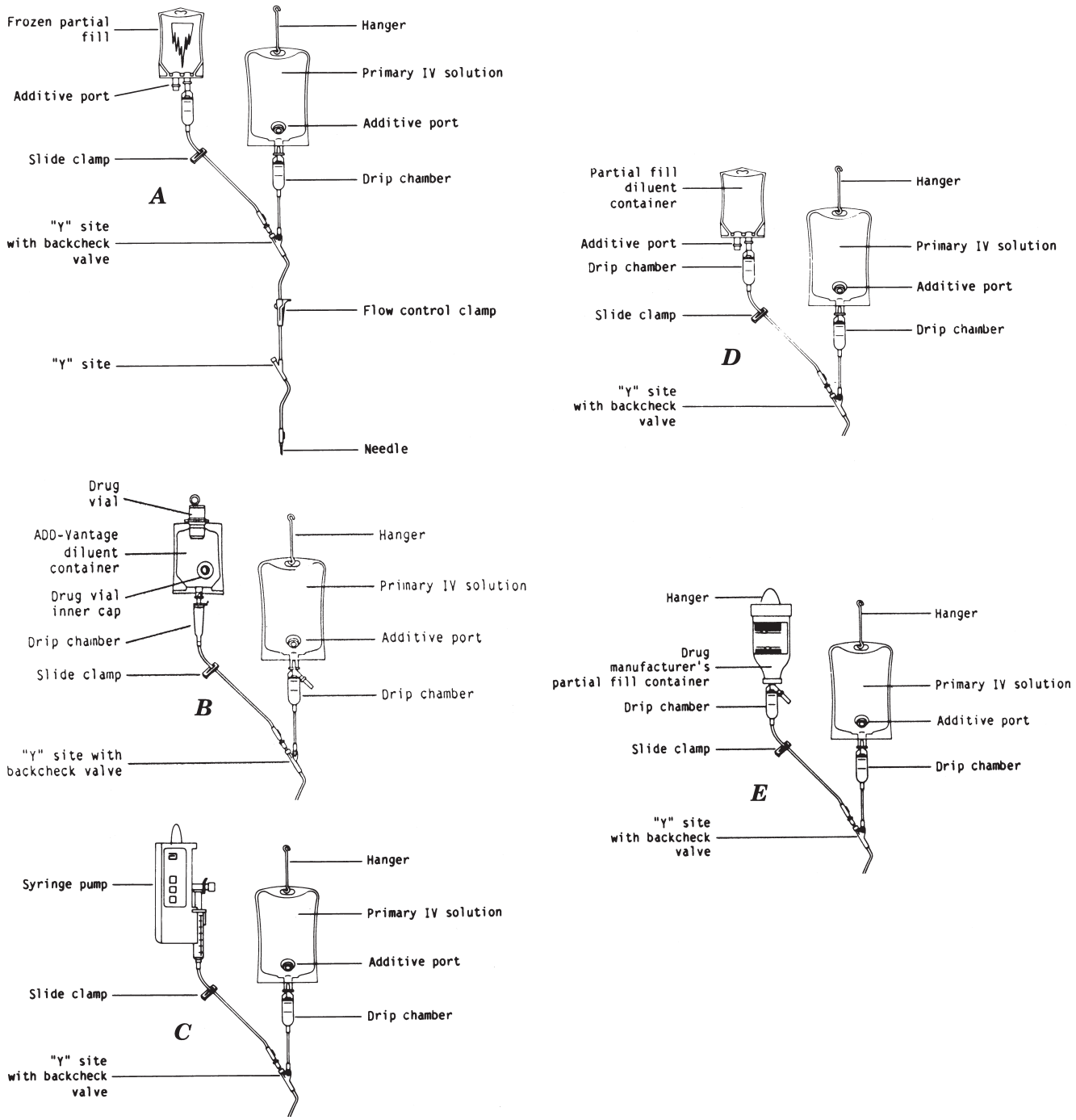

Figure 42-11. Various IV delivery systems. *A,* Frozen partial fill; *B,* ADD-Vantage; *C,* syringe pump; *D,* partial-fill diluent container; *E,* drug manufacturer's partial-fill piggyback (DMP) (courtesy, Abbott). The flow control clamp, "Y" site, needle, and associated tubing for *B* through *E,* are the same as in *A*. (Fig 42-11 is continued on the next page.)

implantable ports can be used for the injection of IV fluids, total parenteral nutrition, chemotherapy, antibiotics, and other drugs.

Some advantages of implantable devices include

The need for a long-term access site to venous, arterial, and spinal systems
An increased dependence on non-hospital treatment of chronic disease states
The direct infusion in a target organ or tumor
A decrease in infection rates that are seen with percutaneous catheters or repeated spinal taps
A greater mobility for the patient (a return to normal function)

Implantable Pump (Infusaid)—The Infusaid Implantable Pump was approved for selected drug administration. This pump is the size of a hockey puck and weighs approximately 6 1/2 oz. The construction is titanium, stainless steel, and polypropylene. The injection port is constructed of silicone rubber and has a usable life of at least 2000 punctures. Under normal use this device lasts more than 8 years.

The internal power supply uses Freon in equilibrium between the gaseous and liquid states and is recharged with each refilling process, thus supplying a power supply for as long as the pump is needed. As the pump is refilled, it compresses the gas back into the liquid state, allowing a fresh supply of energy

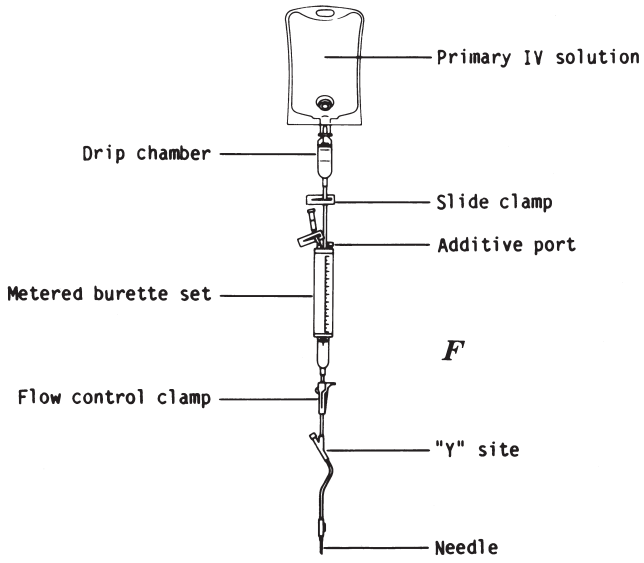

Figure 42-11 (continued). *F,* burette set (courtesy, Abbott).

for the next cycle. The capacity of this pump is 50 mL, which can be administered over a 14-day period. The pump accuracy is stated as over 3%. The cost of one model is approximately $4000.00, not including the surgical implant procedure. The 14-day cycle cannot be altered to any degree.

Model 400 Implantable Drug Delivery System (*Infusaid*) is designed for long-term therapy in the ambulatory patient. The Model 400 with a 47-mL usable drug volume delivers a precise, continuous flow to a selected organ or site via a soft, nontraumatic, nonthrombogenic, silicone rubber catheter. The Model 400 also features an auxiliary Sideport septum, completely bypassing the pumping mechanism, for delivery of direct bolus injections to the target site. Thus the clinician can easily supplement the continuous infusion with additional drugs, objectively assess the disease state, or monitor catheter location and drug perfusion with the use of radiolabeled microspheres.

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 and freedom from particulate matter and pyrogens, it is imperative that they be manipulated in a suitable environment by use of aseptic techniques.

ENVIRONMENT—Proper conditions for aseptic handling can be provided by laminar-flow hoods (see Chapters 40 and 41). 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 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 used properly by operators with proper aseptic techniques.

Before working in a laminar-flow hood, operators wash their hands thoroughly and scrub them with a suitable disinfectant. Some institutions may require gowning and use of 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 ensure 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 operators work 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 operators stand in front of the hood, their bodies act as a barrier to the laminar air flow causing it to pass around them and create backflow patterns that can carry room air into the front of the hood.

Laminar-flow hoods must be maintained and evaluated periodically to ensure 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 dioctylphthalate (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 by use of 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 with 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 42-12). 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.

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. 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.

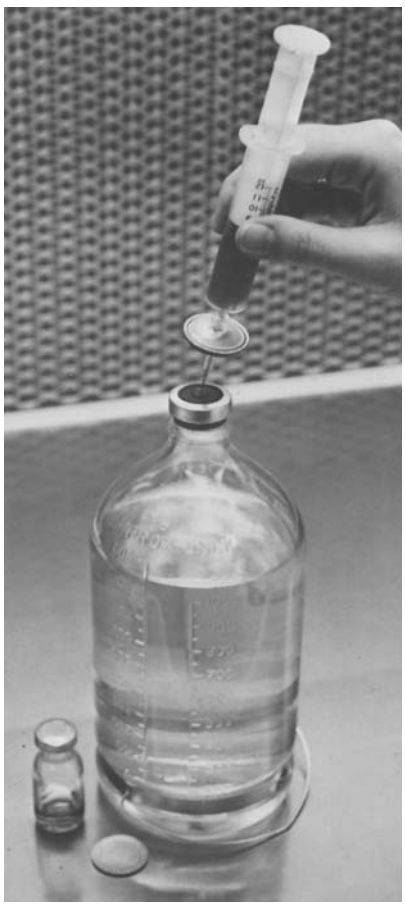

Figure 42-12. Placing an additive into an IV fluid with filtration through a membrane filter (courtesy, Millipore)

There is an increasing awareness of the potential hazard to pharmacists handling antineoplastic drugs.[6] Although the evidence is not conclusive, it appears that measures should be taken to minimize unnecessary exposure.[7,8] These precautions include the use of vertical laminar-flow hoods and biological safety cabinets for the preparation and reconstitution of these agents, the wearing of gloves and masks by the personnel, special labeling of the containers to ensure 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 are described in Table 42-2.

Abbott Glass Containers (Fig 42-2)

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, to mix thoroughly.
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 42-3)

1. Remove the aluminum tear seal and the aluminum disk 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 triangular 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 42-4)

1. Remove the additive port protective sleeve and swab the injection port plug with a suitable disinfectant.
2. Additives are placed in container by piercing the additive port, mix thoroughly.
3. After each addition, milk the container to ensure 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.

PHARMACY BULK PACKAGE—The manufactured bulk package is a sterile container for parenteral use that contains many single doses. These containers are intended for use in admixture programs in which large numbers of doses are prepared. It is designed so that the rubber closure is penetrated only once. It is used in laminar-flow hoods. Pharmacy bulk packages are exempt from the USP requirement that multiple-dose containers have a volume not greater than 30 mL. They also have an exemption in that they are not required to have a bacteriostatic agent. Pharmacy bulk packages have special labeling and storage requirements.

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 pharmacological 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 with 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.[9] 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 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 to 6.5, thus ensuring 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,[10–12] 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,[13] reference books,[14,15] and literature reports of studies with specific parenteral drugs.[16] 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 alternative 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 ensure 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.[17] The efforts of the hospital pharmacy should be no less than those of the industry in following Current Good Manufacturing Practice to ensure 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 (PN).[18] Originally, the term hyperalimentation was used to describe the procedure, but it is being replaced by PN, 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 PN by way of the subclavian vein into the superior vena cava where the solution is diluted rapidly by the large volume of blood available, thus minimizing the hypertonicity of the solution. For administration of the PN fluids, a catheter is inserted and retained in place in the subclavian vein. PN is indicated for patients who are unable to ingest food due to carcinoma or extensive burns and 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 PN fluids is the carbohydrate dextrose. In IV fluid kits commercially available for the preparation of PN 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 PN fluids is crystalline amino acids (Aminosyn, *Abbott;* FreAmine III, *B.Braun;* Travasol, *Baxter*). The crystalline amino acid injections contain all the essential and nonessential amino acids in the L-form. For optimum use 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 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 to 120 mEq; potassium, 80 to 120 mEq; magnesium, 8 to 16 mEq; calcium, 5 to 10 mEq; chloride, 100 to 120 mEq; and phosphate, 40 to 60 mEq. It is better to keep a 1:1 ratio between sodium and chloride ions. 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 PN fluids. Trace elements such as zinc, copper, manganese, and chromium are a concern only in long-term cases and can be added when required.

A lack of knowledge concerning preparation of PN admixtures may present a life-threatening hazard to patients. Several deaths have been reported as a result of chemical incompatibility.[19]

Table 42-3. Typical IV Orders (Parenteral Prescriptions)

PRESCRIPTION	COMMENT
1. ℞ NS 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 D5W + NS + 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 D5W + 1/2NS 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/hr.
4. ℞ 1000 cc D5W + 1/2NS 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/hr). Additional orders of the same can be anticipated.
5. ℞ 1000 cc D5W + 1/2NS + 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	1 L of the hospital's basic PN 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 PN (FreAmine) + 40 mEq $NaHCO_3$ + 30 mEq KCl + Vits + 5U Reg Insulin to run 80 cc/hr	1 L of the basic PN 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/hr (approximately 12 hr).
8. ℞ 1000 PN + 40 mEq NaCl + 10 KCl + 10 Insulin + 10 cal gluconate	1 L of the hospital's basic PN 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. ℞ Cefazolin 500 mg D5W q 6 hr	Cefazolin 500 mg, 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 minibag 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/min).

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 or sent via pneumatic tube or fax. 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-hr therapy period; the patient's chart is reviewed and new orders are written daily. 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

Table 42-4. Product Stability

TRADE NAME	PHYSICAL FORM	SHELF LIFE
Humulin	Liquid solution	2 yr at 2–8°
Protropin	Lyophilized powder	2 yr at 2–8°
Humatrope		
Roferon-A	Lyophilized powder	3 yr at 2–8°
Intron A	Lyophilized powder	2 yr at 2–8°
Activase	Lyophilized powder	2 yr at 2–30°
Recombivax-HB	Liquid solution	
Engerix-B	Liquid solution	
Orthoclone	Liquid solution	1 yr at 2–8°
Epogen	Liquid solution	

Table 42-5. Stability after Reconstitution (Lyophilized Products)

TRADE NAME	SHELF LIFE
Roferon	1 mo at 2–8°
Intron A	1 mo at 2–8°
Humatrope	14 days at 2–8°
Protropin	7 days at 2–8°
Activase	8 hr at 2–30°

Table 42-6. Recombinant Protein Drugs

TRADE NAME	VIAL STRENGTH
Humulin	1000 units
Protropin	5 mg
Humatrope	5 mg
Roferon-A	3 and 18 million units solution 3 and 18 million units lyo
Intron A	3, 5, 10, 25, and 50 million units
Activase	20, 50 mg
Recombivax HB	5, 10 μg
Engerix-B	20 μg
Orthoclone OKT3	5 μg
Epogen	2, 4, and 10 thousand units

allergies, and stability. Additives usually are given an expiration period of 24 hr 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 the label and preparing 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 or via computer. 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 so 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 hr), it is stored under refrigeration; if refrigerated, it must be used within 24 hr. 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 42-3.

PARENTERALS DERIVED BY BIOTECHNOLOGY

In 1993, 14 biotechnology drugs had been approved for clinical use; 21 were in Phase III clinical studies awaiting approval, and over 130 were in various phases of development. The Center for Biologics Evaluation and Review (CBER) had over 3200 Investigational New Drug Applications (INDs) under review. In 1996, 35 biotechnology drugs had been approved for clinical use, with 284 products in testing.

As a result of the stability sensitivities of proteins, the 35 biotechnology pharmaceuticals currently available are all manufactured as parenterals. Many are available as lyophilized parenterals (Table 42-4). Most have limited shelf life after reconstitution (Table 42-5). All are supplied in low dosage, which attests to their potency (Table 42-6).

For a complete treatment of biotechnology and drugs, see Chapter 49, and for more information on the drug approval process, refer to Chapter 48.

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CHAPTER 43

Ophthalmic Preparations

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INTRODUCTION[1]

Ophthalmic preparations are specialized dosage forms designed to be instilled onto the external surface of the eye (topical), administered inside (intraocular) or adjacent (periocular such as juxtascleral or subtenon) to the eye, or used in conjunction with an ophthalmic device. The latter include preparations used in conjunction with surgical implantation (such as an intraocular lens), dry eye formulations compatible with a punctal appliance such as a punctal plug, and extends to a variety of solutions utilized in maintenance of contact lenses. The preparations may have any of several purposes, therapeutic, prophylactic or palliative for topically administered agents, but includes mechanical, chemical and biochemical actions of agents used in the care of ocular appliances, and tissue prophylaxis during or following surgery. Because of the dangers associated with their administration, or repetitive administration, intraocular and periocular preparations are restricted to therapeutic applications or surgical adjuncts.

The versatility of dosage forms enables them to be suitable for the function of the preparation. Therapeutically active formulations may be designed to provide extended action for either convenience or reduction in risk of repetitive administration, improved bioavailability of the agent, or improved delivery to a targeted tissue. The residence of an ocular preparation may range from a few seconds needed for tears to clear an irritating substance, to hours for a gel, a gel-forming solution or an ointment, to months or years for an intraocular or periocular dosage form. The preparation may be strictly therapeutic, or may be administered for its prophylaxis. The latter include surgical adjunctives to maintain the health of fragile cells, post-surgical or post-trauma preparations designed to prevent or reduce the likelihood of infection. Another form of prophylaxis, that for a device, is the antisoiling function provided by some contact lens solutions.

Ophthalmic preparations are similar to parenteral dosage forms in their requirement for sterility as well as considerations for osmotic pressure (tonicity), preservation, tissue compatibility, the avoidance of pyrogens in intraocular dosage forms, particulate matter and suitable packaging.

Topical therapeutic dosage forms have customarily been restricted to solutions, suspensions and ointments. But with advances in material science, the range of ophthalmic dosage forms has expanded significantly to include gels, either preformed or spontaneous gels responsive to the ocular environment, and ocular inserts, both forms reducing dosage frequency. These are most often multi-dose products containing suitable preservative(s) to meet compendial preservative effectiveness test (eg, USP,[2] Pharm. Europa,[3] or JP[4]) requirements. Now, however, single-dose units, also referred to as unit-dose products, that are preservative-free preparations generally packaged in form-fill-seal plastic containers with 0.25 mL to up to 0.8 mL, have become available. These unit dose containers are designed to be discarded after a single use or after a single day's use if the container has a reclosable feature and the product is so labeled.

Injections and implants have been developed for intraocular drug delivery. Irrigating solutions and viscoelastic gels are available specifically for adjunctive use in ophthalmic surgery. Specialized formulations are now available for use in the care of contact lenses. The designs of these preparations meeting all of the requirements for safety, efficacy, component compatibility, tissue acceptability, storage, shipping, and shelf life are beyond the scope of this review. Nonetheless, a description of the requirements and the designs for some of these formulations should be illustrative and didactic.

From a historical perspective, preparations intended for treatment of eye disorders can be traced to the writings of the Egyptians, Greeks, and Romans. In the Middle Ages, *collyria* were referred to as materials that were dissolved in water, milk or egg white and used as eyedrops. One such collyrium contained the mydriatic substance belladonna to dilate the pupils of miladys' eyes for cosmetic purpose.

From the time of belladonna collyria, ophthalmic technology progressed at a pharmaceutical snail's pace until after World War II. Prior to WWII and into the 1950s, ophthalmic preparations were mostly compounded by the pharmacist for immediate use. Not until 1953 was there a legal requirement by FDA that all manufactured ophthalmic solutions be sterile. The range of medicinal agents to treat eye disorders was limited as was the state of eye surgery and vision correction, which was limited to eyeglasses. In the past fifty years, a modern pharmaceutical industry specializing in ophthalmic preparations has developed to support the advances in diagnosis and treatment of eye diseases, eye surgery and contact lenses. Because of the variety of ophthalmic products readily available commercially, the pharmacist now is rarely required to compound a patient's ophthalmic prescription. More important, however, is for the pharmacist to appreciate even subtle differences in formulations that may impact efficacy, comfort, compatibility or suitability of a preparation for particular patients.

Currently and in the future, in addition to the advances in dosage-form technology, drug molecules will be designed and optimized specifically for ophthalmic application. New therapies may become available for preventing blindness caused by degenerative disease - including age-related macular degeneration (AMD), macular edema, and diabetic retinopathy. Biotechnological products may also become available to treat causes of multifactorial eye disorders like glaucoma. Such specialized therapeutic agents also will require carefully designed compatible dosage forms.

Because dosage forms are fashioned to complement the requirements of the therapeutic agent, and the latter are selected for their action upon particular tissues in order to modify their function, we will now turn to a description of ocular tissues and their physiology.

ANATOMY AND PHYSIOLOGY OF THE EYE

In many ways the human eye is an ideal organ for studying drug administration and disposition, organ physiology and function. Unlike many bodily organs, most of its structure can be inspected without surgical intervention. Its macroscopic responses can be investigated by direct observation. Its miraculous function so intricate and complex - converting a physical electromagnetic stimulus into a chemical signal that is coupled to distant neurons for signal processing by an electrochemical wave - can be detected by sensitive instruments attached to external tissues. The basis for the function and protection of this important organ that links man to his external environment are the tissues comprising it. The structures to be described are illustrated in Figures 43-1 to 43-3. The first figure[5] provides a horizontal section of the eyeball identifying the major structures and their interrelationships. The second figure[6] shows in greater detail the anterior portion of the eye and eyelids, in vertical section, emphasizing some of the structures associated with tear apparatus. The third figure[6] emphasizes the flow of tears into the nasal structures. This brief introduction will focus on the anatomical structures comprising the eye, and their function.

Eyelids

Eyelids serve two purposes: mechanical protection of the globe and creation of an optimum milieu for the cornea. The inner surfaces of the eyelids and the outermost surfaces of the eye are lubricated by the tears, a composite of secretions from both lacrimal glands and specialized cells residing in both the bulbar (covering the sclera) and palpebral (covering the inner surface of the lids) conjunctiva. The antechamber has the shape of a narrow cleft directly over the front of the eyeball, with pocket-like extensions upward and downward. The pockets are called the superior and inferior fornices (vaults), and the entire space, the cul-de-sac. The elliptical opening between the eyelids is called the palpebral fissure and the corner of the eyes where the eyelids meet are the canthi.

Overview of Structure and Function of the Eyeball

STRUCTURE

The eyeball is housed in the bones of the skull, joined to form an approximately pyramid-shaped housing for the eyeball, called the orbit. The wall of the human eyeball (bulbus, globe) is composed of three concentric layers that envelop the fluid and lenticular core.[7–9]

Outer Fibrous Layer: The outer scleral layer is tough, pliable, but only slightly elastic. The anterior third is covered by the conjunctiva, a clear transparent mucous surface. The most anterior portion of the outer layer forms the cornea, a structure so regular and the water content so carefully adjusted that it acts as a clear, transparent window. It is devoid of blood vessels. Over the remaining two-thirds of the globe the fibrous collagen-rich coat is opaque (the *white* of the eye) and is called the sclera. It contains the microcirculation, which nourishes the tissues of this anterior segment, and is usually white except when irritated vessels become dilated.

The cornea, slightly thicker than the sclera and ranging in thickness from 500 microns to one millimeter, consists of five

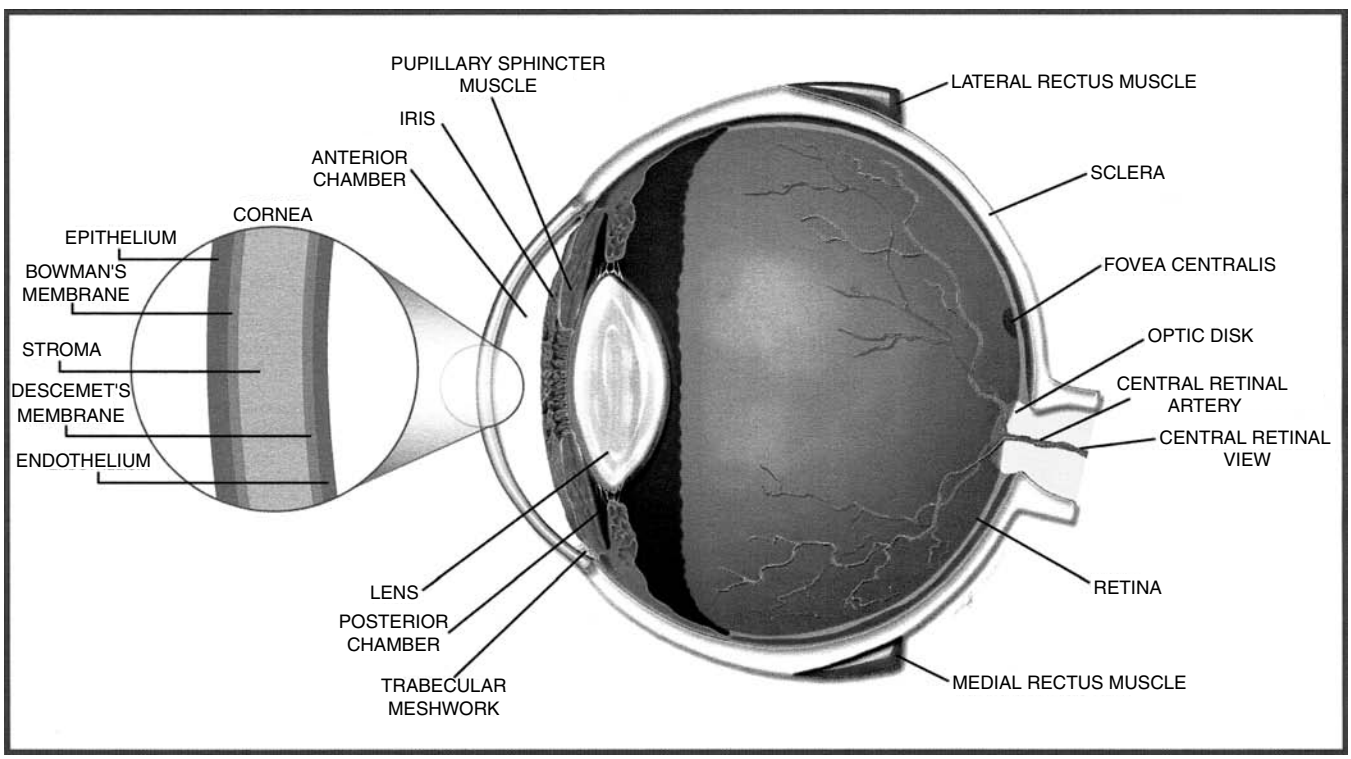


Figure 43-1. A cutaway horizontal section of the eyeball illustrating the important anatomic structures and their interrelationships diagramatically. The different layers of the cornea are illustrated in the magnified view. Relative sizes are suggestive and not proportional. The diameter of a mature eyeball is generally slightly greater than one inch (courtesy, Alcon, Inc., Fort Worth, TX). See Color Plate 19.

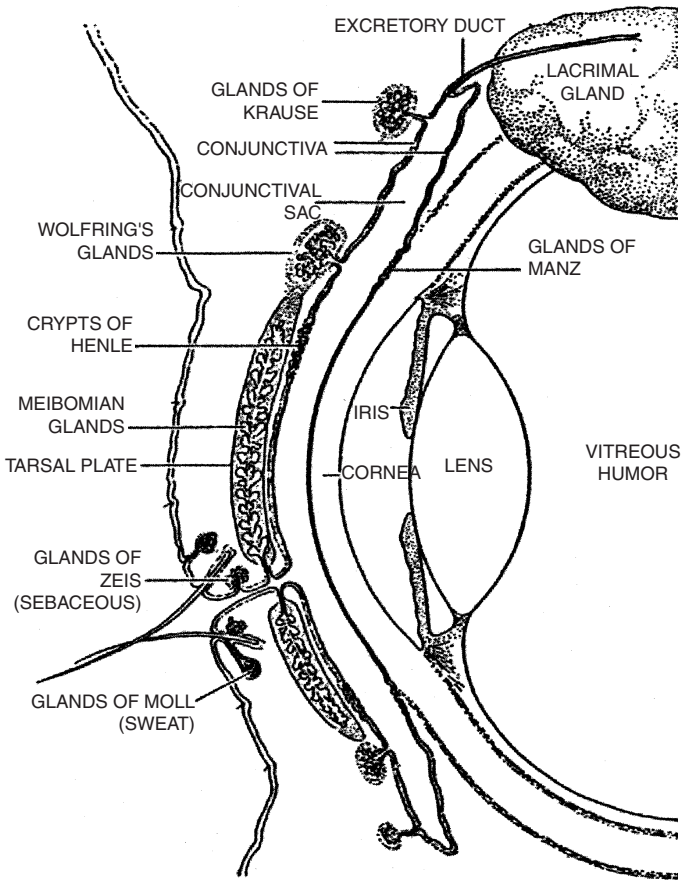


Figure 43-2. The front half of the eye, in vertical section, identifying the important structures associated with cornea and the front of the eye, including the eyelids and the glands associated with tears.

identifiable layers. Proceeding from the most anterior layer, these are the hydrophobic stratified squamous epithelium, which is underlaid by Bowman's membrane, then the stroma and Descemet's membrane, and then the innermost layer, the endothelium. The stroma is a hydrophilic elastic network of highly organized connective tissue and is the thickest layer of the cornea. The fibrous collagen-rich Descemet's membrane separates the stroma from the single-squamous-cell layer of endothelium, the location of the pump that keeps the cornea in its relatively dehydrated transparent state. Functionally, the cornea serves as a bilayer barrier, the hydrophobic epithelium being the primary barrier to hydrophilic molecules, and the hydrophilic stroma, the primary barrier to hydrophobic molecules. A schematic drawing of the cornea is provided in Figure 43-1.

Middle Vascular Layer: The middle vascular layer, or uvea, provides nourishment to the eye and consists, moving from the back of the eye forward, of the choroid, the ciliary body, and the iris. The choroid consists of a pigmented vascular layer, colored by melanocytes and traversed by medium-sized arteries and veins, with the choriocapillaris containing a network of small vessels that nourish the neural retina. The ciliary body contains muscles that control the extension of the lens allowing visual accommodation, as well as the ciliary processes that secrete aqueous humor into the posterior chamber to maintain the intraocular pressure that in turn keeps the eyeball fully expanded. The pigmented iris is a ring of muscular tissue around the pupil, a round centric hole that acts as a variable aperture to control pupil diameter, and thereby the level of light entering the eye. The canal of Schlemm, one of the important paths for outflow of the aqueous humor, resides in the angle of the iris. Bruch's membrane separates the choroid from the retina.

Neural Retina: This innermost layer of the eyeball is a complex tissue that supports the harvesting of light through the action of photoreceptors - nerve cells specialized for distinguishing white from black (rods), or discerning color (cones). In addition, the retina consists of cells that support metabolism (like the heavily pigmented retinal pigmented epithelium, the RPE, which purges photoreceptors of spent molecules and metabolites, and regenerates the *cis*-retinal), provide structure (astrocytes and Mueller cells), or contribute to the primary function of photodetection / signal processing (the ganglion cells that begin to process the electrochemical information transmitted from the photoreceptors).

Ocular Core: Within the globe, the crystalline lens spans the interior fluid-filled center close to the iris and is anchored by zonule fibers to the ciliary body. The lens is composed of a single layer of replicating epithelial cells that with age flatten into layers of long thin crystalline-filled lamellar fibers. The lens is the only tissue in the body that retains all cells ever produced, a fact that contributes to age-related alterations in size, clarity and extensibility. A tough thin transparent membrane called the capsule covers the outermost layer of the lens.

The aqueous and vitreous humors are interposed between the solid structures of the eye. The clear, fluid aqueous humor fills the globe anterior to the lens and is primarily responsible for maintaining correct intraocular pressure. The gel-like vitreous humor accounts for most of the weight of the eye and resides posterior to the lens in direct contact with the retina.

FUNCTION

The eyeball houses the optical apparatus that causes inverted reduced images of the outside world to form on the neural retina.

Dimensional Stability: The optical function of the eye calls for stability of its dimensions, which is provided partly by the fibrous outer coat, but more effectively by the intraocular pressure (IOP), which exceeds the pressure prevailing in the surrounding tissues. This intraocular pressure is the result of a steady production of specific fluid, the aqueous humor, which

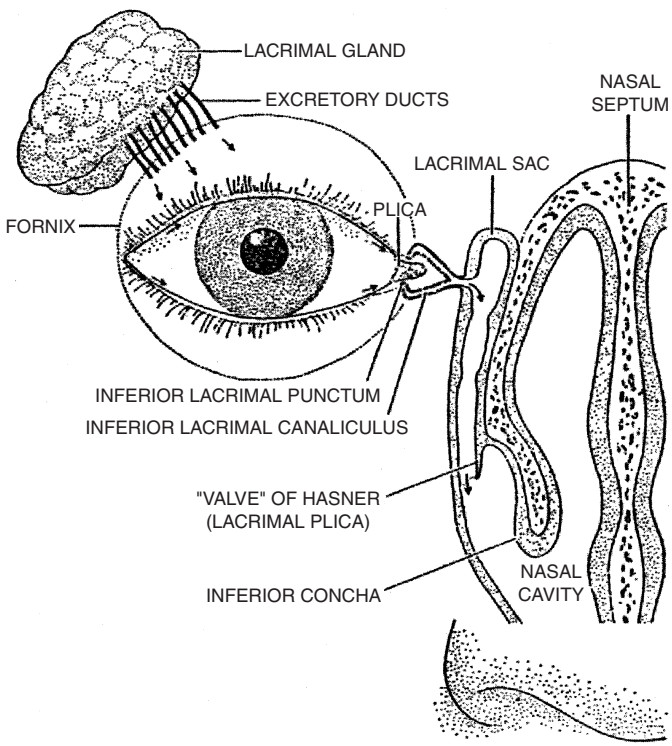


Figure 43-3. The structures associated with the tears and lacrimal flow and access to the nasolacrimal system.

originates from the ciliary processes anterior to the lens and leaves the eye by an intricate system of outflow channels. The resistance encountered during this passage and the rate of aqueous production are the principal factors determining the level of the intraocular pressure. In addition to this hydromechanical function, the aqueous humor acts as a carrier of nutrients, substrates, and metabolites for the avascular tissues of the eye.[10]

Optical Pathway: The optical pathway consists, in sequence, of the precorneal tear film, the cornea, the aqueous humor, the pupil, the crystalline lens, the vitreous humor, and the retina. The chief refraction of light for the eye occurs at the outer surface of the cornea where the index of refraction changes from that of air (1.00) to that of precorneal substance (1.38). After traversing the cornea, light passes through the clear aqueous humor to the pupil, where the amount of light entering the eye is regulated by the pupillary diameter, and to the second refractive element of the eye, the lens, whose variable focal length allows objects both near and far to be brought into focus (accommodation). The shape of the lens, controlled by the muscles of the ciliary body, refracts and focuses the reduced inverted image on the retina. That image is sharp and clear, in part, because of the high transparency of the vitreous humor, which because of its gel-like state keeps debris and cells from entering the pathway for the light. The image formed by the electromagnetic light signal on the neural retina is converted to a chemical signal, changing *cis-* to *trans-* retinal, which in turn is processed by neural cells into an electrochemical signal transported through axons to central nerve bodies. This continuous conversion of the excitation associated with a retinal image to processable information, is integral to the functioning of the retina, and is the reason retinal tissue is amongst the most rapidly metabolizing tissues in the body. The dependence of the neural retina on the metabolic support provided by the underlying cell layer, the RPE, explains why damage to the tissue - such as detachment of the retina or diminished blood supply - can result in nearly immediate and permanent loss of vision.[11]

Tissues Responsible for Refraction: Any alteration in the shape or transparency of the *cornea* interferes with the formation of a clear image; therefore, any pathological process, however slight, may interfere seriously with the resolving power or visual acuity of the eye. Transparency of the cornea is largely attributable to its organized laminar arrangement of cells and fibers and the absence of blood vessels. The normal cornea possesses no blood vessels except at the corneoscleral junction, the limbus. The cornea, therefore, must derive its nutrition by diffusion and must have certain permeability characteristics; it also receives nourishment from the fluid circulating through the chambers of the eye and from the air. The fact that the normal cornea is devoid of blood vessels is an important feature in surgical grafting.

Cloudiness of the cornea may occur as a result of disease (eg, excess pressure in the eyeball, a symptom associated with glaucoma), the presence of scar tissue due to injury, infection, deficiency of oxygen or excess hydration such as may occur during the wearing of improperly fitted contact lenses. A wound of the cornea may heal as an opaque patch that can be a permanent impairment of vision unless it is located in the periphery of the cornea.

The corneal nerves do not supply all forms of sensation to the cornea, but pain and cold are well supplied. The pain fibers have a very low threshold, which makes the cornea one of the most sensitive areas on the surface of the body. It now is agreed that the cornea possesses a true sense of touch; nerve endings supplying the sensation of heat appear to be lacking.

The corneal epithelium provides an efficient barrier against bacterial invasion. Unless its continuity has been broken by an abrasion (a traumatic opening or defect in the epithelium), pathogenic bacteria, as a rule, cannot gain a foothold. Trauma, therefore, plays an important part in most of the infectious diseases of the cornea that occur exogenously. A means of detecting abrasions on the corneal surface is afforded by staining the cornea with sodium fluorescein. Any corneal abrasion is subject to infection.

As with the cornea, any change in the transparency of the *lens* as a result of age or disease can significantly affect visual clarity. Loss of flexibility of the lens can reduce visual accommodation and cause difficulty in focusing on near objects. Also on aging, or as a result of trauma, the lens may generate opacities caused by the oxidation and crosslinking of lens proteins. When cataract surgery is required in order to restore clarity to cloudy vision, the natural lens is removed and replaced by an artificial one. The capsule, though, is preserved so that it may provide scaffolding for the implanted synthetic intraocular lens (IOL).

LACRIMAL SYSTEM—The conjunctival and corneal surfaces are covered and lubricated by a precorneal tear film, a fluid secreted by the conjunctival and lacrimal glands.[11] The clear watery secretion of the lacrimal gland, delivered through a number of fine ducts into the conjunctival fornix, contains numerous salts, glucose, other organic compounds, and approximately 0.7% protein, including the enzyme lysozyme. Small accessory lacrimal glands are situated in the conjunctival fornices. The tear film, compatible with both aqueous and lipid ophthalmic preparations, is composed of a thin outer lipid layer, a thicker middle aqueous layer, and a thin inner mucoid layer. It is renewed during blinking and when blinking is suppressed may dry in patches. It seems to be unaffected by the addition of concentrations of up to 2% sodium chloride to conjunctival fluid. A pH below 4 or above 9 causes derangement of the film. The film affects the movement of contact lenses and forms more easily on hydrophilic than on hydrophobic prostheses.

The innermost mucin-protein layer of the film is especially important in maintaining the stability of the film and is postulated to be held in place by the microvilli of the corneal epithelial cells. Sebaceous Meibomian glands of the eyelids secrete an oily fluid that forms the outer layer of the tears, helps to prevent overflow at the lid margin, and reduces evaporation from the exposed surfaces of the eye.

Spontaneous blinking replenishes the fluid film by pushing a thin layer of fluid ahead of the lid margins as they come together. The excess fluid is directed into the lacrimal lake—a small, triangular area lying in the angle bound by the innermost portions of the lids. The skin of the eyelids is the thinnest in the body and folds easily, thus permitting rapid opening and closing of the palpebral fissures, at velocities of tens of cm /sec. The movement of the eyelids includes a narrowing of the palpebral fissures in a zipper-like action from lateral to medial canthus. This aids transport or movement of fluid toward the lacrimal lake and elimination of unwanted contaminants.

Tears are drained from the lacrimal lake through two small openings, the superior and inferior puncta, which drain into connecting small tubes, the lacrimal canaliculi, which themselves join at the common canaliculus that leads into the upper part of the nasolacrimal duct, the beginning of which is the lacrimal sac, as shown in Figure 43-3 The drainage of tears into the nose does not depend merely on gravity. Fluid enters and passes along the lacrimal canaliculi by capillary action, aided by aspiration resulting from contraction of muscles embedded in the eyelids, and by peristalsis in the muscles near the canaliculi. When the lids close, as in blinking, contraction of the muscle causes dilatation of the upper part of the lacrimal sac and compression of its lower portion. Tears aspirated into the sac are forced down the nasolacrimal duct toward its opening into the nose. As the lids open, the muscle relaxes. The upper part of the sac then collapses and forces fluid into the lower part, which at the same time is released from compression. Thus, the act of blinking exerts a suction force-pump action in removing tears from the lacrimal lake and emptying them into the nasal cavity. Lacrimation is induced reflexively by stimulation of nerve endings of the cornea or conjunctiva. This reflex is abolished by anesthetization of the surface of the eye and by disorders affecting its nerve function.

The normal cul-de-sac is maintained free of pathogenic organisms in part by the chemical action of enzymes, such as lysozyme, which normally destroy saprophytic organisms with limited action against pathogens, and in part by the continuous physical flow of normally sterile secretions, which constantly

wash the bacteria, dust, *etc.*, away from the eye down into the nose. In certain diseases or on aging the lacrimal gland, like other glandular structures in the body, may undergo involution, with the result that the lacrimal fluid becomes scanty. Changes in the conjunctival glands may lead to alteration in the character of the secretion so that quality as well as quantity of tears may be abnormal. This can lead to symptoms of dryness, burning, and general discomfort, and ultimately may interfere with visual acuity.

SUMMARY—This brief overview of the structure and function of the eye should provide a basis for understanding the highly integrated tissues comprising this miraculous organ, and suggest the importance of providing medications that in no way impair the balance of functions required for maintaining normal functioning of the eye.

BIOAVAILABILITY

Therapeutic Targets

Bioavailability of pharmacological agents is dictated by ocular structure and physiology just discussed. But bioavailability also is controlled by physical constraints and tissue biochemistry to be discussed in the next subsections, by physical and chemical characteristics of the therapeutic agents and the preparations by which they are presented. The bioavailability and potential efficacy of an agent also is determined by the therapeutic targets, which are governed by disease etiology.

For example, treatment of a superficial infection of the cornea, while possibly requiring sustained delivery in order to provide less frequent administration of antimicrobial therapy, does not involve special considerations of corneal permeation or access to the target tissue. In this circumstance, product design might be directed toward the reduction of any corneal or scleral transport, since these would be regarded as drug lost from the target site. On the other hand a recalcitrant case of uveitis may require both topical and systemic administration of anti-inflammatory agents in order to eliminate the condition. But in this case transport to the uvea, an internal tissue, is desirable.

Chronic diseases associated with aging, like glaucoma, may be amenable to routine administration of a topical medication. The target, however, may be determined by the particular mechanism for treating the disease. For instance, a drug influencing the generation of aqueous humor may target the iris ciliary body, whereas a drug influencing the outflow of aqueous humor might target the trabecular meshwork that opens into the canal of Schlemm. The inherent characteristics of the drug also will determine, in part, any need for sustained delivery. In general, a lipophilic agent will be absorbed readily into the lipophilic corneal epithelium, whereas an ionic or hydrophilic agent will be absorbed more slowly. But corneal permeation may still be a significant barrier to delivery at the target tissue even for a lipophilic drug since transport through the largely aqueous stroma is still required. The capacity of the epithelium for the drug, in part controlled by its partitioning characteristics, may govern any need for sustained administration as well as the dosing regimen. The solubility of the drug, especially for often relatively insoluble hydrophobic lipophilic agents, can limit the size of the reservoir of drug administered, or the exposure to the drug, where the latter is defined as the AUC (the area under the curve in a concentration vs. time plot of drug residence).

Recently treatments for ocular diseases of the deep tissues have invoked techniques more commonly utilized in targeted systemic delivery. For example, the treatment of retinal infection with cytomegalovirus, accompanying end-stage HIV infections, has engendered treatments delivering drug directly to the vitreous humor, either with intracameral injection or an implant. Photodynamic therapy utilizes a radiation—generally light—to activate a drug delivered systemically. Angiostatic agents for the treatment of wet AMD (age-related macular degeneration) are delivered from an implant. As Higuchi years ago and others more recently have described, the rate of delivery from such devices can be controlled either by the design of the device, drug characteristics (primarily solubility), or a balance of both.[12]

Nonetheless, eye drops remain the most common modality for administration of therapeutic agents, and so considerations of the quantitative relationships governing the balance of effects controlling access of these agents to their target tissues are of significance and will be summarized in the next few sections. The approach will be primarily hydrodynamic,[13,14] though molecular theories are now available to give rationale for the macroscopic transport laws.[15] More intricate transport characteristics, such as those occurring when membranes actively transport the therapeutic agent, are less frequent than simple passive diffusion and for this introduction will be neglected. The approach highlights the interrelationships of phenomena whose subtle control in commercial products improves their efficacy. While transmembrane transport is most relevant to transcorneal delivery, some of the same considerations apply to actives delivered from implants, since these drug reservoirs serve only as a source for the agents that need to traverse tissues or tissue boundaries to reach their target sites.[16]

Corneal Absorption and Drug Access

Physical and Chemical Considerations

Under normal conditions the human tear volume averages about 7 μL.[17] The estimated maximum volume of the cul-de-sac is about 30 μL, with drainage capacity far exceeding lacrimation rate. The outflow capacity accommodates the sudden large volume resulting from the instillation of an eyedrop. Most commercial eyedrops range from 25 to 50 μL in volume.

Within the rabbit cul-de-sac, the drainage rate has been shown to be proportional to the instilled drop volume. Multiple drops administered at intervals produced higher drug concentrations. Ideally, a high concentration of drug in a minimum drop volume is desirable. Patton[18] has shown that approximately equal tear-film concentrations result from the instillation of 5 μL of 1.61×10^{-2} *M* pilocarpine nitrate or from 25 μL of 1.0×10^{-2} *M* solution. The 5 μL contains only 38% as much pilocarpine, yet its bioavailability is greater because of decreased drainage loss. Human responses can be expected to be similar, and this is supported by studies of gamma scintigraphy.[19] However, human tear responses are much more significant, and variable, than those in some *in vivo* models. When the therapeutic agents themselves are irritating, excess tearing may occur that may influence bioavailability in affected individuals. There is a practical limit or limits to the concept of minimum dosage volume. There is a difficulty in designing and producing a dropper configuration that will deliver small volumes reproducibly.[20] Also, the patient often cannot detect the administration of such a small volume. This sensation or lack of sensation is particularly apparent at the 5.0 to 7.5-μL dose-volume range.

The concept of dosage-volume drainage and cul-de-sac capacity directly affects the prescribing and administering of separate ophthalmic preparations. The first drug administered may be diluted significantly by the administration of the second. On this basis combination drug products for use in ophthalmology have considerable merit.

While generally not a major concern, an instilled drug can be subject to protein binding in the tear fluid and metabolic degradation by enzymes such as lysozyme. Stability, however, always is a primary consideration, both in the bottle and in the tissues. Rapid conversion of a drug to a metabolite is generally to be avoided unless by design (pro-drugs).

Corneal Absorption

Penetration of drugs administered topically occurs primarily through the cornea. Drugs administered by instillation must penetrate the eye and do so primarily through the cornea. Corneal absorption is generally more effective than scleral or

conjunctival absorption, in which drug is removed by circulatory flow into the general circulation. This is also true because most therapeutic agents tend to be reasonably lipophilic. In the case of more hydrophilic materials, which as mentioned earlier are more slowly absorbed into the corneal epithelium, there is evidence to suggest that a scleral route may be more common. A practical example comes from studies of carbonic anhydrase inhibitors,[21] a class of drug used in the treatment of glaucoma.

Many ophthalmic drugs are weak bases and are conveniently applied to the eye as aqueous solutions of their salts. If the molecule is maintained in an ionized state, for example by employing a weakly acidic buffered vehicle, stability of the drug often may be prolonged. If the buffer is weak little discomfort is generally experienced at the time of instillation. Once neutralized by the tears, the fraction of free base may increase and this may be the form of the drug most readily absorbed by the corneal epithelium. Nonetheless, during transport through the hydrophilic stroma, an important fraction of the agent may be ionized. Similarly, the form transported through the endothelium may be the free base and that presented to the ciliary body (one of the sites of pharmacological action) in transport from the aqueous humor may be the ionized salt. This scenario is described simply to suggest the complexity that may be exploited in targeting an ophthalmic drug, as well as complementary considerations involved in providing a preparation capable of the requisite stability for conventional 2-year shelf life.

The cornea can be penetrated by ions to a small, but measurable, degree. Under comparable conditions, the permeabilities are similar for all ions of low molecular weight, which suggests that the passage is through extracellular spaces. The diameter of the largest particles that can pass across the cellular layers seems to be in the range of 10 to 25 Å. Some effort has been directed toward increasing the upper molecular weight limit for water-soluble therapeutic agents by utilizing a class of molecules referred to as penetration, or permeation, enhancers. These molecules are selected for their capacity to increase transiently permeation of larger molecules while producing minimal discomfort or toxicity.

Since highly water-soluble drugs generally penetrate the cornea less readily and since the cornea is known to be a membrane including both hydrophilic and lipophilic barrier layers, most effective penetration is obtained with drugs having both lipophilic and hydrophilic properties. As an example highly water-soluble steroid phosphate esters penetrate the cornea poorly. Better penetration is achieved with the poorly soluble but more lipophilic steroid alcohol; still greater absorption is seen with the steroid acetate form.

Work on transport of drugs through the cornea, dating from the work of Edelhauser,[13] Lee and Robinson in 1976[22] and later in 1990,[23] have indicated the interplay of physical properties that regulate access of drugs to ophthalmic tissues. The hydrodynamic principles are well known and will be outlined here. From the physical chemistry of passive diffusion across a simple membrane capable of sustaining a concentration difference (and discussed in other chapters of this volume), the main mechanism of entry into the eye,

$$J = -D\, dC_m/dx \tag{1}$$

according to Fick's first law of diffusion, where J is the flux of drug across the membrane (amount per area per time), D is the diffusion coefficient, the derivative of C_m is the spatial concentration gradient in the membrane (at steady-state, constant across the membrane).[24] Even from this simple relationship the consequences of the physical properties of the drug can be inferred. As the solubility of the drug increases the gradient will increase, so the driving force for entry of the agent into the aqueous humor will be increased. Experiment similarly has shown specific characteristics of the diffusion coefficient; namely the diffusion coefficient decreases with increasing molecular size (and hence molecular weight of the compound). So all else being equal, one need balance the increased specificity and targeting of a larger active against the loss in rate of membrane transport. The equation also makes clear that any means for maintaining the concentration on the donor side of the membrane, thereby sustaining the gradient term for a longer period of time, will increase the mean total flux.

In order to perceive the consequences of partitioning in a more complicated bilayer membrane (a good model for the cornea since the major layers serving as barriers to drug entry are the epithelium and stroma), one need look at the diffusion equation for a bilayer:

$$J \cong \frac{PC_w}{\frac{Pl_s}{D_s} + \frac{l_e}{D_e}} \tag{2}$$

where P is the distribution coefficient (for example the octanol:water partition coefficient wherein it is a good approximation of the partitioning into the epithelium), the subscripts designate either stroma (s) or epithelium (e), l is the length representing the thickness of the layer, and C_w is the concentration of drug at the donor side of the membrane, *i.e.* in the concentration of drug in the tears.[25] This equation is an approximation to the differential equation. One source of approximation is that it presumes the concentration on the donor side (in the eye, the concentration of active in the tears) is much higher than on the receiver side of the membrane (the concentration in the aqueous humor). From this equation one can observe that as the partitioning increases the effectiveness of the epithelium as a barrier diminishes and is replaced nearly exclusively by the stroma. Similarly, as the partitioning decreases, the epithelium becomes the dominant barrier. Of course, this is just a mathematical representation of an anticipated phenomenon. Clearly there is an advantage to increasing the lipophilicity of the agent in order to improve absorption and transport. A precaution to be kept in mind, however, is that ordinarily when the lipophilicity is increased the aqueous solubility (which C_w may approach) generally decreases. This is an example of the need to balance a number of characteristics, as was mentioned above.

There are circumstances, especially when the drug is sufficiently hydrophilic to limit severely absorption directly into the corneal epithelium, when sustaining the presence and concentration of the drug in the tear volume is important. From the equations for a stirred-tank chemical reactor, which is undergoing a steady-state flow of fluid with a solvent entering and a solution of mixed chemicals flowing from it, one expects

$$C_W(t) = C_I \cdot \exp\left(\frac{-\dot{V}_T \,.\, t}{V_T}\right) \tag{3}$$

where the time dependence of C_w is explicitly indicated, C_I is the initial concentration, V_T is the volume of the reactor (here the tear volume) and its derivative is the rate of flow through the reactor, essentially the rate of tear generation. A number of characteristics of drug delivery are apparent from this equation. One is that if the drug is uncomfortable and increases the rate of tearing, $\dot{V}_T$ in the equation, then the concentration in the tears is depleted more rapidly. Analogously, if the preparation includes a means for retaining a drug carrier in the cul-de-sac, then only a fraction of the drug present is released free into the tears, and $C_w(t)$ no longer changes with time, and until the reservoir is depleted may be approximately constant. Since what is important is the total amount of drug reaching the target tissue over a time period,

$$N_{eff} = A \cdot \int dt\, J(t) \tag{4}$$

the effect of reducing the loss rate from tear flow may counterbalance the consequence of reducing the total level in the tears. Note, in the circumstance where there is a means for sustaining drug release equations (2) and (3) need to be modified, in any event, since C_I is no longer the total initial concentration but the fraction in the tears that is transportable through the cornea. This introduction should provide some notion of the types of complexity involved in achieving improved delivery of a therapeutic agent! When more is known about the details of ocular function, characteristics of the therapeutic agents and vehicles, it is possible to solve the differential equations nu-

merically in order to improve the design of topically applied medications.[26–28]

This summary would be incomplete if it did not indicate that precisely the approach outlined at the end of the last paragraph is that taken to model and refine the design of preparations used in implants.[29–32] The significance of these activities, ongoing research, is difficult to overstate since the diseases being addressed—AMD, macular edema, diabetic retinopathy - are sight-threatening. The devices used to deliver the drug need to limit invasiveness and restrict frequency of any implanting procedure, providing durations of delivery ranging from months to years. A practical consequence is that the testing period for an implanted device is extended appreciably.

Finally, while the approach described in this section has been primarily macroscopic and phenomenological, microscopic models and calculations of transport based on them have provided additional detail about the molecular features of ocular drug transport. For example, it is generally believed that lipophilic drugs permeate the corneal epithelium by transcellular transport whereas more hydrophilic drugs permeate the corneal epithelium by paracellular transport. A model of these different mechanisms has indicated that the transcellular transport probably is along the lipophilic bilayers of the cell outer membranes, whereas the paracellular transport is probably along the extracellular space, the 'pores' of a macroscopic model.[24] These models provide insight into mechanisms of transport and how these may be manipulated to improve drug delivery while maintaining safety.

TYPES OF OPHTHALMIC DOSAGE FORMS

Ophthalmic products include prescription and OTC drugs, products for the care of contact lenses and products used in conjunction with ocular surgery. This section will focus on the pharmaceutical aspects of the various ophthalmic dosage forms encompassed by these types of products. The therapeutic uses of individual products can be found in several reference books along with the individual products' labeling.[33,34]

Ophthalmic Solutions

These are by far the most common dosage forms for delivering drugs to the eye. By definition, ingredients are completely soluble such that dose uniformity is not an issue and there is little physical interference with vision. The principal disadvantage of solutions is their relatively brief contact time with the drug and the absorbing tissues of the external eye. Contact time may be increased by the inclusion of a viscosity-imparting agent; however, their use is limited to relatively low viscosities so that the eyedrop can be dispensed from the container or eyedropper and to minimize excessive blurring of vision. A viscous solution can produce a residue on the eyelashes and around the eye when any excess spills out of the eye and dries. The residue can usually be easily removed by careful wiping with a moist towel to the closed eye.

Gel-Forming Solutions

Ophthalmic solutions, usually aqueous based, which contain a polymer system that is a low-viscosity liquid in the container and gels on contact with the tear fluid, have increased contact time and can provide increased drug absorption and prolonged duration of therapeutic effect. The liquid to gel phase transition can be triggered by a change in temperature, pH, ionic strength or presence of tear proteins depending on the particular polymer system employed. Timolol maleate gel-forming solutions formulated with specific patented gellan or xanthan gums have clinically demonstrated prolonged duration of IOP-lowering such that their dosing frequency can be reduced from twice to once a day.[35, 36] Review the labeling for commercial gel-forming solutions prior to dispensing for current instructions related to patient administration.

Powders for Solutions

Drugs that have very limited stability in aqueous solution can sometimes be prepared as sterile powders for reconstitution by the pharmacist prior to dispensing to the patient. The sterile powder should be aseptically reconstituted with the accompanying sterile diluent that has been optimized for dissolution, preservation and stability. The pharmacist must convey to the patient any special storage instructions including the expiration dating.

Ophthalmic Suspensions

Suspensions are dispersions of finely divided, relatively insoluble, drug substances in an aqueous vehicle containing suitable suspending and dispersing agents. The vehicle is, among other things, a saturated solution of the drug substance. Because of a tendency of particles to be retained in the cul-de-sac, the contact time and duration of action of a suspension could theoretically exceed that of a solution. The drug is absorbed from solution, and the solution concentration is replenished from retained particles. Each of these actions is a function of particle size, with solubility rate being favored by smaller size and retention favored by a larger size; thus, optimum activity should result from an optimum particle size.

For aqueous suspensions the parameters of intrinsic solubility and dissolution rate must be considered. The intrinsic solubility determines the amount of drug actually in solution and available for immediate absorption upon instillation of the dose. As the intrinsic solubility of the drug increases, the concentration of the drug in the saturated solution surrounding the suspended drug particle also increases. For this reason, any comparison of different drugs in suspension systems should include their relative intrinsic solubilities. The observed differences in their biological activities may be ascribed wholly or in part to the differences in this physical parameter. As the drug penetrates the cornea and the initial saturated solution becomes depleted, the particles must dissolve to provide a further supply of the drug. The requirement here is that the particles must undergo significant dissolution within the residence time of the dose in the eye if any benefit is to be gained from their presence in the dosing system.

For a drug whose dissolution rate is rapid, the dissolution requirement may present few problems, but for a slowly soluble substance the dissolution rate becomes critical. If the dissolution rate is not sufficiently rapid to supply significant additional dissolved drug, there is the possibility that the slowly soluble substance in suspension provides no more drug to the aqueous humor than does a more dilute suspension or a saturated solution of the substance in a similar vehicle. Obviously, the particle size of the suspended drug affects the surface area available for dissolution. Particle size also plays an important part in the irritation potential of the dosing system. This consideration is important, since irritation produces excessive tearing and rapid drainage of the instilled dose, as discussed earlier. It has been recommended that particles be less than 10 μm in size to minimize irritation to the eye. It should be kept in mind, however, that in any suspension system the effects of prolonged storage and changes in storage temperature might cause the smallest particles to dissolve and the largest particles to become larger.

The pharmacist should be aware of two potential difficulties inherent in suspension dosage forms. In the first instance dosage uniformity nearly always requires brisk shaking to distribute the suspended drug. Adequate shaking is a function of the suitability of the suspension formulation but also, and most importantly, patient compliance. Studies have demonstrated that a significant number of patients may not shake the container at all; others may contribute a few trivial shakes. The pharmacist should use a "Shake Well" label and counsel the patient whenever an ophthalmic suspension is dispensed. An improved ophthalmic suspension has been developed for insoluble drugs such as steroids which tend to cake upon settling.[37] The improved suspension controls the flocculation of the drug particles such that they remain substantially resuspended for

months and provides for easy resuspension of any settled particles. Nonetheless, the pharmacist also should be aware of the possibility of crystal growth over time. This potential stability problem is especially problematic for drug substances with significant temperature-dependence of their solubility. The majority of suspension products have a "Do Not Freeze" warning on the label because they are likely to agglomerate on freezing and will not be resuspended by simple shaking.

A second and infrequent characteristic of suspensions is the phenomenon of polymorphism or the ability of a substance to exist in several different crystalline forms. A change in crystal structure may occur during storage, resulting in an increase (or decrease) in crystal size and alteration in the suspension characteristics, causing solubility changes reflected in increased or decreased bioavailability. Manufacturers of commercial suspensions take these possibilities into account in the development and testing of the final formulation and the labeled storage conditions.

In some cases a water-soluble drug has been converted to an insoluble form and formulated as a suspension to improve stability or compatibility of the drug or improve its bioavailability or patient tolerance. The insoluble forms of steroids such as prednisolone and dexamethasone have better ocular bioavailability and are considered more potent anti-inflammatories for topical ocular use. A resin-bound form of the beta-blocker betaxolol has been formulated as a suspension and is prepared *in situ* using a carbomer polymer.[38] The novel suspension formulation improves both comfort and ocular bioavailability of betaxolol, the 0.25% suspension therapeutically equivalent to a 0.5% solution.

Ophthalmic Ointments

Ophthalmic ointments are primarily anhydrous and contain mineral oil and white petrolatum as the base ingredients that can be varied in proportions to adjust consistency and the melting temperature. Dosage variability probably is greater than with solutions (although probably not with suspensions). Ointments will interfere with vision and their use is usually limited to bedtime instillation. They remain popular as a pediatric dosage form and for postoperative use. The anhydrous nature of the base enables its use as a carrier for moisture sensitive drugs. The petrolatum base can be made more miscible with aqueous components by the addition of liquid lanolins.

Ointments do offer the advantage of longer contact time and greater total drug bioavailability, albeit with slower onset and time to peak absorption. The relationship describing the availability of finely divided solids dispersed in an ointment base was given by Higuchi,[39] where the amount of solid (drug) released in unit time is a function of concentration, solubility in the ointment base, and diffusivity of the drug in the base.

Ophthalmic Emulsions

An emulsion dosage form offers the advantage of being able to deliver a poorly water-soluble drug in a solubilized form as an eyedrop. The drug is dissolved in a nonaqueous vehicle such as castor oil and emulsified with water using a nonionic surfactant and if needed an emulsion stabilizer. An emulsion with water as the external phase can be less irritating and better tolerated by the patient than use of a purely nonaqueous vehicle. Such an emulsion is used to deliver cyclosporin topically for the treatment of chronic dry eye conditions.[40]

Ophthalmic Gels

Gel-forming polymers such as carbomer have been used to develop aqueous, semi-solid dosage forms which are packaged and administered the same as ointments. The viscous gels have significantly increased topical residence time and can increase drug bioavailability and decrease dosage frequency compared to solutions. Although they contain a large proportion of water, they can still cause blurring of vision. A carbomer gel of pilocarpine administered at bedtime has been shown to prolong the IOP-lowering effect in patients for up to 24 hours.[41]

Ocular Inserts

Ocular inserts have been developed in which the drug is delivered on the basis of diffusional mechanisms. Such a solid dosage form delivers an ophthalmic drug at a near-constant known rate, minimizing side effects by avoiding excessive absorption peaks. The delivery of pilocarpine by such an insert was commercialized in 1975 (Ocusert Pilo) by *Alza Corporation*. The Ocusert is designed to be placed in the lower cul-de-sac to provide a weekly dose of pilocarpine at which time the system is removed and replaced by a new one. The near zero-order rate delivery is based on the selection of a non-eroding copolymer membrane enclosing the drug reservoir.[42]

Ocular inserts are plagued with some of the same manipulative disadvantages as conventional eyedrops. The insert must be placed in the eye in a manner similar to the insertion of a contact lens. Additionally, the insert, exhausted of its drug content, must be removed from the eye. Such manipulations can be difficult for the elderly patient. Nonetheless, such therapeutic inserts represent a notable commercialized scientific achievement in pharmaceutical sciences. The Ocusert Pilo product is no longer marketed as the drug has largely been replaced in glaucoma therapy by the use of topical beta-blockers.

Ocular inserts that gradually erode in the tear fluid have been studied but not commercially developed as ocular drug delivery systems.[43] In theory, an erodible insert would be advantageous since it would not have to be removed at the end of its therapeutic cycle, would provide precise unit dosing and if anhydrous would not require a preservative. It may also increase ocular bioavailability and reduce the therapeutic dosage and possible systemic effects. The chief disadvantages may be related to patient use issues, control of erosion and drug release rates and sterilization.

An erodible insert is available (Lacrisert) for treatment of dry eye. It is molded in the shape of a rod from a hydroxypropyl cellulose polymer that is the active ingredient. When inserted into the lower cul-de-sac, the polymer imbibes tear fluid and forms a gel-like mass that gradually erodes while thickening the tear film over a period of several hours. The unit dose insert is anhydrous and no preservative is required, beneficial for some sensitive patients.

DRUG ADMINISTRATION

Topical Administration

The instillation of eyedrops remains one of the less precise, yet one of the more accepted means of topical drug delivery. The method of administration is cumbersome at best, particularly for the elderly, patients with poor vision who have difficulty seeing without eyeglasses, and patients with other physical handicaps. Perhaps surprisingly, most patients become quite adept at routine instillation.

The pharmacist should advise each patient to keep the following points in mind to aid in the instillation of eyedrops or ointments:

METHODS OF USE FOR TOPICAL ADMINISTRATION

How to Use Eyedrops

1. Wash hands.
2. With one hand, gently pull lower eyelid down.
3. If dropper is separate, squeeze rubber bulb once while dropper is in bottle to bring liquid into dropper.
4. Holding dropper above eye, drop medicine inside lower lid while looking up; do not touch dropper to eye or fingers.

5. Release lower lid. Try to keep eye open and not blink for at least 30 seconds.
6. If dropper is separate, replace on bottle and tighten cap.

Precautions When Using Eyedrops

- If dropper is separate, always hold it with the tip down.
- Never touch dropper to any surface.
- Never rinse dropper.
- When dropper is at top of bottle, avoid contaminating cap when removed.
- When dropper is a permanent fixture on the bottle, *i.e.*, when supplied by a pharmaceutical manufacturer to the pharmacist, the same rules apply to avoid contamination.
- Never use eye drops that have changed color.
- If you have more than one bottle of the same kind of drops, open only one bottle at a time.
- If you are using more than one kind of drop at the same time, wait several minutes before use of other drops.
- It may be helpful to practice use by positioning yourself in front of a mirror.
- After instillation of drops, do not close eyes tightly and try not to blink more often than usual, as this removes the medicine from the place on the eye where it will be effective.

How to Use Ophthalmic Ointments/Gels

1. Wash hands.
2. Remove cap from tube.
3. With one hand, gently pull lower eyelid down.
4. While looking up, squeeze a small amount of ointment (about 1/4 to 1/2 inch) inside lower lid. Be careful not to touch tip of tube to eye, eyelid, fingers, etc.
5. Close eye gently and roll eyeball in all directions while eye is closed. Temporary blurring may occur.
6. The closed eyelid may be rubbed very gently by a finger to distribute the drug throughout the fornix.
7. Replace cap on tube.

Precautions When Using Ophthalmic Ointments/Gels

- Take care to avoid contaminating cap when removed.
- When opening ointment tube for the first time, squeeze out the first 1/4 inch of ointment and discard, as it may be too dry.
- Never touch tip of tube to any surface.
- If you have more than one tube of the same ointment, open only one at a time.
- If you are using more than one kind of ointment at the same time, wait about 10 minutes before use of another ointment.
- To improve flow of ointment, hold tube in hand several minutes to warm before use.
- It may be helpful in use of the ointment to practice use by positioning yourself in front of a mirror.

Nasalacrimal Occlusion

To limit absorption of topically applied drugs directly into the bloodstream from the highly vascular areas of the nasal cavity, the patient should be instructed to close the eye immediately after eyedrop instillation and place a finger between the eyeball and the nose and apply pressure for several minutes. This will temporarily occlude both superior and inferior canaliculi, preventing nasolacrimal drainage.

Intraocular Preparations

Ophthalmic products introduced into the anterior chamber or vitreous chamber of the internal eye structure are specialized dosage forms requiring additional pharmaceutical considerations in their formulation, packaging and manufacture. They are essentially parenteral-type products requiring both sterility and nonpyrogenicity as well as strict control of particulate matter, being restrictive in formulation to assure they are compatible with sensitive internal tissues critical to visual acuity. In some cases in which the product may be introduced into the sterile field during surgery, sterility of the exterior of the primary package is required. Since preservatives commonly used in topical ophthalmic products can be toxic to sensitive intraocular tissues such as the corneal endothelium, intraocular products are designed and packaged as preservative-free single use products.

Present technologies are summarized in the next subsections, but many novel technologies can be expected in the next several years with the advent of new therapeutics and approaches to delivery for such devastating diseases as AMD, diabetic retinopathy, and cystoid macular edema, diseases of the back of the eye.

IRRIGATING SOLUTIONS

During ocular surgery an irrigating solution is used to maintain hydration and clarity of the cornea providing the surgeon a clear view of the surgical field. The irrigating solution also provides a physiologic medium for removing blood and cellular debris and replacing the natural aqueous intraocular fluid. A balanced salt solution (BSS) is the primary intraocular irrigating solution which includes the key ionic components to maintain corneal endothelial integrity; sodium, potassium, calcium, magnesium and chloride, as well as a neutral to slightly alkaline pH and osmolality of about 305 mOsm.[44] An enriched balanced salt solution (BSS Plus) is also available to provide enhanced physiological compatibility when required in an irrigating solution. The enriched solution contains oxidized glutathione, dextrose and bicarbonate in addition to the critical ionic components.[45] The additional ingredients in the enriched solution require, for maximum shelf-life stability, that the product be packaged in a two-part system to be aseptically reconstituted just prior to its use. Intraocular solutions do not contain a preservative and should be discarded after initial use. These irrigating solutions are also designed to be used without additional additives as there is potential for intraocular toxicity. An acidic epinephrine injection containing sodium bisulfite antioxidant when added to an intraocular irrigating solution and diluted as much as 500-fold has been reported to produce intraocular toxicity.[46]

INTRAOCULAR INJECTIONS

Products approved for direct injection into the eye include miotics and viscoelastics for ocular surgery and two antiviral agents to treat cytomegalovirus retinitis (CMV). The miotics carbachol and acetylcholine are used at the end of cataract surgery to constrict the pupil allowing the iris to cover the implanted intraocular lens. Both products are specially packaged such that the exterior of the primary vial is sterile. This is accomplished by use of a special outer container that is permeable to sterilant gas and prevents contamination of the exterior of the vial.

Solutions with viscoelastic properties are injected into the eye during surgery to provide a mechanical barrier between tissues and allow the eye surgeon more space for manipulation with less potential for trauma to very sensitive intraocular tissues. The primary viscoelastic substance is a highly purified fraction of sodium hyaluronate. Purification is required to remove foreign proteins to be nonantigenic and noninflammatory for intraocular use. The viscoelasticity can be varied by use of different molecular weight fractions and concentrations. Chondroitin sulfate and purified hydroxypropyl methylcellulose are also utilized as viscoelastic and viscoadherent surgical adjuncts. The viscoelastic products are packaged and sterilized such that the primary package can be placed in the sterile surgical field prior to use. Sodium hyaluronate viscoelastic products usually require refrigeration during storage to maintain their integrity.

INTRAVITREAL INJECTIONS/IMPLANTS

Two antivirals have been approved for treatment of the ocular sequelae of AIDS with direct implacement in the vitreous cav-

ity in order to provide high localized ocular therapeutic concentrations. A sterile tablet containing ganciclovir, called a Vitrasert,[47] is implanted by the surgeon in the vitreous cavity where it releases drug over a period of several months and then is removed and replaced with a new tablet. The tablet is formulated with magnesium stearate as the drug carrier and coated with polymers that provide the prolonged drug release. It is important that during handling this polymer coating is not damaged and the special sterile packaging not be compromised. A sterile solution of fomivirsen is also available for intravitreal injection to treat CMV retinitis. It is supplied in single use vials and is injected intravitreally without requiring surgery but must be repeated every 2 to 4 weeks.

JUXTASCLERAL INJECTIONS

Certain disease conditions in the back of the eye are usually untreatable through topical administration to the eye. For example, CME (cystoid macular edema) - associated with trauma, chronic inflammation and diabetes–results in swelling of the macula and, if left untreated, loss of vision. At present there is no effective treatment available for AMD (age-related macular degeneration), whose incidence and severity increases with age resulting in progression from accumulation of proteins and glycosaminoglycans (drusen) to leakage of blood vessels (hemorrhage) and eventual blindness. For such conditions localized intravitreal or juxtascleral injections may be preferable to systemic administration of drugs (either alone or accompanied by laser initiated events such as photodynamic therapy).

Other Modes of Administration

PACKS

These sometimes are used to give prolonged contact of a drug solution with the eye to maximize absorption. Sterile cotton pledgets placed in the lower cul-de-sac have been used in this manner but more recently corneal shields and soft contact lenses developed as bandages have been utilized to protect the cornea during healing.[48] Corneal shields are made of collagen that is cross-linked to control the rate of erosion, usually 12 to 72 hours. Hydrophilic polymers used for soft contact lenses without vision correction have also been utilized as a drug reservoir. The soft lenses remain intact and therefore require removal.

INTRACAMERAL INJECTIONS

Injections may be made directly into the anterior chamber (eg, acetylcholine chloride, alpha-chymotrypsin, carbamylcholine chloride, certain antibiotics, and steroids) or directly into the vitreous chamber (eg, amphotericin B, gentamicin sulfate, and certain steroids).

IONTOPHORESIS

This procedure keeps the solution in contact with the cornea by means of an eyecup bearing an electrode. Diffusion of an ionic drug has imposed on it a driving force generated by a difference in electrical potential, which acts as an electrochemical driving force to transport the drug in the direction of the potential gradient.[49]

SUBCONJUNCTIVAL INJECTIONS

Subconjunctival injections (Fig 43-4)[50] are used frequently to introduce medications that if applied topically either do not penetrate into the anterior segment or penetrate too slowly to attain the concentration required. The drug is injected underneath the conjunctiva and probably passes through the sclera and into the eye by simple diffusion. The most common use of subconjunctival injection is for the administration of antibiotics in infections of the anterior segment of the eye. Subconjunctival injections of mydriatics and cycloplegics also are used to achieve maximal pupillary dilation or relaxation of the ciliary muscle. If the drug is injected underneath the conjunctiva and the underlying Tenon's capsule in the more posterior portion of the eye, effects on the ciliary body, choroid, and retina can be obtained.

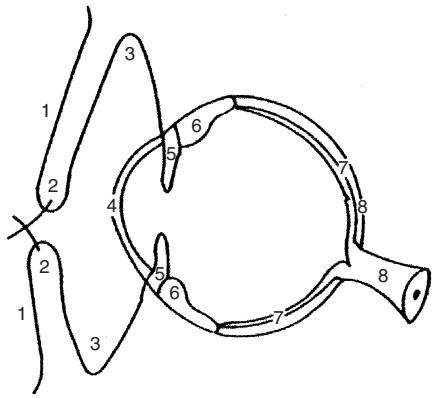


Figure 43-4. The locations for administration and target of therapy. Ointment: regions 1–5. Drops: regions 3–5. Parenteral injections—subconjunctival: regions 4–6, deep subtenons: regions 6–8, retreobulbar: region 8.

RETROBULBAR INJECTIONS

Drugs administered by retrobulbar injection (Fig 43-4) may enter the globe in essentially the same manner as the medications given subconjunctivally. The orbit is not well vascularized, and the possibility of significant removal via-bloodstream effects from these injections is remote. In general, such injections are given for the purpose of getting medications (eg, antibiotics, local anesthetics, enzymes with local anesthetics, steroids, vasodilators) into the posterior segment of the globe and to affect the nerves and other structures in that space for a sustained period of time.

PREPARATION

Commerical Manufacture

Pharmaceutical manufacturers provide finished ophthalmic products manufactured and tested for quality according to stringent industrial and governmental standards. The products' sterility and, where required, their nonpyrogenicity as well as other important quality standards are assured by end-product testing of each batch and also the use of validated manufacturing processes developed for each individual product. The products' manufacturing and quality control is governed largely by the Current Good Manufacturing Practice (cGMP) regulations[51] promulgated and enforced by the Food and Drug Administration (FDA). If the product is a new or generic drug or medical device and has received FDA marketing approval, the manufacturer must also meet the requirements specified in the approved application for chemistry, microbiology, manufacturing and quality control. Significant changes to the approved requirements must be submitted and approved by the FDA. For products not requiring prior FDA approval to market such as monographed OTC drug products,[52] the manufacturer must meet the quality standards of applicable USP or NF compendial monographs in addition to the cGMP regulations.

The manufacturer is subject to preapproval inspections and periodic GMP postapproval inspections by FDA. FDA also conducts inspections of the suppliers of active ingredients, both foreign and domestic, and certain inactive ingredients and packaging operations. The manufacture is subject to recalls of batches of product that do not meet quality requirements. In some cases a recall may result not from actual failed test results but from a lack of assurance that the product will continue to meet quality requirements through its shelf life.

Pharmacy Compounding

Compounding of individual patient prescriptions by pharmacists has been and continues in some areas to be an integral part of pharmacy practice. The need to routinely compound sterile ophthalmic products is no longer required with the broad range of commercially manufactured products available today. Most of the new and generic prescription ophthalmic products marketed today have been subjected to FDA's rigorous requirements for proof of safety and efficacy or bioequivalence as well as the above-described manufacturing and quality requirements.

If the pharmacist is requested to compound a prescription for a noncommercial product such as a preservative-free version or pediatric strength, he or she should be well versed in the preparation of sterile products, have the proper equipment and facilities and be knowledgeable about the special requirements for ophthalmic formulations and packaging. Reference information on the standards and technology for pharmacy compounding with special emphasis on preparation of sterile products should be consulted.[53, 54] The pharmacist must also consult the rules and regulations of the applicable state board of pharmacy concerning sterile pharmacy compounding as well as any federal regulatory requirements promulgated by the FDA. Congress included in the 1997 FDA Modernization Act certain legal conditions for which compounding as defined in the Act would be exempt from FDA regulation. The pharmacy compounding section of the Act was subsequently litigated and overturned in its entirety because it contained unconstitutional restrictions on commercial speech. FDA may seek new legislation to address their concerns regarding manufacturing in the guise of compounding. In the meantime, FDA has issued a guidance document on how the Agency intends to regulate pharmacy compounding of human drugs considered to be outside the bounds of traditional pharmacy practice and in violation of the Food, Drug and Cosmetic Act (www.fda.gov/cder/pharmcomp).

STERILIZATION

Common methods of sterilization include moist heat under pressure (autoclave), dry heat, filtration, gas sterilization, and ionizing radiation. Please refer to Chapter 40 where these sterilization procedures are described in detail.

DANGERS OF NONSTERILE MEDICATIONS—The possibility of serious ocular infection resulting from the use of contaminated ophthalmic solutions has been documented amply in the literature. Such solutions have been the cause repeatedly of corneal ulcers and even loss of eyesight. Contaminated solutions have been found in use in physicians' offices, eye clinics, and industrial infirmaries, and dispensed on prescription in community and hospital pharmacies. The microbe most frequently found as a contaminant is the Staphylococcus group. *Pseudomonas aeruginosa* is a less frequent contaminant, and the solution most often found contaminated is sodium fluorescein.

P. aeruginosa (*B. pyocyaneus; Pseudomonas pyocyanea;* blue pus bacillus) is a very dangerous and opportunistic organism that grows well on most culture media and produces both toxins and antibacterial products. The latter tend to kill off other contaminants and allow the *P. aeruginosa* to grow in pure culture. This gram-negative bacillus also grows readily in ophthalmic solutions, which may become the source of extremely serious infections of the cornea. It can cause complete loss of sight in 24 to 48 hr. In concentrations tolerated by tissues of the eye, it seems that all the antimicrobial agents discussed in the following sections may be ineffective against some strains of this organism.

A sterile ophthalmic solution in a multiple-dose container can be contaminated in a number of ways unless precautions are taken. For example, if a dropper bottle is used, the tip of the dropper while out of the bottle can touch the surface of a table or shelf if laid down, or it can touch the eyelid or eyelash of the patient during administration. If the Drop-Tainer (*Alcon*) type of bottle is used, the dropper tip can touch an eyelash or the cap while removed to permit administration, or its edge may touch a table or finger, and that edge can touch the dropper tip as the cap is replaced.

The solution may contain an effective antimicrobial, but the next use of the contaminated solution may occur before enough time has elapsed for all of the organisms to be killed, and living organisms can find their way through an abrasion into the corneal stroma. Once in the corneal stroma, any residual traces of antimicrobial agents are neutralized by tissue components, and the organisms find an excellent culture medium for rapid growth and dissemination through the cornea and the anterior segment of the eye.

OTHER ORGANISMS—*Bacillus subtilis* may produce a serious abscess when it infects the vitreous humor. The pathogenic fungus considered of particular importance in eye solutions is *Aspergillus fumigatus*. Other fungi or molds may be harmful by accelerating deterioration of the active drugs.

With regard to viruses, as many as 42 cases of epidemic keratoconjunctivitis were caused by one bottle of virus- contaminated tetracaine solution. Virus contamination is particularly difficult to control because none of the preservatives now available is virucidal. Moreover, viruses are not removable by filtration. However, they are destroyed by autoclaving. The pharmacist and physician have not been made adequately aware of the dangers of transmitting viral infection via contaminated solutions. This is particularly pertinent to the adenoviruses (Types III and VIII), now believed to be the causative agents of viral conjunctivitis such as epidemic keratoconjunctivitis.

The danger of non-sterile preparations is exponentially increased for products intended to be injected within the eyeball. Endophthalmitis and loss of vision can occur within a short time of onset of a bacterial infection.

Methods

STEAM UNDER PRESSURE—Terminal sterilization by autoclaving is an acceptable, effective method of sterilization; however, the solution or suspension components must be sufficiently heat-resistant to survive the procedure. If sterilization is carried out in the final container, the container also must be able to survive heat and pressure. A recent addition to this technique is the so-called air-over-steam autoclave. This combination allows pressure adjustments to be made during the autoclave cycle. Pressure manipulations permit the autoclave sterilization of materials that while heat-resistant tend to deform (ie, polypropylene containers). The sterilization cycle for a product should be carefully validated and assure that sterilization temperature and time are monitored at the coldest spot of the autoclave load to assure sterility of the product.

FILTRATION—The USP states that sterile membrane filtration under aseptic conditions is the preferred method of sterilization. Membrane filtration offers the substantial advantage of room temperature operation with none of the deleterious effects of exposure to heat or sterilizing gas.

Sterilization by filtration does involve the transfer of the finished sterile product into previously sterilized containers, using aseptic techniques. The membrane filtration equipment itself usually is sterilized as an assembly by autoclaving.

Several types of membrane filtration equipment are available for small-scale processing, as described in Chapter 40.[54] Particular interest has been shown in the Swinney adapter fitted on a syringe and in the *Millipore* Swinnex disposable filter units. Empty sterile plastic *squeeze* containers and sterile plastic filtration units can be purchased directly from the manufacturers, eg, *Wheaton* (polyethylene containers) and *Millipore* (Swinnex filter units). They permit extemporaneous preparation of ophthalmic solutions that have a high probability of being sterile if the work is carried out under aseptic conditions. A supplementary device can permit automatic refilling of the syringe. The filter unit must be replaced after use. To avoid contamination, the pharmacist should fill sterile filtered solutions into pre-sterilized containers closed with appropriate fitments and closure under laminar-flow using aseptic techniques. The Parenteral Drug Association has produced several audio-visual teaching materials for aseptic techniques and processing. The reader should refer to these guidelines for reference.

GAS—Gas sterilization of heat-sensitive materials may be carried out by exposure to ethylene oxide gas in the presence of moisture. Ethylene oxide (EtO) gas for sterilization use is available commercially, diluted with either carbon dioxide or halogenated hydrocarbons. Ethylene oxide sterilization requires careful consideration of conditions required to effect sterility. Temperature and pressure conditions are quite nominal in contrast to wet or dry heat; however, careful control of exposure time, EtO concentration, and moisture is essential.

Gas sterilization requires the use of specialized, but not necessarily elaborate, equipment. Gas autoclaves may range from very large walk-in units to small, laboratory bench–scale units suitable for small hospitals, laboratories, or pharmacies. In using gas sterilization the possibility of human toxicity must be kept in mind. Care should be taken to restrict exposure to ethylene oxide during the loading, venting, and unloading of the sterilizer. Ethylene oxide sterilization produces irritating by-products that remain as residues in or on the articles sterilized. Residues include ethylene glycol and ethylene chlorohydrin (when in contact with chloride ions) in addition to EtO itself. To minimize such residues the sterilized articles should be aerated for at least 72 hr, preferably at 40 to 50°C.

Ambient aeration time for sterilized polyethylene bottles should be about 48 hr. Ethylene oxide is recommended for the sterilization of solid materials that will not withstand heat sterilization. The FDA has recommended maximum residues in the parts per million range for EtO, ethylene glycol, and ethylene chlorohydrin.

Extreme caution should be exercised when using EtO gas sterilization. The previously accepted 12:88 mixture of EtO:Freon has been replaced with 100% EtO for environmental reasons. This gas is explosive and all workers also should be protected from accidental exposure due to concern for carcinogenicity and other toxic reactions to ethylene oxide. This method at present is used as a last resort when no other methods can be used.

RADIATION—Sterilization by exposure to ionizing radiation is an acceptable procedure for components of ophthalmic preparations or indeed for the total product, such as certain ophthalmic ointments. Sources of radiation are twofold and include linear electron accelerators and radioisotopes. The linear accelerators produce high-energy electrons with very little penetrating power. Radioisotopes, particularly ^{60}Co, are employed more widely for sterilization. Sterilization by radiation may produce untoward effects such as chemical changes in product components as well as changes in color or physical characteristics of package components. Gamma sterilization is currently used in place of EtO for sterilizing most of the packaging components. Gamma sterilization of containers may alter the surface characteristics and this can increase degradation of drug molecules and or some of the excipients used in the formulation. Some plastic manufacturers have developed special grades of polypropylene resin that is stabilized to withstand gamma irradiation.

OPHTHALMIC PREPARATION CHARACTERISTICS

CLARITY—Ophthalmic solutions by definition contain no undissolved ingredients and are essentially free from foreign particles. Clarity may be enhanced in some cases by filtration. It is essential that the filtration equipment be clean and well-rinsed so that particulate matter is not contributed to the solution by equipment designed to remove it. Operations performed in clean surroundings, the use of laminar-flow hoods, and proper nonshedding garments will contribute collectively to the preparation of clear solutions essentially free from foreign particles. In many instances clarity and sterility may be achieved in the same filtration step. If viscosity-imparting polymers are used, a polish-filtering step may be required prior to the final filtration.

Both container and closure must be thoroughly clean, sterile, and nonshedding, neither contributing particulate matter to the solution during prolonged contact for the duration of the shelf life. Normally this is established by thorough stability testing, which also will indicate if insoluble particles are generated by drug degradation (by-products with lower solubility). Solution formulations also may contain viscosity imparting polymers that can diminish clarity. In these situations it may be important both to define the visual clarity of the product and monitor its stability. The European Pharmacopoeia describes visual clarity and recommends standards that can be used for clarity specifications.

STABILITY—The stability of a drug in an ophthalmic product depends on a number of factors including the chemical nature of the drug substance, whether it is in solution or suspension, product pH, method of preparation (particularly temperature exposure), solution additives, and type of packaging. A pharmaceutical manufacturer strives for a shelf-life measured in years at controlled room temperature conditions whereas the compounding pharmacist often is not certain about the shelf life of his preparation and thus provides relatively small quantities at one time and assigns a shelf life in terms of days or weeks and may specify refrigerated storage as a further precaution. The attainment of optimum stability often imposes some compromises in the formulation, packaging and preparation of the final product.

The product's pH is often the stability-controlling factor for many drugs. Drugs such as pilocarpine and physostigmine are both active and comfortable in the eye at a pH of 6.8; however, at this pH chemical stability (or instability) can be measured in days or months. With either drug, a substantial loss in chemical stability will occur in less than 1 year. On the other hand, at pH 5 both drugs are stable for a period of several years.

In addition to optimal pH, if oxygen sensitivity is a factor, adequate stability may require inclusion of an antioxidant or special packaging. Plastic packaging, *ie*, the low-density polyethylene containers such as the Drop-Tainer (*Alcon*) that represents a patient convenience, may prove detrimental to stability by permitting oxygen permeation resulting in oxidative decomposition of the drug substance. To develop an epinephrine solution with 2 to 3 years stability in a plastic package requires the use of a pH of about 3 for protection from oxidation whereas an epinephrine borate solution formulated at a pH of about 7, which is more comfortable to the patient, requires an antioxidant system and the use of glass packaging. The prodrug of epinephrine, dipivefrin, significantly increases ocular bioavailability and is effective at one-tenth the concentration of epinephrine. The structure of the chemical derivative protects the active epinephrine portion from oxidation enabling it to be packaged in plastic. However, the prodrug introduces a labile ester linkage and as a result must be formulated at a pH of about 3 to minimize hydrolysis and still can only achieve a room temperature shelf life of less than 18 months.

Pharmaceutical manufacturers conduct comprehensive stability programs to assure the assigned expiration dating for each product. In addition to the standard chemical and physical stability of the pharmaceutical, the stability of the preservative is monitored by chemical means or by actual challenge of

the preservative efficacy with appropriate test organisms. Sterility is not a stability parameter per se but each container-closure system can be tested by microbial challenge to assure integrity of the package against environmental contamination prior to opening.

Some of the newer classes of ophthalmic drugs, like prostaglandins, are very hydrophobic and have very low concentrations. For example, in the product Xalatan latanoprost is present at 0.005% and in the product Travatan travoprost is present at 0.004%. Actives at such low concentrations present a challenge for formulators since the loss of even small amounts of drug, eg, from adsorption losses to packaging, may become significant. Pharmacia's Xalatan requires refrigerated storage, and as indicated earlier, temperature cycling also can reduce the concentration of active. It is important for the pharmacist to know the properties of the drug substance so that product quality is maintained throughout the shelf life of the product.

BUFFER AND pH—Ideally, ophthalmic preparations should be formulated at a pH equivalent to the tear fluid value of 7.4. Practically, this seldom is achieved. The large majority of active ingredients used in ophthalmology are salts of weak bases and are most stable at an acid pH. This generally can be extended to suspensions of insoluble corticosteroids. Such suspensions usually are most stable at an acid pH.

Optimum pH adjustment generally requires a compromise on the part of the formulator. The pH selected should be optimized for stability. The buffer system selected should have a capacity adequate to maintain pH within the stability range for the duration of the product shelf life. Buffer capacity is the key in this situation.

It generally is accepted that a low (acid) pH *per se* necessarily will not cause stinging or discomfort on instillation. If the overall pH of the tears, after instillation, reverts rapidly to pH 7.4, discomfort is minimal. On the other hand, if the buffer capacity is sufficient to resist adjustment by tear fluid and the overall eye pH remains acid for an appreciable period of time, then stinging and discomfort may result. Consequently, buffer capacity should be adequate for stability but minimized, so far as possible, to allow the overall pH of the tear fluid to be disrupted only momentarily. Special care in formulating intraocular products is required regarding their pH and buffer capacity. The corneal endothelium can tolerate much less deviation from physiological conditions compared to the external corneal epithelium.[55]

TONICITY—Tonicity refers to the osmotic pressure exerted by salts in aqueous solution. An ophthalmic solution is isotonic with another solution when the magnitudes of the colligative properties of the solutions are equal. An ophthalmic solution is considered isotonic when its tonicity is equal to that of a 0.9% sodium chloride solution (290 mOsm). However, the osmotic pressure of the aqueous intraocular fluid is slightly higher than tears measuring about 305 mOsm.

In actuality the *external* eye is much more tolerant of tonicity variations than was at one time suggested and usually can tolerate solutions equivalent to a range of 0.5 to 1.8% sodium chloride. Given a choice, isotonicity is desirable and particularly is important in intraocular solutions.[56] However, in certain cases a non-isotonic topical product is desirable. Tear fluid in some cases of dry eye (keratoconjunctivitis sicca) is reported to be hypertonic and a hypotonic artificial tear product is used to counteract this condition. Hypertonic ophthalmic products are used to relieve corneal edema and solutions and ointments containing 2% or 5% sodium chloride are available for this use.

The tonicity of ophthalmic (and parenteral) solutions has been investigated intensively over the years. These studies have resulted in the accumulation and publication of a large number of sodium chloride equivalents that are useful in calculating tonicity values. See Chapter 18 for a thorough discussion of the measurement and calculation of tonicity values.

VISCOSITY—Ophthalmic solution and suspension eyedrops may contain viscosity-imparting polymers to thicken the tear film and increase corneal contact time, ie, reduce the rate of tear fluid drainage. For suspensions, the increased viscosity also serves to retard the settling of particles between uses and at the same time maintains their suspension for uniform dosing. However, added viscosity may make initial resuspension more difficult particularly in a suspension that has a tendency to cake during storage. The hydrophilic polymers most often used for these purposes are methylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose and polyvinyl alcohol. They are used at concentrations that produce viscosities in the range of about 5 to 100 cps. These polymers are also used themselves as the active ingredients in artificial tear solutions for their lubrication and moisturizing properties in dry eye therapy. Viscosity agents can have several disadvantages in that they sometimes produce blurring of vision and can leave a residue on the eyelids. These effects are most often seen at the higher end of the viscosity range. The added viscosity can make filtration more difficult particularly for the small pore size filters used to sterilize solutions.

Newer ophthalmic dosage forms such as gel-forming solutions and semi-solid aqueous gels utilize increased viscosity and gel elasticity to improve significantly drug bioavailability and duration of effect. With these advances, the frequency of dosing can be reduced and patient compliance improved. These newer dosage forms utilize novel polymer systems with special rheological properties to enhance their effect. Their complex rheology and intricate dependence on environment, however, increase the complexity of the sterile manufacturing process.

ADDITIVES—Additives or pharmaceutical excipients are used as inactive ingredients in most ophthalmic dosage forms. Because of the need for tissue compatibility, the use of additives is perhaps more limited in ophthalmics, particularly in intraocular products.

The most common inactive ingredient is the product's vehicle. For topical dosage forms, Purified Water USP is used. Because of the requirement for nonpyrogenicity, Water for Injection USP is used for intraocular products. While a mineral oil and petrolatum combination is the vehicle used for ophthalmic ointments, nonaqueous liquids are rarely used in topical eyedrops due to their potential for ocular irritation and poor patient tolerance. Some mineral and vegetable oils have been used for very moisture-sensitive or poorly water-soluble drugs. The purest grade of oil such as those used for parenteral products should be used.

Microbiological preservatives are commonly used in multiple dose topical ophthalmic products and will be discussed in a later section. Other commonly used additives in topical eye products are ingredients to adjust and buffer pH and adjust tonicity in addition to the viscosity agents previously discussed. Ingredients to adjust pH and tonicity and buffer pH are essentially the same as those used in parenteral products. Less commonly used additives are antioxidants such as sodium bisulfite, ascorbic acid and acetylcysteine.

Surfactants are sometimes used in topical eye products for dispersing insoluble ingredients or to aid in solubilization. They are used in the smallest concentration possible to perform the desired function since they can be irritating to sensitive ocular tissues. Nonionic surfactants are used most often since they are generally less irritating than ionic surfactants. Polysorbate 80 is used in the preparation of an ophthalmic emulsion. Polyoxyl 40 stearate and polyethylene glycol have been used to solubilize a drug in an anhydrous ointment so that it can be filter sterilized. Surfactants are often used to stabilize more hydrophobic drugs, for example preventing loss to adsorption on the container walls. For example, a nonionic surfactant like polyoxyl 40 hydrogenated castor oil (HCO-40) has been used to stabilize travoprost, a prostaglandin derivative.[57] Similarly Cremophore EL has been used to stabilize diclofenac in the Voltaren formulation marketed by *Novartis*.

The FDA has published a list of all inactive ingredients used in approved drug products on their Internet website at www.fda.gov/cder. The list includes dosage forms and concentration ranges.

PACKAGING

Currently almost all commercially available ophthalmic products are packaged in plastic containers. Obvious advantages - ease of use, little breakage, less spillage - have led to universal acceptance of these plastic packaging components, consisting of bottle, fitment and closure. Alcon was the first company to introduce these packaging components, identified as a Drop-Tainer for ophthalmic products, in the late 1940s and then saw them adopted by the industry as the standard for packaging topical ophthalmic products. These bottles are generally of low-density polyethylene, either without any colorants or with opacifying agents or other colorants for light protection. Polypropylene or high-density polyethylene resins are also used to meet specific product requirements. The fitments determine drop size of the product and may contain additional features to prevent streaming of product at the time of use. Caps or closures are generally made from polypropylene and basically seal the container to prevent contamination or leakage of the product.

The FDA and other health authorities are also concerned about leachable impurities extracted from either the packaging components themselves or even occasionally from the label adhesives or ink used in printing the labels. Normally as a part of a stability program, actual package-formulation compatibility studies are required, including monitoring any extractables that come out in the product as a function of the duration of storage. Selection of compatible packaging material has become a critical issue for newer drug products, especially those in which the concentration of active is extremely low, like prostaglandins described earlier. The prostaglandin travoprost, the active in Travatan, required re-engineering of the total packaging, starting with the resin (syndiotactic polypropylene) to stabilize the drug, as well as altering size and shape to maintain squeezability of the bottle.[58] Travoprost was found not to be stable when stored in low-density polyethylene containers, the compound being lost to adsorption onto and absorption into surfaces even at room temperature. Consequently, chemical assay of marketed product must be conducted in a manner that does not deplete the concentration.

Specialized containers, like those developed by *Merck* for their Timolol/Pilocarpine combination product, maintain two solutions in different chambers adjusted separately to provide optimal chemical stability. At the time of dispensing the product, fractions of both solutions are combined and reconstituted by the pharmacist. For example, the final Timolol/Pilocarpine product once reconstituted would be at a nearly physiological pH, would provide pilocarpine as stable for one month at room temperature, and will be found comfortable to patients. Alcon also has developed a proprietary package[59] that can keep unstable or reactive components separate during storage, and that permits the pharmacist, at the time of dispensing to the patient, to rupture a diaphragm allowing the disparate fractions to be mixed. After mixing, the product is expected to remain stable for a month at room temperature. This container is designed to handle either liquid/liquid two-part or solid/liquid two-part components.

Pharmacists also should be aware of unit-dose products currently available in form-fill-seal containers that are preservative free. These products are discarded after single use. These products are most suited for patients who are sensitive or allergic to common preservatives and require chronic administration of a product. Specialized manufacturing technology involves melting a plastic resin to form the container walls, filling with the drug solution (usually 0.2 to 0.8 ml), and then sealing to maintain sterility. At the time of use the tip is broken off, the solution is dosed, and then the package is discarded. For technical reasons relating to manufacturing and filling capabilities as well as the need to minimize evaporation rate, these containers contain an excess volume of the product. The disadvantage is that patients may desire to use the entire volume and risk using an accidentally contaminated product. Recently, some unit-dose containers have been modified to allow the product to be recapped after use. These containers are designed and labeled to be discarded after a single day's use (12 hours) in order to reduce the risk of significant contamination yet make them more economical for the patient.

In only a very few instances are glass containers still in use, usually because of stability limitations. Large-volume intraocular solutions of 250 and 500 mL have been packaged in glass, but even these parenteral-type products are beginning to be packaged in specially fabricated polyethylene/polypropylene containers or flexible bags. Type 1 glass vials with appropriate stoppers are used for intraocular ophthalmic products administered by injection. These packaging components should meet the same requirements as parenteral products. Products injected intraocularly also are required to meet endotoxin limits. Readers should refer to the Chapter 41 *Parenteral Preparations* & 42 *Intravenous Preparations* for more details.

Plastic packaging, usually low-density polyethylene, is by no means interchangeable with glass, however. Plastic packaging is permeable to a variety of substances including light and air. The plastic package may contain a variety of extraneous substances such as mold-release agents, antioxidants, reaction quenchers, and the like, which may leach out of the plastic and into the contained solution. Label glues, inks, and dyes also may penetrate polyethylene. Conversely, confined volatile or lipophilic materials may permeate from solution into or through plastic walls. Sterilization, depending on the method, may influence the resin properties; for example gamma irradiation may increase acid extractables or generate sites that may degrade certain drugs. For these products ethylene oxide gas sterilization may be the only remaining option. However, gas sterilization also may degrade active molecules or leave harmful residuals, and certainly requires aeration under forced air to remove the traces of the gas and volatile residues. Whatever process is selected will need to be validated and monitored, assuring the process neither degrades the active nor generates toxic residues.

Patients may be prescribed more than one ophthalmic medication for the same or different conditions and this can lead to confusion as to which medication is for which use. Historically, red caps have been used for mydriatic drops and green caps for miotic drops such as pilocarpine. FDA now requires the use of certain colored caps on several additional types of ophthalmic drugs as a result of a cooperative effort between FDA, the ophthalmic industry and the Academy of Ophthalmology. The intent is to help patients' prevent medication errors and improve patient compliance. The pharmacist should counsel the patient or caregiver about the purpose of the cap color coding and the importance of opening only one container at a time so that the cap is replaced on the correct container. A listing of the current coding is provided in Table 43-1.

Glass containers remain a convenient package material for extemporaneous preparation of ophthalmic solutions. Type 1 glass should be used. The container should be well rinsed with sterile distilled water and may be sterilized by autoclaving. Droppers normally are available presterilized and packaged in a convenient blister pack.

Ophthalmic ointments invariably are packaged in metal tubes with an ophthalmic tip. Such tubes are sterilized conveniently by autoclaving or by ethylene oxide. In rare cases of metal reactivity or incompatibility, tubes lined with epoxy or vinyl plastic may be required.

Table 43-1. Ophthalmic Cap Color Coding

COLOR	PHARMACEUTICAL CLASS
Yellow or Blue	beta-blockers
Grey	non-steroids
Pink	steroids
Brown or Tan	anti-infectives
Orange	carbonic anhydrase inhibitors
Turquoise	prostaglandins
Red	mydriatics
Green	miotics

Regardless of the form of packaging, some type of tamper-evident feature must be used for consumer protection. The common tamper-evident feature used on most ophthalmic preparations is the moisture- or heat-sensitive shrink band. The band should be identified in such a way that its disruption or absence constitute a warning that tampering, either accidental or purposeful, has occurred.

The eyecup, an ancillary packaging device, fortunately seems to have gone the way of the community drinking cup. An eyecup should not be used. Its use inevitably will spread or aggravate eye infections. Pharmacists should not fail to discourage such use just as they should take the time to instruct patients in the proper use and care of eye medications. While ophthalmic administration may seem simple enough, it may be a foreign and difficult task for many people. The suggestions and precautions given elsewhere (under *Types of Dosage Forms*) may be useful in instructing patients.

ANTIMICROBIAL PRESERVATIVES[60]

A preservative is a substance or mixture of substances added to a product formulation to prevent the growth of, or to destroy, microorganisms introduced accidentally once the container is opened for use.[61,62] The preservative is not intended to be a means of preparing a sterile solution. Other appropriate techniques, discussed elsewhere, are to be employed to prepare sterile solutions.

Preservatives are used for topical ophthalmic products packaged in multiple dose containers unless the formulation itself is self-preserving, as is the case with some antimicrobial products like the ophthalmic solution Vigamox (moxifloxacin). FDA regulations (21 CFR 200.50) allow unpreserved ophthalmic liquid products to be packaged in multiple dose containers only if they are packaged and labeled in a manner that affords adequate protection and minimizes the hazards resulting from accidental contamination during patient use. This can be accomplished by using a reclosable container with a minimum number of doses that is to be discarded after 12 hours from initial opening, and so long as the container is labeled appropriately.

Preservatives are not to be used in solutions intended for intraocular use because of the risk of irritation and damage to these delicate tissues, or in chronic topical applications for patients who cannot tolerate preservatives. Unit dose ophthalmic solutions are especially useful for patients sensitive to preservatives yet who require daily medication, such as glaucoma patients or individuals requiring chronic application of palliatives for dry eye. Ophthalmic solutions prepared and packaged for a single application, *i.e.* a unit dose, need not contain a preservative because they are not intended for reuse.

The need for proper control of ophthalmic solutions to prevent serious contamination was recognized in the 1930s. The first preservative recommended for use in ophthalmics was chlorobutanol, as an alternative to daily boiling!

The selection of an ophthalmic preservative can be a rather difficult task, in part because of the relatively small number of suitable candidates. There is, of course, no such thing as an ideal preservative; however, the following criteria may be useful in preservative selection.

1. The agent should have a broad spectrum and be active against gram-positive and gram-negative organisms as well as fungi. The agent should exert a rapid bactericidal activity, particularly against known virulent organisms such as *P. aeruginosa* strains.
2. The agent should be stable over a wide range of conditions including autoclaving temperatures and pH range.
3. Compatibility should be established with other components of the preparation and with package systems.
4. Lack of toxicity and irritation should be established with a reasonable margin of safety.

Preservative substances must be evaluated as a part of the total ophthalmic preparation in the proposed package. Only in this way can the adequacy of the preservative be established. Criteria for preservative effectiveness in ophthalmic products are official compendial requirements in the USP, Pharm. Europe, and JP. Health authorities expect products will meet these preservative effectiveness criteria throughout their approved shelf lives, in the final packaging, and at the recommended storage conditions.[2-4]

In addition to preservative effectiveness as an immediate measure, its adequacy or stability as a function of time also must be ascertained. This often is done by measuring both chemical stability and preservative effectiveness over a given period of time and under varying conditions.

Many of these test procedures are not completely pertinent to the preparation of an extemporaneous ophthalmic solution. In such a situation the pharmacist must make selections based upon known conditions and physical and chemical characteristics, and should be guided by those used in commercial ophthalmic preparations. In these circumstances it would be prudent to prepare only minimum volumes for short-term patient use.

The choice of preservatives suitable for ophthalmic use is surprisingly narrow. The classes of compounds available for such use are described in Table 43-2.[63] In each case or category there are specific limitations and shortcomings.

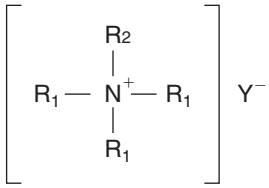
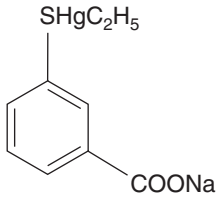
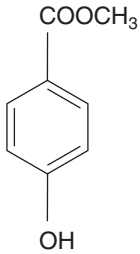
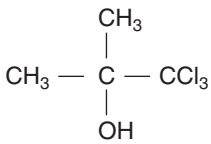
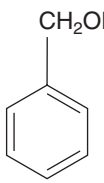
QUATERNARY AMMONIUM COMPOUNDS—Benzalkonium chloride (BAC) is a typical quaternary ammonium compound and is, by far, the most common preservative used in ophthalmic preparations. Over 65% of commercial ophthalmic products are preserved with benzalkonium chloride. Despite this broad use the compound has definite limitations. As a cationic surface-active material of high molecular weight it is not compatible with anionic compounds. It is incompatible with salicylates and nitrates and may be inactivated by high-molecular-weight nonionic compounds. Conversely, benzalkonium chloride has excellent chemical stability and very good antimicrobial characteristics. Given the alternative, often it is preferable to modify a formulation to remove the incompatibility, rather than to include a compatible but less effective preservative. The presence of a surfactant, for example, may require higher levels of BAC to achieve an adequate level of preservation.

The literature on benzalkonium chloride is somewhat mixed; however, this is not unexpected given the wide variation in test methods and, indeed, the chemical variability of benzalkonium chloride itself. The official substance is defined as a mixture of alkyl benzyldimethylammonium chlorides including all or some of the group ranging from n-C_8H_{17} through n-$C_{16}H_{33}$. The n-$C_{12}H_{25}$ homolog content is not less than 40% on an anhydrous basis.

Reviews[64] of benzalkonium chloride indicate that it is well suited for use as an ophthalmic preservative. Certain early negative reports have been shown to be quite erroneous; in some cases adverse tissue reactions were attributed to benzalkonium chloride when, in fact, a totally different compound was used as the test material. Although benzalkonium chloride is by far the most common quaternary preservative, others occasionally referred to include benzethonium chloride and cetyl pyridinium chloride. All are official compounds. More recently, quaternary ammonium functionality has been attached to soluble, reasonably high molecular weight polymers. These agents possess good antimicrobial effectiveness with fewer compatibility problems than the official quaternary preservatives.

Search for milder, safer, gentler preservatives for ophthalmic products, specifically artificial tear products and products that are for chronic use, has been a challenge for many companies. Newer preservatives as a result of this research have led to commercial products where these agents are employed as preservatives. Alcon has introduced many lens care and ophthalmic products with Polyquad. Polyquad represents a newer preservative of the same class as, but with less cytotoxicity than BAC. These agents are more effective and are used at a lower concentration than BAC. Their concentration in the product can range from 0.005% to 0.0005% and yet still meet compendial preser-

Table 43-2. Ophthalmic Preservatives[57]

TYPE	TYPICAL STRUCTURE	CONCENTRATION RANGE	INCOMPATIBILTIES
Quaternary ammonium compounds		0.004–0.02%, 0.01% most common	Soaps Anionic materials Salicylates Nitrates
Organic mercurials		0.001–0.01%	Certain halides with phenylmercuric acetate
Parahydroxy benzoates		Maximum 0.1%	Adsorption by macromolecules; marginal activity
Chlorobutanol		0.5%	Stability is pH-dependent; activity concentration is near solubility
Aromatic alcohols		0.5–0.9%	Low solubility in water; marginal activity

vative efficacy requirements. Polyquad has been used widely in many lens care and artificial tear products.

OXIDIZING AGENTS—Systems based on either sodium perborate or a stabilized oxychloro complex (SOC) are being used as preservatives based on their ability to generate a mild oxidative and cytotoxic effect in aqueous media. Sodium perborate produces hydrogen peroxide as the oxidative species and the SOC is a mixture of oxychloro species but primarily made up of chlorite and a trace of chlorine dioxide. Once in the eye the active agents in either system are spontaneously reduced to harmless byproducts and have been marketed as so-called disappearing preservatives in OTC products for dry eye treatment.

ORGANIC MERCURIALS—It generally is stated that phenylmercuric nitrate or phenylmercuric acetate, in 0.002% concentration, should be used instead of benzalkonium chloride as a preservative for salicylates and nitrates and in solutions of salts of physostigmine and epinephrine that contain 0.1% sodium sulfite. The usual range of concentrations employed is 0.002 to 0.004%. Phenylmercuric borate sometimes is used in place of the nitrate or acetate.

Phenylmercuric nitrate has the advantage over some other organic mercurials of not being precipitated at a slightly acid pH. As with other mercurials, it is slow in its bactericidal action, and it also produces sensitization reactions. Phenylmercuric ion is incompatible with halides, as it forms precipitates.

The effectiveness of phenylmercuric nitrate against *P. aeruginosa* is questionable; it has been found that pseudomonads survive after exposure to a concentration of 0.004% for longer than a week.

Development of iatrogenic mercury deposits in the crystalline lens resulting from use of miotic eye drops containing 0.004% phenylmercuric nitrate, 3 times daily, for periods of 3 to 6 years, has been reported. No impairment of vision was found, but the yellowish brown discoloration of the lens capsule is reported to be permanent.

Thimerosal (Merthiolate, *Lilly*) is an organomercurial with bacteriostatic and antifungal activity and is used as an antimicrobial preservative in concentrations of 0.005 to 0.02%. Its action, as with other mercurials, has been reported to be slow.

PARA-HYDROXYBENZOIC ACID ESTERS—Mixtures of methylparaben and propylparaben sometimes are used, mostly in ophthalmic ointments, as antimicrobial preservatives; the concentration of methylparaben is in the range of 0.1 to 0.2%, while that of propylparaben approaches its solubility in water (~0.04%). They are not considered efficient bacteriostatic agents and are slow in their antimicrobial action. Ocular irritation and stinging have been attributed to their use in ophthalmic preparations.

SUBSTITUTED ALCOHOLS AND PHENOLS—Chlorobutanol is stated to be effective against both gram-posi-

tive and gram-negative organisms, including *P. aeruginosa* and some fungi. It is broadly compatible with other ingredients and normally is used in a concentration of 0.5%. One of the products of hydrolysis is hydrochloric acid, which causes a decrease in the pH of aqueous solutions. This decomposition occurs rapidly at high temperatures and slowly at room temperature, in unbuffered solutions that were originally neutral or alkaline. Therefore, ophthalmic solutions that contain chlorobutanol should be buffered between pH 5 and 5.5 and generally packaged in glass containers. At room temperature it dissolves slowly in water, and although it dissolves more rapidly on heating, loss by vaporization and decomposition is accelerated.

A combination of chlorobutanol and phenylethyl alcohol (0.5% of each) has been reported to be more effective against *P. aeruginosa, Staphylococcus aureus,* and *Proteus vulgaris* than either antimicrobial singly. In addition, dissolving chlorobutanol in phenylethyl alcohol before dissolution in water eliminated a need for heating the solution.

OVER-THE-COUNTER (OTC) PRODUCTS FOR DRY EYE

Dry eye is a condition that can be an annoying irritation in its mild form, or a painful and destructive pathology in its severe form damaging the corneal surface and interfering with vision. Dry eye can be caused by decreased tear production, increased tear evaporation rate or an abnormality of the tear film that decreases its natural capacity to protect and lubricate the epithelial tissues. It is one of the most common complaints of patients seeking treatment from their eyecare doctor. This condition is somewhat unique in that it is largely treated with OTC monograph drug products and the pharmacist is often asked to assist in its selection.[65] These products are variously known as artificial tears, ocular lubricants, demulcents or emollients and are available as solutions, gels or ointments. Also unique is that these dry eye products are often the essential viscous vehicle component of therapeutic ophthalmic products. The compositions of the various commercial dry eye products can be found in several reference books.[33, 34]

OTC dry eye products contain water-soluble polymers as active ingredients that protect and lubricate the mucous membrane surfaces of the conjunctiva and cornea providing temporary relief of the symptoms of dryness and irritation. The polymers thicken the tear film and decrease the rate of tear loss in addition to lubricating and protecting the tissues. Mucin is a natural lubricating component of tears and thus dry eye products are expected to provide a mucomimetic effect. The active ingredient demulcent (lubricant) polymers in these products along with their permitted concentrations and labeling are defined in an OTC Monograph issued by FDA.[66] The Monograph does not specify viscosity grades and therefore a wide range of product viscosities are available. The more viscous products can provide longer duration of relief, however, they are also more likely to blur vision and leave a residue of polymer on the eyelids. The OTC products vary in their choice of polymer or combination of polymers, concentrations and viscosity. The majority of OTC dry eye products contain one or more of the following permitted polymers: cellulosics such as hydroxypropyl methylcellulose (hypromellose) or carboxymethylcellulose sodium; polyol liquids such as glycerin, polyethylene glycol, or polysorbate 80; polyvinyl alcohol; or povidone. Dextran 70 can be used only in combination with another permitted demulcent polymer.

The inactive components of OTC dry eye products are similar to those used in therapeutic ophthalmic products and must be selected just as carefully keeping in mind that the Monograph products are labeled for use as often as needed and thus must be nonirritating and physiologically compatible. In the moderate to severe forms of dry eye, the product may be dosed as often as every hour and in the especially severe cases as often as every 15 minutes. The preferred vehicle is aqueous for replenishing natural tears and dissolving the active and inactive ingredients. The vehicle is usually adjusted to be isotonic with sodium chloride and in some cases other salts are used as well as nonionic ingredients such as dextrose and mannitiol. Some cases of dry eye have been reported to produce tears that are hypertonic and several products feature a slightly hypotonic formula to restore the natural tear osmotic pressure. The products generally are adjusted or buffered to provide a pH of about 7.4 but rarely outside of the range of about 7 to 8.

Some polymers notably polyvinyl alcohol can lead to a more acidic pH upon storage of the solution. The preservative chlorobutanol also produces an acidic pH as it degrades in solution. Bicarbonate is included in some products as a more physiological buffer and requires a hermetically-sealed secondary package for stability. Some products include both mono and divalent chloride salts in their vehicles in an attempt to mimic the electrolyte composition of natural tears.

The majority of dry eye products contain a preservative and are packaged in multiple dose plastic ophthalmic containers. As in therapeutic products, benzalkonium chloride is the most widely used preservative. Newer preservatives having improved compatibility with ocular tissues such as polyquaternium-1 (Polyquad) are increasingly being used as well as the so-called “disappearing” preservatives sodium perborate and Purite. Sodium perborate forms hydrogen peroxide which can be irritating in the eye but quickly degrades to oxygen and water. Purite is a stabilized oxychloro complex that degrades to sodium chloride and water when exposed to long wavelength UV light.

Preservative-free products are also available and are gaining popularity particularly for patients with chronic dry eye conditions and those that are sensitive to preservatives. These products are packaged in form-fill-seal unit dose containers but due to manufacturing considerations they contain enough product for several doses but are labeled to be discarded after a single dose. This has led to the introduction of a modified package that features a reclosable cap and can be used as a small volume multiple dose container for preservative-free products when they are labeled for safety reasons to be discarded no longer than 12 hours after first opening.

The large majority of dry eye products are solution dosage forms administered as eyedrops but there are also available gel-like and ointment dosage forms. Ointments consisting primarily of a mixture of petrolatum and mineral oil are used for their emollient properties in dry eye treatment or where there is a defect in lid closing to prevent increased tear evaporation. Lanolin is sometimes added to the base to provide some water miscibility. The ratio of oils can be varied for consistency and melting temperature. The ointments are used primarily as a nighttime medication since they usually cause a blurring of vision. Several products are labeled as gels or liquid gels and are aqueous-based dosage forms containing one or more of the permitted lubricant polymers. The gel dosage form identifier is used to designate a more viscous product, however, the dosage directions read the same as for the eyedrop products (instill one or two drops prn) since this dosage statement is the only one permitted for dry eye products marketed using the permitted lubricant polymers under the OTC Monograph.

One disadvantage of most OTC dry eye products is their relatively short duration of effect. Several products have become available which incorporate novel delivery system technology into these products to prolong the duration of the lubricant and protectant effects of the Monograph active ingredients. In one product, AquaSite,[67] the polymer polycarbophil is used and in a more recent product, Systane,[68] a modified hydroxypropyl guar polymer is used to form a gel-like matrix when the product components interact with the tear fluid.

CONTACT LENSES AND THEIR CARE

Historical Background[69–71]

Evidence suggests that the concept of altering corneal power was first envisioned by Leonardo da Vinci early in the sixteen

century. In the next century, more than a hundred years later, Rene Descartes described a device, a glass-filled tube in direct contact with the cornea, capable of implementing this concept though it prohibited blinking and so was not a practical solution. In the early nineteenth century the British astronomer Sir John Herschel described the mathematics of these devices and proposed a means of treating very irregular corneas by using a glass capsule filled with a gelatin solution. Not until 1888 was the original concept executed by the artificial eye maker, Albert Muller. He made a glass protective shell for the cornea of a lagophthalmic patient who had carcinoma of the upper lid. The patient wore the device for 20 years, and corneal clarity was maintained.

But, perhaps the first contact lenses, scleral lenses resting on the bulbar conjunctiva beyond the limbal ring, were fabricated and fit by the German ophthalmologist A. E. Fick working in Zurich, Switzerland, late in the nineteenth century. Contact lenses without scleral portions (corneal lenses) were in existence at least as early as 1912, when they were manufactured by Carl Zeiss. Glass prostheses produced by Fick and others, while conceptually a step forward, suffer from reasonably rapid deterioration in the tear fluid. However they had the advantage that the glass was readily wetted by tears.

Experimentation in the twentieth century led J. Dallos, working in Budapest, to perceive the importance of tear flow underneath the contact lens. Dallos also took impressions of human eyes to improve the fidelity of the ground lens to the shape of the cornea. The first contact lenses, scleral lenses, of plastic made in the late 1930s with polymethyl methacrylate (PMMA) from Rohm and Haas are attributed to W. Mullen and T. Obrig. The advantages of durability and weight reduction far outweighed the slight differences in optical properties. And in 1948 K. Tuohy filed a patent for a plastic corneal contact lens. With the advent of PMMA a flush-fitting shell became possible, a concept developed in England in the 1950s by Ridley. The first corneal lenses to have any measure of commercial success were developed in the early '50s by F. Dickinson and W. Sohnges. Its thickness was about 0.2 mm, considered to be a fairly thick lens. Thinner lenses, about 0.1 mm, were introduced in the early '60s.

The first soft contact lenses were made of silicone, an elastomer nearly devoid of water but with good permeability to oxygen and carbon dioxide. However, the first soft contact lenses to be commercialized were of hydroxyethylmethacrylate hydrogels, developed by O. Wichterle and D. Lim in Czechoslovakia in the early '60s. Continuous improvements have progressed to the present day including milestones such as silicone-acrylate rigid gas permeable lenses in the '70s, disposable inexpensive lenses in the 80's, daily disposable and silicone hydrogel lenses in the '90s.

With the advent of commercialized, relatively comfortable and inexpensive corneal contact lenses, the need for lens care products developed beginning in the 1950s, and as summarized below a great variety of functionality has been provided, depending on the requirements of the individual products.

From a regulatory perspective, during the period from approval of the U.S. Food Drug and Cosmetic Act of 1938 (FDCA) until the U.S. Medical Device Amendments to the FDCA of 1976, contact lenses and contact lens care products were regulated as drugs. While during this period a device was defined in the FDCA, many medical devices were thought to be "used for the cure, mitigation, or prevention of disease" leading to their classification as drugs. With increased activity in industry and significance of biomedical devices in maintaining health, Congressional awareness arose of the advantages for greater regulation. The Amendments made provision for three classes of device, with different requirements for each. Those with least risk were assigned to Class I and those associated with increasing risk, to a progressively higher class. If safety and efficacy of a device could be reasonably assured by "general controls" (including restrictions on design, production, storage, maintenance, use, etc.), then the device was assigned to Class I, which may be exempted from the requirement for a 510 (k) but still require company or product registrations. Under the 1976 Amendments, contact lenses and lens care products were reclassified as Class III devices, requiring a premarket approval application (PMA) and approval by the FDA before marketing.

However by 1990, following years of experience with certain devices in the marketplace and recognition that little purpose was being served duplicating regulatory investigation of substantially equivalent safe and effective devices, Congress passed new legislation. The U.S. Safe Medical Devices Act of 1990 authorized reclassification of certain contact lens and lens care products as Class II devices (requiring special controls [a 510 (k) submission and clearance]). The products covered by this reclassification include solutions, dry products, tablets and disinfecting units used in caring for and disinfecting of soft (hydrophilic) and rigid gas permeable contact lenses. In March of 1994, the downclassification of two types of daily-wear contact lenses, from Class III to Class II, was implemented by a rule in the Federal Register. In July of 1997, a similar downclassification of certain contact lens care products, including multi-purpose solutions and in-eye contact lens solutions, was implemented by a rule in the Federal Register. Extended wear contact lenses remain governed by class III regulations.

Contact Lenses, Current Art

As a consequence of these years of development, there is an enormous selection of contact lenses and lens materials currently available to the consumer. There are basically four classes of lenses, and the identification of these classes is both by polymer type and lens characteristics: hard contact lenses, rigid gas permeable contact lenses, soft hydrophilic contact lenses, and silicone-based flexible hydrophobic lenses. These classes are summarized in Table 43-3. Hard contact lenses are generally fabricated from polymethylmethacrylate or polysili-

Table 43-3. Contact Lens Classes, Characteristics, and Support Products

LENS TYPE	CHEMICAL CLASSIFICATION	MAJOR CHARACTERISTICS	TYPICAL SUPPORT PRODUCTS
Hard, rigid, hydrophobic	PMMA (polymethyl methacrylate)	Negligible gas permeability, low water content, medium wettability	Wetting solutions Soaking solutions Cleaning solutions Combination Artificial tears
Soft, flexible, hydrophilic	HEMA (hydroxyethyl methylmethacrylate)	High water content, low gas permeability, good wettability	Cleaning solutions Disinfection solutions
Flexible hydrophobic	Silicone rubber	Good gas permeability; poor wettability	Wetting solutions Cleaning solutions
	Silicone vinylpyrollidone	Good gas permeability; good wettability	Soaking solutions
Rigid, hydrophilic	CAB (cellulose) acetate butyrate	Good gas permeability; good wettability	Wetting solutions Cleaning solutions Soaking solutions Rewetting solutions

cone acrylate polymers or copolymer blends containing one of these materials. The rigid gas permeable (RGP) contact lenses are generally made from more polarizable and oxygen-permeable materials such as cellulose acetate butyrate, *t*-butyl styrene, or silicone polymers or copolymers. These lenses generally provide superior visual acuity to those of the more flexible soft contact lenses. The U.S. Adopted Names (USAN) designates these hydrophobic lens types with less than 10% water by the suffix *focon*. However, RGPs having low oxygen permeability must be removed after a day's wear, and because of greater lens awareness especially for a new wearer, are recommended to be worn routinely, ie, not intermittently. However, they are durable and the replacement schedule is extended. RGPs with higher oxygen transmissibility tend to be preferred, especially in comparison with hard contact lenses, because the improved exchange of gases assists in maintaining the health of the cornea.

The third class of contact lenses, soft hydrophilic lenses, are fabricated from such a wide variety of materials and their blends and the FDA has grouped them according to two parameters, ionicity and water content (either low or high, less than or greater than 50% water):

- Group I includes the nonionic polymers of low water content such as a Polymacon [a simple poly (hydroxyethylmethacrylate), HEMA],
- Group II includes the nonionic polymers of high water content such as Alphafilcon A (a copolymer of five monomeric units, HEMA, vinyl pyrrolidone, ethylene dimethacrylate, hydroxycyclohexyl methacrylate, and a substituted vinyl carbonate),
- Group III includes ionic polymers of low water content such as Bufilcon (a terpolymer of HEMA, dimethyl oxobutyl acrylamide and the trimethacrylate ester of ethyl t-butane triol with some level of hydrolysis of the esters to the free acid) or Ocufilcon A (a terpolymer with HEMA, methacrylic acid [MA] and ethylene dimethacrylate), and
- Group IV includes ionic polymers of high water content such as a higher water content Ocufilcon B/C or Etafilcon (a terpolymer of HEMA, the salt of MA and the trimethacrylate ester of ethyl *t*-butane triol).

The final class of contact lenses, considered either a group of harder soft lenses or a group of softer RGP lenses with high oxygen solubility and transmission, is the silicone hydrogel lenses. These silicone and fluorosilicone materials are candidates for continuous extended wear applications.

Such diverse functionalities provide distinct properties in addition to water content, ranging from oxygen and metabolite transport, hardness and flexibility, to processability, and to durability and stability. More complete lists of the materials used in contact lens manufacture are available, but in general the USAN designates these hydrophilic lens types with greater than 10% water by the suffix *filcon*.[72–74] While the nomenclature adequately distinguishes monomer components, and the alphabetic trailing designation indicates differences in ratios of monomer units, one must remember that differences in crosslinker (often ethylene glycol dimethacrylate [EGDM]), initiator, catalyst, filler or color additive are not differentiated.

While this is a reasonable overview of the categories of choices for the materials comprising contact lenses, it is still an incomplete list of the properties which otherwise the consumer and his or her practitioner still need to make in selecting a contact lens. In addition to the chemical composition, the following choices need to be made: (1) duration of wear (daily vs. continuous), (2) lens replacement schedule (daily vs. biweekly vs. monthly vs. quarterly), (3) lens design (spherical, toric, bifocal), (4) colored or clear, (5) means of manufacture (lathe-cut or cast-molded), (5) edge design (which can affect lens motion, overall fit, comfort and acuity) and lens thickness, (6) fitting characteristics like the selection available for base curves and lens diameter, and (7) any surface treatment or conditioning. With this multiplicity of choices and the subtlety of competing requirements, the recommendation of the practitioner is vital.

But ultimately, the consumer's metrics—comfort, convenience and cost—also remain significant factors in lens selection. For some, the soft contact lenses are simply too fragile, and they select an RGP lens. For others, comfort dominates and they choose between the higher-water-content lenses, Groups II and IV. Soft lenses can be worn occasionally, and the blurring associated with the transition to eyeglasses is less troublesome than with hard contact lenses. But comfort and their other advantages have been achieved at a cost, and affects practice. Because Group IV lenses, being anionic, tend to accumulate soil such as protein at a more rapid rate than lenses from other groups, and are more sensitive to ionic strength and may bind absorbable impurities or additives such as preservatives, pollutants, cosmetic ingredients and therapeutic agents, they generally require more care than hard contact lenses or more hydrophobic soft contact lenses.

Replacement frequency also affects the choice of lenses. In America where replacement is biweekly, these disadvantages appear not to be troublesome; however in Europe where replacement schedules run longer, there appears to be a preference for the nonionic lenses with high water content, Group II lenses. However, since most lenses are currently replaced every 14-90 days, the influence of this factor appears to be diminishing. Preference for either of the high-water-content lenses is tempered in those individuals who tend toward dry eyes, since these Group II and IV materials appear to accelerate evaporation rates; and as a consequence patients with drier eyes are more likely to prefer Group I lenses.

In addition to their use in vision correction, soft contact lenses, like collagen shields, are occasionally used for therapeutic purposes, serving as bandages providing protection as in their use in bullous keratopathy (or other forms of corneal edema or other corneal irregularities or sources of cicatrization) or for lid abnormalities, and with ulcers, chemical burns, grafts, or dry eye. They can also be used to sustain the delivery of therapeutic agents, as discussed above. The same preparations used in caring for lenses used for refractive correction will be needed for lenses used for these therapeutic purposes.

In summary, both doctors and consumers have been provided with a broad range of alternatives. Current lens materials and the solutions to maintain them (next section) provide a wide selection of properties suitable for individual ocular health requirements and preferences.

Contact Lenses Care Products

GENERAL CONSIDERATIONS

With the previous two sections for background we are ready to discuss those preparations utilized in the care of these devices. For all of the specialized solutions to be discussed it is generally necessary: (1) to adjust pH, tonicity (osmolality), surface and interfacial tensions, and viscosity, (2) preserve and maintain sterility, (3) assure stability and shelf life, and (4) package and sterilize appropriately. In the US, these solutions are Class II medical devices.[71]

WETTING SOLUTIONS

These are lubricating and cushioning preparations designed to furnish a hydrophilic coating over the characteristically hydrophobic surface of PMMA, silicon, acrylate, and other rigid lens surfaces. Typically, wetting solutions include an acceptable viscosity-imparting agent, a surfactant, and a preservative. The surface-activity and viscosity effects may be obtained from a single compound. Agents commonly used include cellulose derivatives, polyvinyl pyrrolidone, polyvinyl alcohol, and polyethylene glycol derivatives. The need for surface-active agents, which facilitate wetting of lenses and spreading of tears, is greater for hard contact lenses because of their hydrophobic surface characteristics. Preservatives include those acceptable for ophthalmic use, including Polyquad and Dymed.

CLEANING SOLUTIONS

Cleaning solutions commonly are used to remove surface contaminants—lipids, protein, organic salts and the like. Cleaning is accomplished by the use of surfactants that preferably are nonionic or amphoteric. Viscosity-imparting agents generally are not included. Some cleaning agents also include a mild abrasive, silica for RGPs or plastic particles for soft lenses.

Adequate cleaning of hydrophilic lenses is a far more complex and challenging problem than for hard-lens cleaning. Because of their permeability characteristics, contaminants penetrate into the lens structure and may bind chemically or physically to the hydroxyethylmethylmethacrylate (HEMA) or ionic portions of the lens material. Contaminants may be surface films or crystals, amorphous aggregates of protein material, cellular debris, or insoluble inorganic salts.

Cleaning products generally are specific to the lens material and require FDA clearance, with proof of cleaning efficacy and safety. Cleaners are based on surface activity, enzyme action, or even abradant action, in which case the abradant material must be softer than the lens itself. Adequate daily cleaning of hydrophilic lens material can enhance disinfection, but in some cases may not be necessary given the choices of today's powerful disinfecting solutions and enzymatic cleaners, in either a tableted or liquid form. Most recently daily-wear planned replacement lenses have found wide acceptance. Conventionally their successful use is reliant on enzymatic cleaning together with special disinfectants. However, extended wear lenses, soiling at a lower rate, require only rewetting drops.

The significance of adequate cleaning cannot be overstated. Improperly or inadequately cleaned and maintained lenses are perhaps the most important contributors to complications associated with the wear of contact lenses such as discomfort, loss of visual acuity, conjunctivitis and keratitis.

There are two types of cleaning solutions, daily and weekly cleaners. Weekly cleaning solutions may include proteolytic enzymes like *Subtilisin* or a broad-spectrum less-toxic enzyme like pancreatin (which contains protease, lipase and amylase activity), or concentrated surfactants. Daily cleaning solutions achieve cleaning using less aggressive surface active agents and polymers, often nonionic but nonsolubilizing agents that will be less toxic if carried over into the eye. Examples include Tweens and Tyloxapols. A daily cleaning solution containing even a nontoxic enzyme is available (SupraClens).

The goal is to provide thorough cleaning of the lenses, for the benefits described above, without causing any degradation of the lenses.

DISINFECTING SYSTEMS

Disinfection of the first hydrophilic lens approved by the FDA was accomplished using a heating device that generated steam from a saline solution. The latter was either prepared by the user or available from the manufacturer. Subsequent to the so-called thermal systems, requiring heating at 80°C for ten minutes, disinfection solutions were developed that met the requirements for FDA approval while not damaging the more delicate soft lens materials. Because of the sorption characteristics of hydrophilic lens materials, many of the accepted ophthalmic preservatives are unsatisfactory for use in soft-lens disinfecting systems, including the ubiquitous benzalkonium chloride. Once again, however, the use of a quaternary disinfectant covalently bonded to a soluble, relatively high molecular weight polymer has met with some success. These have to a large extent replaced chemical antimicrobial agents like sorbic acid, thimerosal (mercury containing), and hydrogen peroxide amongst many others. Perhaps the most common in current use are a cationic polymer, Polyquad, and a poly biguanide, called PHMB or Dymed.

In addition to possessing satisfactory disinfecting activity, such a preparation must be isotonic, in an acceptable pH range, and nonreactive (nonbinding) with lens materials and, over a normal use period, induce or bring about no physical, chemical, or optical changes in the lens. It is of course sterile and safe for use in the eye, even though direct instillation into the eye is not intended.

SOAKING SOLUTIONS

Soaking or storage solutions, as the name suggests, are used to store and hydrate hard or RGP lenses but, most importantly, to disinfect such lenses. Disinfection should be rapid and as complete as possible making use, once again, of acceptable ophthalmic preservative substances. Soaking solutions typically contain chlorhexidine (gluconate), benzalkonium, or quaternary/polymer compounds enhanced by sodium edetate. Soaking solutions are intended to be rinsed off lenses before insertion.

REWETTING SOLUTIONS

Solutions intended to rewet hard or RGP lenses *in situ* are referred to as rewetting solutions or lubricating drops. Such preparations are intended to reinforce the wetting capacity of the normal tear film. Early products of this type tended to be somewhat viscous wetting solutions acceptable for direct instillation into the eye. More-recent preparations mimic tears more accurately, and their viscosity may be rather low to improve user acceptability, or adjusted to be responsive and to improve retention and duration of the wetting characteristics.

MULTIPURPOSE SOLUTIONS

By combining the actions of two or more of the solutions just described, these products have simplified regimens, improved compliance, generally increased comfort of contact lens products, and greatly increased convenience of using contact lenses. For soft contact lenses multipurpose solutions need combine only the functions of cleaning and disinfection, whereas for a complete multipurpose solution for a hard or RGP lens some level of wetting also need be provided. Suffice it to say that these solutions, which contain an intricate balance of ingredients, have grown in popularity significantly, because of the greatly increased level of convenience they provide. Their efficacy often precludes the need for separate cleaning solutions for many patients.

GUIDELINES FOR SAFETY AND EFFICACY TESTING

The FDA periodically issues or updates guidelines describing recommended test procedures for contact lens–care products. The reader is advised to review the most recent guidelines for appropriate requirements.

Current guidelines cover all lens care products. Applicable guidelines are determined by the type of product (eg, saline solution, cleaning solution, multipurpose solution, rewetting drops) and the claim (eg, disinfection in a regimen vs. a standalone process). Safety testing includes determinations of cytotoxicity, oral toxicity, potential for sensitization, and single to multiple exposure in an animal (rabbit) eye. The tests designated depend on the active ingredient (eg, if it is a new entity or has been in previous products) and its concentration (eg, if it is the same or different from that used in a currently approved product). Efficacy of preservation, disinfection and cleaning, compatibility with lens or lens types, and clinical trials are also required with their type and scope dependent on product type, characteristics, ingredients and claims.

SUMMARY

Considerable progress has been made in ophthalmic pharmaceutics and in lens-care products during the last decade. Very substantial advances have been made in designing vehicles and

packaging for highly potent actives presented at very low concentrations, in increasing ophthalmic bioavailability and controlling factors influencing ophthalmic drug absorption, in the design of implants and means of delivering them for providing therapeutic agents to the retina and other deep ophthalmic tissues, and in devising robust yet delicately balanced multipurpose solutions for contact lens wearers. Continuing advances in the general field of ophthalmic pharmaceutics and pharmacokinetics can be expected to assist in maintaining and improving ocular health.

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CHAPTER 44

Medicated Topicals

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The application of medicinal substances to the skin or various body orifices is a concept as old as humanity. The papyrus records of ancient Egypt describe a variety of these 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. Ophthalmics and topical aerosol products will not be discussed in this chapter. Ophthalmic use imposes particle size, viscosity, and sterility specifications that require separate, detailed discussion (see Chapter 43). The complexity of pharmaceutical aerosol systems necessitates their inclusion elsewhere (see Chapter 50).

BIOPHARMACEUTIC ASPECTS OF THE ROUTES OF ADMINISTRATION

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 44-1).

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, linked by intercellular bridges and compressed into about 15 layers. The lipid-rich intercellular space in the stratum corneum comprises lamellar matrices with alternating hydrophilic layers and lipophilic bilayers formed during the process of keratinization. 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 toward 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 and 6.5, depending on the area tested) made up of emulsified lipids covers the surface of the stratum corneum.

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.

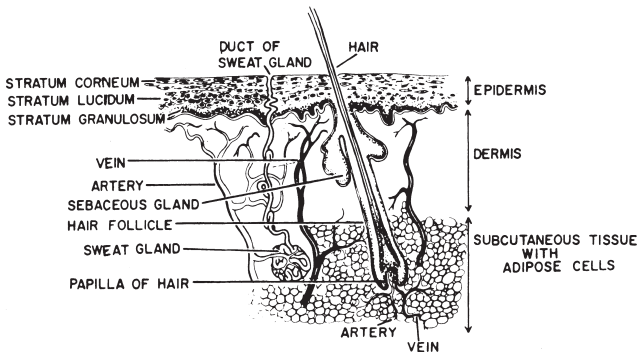

Figure 44-1. Vertical section of human skin.

PILOSEBACEOUS UNITS—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. Follicular density varies considerably as well, from values of about 250 follicles per cm^2 for the scalp to 50 per cm^2, or less, for the thigh and other relatively nonhirsute areas. Follicular density is determined genetically, ie, no new follicles are formed after birth. One characteristic human trait is that although most of the body hairs never develop beyond the rudimentary vellus state, the only hairless areas are confined, primarily, to the palmar and plantar surfaces. 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. Population in the scalp, face, and anogenital areas may vary from 400 to 900/cm^2. Fewer than 100/cm^2 are found in other areas. Sebaceous glands are richly supplied with blood vessels.

Sebaceous cells synthesize and accumulate lipid droplets. This accumulation results in enlarged cells that fragment to form sebum. Sebum is made up of a mixture of lipids, approximately as shown in Table 44-1.

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.

SWEAT GLANDS—Sweat glands are classified as apocrine and eccrine. Apocrine glands are secretory but are not necessarily responsive to thermal stimulation. Such glands do not produce sweat in the normal sense of the word. Apocrine glands, however, often are associated with eccrine sweat glands, particularly in the axilla.

Eccrine sweat glands are coiled secretory glands, equipped with a blood supply, extending from the dermis to the epidermal surface. Eccrine sweat glands function to regulate heat exchange in man. As such, they are indispensable to survival.

About 3 million eccrine glands are thought to be distributed over the human body. Distribution varies from less than 100 to more than 300/cm^2. Gland counts after thermal stimulation do not always agree with anatomical counts.

Table 44-1. Composition of Sebum

CONSTITUENTS	% W/W	CONSTITUENTS	% W/W
Triglycerides	57.5	Cholesterol esters	3.0
Wax esters	26.0	Cholesterol	1.5
Squalene	12.0		

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* fulfills 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 that both penetrates and is substantive to stratum corneum cells. Skin moisturization takes place within the stratum corneum. Whether it involves the hydration of dry outer cells by surface films or the intercalation of water in the lipid-rich intercellular laminae, 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 that exhibit significant skin interaction include benzocaine, estrogens, 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 that 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, or *N,N*-diethyl-*m*-toluamide) over the years. With the commercial introduction of transdermal drug delivery systems for scopolamine, nitroglycerin, clonidine, 17β-estradiol, fentanyl, nicotine, testosterone, lidocaine, and oxybutynin, 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 der-

mis, 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

$$R_{skin} = R_{sc} + R_e + R_{pd}$$

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. On the other hand, liposomal vehicles and microbead (3 to 10 μm diameter) suspensions appear to accumulate selectively in pilosebaceous and perifollicular areas. In the very early stages of absorption, transit through the appendages may be comparatively large, particularly for lipid-soluble molecules and those whose permeation through the stratum corneum is relatively low. Surfactants and volatile organic solvents such as ethanol have been found to enhance drug uptake via the transfollicular route.

Rather than characterizing drug transfer into and through the skin in terms of the diffusional resistances encountered, one could define permeation in terms of the *pathways* followed by the diffusing species. Drug permeation through the intact skin of humans involves either an intercellular or transcellular path in the stratum corneum, for the most part, rather than the so-called shunt pathways (transglandular or transfollicular routes).

The conventional wisdom is that for the most part, lipophilic compounds transfer preferentially into the lipoidal intercellular phase of the stratum corneum, while relatively more hydrophilic compounds transfer into the intracellular domain of the stratum corneum. One should keep in mind that the often-postulated biphasic character of the horny layer—with hydrophilic cells in a lipophilic matrix—is overly simplistic: the hydrophilic cells themselves are enclosed within lipid bilayer membranes, while the lipophilic matrix comprises intercellular lipids that are, in fact, present in lamellar structures that *sandwich in* hydrophilic layers. As Boddé et al[1] have suggested, the intercellular pathway is *bicontinuous,* consisting of a nonpolar and a polar diffusion pathway between the corneocytes. The implications for dermatopharmacokinetic modeling are clear.

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,

$$K_m \text{ is the } \frac{\text{solute sorbed per cm}^3 \text{ of tissue}}{\text{solute in solution per cm}^3 \text{ of solvent}} = \frac{C_m}{C_s},$$

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 *hydrophilic* corneocytes and the lipid-rich lamellar structures in the intercellular space. 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. It has been suggested that one ought to differentiate between two species of horny layer: the palms and soles (up to 600 μm thick), adapted for weight-bearing and friction; and the body horny layer (~10 μm thick), adapted for flexibility, impermeability, and sensory discrimination.

Overall, data suggest the following order for diffusion of simple molecules through the skin: plantar < palmar < arms, legs, trunk, dorsum of hand < scrotal and postauricular < axillary < scalp. 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). The development of iontophoretic devices in recent years may minimize this problem with ionic penetrants. For any specific molecule, the predictability of regional variations in skin permeability continues to elude investigators. This will continue to be true as long as dermatopharmacokinetic models do not adequately reflect the anisotropicity of the skin's composition and structure, its interactions with the drug and the vehicle, and the physiological parameters that affect transfer.

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 or animal skin. *In vivo* studies in recent years have made use of the skin-stripping method, which permits the estimation of the concentration or amount of the penetrating species as a function of depth of the stratum corneum. Layers of the stratum corneum can be removed or stripped successively away by the repeated application and removal of cellulose adhesive tape strips. Skin penetration of a drug and the effect of additives may be studied and evaluated through analysis of individual skin strips, which provide a profile of skin penetration. Rougier et al[2] have championed the use of the skin-stripping method, in conjunction with short-term exposure to the topically applied penetrant, as a predictor of skin permeation.

Clearly, the evaluation of new chemical entities (NCEs) of indeterminate toxicity mandates *in vitro* testing. A diffusion cell frequently used for *in vitro* experiments is shown in Figure

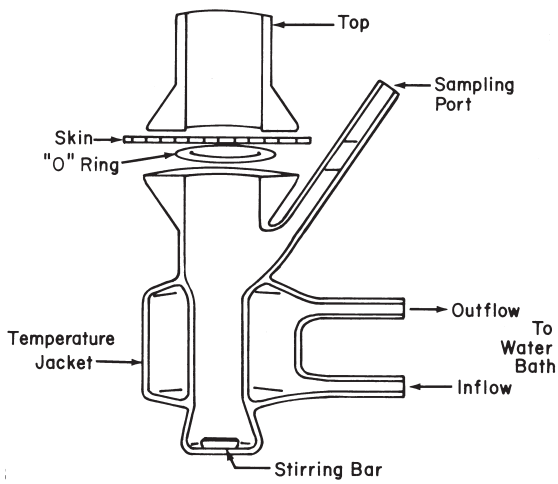

Figure 44-2. Schematic representation of diffusion cell. Top is open to ambient laboratory environment. (From Franz TJ. *J Invest Dermatol* 1975;64:191.)

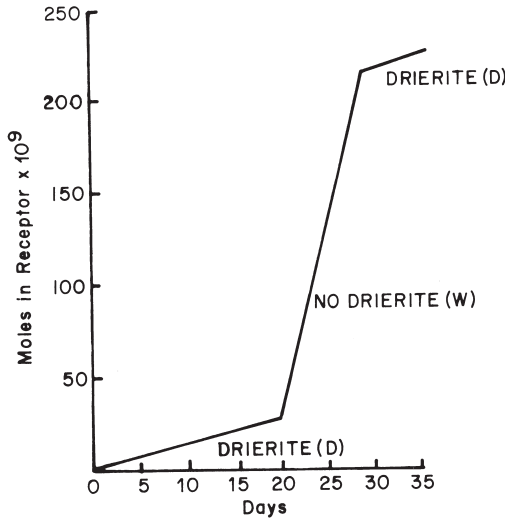

Figure 44-3. Change in cortisone penetration by alternately drying (D) and humidifying (W) the stratum corneum. (From Scheuplein RJ, Ross LW. *J Invest Dermatol* 1974;63:353.)

44-2.[3] 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.

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[4] varied the atmosphere above the skin strip by use of Drierite to simulate dry conditions and wetted paper strips to simulate the effect of occlusion and observed marked reduction in penetration of cortisone under dry conditions but greatly enhanced penetration on humidifying the stratum corneum (Fig 44-3).[4]

The studies of Scheuplein and Ross,[4] and of Franz,[3] 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

PERCUTANEOUS ABSORPTION—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[5] 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 Figure 44-4,[6] illustrate the penetration differences observed with different animal skins.

Subsequently, using a similar *in vivo* technique, Wester and Maibach[7] 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 5 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.

The consensus is that rhesus monkeys and miniature pigs are good *in vivo* models for human percutaneous absorption, while smaller laboratory animals (eg, mouse, rat, rabbit) are not.

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.

As Bronaugh[8] notes, although human skin is preferable for *in vitro* permeation studies, its availability is limited. Additional constraints apply if one is only willing to use freshly obtained viable human skin from surgical specimens or biopsies, as opposed to skin harvested from cadavers.

Concern has been voiced over the notorious variability in barrier properties of excised skin, whether animal or human. Factors responsible for the variability include the source and characteristics of the donor skin (eg, elapsed time from death to harvesting of the skin, age and gender of the donor, health of the skin prior to the donor's death), exposure of the skin to chemicals or mechanical treatment (eg, shaving or clipping prior to harvesting of the skin), etc. The availability of a *living skin equivalent*—comprising a bilayered system of human dermal fibroblasts in a collagenous matrix upon which human corneocytes have formed a stratified epidermis—offers an alternative, less variable, model for evaluating human skin permeation and biotransformation.

Skin-flap methods represent *in vivo* and *in vitro* techniques for evaluating percutaneous absorption in animals or animal models: the general approach entails the surgical isolation of a skin section of an animal such that the blood supply is singular; this ensures that drug can be collected and assayed in the vascular perfusate as it undergoes absorption from the skin surface. The perfused skin flap can be maintained in the intact animal or mounted in an *in vitro* perfusion system, all the while maintaining its viability.

Animals also have been used to detect contact sensitization, measure antimitotic drug activity, measure phototoxicity, and evaluate the comedogenic and comedolytic potential of sub-

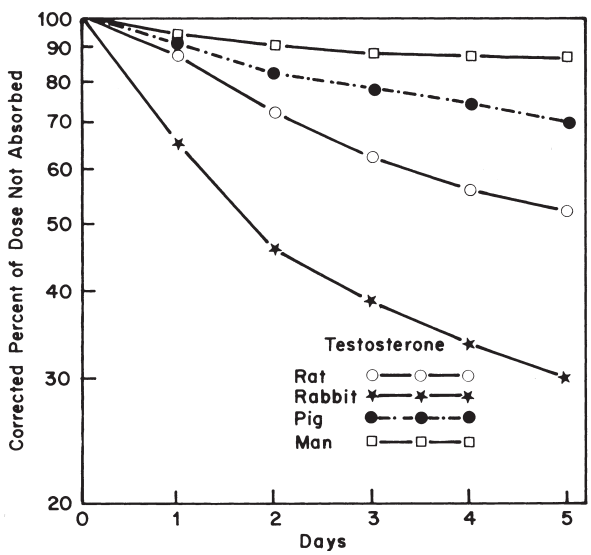

Figure 44-4. Percutaneous absorption of testosterone in rats, rabbits, swine and man for 5 days after application. (From Maibach HI, ed. *Animal Models in Dermatology*. Edinburgh: Churchill Livingstone, 1975.)

stances. 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[9] 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.

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[10] tabulated the potency of various topical steroids, comparing the rat-ear-edema assay with potency measured in humans by use of the vasoconstrictor procedure of Stoughton and McKenzie; the results are given in Table 44-2.[11] 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. However, a number of concerns have been raised over the years that need to be addressed, particularly if this bioassay is to be used to assess the bioequivalence of topical corticosteroid formulations. These concerns include the linearity of the vasoconstrictor response–drug concentration relationship and the visual assessment of the blanching or vasoconstrictor response.

As the *in vivo* vasoconstrictor response generally approaches a maximum, one must know whether the microcirculation of the skin has exceeded its capacity to respond linearly to the corticosteroid concentration attained in the skin. It may be that only relatively minimal responses will be elicited by relatively high concentrations. At the other end of the response-dose relationship, what is the minimum dose that will produce a reliable, replicable response? Rather than relying on the somewhat subjective visual evaluation of the response, investigators ought to make use of chromometers to provide objective, quantifiable data.

PILOSEBACEOUS UPTAKE—The study of the targeted delivery of drugs to follicles and/or sebaceous glands has become necessary in view of the selective uptake or deposition of antiacne drugs such as tretinoin in pilosebaceous units. Fortunately, the anatomical and physiological correspondence of hamster ear pilosebaceous units to those in humans has facilitated studies of the cutaneous and pilosebaceous disposition of drugs following topical application.[12]

Table 44-2. Relative Potency of Anti-Inflammatory Agents

COMPOUND	RAT-EAR EDEMA ASSAY	TOPICAL ANTI-INFLAMMATORY POTENCY HUMAN ASSAY VASOCONSTRICTOR
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 (4.05–7.70)	3
Betamethasone	97.3 (16.7–141)	3–5
Betamethasone 21-acetate	1072.0 (876–1179)	18–33
Fluorometholone	138.3 (57.9–333)	30–40
Fluorometholone acetate	219.5 (9.15–536)	
Fluprednisolone	31.8 (13.3–76.1)	4–6
Fluprednisolone acetate	61.3 (25.6–147)	
Hydrocortisone	1	1

( ) = 95% confidence limits.
From Maibach HI. In Maibach HI, ed. *Animal Models in Dermatology.* Edinburgh: Churchill Livingstone, 1975, p 221.

Other Factors Affecting Drug Absorption from the Skin

Percutaneous absorption of a drug 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 of 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°C), resulting in increased molecular motion and skin permeation.

Hydrocarbon bases that 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.

Transdermal delivery systems, with their occlusive backing, can effect increased percutaneous absorption as a result of increased skin temperature and hydration.

In experiments with healthy volunteers wearing transdermal nitroglycerin delivery systems, investigators[13] showed that exposure of the surrounding skin area to localized heating or cooling could cause extensive changes in nitroglycerin bioavailability, presumably due to changes in regional cutaneous blood flow and subsequent systemic uptake *(see below)*.

One consequence of occlusion of the skin surface, whether by a transdermal delivery system or a hydrocarbon film, is that an aqueous film may form at the formulation-skin interface. This aqueous film or interphase could result in decreased transfer efficiency, and, in the case of a transdermal delivery system, a loss of adhesion. Accordingly, the suppression of perspiration could enhance vehicle-skin partitioning efficiency and drug permeation.

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 44-3).[14,15] 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 that affect skin permeability is water. As noted above, water is a factor even for *anhydrous* transdermal delivery systems due to their occlusive nature. Due to its safety and efficacy, water has been described as the

Table 44-3. Penetration Enhancers

Solvents	Dimethyl formamide
Water	Tetrahydrofurfuryl alcohol
Alcohols	*Amphiphiles*
Methanol	L-α -Amino acids
Ethanol	Anionic surfactants
2-Propanol	Cationic surfactants
Alkyl methyl sulfoxides	Amphoteric surfactants
Dimethyl sulfoxide	Nonionic surfactants
Decylmethyl sulfoxide	Fatty acids and alcohols
Tetradecylmethyl sulfoxide	*Miscellaneous*
Pyrrolidones	Clofibric acid amides
2-Pyrrolidone	Hexamethylene lauramide
N-Methyl-2-pyrrolidone	Proteolytic enzymes
N-(2-Hydroxyethyl) pyrrolidone	Terpenes and sesquiterpenes
	α-Bisabolol
Laurocapram	*d*-Limonene
Miscellaneous solvents	Urea
Acetone	*N,N*-Diethyl-*m*-toluamide
Dimethyl acetamide	

Data from Walters KA. In Hadgraft J, Guy RH, eds. *Transdermal Drug Delivery.* New York: Dekker, 1989, p 197; Ghosh TK, Banga AK. *Pharm Technol* 1993; 17(4):62; 1993; 17(5):68.

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 (Azone) has been shown to function effectively at low concentrations (≤5%). Furthermore, laurocapram'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.[16] 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[17] 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 Figure 44-5.[17] 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.

The importance of blood-flow-limited percutaneous absorption was shown by Benowitz et al[18] who documented the effect of the intravenous administration of nicotine, a known cutaneous vasoconstrictor, on the systemic absorption of nicotine administered concurrently in the form of a transdermal delivery system. Plasma nicotine concentrations rose less rapidly and reached a lower peak at a later time than when nicotine was applied transdermally in the absence of the intravenous nicotine infusion. This raises concerns about the potential cutaneous interactions between vasoconstrictors *or* vasodilators *and* topically applied drugs intended for a systemic effect: bioavailability could be increased or diminished as a result! The assessment of the potency of corticosteroids by corticosteroid-induced skin blanching (ie, vasoconstriction, lends credence to this issue).

On the other hand, Christophers and Kligman[17] demonstrated increased *in vitro* skin permeation by sodium fluorescein in the stratum corneum excised from young and old subjects (Fig 44-6[17]). 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 these studies may not provide data that is indicative of drug permeation through the skin of older subjects or patients.

Roskos, Maibach, and Guy[19] made quantitative measurements of the percutaneous absorption of a number of drugs *in vivo* from the urinary excretion profiles of ^{14}C-radiolabeled drugs in young (18 to 40 years) and old (>65 years) subjects: while permeation of hydrocortisone, benzoic acid, aspirin, and caffeine was significantly lower in older subjects, testosterone and estradiol absorption was comparable in the two groups. Additional comprehensive studies of percutaneous absorption *as a function of age* continue to be warranted.

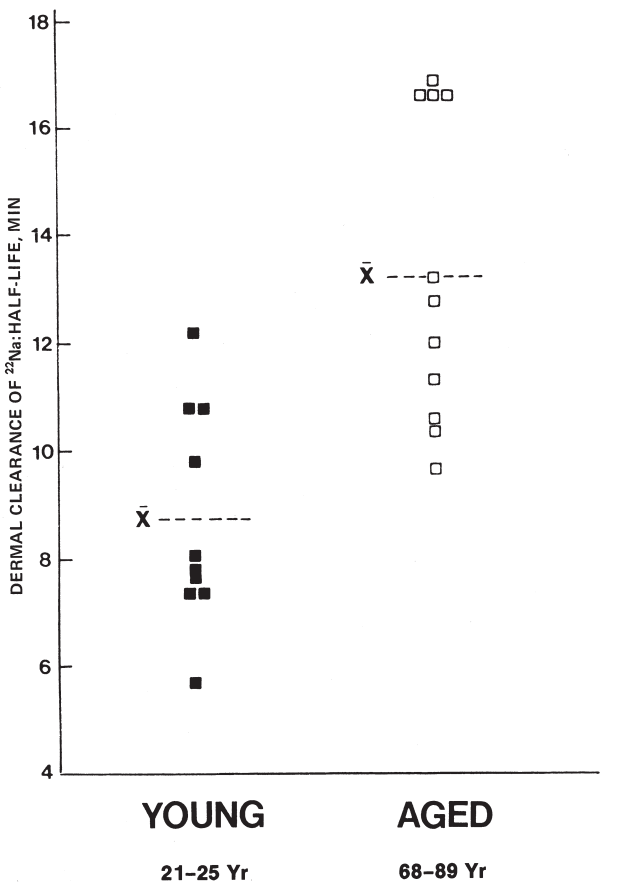

Figure 44-5. Dermal clearance of ^{22}Na in young and aged subjects after intradermal injection. (Data from Christophers E, Kligman AM. In Montagna W, ed. *Advances in the Biology of Skin,* vol 6. Oxford: Pergamon, 1965, p 163.)

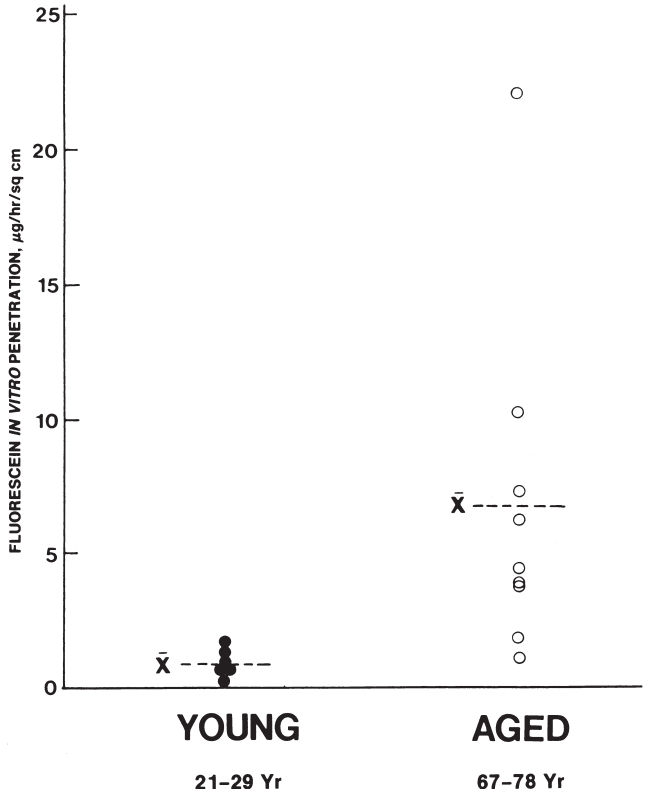

Figure 44-6. Flux of fluorescein through stratum corneum excised from young and aged subjects (Data from Christophers E, Kligman AM. In Montagna W, ed. *Advances in the Biology of Skin,* vol 6. Oxford: Pergamon, 1965, p 163.)

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,[20] for example, synthesized 7-acyloxymethyl derivatives of theophylline that diffuse through the skin far more efficiently than theophylline itself (Fig 44-7[20]) but which are biotransformed rapidly to theophylline. Thus, theophylline delivery to systemic circulation can be enhanced substantially.

Further Considerations for Transdermal Drug Delivery

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.

In Silico Methods

In recent years, *in silico* or *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 that 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.

RECTAL ABSORPTION

The bioavailability of rectally administered drugs is a relatively recent concern despite the antiquity of this dosage form; little was known about drug absorption or drug activity via suppository administration until recent years. Rectally instilled preparations, whether suppositories, 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.[21] 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, and the physicochemical properties of the drug.

ANORECTAL PHYSIOLOGY—The rectum is about 150 mm in length, terminating in the anal opening; its surface area is about 200 to 400 cm^2. In the absence of fecal matter the rec-

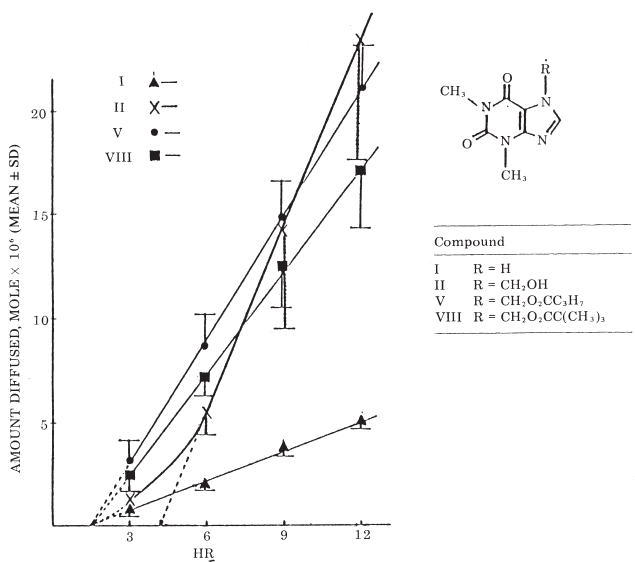

Figure 44-7. Diffusion of theophylline (I) and its derivatives through hairless mouse skin. (From Sloan KB, Bodor N. *Int J Pharm* 1982;12:299.)

tum contains a small amount of fluid (1 to 3 mL) 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. Bottger et al [22] studied the influence of pH on the rectal absorption of sodium benzoate in man by the technique of rectal lumen perfusion. This study demonstrates that strong buffers in rectal solutions induce a drastic effect on the pH of the boundary layer, an effect that is not seen if unbuffered solutions are used.

Most rectal suppositories today are torpedo-shaped, with the apex, or pointed end, tapering to the base, or blunt end, following the recommendation of HS Wellcome in 1893 that rectal suppositories should be inserted with the thicker end foremost so that when the anal sphincter contracts, expulsion is prevented. In the intervening 100 years or so, no study has correlated rectal suppository insertion with anorectal physiology until that of Abd-El-Maeboud et al,[23] who found that ease of insertion, retention, and lack of expulsion were enhanced when the suppository was inserted base or blunt end up. This was ascribed to reversed vermicular contractions of the external anal sphincter, which facilitate movement of the suppository upward into the rectum.

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 are 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.[24]

Parrott[25] 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 depends 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 partition and 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, assuming rapid dissolution, the rate-limiting step in absorption would be transport of the drug through the rectal mucosa.

In the absence of evidence of any substantial carrier-mediated uptake mechanisms, the predominant mechanism of colorectal mucosal permeation appears to involve transcellular passage across cell membranes in accordance with the pH-partition hypothesis. Ease of access to the rectal mucosa has encouraged the evaluation of absorption enhancers. 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 that 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 then must 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 endpoints, 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) near the anterior fornix and the highest (pH ~5) near the cervix.[26]

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[27] 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,[28,29] as well as the marketing of an intrauterine progesterone drug delivery system (Progestasert, *Alza*), has 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.

DOSAGE FORMS AND DRUG DELIVERY SYSTEMS FOR TOPICAL APPLICATION

The array of formulations and compositions employed for topical application confounds attempts at categorization. Nonetheless, if a distinction is made between drug *dosage forms* and drug *delivery systems*, some clarity emerges. **Dosage forms** contain the active drug ingredient in association with nondrug (usually inert) excipients that comprise the vehicle or formulation matrix. A conventional dosage form tends to be empirical in composition; its formulator's focus tends to emphasize stability and esthetics rather than efficacy. On the other hand, **delivery systems** involve a holistic approach to formulation that is optimized for the drug's relevant biopharmaceutic and pharmacokinetic characteristics in the patient population. Thus, a delivery system is formulated with functionality and efficacy in mind, not just stability and esthetics.

The Skin

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 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 endpoint 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, intended product use, site of application, and product type must be combined in a dosage form or delivery system that will release the drug readily when placed in contact with the skin. Further, the release characteristics of the vehicle depend on the physical-chemical properties of the specific drug substance to be delivered to the skin: drug release from a vehicle is a function of the drug's concentration and solubility in the vehicle, and the drug's partition coefficient between the vehicle and the skin. A vehicle optimized for delivery of hydrocortisone may be quite inappropriate for delivery of a different steroid.

Higuchi (see *Bibliography*) discussed equations describing the rate of release of solid drugs suspended in ointment bases. Ostrenga et al[30] discussed the significance of vehicle composition on the percutaneous absorption of fluocinolone acetonide and fluocinolone acetonide 21-acetate (fluocinonide) (Fig 44-8). 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

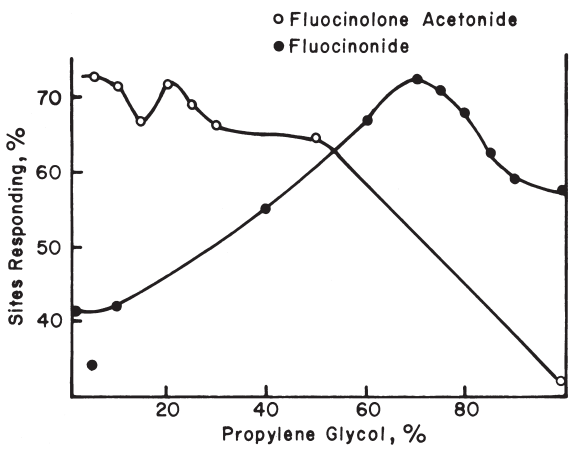

Figure 44-8. *In vivo* response as a function of vehicle composition (24-hour vasoconstriction). (From Ostrenga J, Steinmetz C, Poulsen B. *J Pharm Sci* 1971;60:1175.)

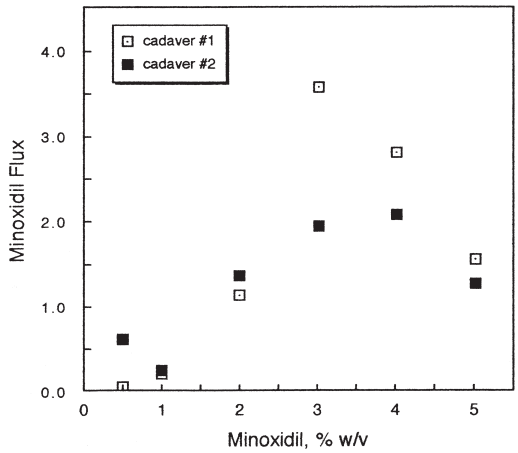

Figure 44-9. Minoxidil flux (x10^4 mg/cm^2/h) through human cadaver skin as a function of minoxidil concentration in the topically applied formulation. (Data from Flynn GL, Weiner ND, et al. *Int J Pharm* 1989;55:229.)

> "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 Figure 44-8, taken from Ostrenga, Steinmetz, and Poulsen.[30]

Experimental work of the kind described by Ostrenga, Steinmetz, and Poulsen 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.

The work of Flynn, Weiner, and others[31] on the physicochemical stability of topical drug-delivery systems *postapplication* has facilitated the exploration of additional formulation factors that are crucial to the success of topical formulations. Flynn notes that the functionality of topical drug delivery systems stands in stark contrast to those of transdermal drug-delivery systems; while both delivery systems are open systems *kinetically* due to the formulation-skin interface, they differ to a considerable extent *thermodynamically* because most topical formulations are left open to the air postapplication, while transdermal delivery systems are self-contained closed systems.

One study focused on a topical delivery system for minoxidil. The vehicle was 60:20:20 ethanol:propylene glycol:water system, with just enough propylene glycol to maintain 2% minoxidil in solution, following the evaporation of the more volatile ethanol and water. Minoxidil fluxes across human cadaver skin, measured as a function of minoxidil concentration, increased as the initial concentration of drug increased, but only to about 3% (Fig 44-9). [31] At initial minoxidil concentrations greater than 3%, transport was disproportionately low, relative to initial concentration, due to early precipitation of the drug.

Evaporation and loss of volatile formulation components such as water or ethanol postapplication can be expected to affect topical drug-delivery system composition and performance. Flynn et al[31] have shown that so-called nonvolatile excipients (eg, propylene glycol) evaporate after topical application. Skin permeation by excipients also may occur after application lead-

ing to further compositional changes in the applied film on the skin surface. The impact of this evaporative and absorptive loss of adjuvants increases as the volume of the applied formulation is reduced. As Flynn et al[31] note, ". . . the momentary compositions, and thus delivery capabilities, of real vehicles are significantly influenced by the amounts applied."

TOPICAL DOSAGE FORMS

OINTMENTS—The USP defines ointments as semisolid preparations intended for external application to the skin or mucous membranes. They usually, but not always, contain medicinal substances. The types of ointment bases used as vehicles for drugs are selected or designed to facilitate drug transfer into the skin. Ointments also contribute emolliency or other quasi-medicinal benefits.

USP Classification and Properties of Ointment Bases

The USP recognizes four general classes of ointment bases: hydrocarbon bases (ie, oleaginous bases), absorption bases, water-removable bases, and water-soluble bases. These various bases are contrasted with one another in Table 44-4. The selection of the optimum vehicle based on the USP classification *per se* may require compromises. For example, stability or drug activity might be superior in a hydrocarbon base; however, patient 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. For some drugs, 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. In other instances, activity and percutaneous absorption may be enhanced by using a hydrophilic base. These problematic aspects of bioavailability of drugs in topical formulations are discussed above.

HYDROCARBON (OLEAGINOUS) 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 polyethylene 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. These 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°C to 60°C; 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 or emollient effect. Skin hydration on the other hand may increase drug activity as discussed earlier.

A gelled mineral oil vehicle (Plastibase) represents a unique member of this class of bases that comprises refined natural products: When approximately 5% of low-density polyethylene is added to liquid petrolatum and the mixture then heated and subsequently 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°C. Excessive heat, ie, above 90°C, will destroy the gel structure.

On the basis of *in vitro* studies, drugs may be released faster from a gelled mineral oil vehicle than from conventional petrolatum. This quicker release has been attributed to easier diffusion of drug through a vehicle with lower microscopic viscosity (ie, a vehicle that is essentially a liquid) than through 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 context refers only to the ability of the base to absorb water.

Hydrophilic Petrolatum USP is an anhydrous absorption base. Its 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 adds to the physical characteristics, particularly firmness and heat stability.

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 pronounced than with hydrocarbon bases.

Table 44-4. Classification and Properties of USP Ointment Bases

	HYDROCARBON BASE	ABSORPTION BASE	WATER-REMOVABLE BASE	WATER-SOLUBLE BASE
Example(s)	White Petrolatum, USP; White Ointment, USP	Hydrophilic Petrolatum, USP; Lanolin, USP	Hydrophilic Ointment, USP	Polyethylene Glycol Ointment, NF
Composition	Hydrocarbons	Anhydrous or W/O emulsion	O/W emulsion	Water-soluble constituents
Occlusiveness	High	Moderate to high	Low to moderate	Minimal
Principal Benefits or Uses	Maintains prolonged contact with application site; emollient effect	Allows incorporation of aqueous solutions; emollient effect	Water-washable; may be diluted with water; allows absorption of serous discharges	Water-washable; no water-insoluble residue

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 (WATER-WASHABLE) BASES— These bases are O/W emulsion bases, commonly referred to as creams, and 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 cosmetic chemistry the formulator of an emulsion base is faced with a bewildering array of potential ingredients. A glance at the cosmetic literature and such volumes as the Cosmetic, Toiletry and Fragrance Association's *International Cosmetic Ingredient Dictionary and Handbook* impresses one with the enormous number and variety of emulsion-base components, particularly surfactants and 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 or delivery systems. Furthermore, the likelihood of drug-excipient interactions, either physical or chemical, increases substantially (as does the cost) as the number of formulation components is increased. Thus the formulator of topical products should minimize the number of excipients in the formulation. Nonetheless, emulsion bases typically include antimicrobial preservatives, stabilizers (such as antioxidants, metal chelating agents, or buffers), and humectants (eg glycerin or propylene glycol), in addition to the emulsifiers, in order to ensure stability and efficacy.

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.

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 (PEGs). Patch tests have shown that these compounds are innocuous, and long-term use has confirmed their lack of irritation. PEGs are relatively inert, non-volatile, water-soluble or water-miscible liquids or waxy solids identified by numbers that are an approximate indication of molecular weight. Polyethylene glycol 400 is a liquid superficially similar to propylene glycol, while polyethylene glycol 6000 is a waxy solid.

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 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. The water-solubility of polyethylene glycol vehicles does not ensure availability of drugs contained in the vehicle. As hydrated stratum corneum is an important factor in drug penetration, the use of polyethylene glycol vehicles, which are anhydrous and nonocclusive, actually may hinder percutaneous absorption due to dehydration of the stratum corneum.

Aqueous gel vehicles containing water, propylene, and/or polyethylene glycol and gelled with a carbomer or a cellulose derivative also are classed as water-soluble bases. Bases of this kind, sometimes referred to as gels, may be formulated to optimize delivery of a drug, particularly steroids. In such a preparation, propylene glycol is often used for its solvent properties as well as for its antimicrobial or preservative effects.

Gelling agents used in these preparations may be nonionic or anionic. Nonionics include cellulose derivatives, such as methylcellulose or hypromellose (hydroxypropyl methylcellulose). Sodium carboxymethylcellulose is an anionic cellulose derivative.

Carbomers are the USP designation for various polymeric acrylic acids, crosslinked with carbohydrates or polyalcohol derivatives, that are dispersible but insoluble in water. When the acid dispersion is neutralized with a base a clear, stable gel is formed. Carbomers for which monographs appear in the USP include carbomers 910, 934, 934P, 940, 941, and 1342, as well as the more complex carbomer copolymer and carbomer interpolymer.

Other gelling agents employed in topical formulations include sodium alginate and the propylene glycol ester of alginic acid (Kelcoloid). 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.

Gels can also be formed or stabilized by the incorporation of finely divided solids such as colloidal magnesium aluminum silicate (Veegum) or colloidal (fumed) silicon dioxide (Aerosil, Cab-O-Sil). These inorganic particulates can function as emulsifiers and suspending agents, as well as gellants. Their compatibility with alcohols, acetone, and glycols makes them particularly useful in topical gel formulations.

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 the drug uniformly throughout the vehicle). Normally, the drug materials are either in finely powdered form or in solution before being dispersed in the vehicle.

Incorporation of Drug by Levigation

The incorporation of a drug powder in small quantities of an ointment (ie, 30-90 g) can be accomplished by using a spatula and an ointment tile (either porcelain or glass). The drug material is levigated thoroughly with a small quantity of the vehicle or a miscible liquid component of the formulation (eg, propylene glycol; light mineral oil) to form a concentrate. The concentrate then is diluted geometrically with the remainder of the base.

If the drug substance is water-soluble it can be dissolved in water and the resulting solution incorporated into the vehicle by use of 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.

On a larger scale, mechanical mixers (eg, Hobart mixers, pony mixers) are used. 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 ensure complete dispersion and reduce any aggregates.

An alternative procedure involves preparing and milling 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 Formulations

Emulsions are prepared generally by combining the "oil"-soluble ingredients (eg, petrolatum, waxes, fats) and heating the admixture to about 75°C (ie, a temperature at which the oil-phase ingredients are molten). The "water"-soluble ingredients

are combined separately and heated to slightly above 75°C. 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°C. 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.

IRRITANCY TESTING OF TOPICAL PRODUCTS

Ointment bases may cause irritant or allergic reactions. Allergic reactions are usually due 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 animals and in man. The consequences of species differences and specificity must be included in the evaluation of animal-test results.

In the past, the most common method for evaluating irritancy was the Draize dermal irritation test in rabbits. In this procedure the test material was applied repeatedly to the clipped skin on the rabbit's back. Endpoints were dermal erythema and/or edema. The assignment of numerical scores for erythema and edema enabled the mathematical and statistical analysis of results.

In the human, a variety of test procedures are used to measure irritancy, sensitization potential, and phototoxicity. Among the most common are the 21-day cumulative irritancy patch test, the Draize-Shelanski repeat-insult patch test, and the Kligman "maximization" test.

21-DAY CUMULATIVE IRRITANCY PATCH TEST—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 are repeated daily for 21 days or until irritation produces a predetermined maximum score. Typical erythema scores range from 0 (no visible reaction) to 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 hours. The challenge sites are read on removal of the patch and again 24 hours 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 hours 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, do not automatically 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 Kligman "maximization" is a potent sensitizer, yet the incidence of sensitization among acne patients is low.

THE EVOLUTION OF TRANSDERMAL DRUG DELIVERY SYSTEMS

Conventional medicated topicals (eg, creams and ointments) seldom permit substantial systemic uptake of the drug or drugs incorporated therein. This is a consequence, in part, of the limited persistence or residence time of the topical formulation on the skin surface. In effect, a drug does not remain in contact with the absorbing surface long enough for sufficient drug to transfer into the skin and, ultimately, into systemic circulation. Furthermore, there is the concomitant problem of the gradual depletion of drug from the region of the topical formulation immediately adjacent to the skin surface and the corresponding reduction in the concentration gradient for drug transfer from the topical formulation to the skin.

The emergence of adhesive transdermal drug-delivery systems (TDDSs) in the early 1980s permitted skin residence times to increase from hours to days. The novel matrix- or reservoir-formulations employed in these TDDSs also provided for the maintenance of relatively uniform concentrations of diffusible drug in the formulation, thereby preventing the formation of drug-depleted regions within the topical formulation and helping to ensure relatively constant drug-release rates. As noted above, skin occlusion by the water-impermeable backing film of TDDSs further facilitates TDDS systemic efficacy by increasing skin hydration and temperature with a corresponding increase in the rate and extent of skin permeation. The inclusion of skin-penetration enhancers in medicated topicals serves to decrease diffusional resistance and increase transport.

Nonetheless, these—by now—*conventional* TDDSs have their limitations: the increased residence time of occlusive TDDSs on the skin surface leads to an increased incidence of skin maceration and adverse cutaneous reactions. In addition, effective skin permeation is limited to relatively small (<1 kD), lipophilic drug molecules. Thus, increasingly more attention is being placed on alternative TDDSs—eg, electrically modulated systems and mechanical systems—which circumvent the need for partitioning and diffusion of the drug out of the formulation matrix and into and through the skin:

Electrically modulated systems, or *electrotransport* systems, facilitate drug transport by an external electrical field. Electrotransport mechanisms include *iontophoresis, electroosmosis,* or *electroporation*.

Mechanically (physically) *modulated* systems are exemplified by systems employing *phonophoresis* or those using *microneedle arrays* to achieve transdermal drug delivery.

ELECTRICALLY MODULATED DRUG DELIVERY THROUGH THE SKIN[32,33]—For some poorly absorbed (ionic) compounds, parenteral administration appears to be the only viable option for regional or systemic delivery, as chemical penetration enhancers (Table 44-3) 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 seconds), 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.

Problematic aspects of electrotransport include cutaneous irritation or erythema and the effect of the electrical field on the integrity and stability of the formulation. Electrically induced alterations in the formulation generally arise as a result of iontophoresis (due to the increased flux of ions) or electroosmosis (due to the electrically induced convective transport of water molecules and associated electrically neutral solutes).[34,35] The use of pulsed or intermittent current electrotransport systems has been suggested as an alternative to continuous current systems. *Electroporation*—the use of pulsed electrical current to provoke the transient formation of pores in biomembranes—also has been suggested as an alternative, or complement, to iontophoresis. In any event, the potential of electrically modulated drug-delivery systems for the effective transdermal delivery of large, polar or ionic molecules (eg, proteins, peptides, DNA) necessitates continued research in this field. One encouraging advance in this area is the development of flexible wafer-thin arrays of conductive layers or filaments for drug delivery systems that are less bulky and potentially more acceptable to patients.

MECHANICALLY MODULATED DRUG DELIVERY— *Phonophoresis,* or *sonophoresis,* is defined as the movement of drug molecules through the skin under the influence of ultrasound. In general, ultrasound frequencies of 1–3 MHz and intensities of 0.01–2 W/cm^2 have been used with varying degrees of effectiveness,[36] although high-frequency, low-intensity ultrasound has been observed to increase transdermal drug flux and decrease percutaneous diffusional lag times.[37] A more recent analysis of ultrasound-enhanced transdermal transport indicates that low-frequency sonophoresis is much more important than high-frequency sonophoresis in enhancing transport.[38] Various thermal and nonthermal changes have been implicated to explain phonophoretically induced increases in drug transport through the skin. Although the effect of temperature increases on molecular diffusivity and flux is clear, nonthermal effects of ultrasound (eg, cavitation) are less clear. Transient ultrasound-induced cavitation (ie, the generation and oscillation of gas bubbles) in the stratum corneum apparently perturbs barrier permeability and solute transport in the aqueous regions of the stratum corneum. Evidence for this is the lack of correlation between phonophoretic permeability and permeant lipophilicity.

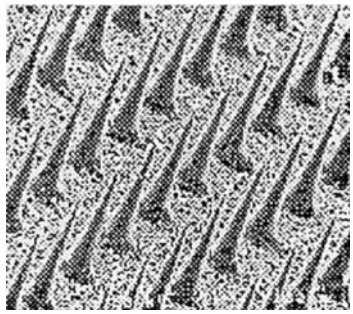

Figure 44-10. Electron micrograph of a microneedle array for transdermal drug delivery (courtesy, Georgia Institute of Technology; ©Georgia Tech Res Corp.).

Silicon microneedle arrays[39] have been proposed recently as painless adjuncts to transdermal delivery systems. The 150-μm long needles (Fig 44-10) can penetrate the stratum corneum, thereby facilitating drug access to the living epidermis and dermis and ultimately to systemic circulation. The needles—prepared by reactive ion etching microfabrication techniques originally developed for integrated circuits—leave holes about 1 μm in diameter when removed from the skin.

SUPPOSITORIES

Suppositories are solid dosage forms of various weights and shapes, usually medicated, for insertion into the rectum, vagina, or urethra. After insertion, suppositories soften, melt, disperse, 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.

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 g.

VAGINAL SUPPOSITORIES—The USP describes vaginal suppositories, or pessaries, 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, or inserts prepared by encapsulation in soft gelatin, however, do meet the definition and represent convenience both of administration and manufacture.

URETHRAL SUPPOSITORIES—Urethral suppositories, or bougies, are not described specifically in the USP, either by weight or dimension. Traditional values, based on the use of cocoa butter as a 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. An intraurethral insert containing the prostaglandin alprostadil is available for the treatment of erectile dysfunction. The commercial formulation, described as a sterile micropellet (1.4 mm in diameter and 6 mm long) consisting of the drug and polyethylene glycol 1450 is inserted 3 cm deep into the urethra by use of a hollow applicator.

SUPPOSITORY VEHICLE—The ideal suppository base should meet the following general specifications:

- The base is nontoxic and nonirritating to mucous membranes.
- The base is compatible with a variety of drugs.
- The base melts or dissolves in rectal fluids.
- The base should be stable on storage; it should not bind or otherwise interfere with release or absorption of drug substances.

Rectal suppository bases can be classified broadly into two types: fatty and water-soluble or water-miscible. The traditional cocoa butter vehicle is immiscible with aqueous tissue fluids but melts at body temperature. Water-soluble or water-miscible vehicles also have been used. In general, formulators have been reluctant to use glycerinated gelatin as a rectal suppository base because of its relatively slow dissolution. More typical of this class is the polyethylene glycol vehicle. Drug absorption from such dissimilar bases can differ substantially. Lowenthal and Borzelleca[40] 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 composed 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.

SUPPOSITORY BASES

The USP lists the following as usual suppository bases: cocoa butter, cocoa butter substitutes (primarily, vegetable oils modified by esterification, hydrogenation, and/or fractionation), glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights, and fatty acid esters of polyethylene glycol.

COCOA BUTTER AND OTHER FATTY BASES—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. Oleaginous vehicles, such as cocoa butter, seldom are used in vaginal preparations for esthetic reasons: many women consider them messy and prone to leakage.

If, in the preparation of suppositories, the theobroma oil is overheated, ie, heated to about 60°C, molded, and chilled, the suppositories formed will melt below 30°C. The fusion treatment of theobroma oil requires maximum temperatures of 40 to 50°C to avoid a change in crystal form and melting point. Theobroma oil, heated to about 60°C and cooled rapidly, will crystallize in an alpha configuration characterized by a melting point below 30°C. The alpha form is metastable and will slowly revert to the beta form, with the characteristic melting point approaching 35°C. 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 these 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.

Various cocoa butter substitutes (hard fat, hydrogenated vegetable oil) are available commercially that offer a number of advantages over cocoa butter such as decreased potential for rancidity and phase transition (melting and solidification) behavior tailored to specific formulation, processing, and storage requirements. However, as with cocoa butter, these semisynthetic glyceride mixtures are also subject to polymorphic transformations. Batch-to-batch variations of the physical properties of all of these bases, whether cocoa butter or cocoa butter substitutes, can play havoc with the final products' characteristics. The formulator should ensure that the melting and congealing behavior of these bases and the formulations prepared from them is evaluated thoroughly.

WATER-SOLUBLE OR DISPERSIBLE SUPPOSITORY BASES—Water-miscible suppository bases are of comparatively recent origin. The majority are composed 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, while prepared rather easily by molding, cannot be prepared satisfactorily by hand-rolling. 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. The USP advises that labels on polyethylene glycol suppositories should instruct patients to moisten the suppository before inserting it.

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.

PEG-based water-miscible suppository bases, devised by Collins, Hohmann, and Zopf,[41] are exemplified by a low-melting formulation employing 96% PEG 1000 and 4% PEG 4000 and a more heat-stable formulation with 75% PEG 1000 and 25% PEG 4000. Both may be 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.

HYDROGELS—In recent years, hydrogels, defined as macromolecular networks that swell but do not dissolve in water, have been advocated as bases for rectal and vaginal drug delivery. The swelling of hydrogels (ie, the absorption of water) is a consequence of the presence of hydrophilic functional groups attached to the polymeric network. Cross-links between adjacent macromolecules result in the aqueous insolubility of these hydrogels.

The use of a hydrogel matrix for drug delivery involves the dispersal of the drug in the matrix, followed by drying of the system and concomitant immobilization of the drug. When the hydrogel delivery system is placed in an aqueous environment (eg, the rectum or the vagina), the hydrogel swells, enabling the drug to diffuse out of the macromolecular network. The rate and extent of drug release from these hydrogel matrices depend on the rate of water migration *into* the matrix and the rate of drug diffusion *out of* the swollen matrix.

Hydrogels employed for rectal or vaginal drug administration have been prepared from polymers such as polyvinyl alcohol, hydroxyethyl methacrylate, polyacrylic acid, or polyoxyethylene. Although hydrogel-based drug-delivery systems have yet to appear in suppository or insert form commercially,

research efforts in this direction are increasing, given their potential for controlled drug delivery, bioadhesion, retention at the site of administration, and biocompatibility.

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%) then is 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 preparing 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:

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 that is kept between the mass and the hands during the kneading and rolling procedure. By quick, rotary movements of the hands, the mass is rolled to a ball, which immediately is placed on a pill tile. A suppository cylinder is formed by rolling the mass on the tile with a flat board, partially aided by the palm of the other hand, if weather conditions permit. The suppository *pipe* frequently will show a tendency to crack in the center, developing a hollow core. This occurs when the mass has not been kneaded and softened sufficiently, with the result that the pressure of the roller board is not carried uniformly throughout the mass but is exerted primarily on the surface. The length of the cylinder usually corresponds to about four spaces on the pill tile for each suppository, thus making the piece, when cut, practically a finished suppository except for the shaping of the point. When the cylinder has been cut into the proper number of pieces with a spatula, the conical shape is given it by rolling one end on the tile with a spatula, or in some cases even by shaping it with the fingers to produce a rounded point.

COMPRESSION-MOLDED (FUSED) SUPPOSITORIES—This method of suppository preparation also avoids heat. The suppository mass, such as a mixture of grated theobroma oil and drug, is forced into a mold under pressure, using a wheel-operated press. The mass is forced into mold openings, pressure is released, and 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.

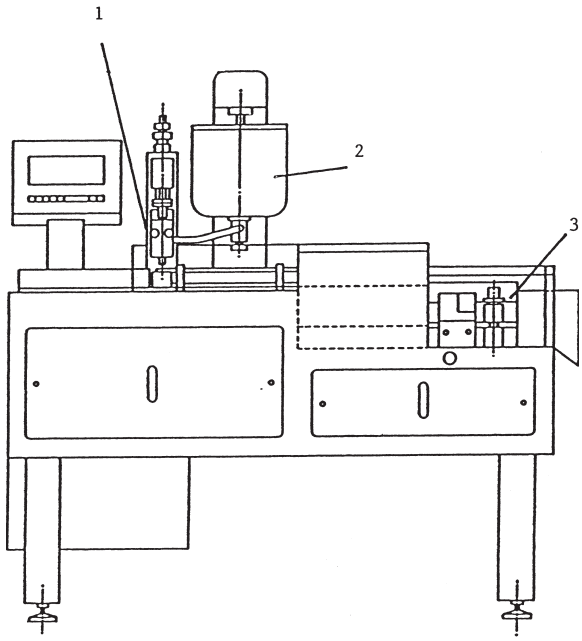

Figure 44-11. A cross-section of the Sarong SpA semiautomatic equipment for the production of suppositories in preformed plastic or foil shells. The fully jacketed piston-type *dosing pump* (1) meters the suppository melt in the jacketed tank (2) into preformed shells that pass directly beneath injection nozzles. The strips of filled preformed shells continue into a cooling chamber (3) prior to sealing and cartoning.

The method of choice for commercial suppository production (Fig 44-11) involves the automated filling of molds or preformed shells by a volumetric dosing pump that meters the melt from a jacketed kettle or mixing tank directly into the molds or shells. Strips of preformed shells pass beneath the dosing pump and are filled successively, passed through cooling chambers (to promote solidification), sealed, and then packaged. Quality control procedures (eg, weight, fill volume, leakage) are conducted readily *online*.

An alternative to the melt-and-pour processes described above is that of injection molding, which has been described by Snipes.[42] This process is distinctive in that it makes use of the injection-molding technique developed for the fabrication of plastics. Polyethylene glycols are the excipients of choice in this process, with polyethylene oxide, povidone, or silicon dioxide added to adjust viscosity or plasticity. Long-chain saturated carboxylic acids also have been added to reduce the hygroscopicity inherent with the use of the polyethylene glycols. Typically, the molten excipient admixture is extruded or injected under pressure into precision-machined multicavity molds, followed by the ejection of the molded units from the mold cavities. Advantages claimed for this method include the wide range of shapes and sizes that can be prepared at very high production rates with great precision.

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 compared with cocoa butter (see Table 44-5).[43,44] 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 44-5 indicates the density fac-

Table 44-5. Density Factors for Cocoa Butter Suppositories

MEDICATION	FACTOR	MEDICATION	FACTOR
Alum	1.7	Menthol	0.7
Aminophylline	1.1	Morphine HCl	1.6
Aminopyrine	1.3	Opium	1.4
Aspirin	1.3	Paraffin	1.0
Barbital	1.2	Peruvian balsam[a]	1.1
Belladonna extract	1.3	Phenobarbital	1.2
Benzoic acid	1.5	Phenol[a]	0.9
Bismuth carbonate	4.5	Potassium bromide	2.2
Bismuth salicylate	4.5	Potassium iodide	4.5
Bismuth subgallate	2.7	Procaine	1.2
Bismuth subnitrate	6.0	Quinine HCl	1.2
Boric acid	1.5	Resorcinol	1.4
Castor oil	1.0	Salicylic acid	1.3
Chloral hydrate	1.3	Sodium bromide	2.3
Cocaine HCl	1.3	Spermaceti	1.0
Digitalis leaf	1.6	Sulfathiazole	1.6
Gallic acid	2.0	Tannic acid	1.6
Glycerin	1.6	White wax	1.0
Ichthammol	1.1	Witch hazel fluidextract	1.1
Iodoform	4.0	Zinc oxide	4.0
		Zinc sulfate	2.8

[a] Density adjusted taking into account white wax in mass.
Data from Davis H. *Bentley's Text-Book of Pharmaceutics,* 7th ed. London: Bailliere, Tindall & Cox, 1961 and Buchi J. *Pharma Acta Helv* 1940;20:403.

tor, or the density 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 the densities of both 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 weights 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 x 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 jacket 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 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 that hold the suppositories upright. Glycerin and glycerinated gelatin suppositories often are packaged in tightly closed screwcapped glass containers. Though many commercial suppositories are wrapped individually in aluminum foil or PVC-polyethylene, strip-packaging is commonplace.

Alternatively, suppositories may be molded directly into their 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

Poultices (Cataplasms)

Poultices, or cataplasms, represent one of the most ancient classes of pharmaceutical preparations. A poultice 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

The USP defines pastes as semisolid dosage forms that contain one or more drug substances intended for topical application. Pastes are divided into fatty pastes (eg, Zinc Oxide Paste) and those made from a single-phase aqueous gel (eg, Carboxymethylcellulose Sodium Paste). Another official paste is Triamcinolone Acetonide Dental Paste.

The term *paste* is applied to ointments in which large amounts of solids have been incorporated (eg, Zinc Oxide Paste). In the past, pastes have been defined as concentrates of absorptive powders dispersed (usually) in petrolatum or hydrophilic petrolatum. These fatty pastes are stiff to the point of dryness and are reasonably absorptive considering they have a petrolatum base. Pastes often are used in the treatment of oozing lesions, where they act to absorb serous secretions. Pastes also are used to limit the area of treatment by acting both as an absorbent and a 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 may be removed from the skin by the use of mineral oil or a vegetable oil. This is particularly necessary when the underlying or surrounding skin is traumatized easily.

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 composed 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 to 75 μm). 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 in the USP 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 removal (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.

Preservatives in Topical Formulations

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 *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 tested for the presence of *P aeruginosa* and *S aureus*. In addition, products intended for rectal, urethral, or vaginal administration should be tested for yeasts and molds.

The attributes of an ideal preservative system have been defined by various authors as

- Effective at relatively low concentrations against a broad spectrum or variety of microorganisms that could cause disease or product deterioration
- Soluble in the required concentration
- Nontoxic and nonsensitizing at in-use concentrations
- Compatible with ingredients of the formulation and package components
- Free from objectionable odors and colors
- Stable over a wide range of conditions
- 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 more than 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 spite of concerns about contact sensitization, 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 topical formulations, together with comments on possible limitations, are given in Table 44-6.[45] It is probably sensible to

Table 44-6. Topical Preservatives: Benefits and Risks

PRESERVATIVES	LIMITATIONS RELATIVE TO USE IN COSMETIC/DERMATOLOGIC FORMULATIONS
Quaternary ammonium compounds	Inactivated by numerous ingredients including anionics, nonionics, and proteins
Organic mercurial compounds	Potentially toxic; many sensitize the skin Limited use in formulations used near or in the eye
Formaldehyde	Volatile compound with an objectionable odor Irritating to the skin High chemical reactivity
Halogenated phenols[a]	Objectionable odor Often inactivated by nonionics, anionics or proteins Limited gram-negative antibacterial activity
Sorbic acid, potassium sorbate	pH-dependent (can be used only in formulations below the pH of 6.5 to 7.0) Higher concentrations are oxidized by sunlight resulting in product discoloration Limited antibacterial activity
Benzoic acid, sodium benzoate	pH-dependent (limited to use in formulations with pH of 5.5 or less) Replaced by newer antimicrobials because of its limited antimicrobial activity

[a]eg, hexachlorophene, *p*-chloro-*m*-cresol (PCMC), *p*-chloro-*m*-xylenol (PCMX), dichloro-*m*-xylenol (DCMX).

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.

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.

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CHAPTER 45

Oral Solid Dosage Forms

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Drug substances most frequently are administered orally by means of solid dosage forms such as tablets and capsules. Large-scale production methods used for their preparation, as described later in the chapter, require the presence of other materials in addition to the active ingredients. Additives also may be included in the formulations to facilitate handling, enhance the physical appearance, improve stability, and aid in the delivery of the drug to the bloodstream after administration. These supposedly inert ingredients, as well as the production methods employed, have been shown in many cases to influence the absorption or bioavailability of the drug substances.[1] Therefore, care must be taken in the selection and evaluation of additives and preparation methods to ensure that the drug-delivery goals and therapeutic efficacy of the active ingredient(s) will not be diminished.

In a number of cases it has been shown that the drug substance's solubility and other physicochemical characteristics have influenced its physiological availability from a solid dosage form. These characteristics include its particle size, whether it is amorphous or crystalline, whether it is solvated or nonsolvated, and its crystalline, or polymorphic form. After clinically effective formulations are obtained, such variations among dosage units of a given batch, as well as batch-to-batch differences, should be reduced to a minimum through proper in-process controls and good manufacturing practices. The recognition of the importance of performance qualification, and validation for both equipment and processes has enhanced assurance in the reproducibility of solid dosage formulations greatly. It is in these areas that significant progress has been made with the realization that large-scale production of a satisfactory tablet or capsule depends not only on the availability of a clinically effective formulation but also on the raw materials, facilities, personnel, documentation, validated processes and equipment, packaging, and the controls used during and after preparation (Fig 45-1).

TABLETS

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and have been traditionally prepared by either compression, or molding methods. Recently, punching of laminated sheets, electronic deposition methods, and three-dimensional printing methods have been used to make tablets. Tablets have been in widespread use since the latter part of the 19th century, and their popularity continues. The term *compressed tablet* is believed to have been used first by John Wyeth and Brother of Philadelphia. During this same period, molded tablets were introduced to be used as *hypodermic* tablets for the extemporaneous preparation of solutions for injection. Tablets remain popular as a dosage form because of the advantages afforded both to the manufacturer (eg, simplicity and economy of preparation, stability, and convenience in packaging, shipping, and dispensing) and the patient (eg, accuracy of dosage, compactness, portability, blandness of taste, and ease of administration).

Although the basic mechanical approach for most tablet manufacture has remained the same, tablet technology has undergone great improvement and experimentation. Efforts are being made continually to understand more clearly the physical characteristics of powder compaction and the factors affecting the availability of the drug substance from the dosage form after oral administration. Tableting equipment continues to improve in both production speed and the uniformity of tablets compressed. Recent advances in tablet technology have been reviewed.[2–13]

Although tablets frequently are discoid in shape, they also may be round, oval, oblong, cylindrical, or triangular. Other geometric shapes, such as diamonds and pentagons, and hexagons have also been used. They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration. Most commercial tablets can be divided into two general classes by whether they are made by compression or molding. Compressed tablets usually are prepared by large-scale production methods, while molded tablets generally involve small-scale operations. The various tablet types and abbreviations used in referring to them are listed below.

COMPRESSED TABLETS (CT)—These tablets are formed by compression and in their simplest form, contain no special coating. They are made from powdered, crystalline, or granular materials, alone or in combination with binders, disintegrants, controlled-release polymers, lubricants, diluents, and in many cases colorants. The vast majority of tablets commercialized today are compressed tablets, either in an uncoated or coated state.

Sugar-Coated Tablets (SCT)—These are compressed tablets surrounded by a sugar coating. Such coatings may be colored and are beneficial in covering up drug substances possessing objectionable tastes or odors and in protecting materials sensitive to oxidation. These coatings were once quite common, and generally lost commercial appeal due to the high cost of process validation. Recently, they have made a comeback due to patient popularity and technical advances.

Film-Coated Tablets (FCT)—These are compressed tablets that are covered with a thin layer or film of a water-soluble material. A number of polymeric substances with film-forming properties may be used. Film coating imparts the same general characteristics as sugar coating,

Figure 45-1. Tablet press operators checking batch record in conformance with Current Good Manufacturing Practices (courtesy, Lilly).

with the added advantage of a greatly reduced time period required for the coating operation. Advances in material science and polymer chemistry has made these coatings the first-choice of formulators.

Enteric-Coated Tablets (ECT)—These are compressed tablets coated with substances that resist solution in gastric fluid but disintegrate in the intestine. Enteric coatings can be used for tablets containing drug substances that are inactivated or destroyed in the stomach, for those that irritate the mucosa, or as a means of delayed release of the medication.

Multiple Compressed Tablets (MCT)—These are compressed tablets made by more than one compression cycle. This process is best used when separation of active ingredients is needed for stability purposes, or if the mixing process is inadequate to guarantee uniform distribution of two or more active ingredients.

Layered Tablets—Such tablets are prepared by compressing additional tablet granulation on a previously compressed granulation. The operation may be repeated to produce multilayered tablets of two or three, or more layers. Special tablet presses are required to make layered tablets such as the Versa press *(Stokes/Pennwalt)*.

Press-Coated Tablets—Such tablets, also referred to as dry-coated, are prepared by feeding previously compressed tablets into a special tableting machine and compressing another granulation layer around the preformed tablets. They have all the advantages of compressed tablets (ie, slotting, monogramming, speed of disintegration) while retaining the attributes of sugar-coated tablets in masking the taste of the drug substance in the core tablets. An example of a press-coated tablet press is the *Manesty* Drycota. Press-coated tablets also can be used to separate incompatible drug substances; in addition, they can provide a means of giving an enteric coating to the core tablets. Both types of multiple-compressed tablets have been used widely in the design of prolonged-action dosage forms.

Controlled-Release Tablets (CRT)—Compressed tablets can be formulated to release the drug slowly over a prolonged period of time. Hence, these dosage forms have been referred to as *prolonged-release* or *sustained-release* dosage forms as well. These tablets (as well as capsule versions) can be categorized into three types: (1) those that respond to some physiological condition to release the drug, such as enteric coatings; (2) those that release the drug in a relatively steady, controlled manner; and (3) those that combine combinations of mechanisms to release *pulses* of drug, such as repeat-action tablets. The performance of these systems is described in more detail in Chapter 47. Other names for these types of tablets can be: *Extended Release, Sustained Release, Prolonged Release, Delayed Release*, and in the case of pulsatile tablets, *Repeat Action, Pulsatile Release* or *Pulse Release.*

Tablets for Solution (CTS)—Compressed tablets to be used for preparing solutions or imparting given characteristics to solutions must be labeled to indicate that they are not to be swallowed. Examples of these tablets are Halazone Tablets for Solution and Potassium Permanganate Tablets for Solution.

Effervescent Tablets—In addition to the drug substance, these contain sodium bicarbonate and an organic acid such as tartaric or citric. In the presence of water, these additives react, liberating carbon dioxide that acts as a distintegrator and produces effervescence. Except for small quantities of lubricants present, effervescent tablets are soluble.

Compressed Suppositories or Inserts—Occasionally, vaginal suppositories, such as Metronidazole tablets, are prepared by compression. Tablets for this use usually contain lactose as the diluent. In this case, as well as for any tablet intended for administration other than by swallowing, the label must indicate the manner in which it is to be used.

Buccal and Sublingual Tablets—These are small, flat, oval tablets. Tablets intended for buccal (the space between the lip and gum in the mouth) administration by inserting into the buccal pouch may dissolve or erode slowly; therefore, they are formulated and compressed with sufficient pressure to give a hard tablet. Progesterone tablets may be administered in this way. Some newer approaches have employed materials that act as bioadhesives to increase absorption of the drug.

Some other approaches use tablets that melt at body temperatures. The matrix of the tablet is solidified while the drug is in solution. After melting, the drug is automatically in solution and available for absorption, thus eliminating dissolution as a rate-limiting step in the absorption of poorly soluble compounds. Sublingual tablets, such as those containing nitroglycerin, isoproterenol hydrochloride, or erythrityl tetranitrate, are placed under the tongue. Sublingual tablets dissolve rapidly, and the drug substances are absorbed readily by this form of administration.

MOLDED TABLETS OR TABLET TRITURATES (TT)—Tablet triturates usually are made from moist material, using a triturate mold that gives them the shape of cut sections of a cylinder. Such tablets must be completely and rapidly soluble. The problem arising from compression of these tablets is the failure to find a lubricant that is completely water-soluble.

Dispensing Tablets (DT)—These tablets provide a convenient quantity of potent drug that can be incorporated readily into powders and liquids, thus circumventing the necessity to weigh small quantities. These tablets are supplied primarily as a convenience for extemporaneous compounding and should never be dispensed as a dosage form.

Hypodermic Tablets (HT)—Hypodermic tablets are soft, readily soluble tablets and originally were used for the preparation of solutions to be injected. Since stable parenteral solutions are now available for most drug substances, there is no justification for the use of hypodermic tablets for injection. Their use in this manner should be discouraged, since the resulting solutions are not sterile. Large quantities of these tablets continue to be made, but for oral administration. No hypodermic tablets ever have been recognized by the official compendia.

Compressed Tablets (CT)

For medicinal substances, with or without diluents, to be made into solid dosage forms with pressure, using available equipment, it is necessary that the material, either in crystalline or powdered form, possess a number of physical characteristics. These characteristics include the ability to flow freely, cohesiveness, and lubrication. The ingredients such as disintegrants designed to break the tablet up in gastrointestinal (GI) fluids and controlled-release polymers designed to slow drug release ideally should possess these characteristics or not interfere with the desirable performance traits of the other excipients. Since most materials have none or only some of these properties, methods of tablet formulation and preparation have been developed to impart these desirable characteristics to the material that is to be compressed into tablets.

The basic mechanical unit in all tablet-compression equipment includes a lower punch that fits into a die from the bottom and an upper punch, with a head of the same shape and dimensions, which enters the die cavity from the top after the tableting material fills the die cavity (Fig 45-2). The tablet is formed by pressure applied on the punches and subsequently is ejected from the die. The weight of the tablet is determined by the volume of the material that fills the die cavity. Therefore, the ability of the granulation to flow freely into the die is important in ensuring a uniform fill, as well as the continuous movement of the granulation from the source of supply or feed hopper. If the tablet granulation does not possess cohesive properties, the tablet after compression will crumble and fall apart on handling. As the punches must move freely within the

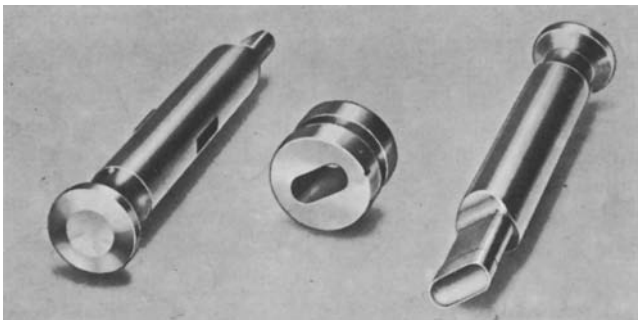


Figure 45-2. Basic mechanical unit for tablet compression: lower punch, die, and upper punch (courtesy, Vector/Colton).

die and the tablet must be ejected readily from the punch faces, the material must have a degree of lubrication to minimize friction and allow the removal of the compressed tablets.

There are three general methods typically used for commercial tablet preparation: the wet-granulation method, the dry-granulation method, and direct compression. The method of preparation and the added ingredients are selected to give the tablet formulation the desirable physical characteristics allowing the rapid compression of tablets. After compression, the tablets must have a number of additional attributes such as appearance, hardness, disintegration ability, appropriate dissolution characteristics, and uniformity, which also are influenced both by the method of preparation and by the added materials present in the formulation. In the preparation of compressed tablets, the formulator also must be cognizant of the effect that the ingredients and methods of preparation may have on the availability of the active ingredients and, hence, the therapeutic efficacy of the dosage form. In response to a request by physicians to change a dicumarol tablet so that it might be broken more easily, a Canadian company reformulated to make a large tablet with a score. Subsequent use of the tablet, containing the same amount of drug substance as the previous tablet, resulted in complaints that larger-than-usual doses were needed to produce the same therapeutic response. On the other hand, literature reports indicate that the reformulation of a commercial digoxin tablet resulted in a tablet that, although containing the same quantity of drug substance, gave the desired clinical response at half its original dose. Methods and principles that can be used to assess the effects of excipients and additives on drug absorption have been reviewed.[2,14,15]

TABLET INGREDIENTS

In addition to the active or therapeutic ingredient, tablets contain a number of inert materials. The latter are known as additives or *excipients*. They may be classified according to the part they play in the finished tablet. The first group contains those that help to impart satisfactory processing and compression characteristics to the formulation. These include diluents, binders, glidants, and lubricants. The second group of added substances helps to give additional desirable physical characteristics to the finished tablet. Included in this group are disintegrants, surfactants, colors, and, in the case of chewable tablets, flavors, and sweetening agents, and in the case of controlled-release tablets, polymers or hydrophobic materials, such as waxes or other solubility-retarding materials. In some cases, anti-oxidants or other materials can be added to improve stability and shelf-life.

Although the term *inert* has been applied to these added materials, it has become apparent that there is an important relationship between the properties of the excipients and the dosage forms containing them. Preformulation studies demonstrate their influence on stability, bioavailability, and the processes by which the dosage forms are prepared. The need for acquiring more information and use standards for excipients has been recognized in a joint venture of the Academy of Pharmaceutical Sciences and the Council of the Pharmaceutical Society of Great Britain. The result is called the *Handbook of Pharmaceutical Excipients*. This reference now is distributed widely throughout the world.[16]

Diluents

Frequently, the single dose of the active ingredient is small, and an inert substance is added to increase the bulk to make the tablet a practical size for compression. Compressed tablets of dexamethasone contain 0.75 mg steroid per tablet; hence, it is obvious that another material must be added to make tableting possible. Diluents used for this purpose include dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such tablets commonly are called *chewable tablets*. Upon chewing, properly prepared tablets will disintegrate smoothly at a satisfactory rate, have a pleasant taste and feel, and leave no unpleasant aftertaste in the mouth. Diluents used as excipients for direct compression formulas have been subjected to prior processing to give them flowability and compressibility. These are discussed under *Direct Compression.*

Most formulators of immediate-release tablets tend to use consistently only one or two diluents selected from the above group in their tablet formulations. Usually, these have been selected on the basis of experience and cost factors. However, in the formulation of new therapeutic agents, the compatibility of the diluents with the drug must be considered; eg, calcium salts used as diluents for the broad-spectrum antibiotic tetracycline have been shown to interfere with the drug's absorption from the GI tract. When drug substances have low water solubility, it is recommended that water-soluble diluents be used to avoid possible bioavailability problems. Highly adsorbent substances (eg, bentonite and kaolin) are to be avoided in making tablets of drugs used clinically in small dosage, such as the cardiac glycosides, alkaloids, and the synthetic estrogens. These drug substances may be adsorbed after administration. The combination of amine bases with lactose, or amine salts with lactose in the presence of an alkaline lubricant results in tablets that discolor on aging.

Microcrystalline cellulose (Avicel) usually is used as an excipient in direct-compression formulas. However, its presence in 5–15% concentrations in wet granulations has been shown to be beneficial in the granulation and drying processes in minimizing case-hardening of the tablets and in reducing tablet mottling.

Many ingredients are used for several different purposes, even within the same formulation (eg, cornstarch can be used in paste form as a binder). When added in drug or suspension form, it is a good disintegrant. Even though these two uses are to achieve opposite goals, some tablet formulas use cornstarch in both ways. In some controlled-release formulas, the polymer hydroxypropyl methylcellulose (HPMC) is used both as an aid to prolong the release from the tablet as well as a film-former in the tablet coating. Therefore, most excipients used in formulating tablets and capsules have many uses, and a thorough understanding of their properties and limitations is necessary to use them rationally.

Binders

Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators. They impart a cohesiveness to the tablet formulation that ensures the tablet remaining intact after compression, as well as improving the free-flowing qualities by the formulation of granules of desired hardness and size. Materials commonly used as binders include

starch, gelatin, and sugars such as sucrose, glucose, dextrose, molasses, and lactose. Natural and synthetic gums that have been used include acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, Veegum, and larch arabogalactan. Other agents that may be considered binders under certain circumstances are polyethylene glycol, ethylcellulose, waxes, water, and alcohol.

The quantity of binder used has considerable influence on the characteristics of the compressed tablets. The use of too much binder or too strong a binder will make a hard tablet that will not disintegrate easily and will cause excessive wear of punches and dies. Differences in binders used for CT Tolbutamide resulted in differences in hypoglycemic effects observed clinically. Materials that have no cohesive qualities of their own will require a stronger binder than those with these qualities. Alcohol and water are not binders in the true sense of the word, but because of their solvent action on some ingredients such as lactose, starch, and celluloses, they change the powdered material to granules, and the residual moisture retained enables the materials to adhere together when compressed.

Binders are used both as a solution and in a dry form, depending on the other ingredients in the formulation and the method of preparation. However, several *pregelatinized* starches available are intended to be added in the dry form so that water alone can be used as the granulating solution. The same amount of binder in solution will be more effective than if it were dispersed in a dry form and moistened with the solvent. By the latter procedure, the binding agent is not as effective in reaching and wetting each of the particles within the mass of powders. Each of the particles in a powder blend has a coating of adsorbed air on its surface, and it is this film that must be penetrated before the powders can be wetted by the binder solution. After wetting, a certain period of time is necessary to dissolve the binder completely and make it completely available for use. Since powders differ with respect to the ease with which they can be wetted and their rate of solubilization, it is preferable to incorporate the binding agent in solution. By this technique it often is possible to gain effective binding with a lower concentration of binder.

The direct-compression method for preparing tablets requires a material that is not only free-flowing but also sufficiently cohesive to act as a binder. This use has been described for a number of materials including microcrystalline cellulose, microcrystalline dextrose, amylose, and polyvinylpyrrolidone. It has been postulated that microcrystalline cellulose is a special form of cellulose fibril in which the individual crystallites are held together largely by hydrogen bonding. The disintegration of tablets containing the cellulose occurs by breaking the intercrystallite bonds by the disintegrating medium.

STARCH PASTE—Cornstarch is used widely as a binder. The concentration may vary from 10% to 20%. It usually is prepared as it is to be used, by dispersing cornstarch in sufficient cold purified water to make a 5–10% *w*/*w* suspension and warming in a water bath with continuous stirring until a translucent paste forms. It has been observed that during paste formation, not all of the starch is hydrolyzed. Starch paste then is not only useful as a binder, but also as a method to incorporate some disintegrant inside the granules.

GELATIN SOLUTION—Gelatin generally is used as a 10–20% solution; gelatin solutions should be prepared freshly as needed and used while warm or they will solidify. The gelatin is added to cold purified water and allowed to stand until it is hydrated. It then is warmed in a water bath to dissolve the gelatin, and the solution is made up to the final volume on a weight basis to give the concentration desired.

CELLULOSIC SOLUTIONS—Various cellulosics have been used as binders in solution form. Hydroxypropyl methylcellulose (HPMC) has been used widely in this regard. Typical of a number of cellulosics, HPMC is more soluble in cold water than hot. It also is more dispersable in hot water than cold. Hence, to obtain a good, smooth gel that is free from lumps or *fisheyes,* it is necessary to add the HPMC in hot, almost boiling water and, under agitation, cool the mixture down as quickly as possible, as low as possible. Other water-soluble cellulosics such as hydroxyethylcellulose (HEC) and hydroxypropylcellulose (HPC) have been used successfully in solution as binders.

Not all cellulosics are soluble in water. Ethylcellulose can be used effectively when dissolved in alcohol or as a dry binder that then is wetted with alcohol. It is used as a binder for materials that are moisture-sensitive.

POLYVINYLPYRROLIDONE—PVP can be used as an aqueous or alcoholic solution, and this versatility has increased its popularity. Concentrations range from 2% and vary considerably.

It will be noted that binder solutions usually are made up to weight rather than volume. This is to enable the formulator to determine the weight of the solids that have been added to the tablet granulation in the binding solution. This becomes part of the total weight of the granulation and must be taken into consideration in determining the weight of the compressed tablet, which will contain the stated amount of the therapeutic agent.

As can be seen by the list of binders in this chapter, most modern binders used in solution are polymeric. Because of this, the flow or spreadability of these solutions becomes important when selecting the appropriate granulating equipment. The rheology of polymeric solutions is a fascinating subject in and of itself and should be considered for these materials.

Lubricants

Lubricants have a number of functions in tablet manufacture. They prevent adhesion of the tablet material to the surface of the dies and punches, reduce interparticle friction, facilitate the ejection of the tablets from the die cavity, and may improve the rate of flow of the tablet granulation. Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, glyceryl behanate, hydrogenated vegetable oils, and polyethylene glycol (PEG). Most lubricants, with the exception of talc, are used in concentrations below 1%. When used alone, talc may require concentrations as high as 5%. Lubricants are in most cases hydrophobic materials. Poor selection or excessive amounts can result in *waterproofing* the tablets, resulting in poor tablet disintegration and/or delayed dissolution of the drug substance.

The addition of the proper lubricant is highly desirable if the material to be tableted tends to stick to the punches and dies. Immediately after compression, most tablets have the tendency to expand and will bind and stick to the side of the die. The choice of the proper lubricant will overcome this effectively.

The method of adding a lubricant to a granulation is important if the material is to perform its function satisfactorily. The lubricant should be divided finely by passing it through a 60- to 100-mesh nylon cloth onto the granulation. In production this is called *bolting* the lubricant. After adding the lubricant, the granulation is tumbled or mixed gently to distribute the lubricant without coating the particles too well or breaking them down to finer particles. Some research has concluded that the order of mixing of lubricants and other excipients can have a profound effect on the performance of the final dosage form. Thus, attention to the mixing process itself is just as important as the selection of lubricant materials.

These process variables can be seen in the prolonged blending of a lubricant in a granulation. Overblending materially can affect the hardness, disintegration time, and dissolution performance of the resultant tablets.

The quantity of lubricant varies, being as low as 0.1% and, in some cases, as high as 5%. Lubricants have been added to the granulating agents in the form of suspensions or emulsions. This technique serves to reduce the number of operational procedures and thus reduce the processing time.

In selecting a lubricant, proper attention must be given to its compatibility with the drug agent. Perhaps the most widely in-

vestigated drug is acetylsalicylic acid. Different talcs varied significantly the stability of aspirin. Talc with a high calcium content and a high loss on ignition was associated with increased aspirin decomposition. From a stability standpoint, the relative acceptability of tablet lubricants for combination with aspirin was found to decrease in the following order: hydrogenated vegetable oil, stearic acid, talc, and aluminum stearate.

The primary problem in the preparation of a water-soluble tablet is the selection of a satisfactory lubricant. Soluble lubricants reported to be effective include sodium benzoate, a mixture of sodium benzoate and sodium acetate, sodium chloride, leucine, and polyethylene glycol/Carbowax 4000. However, it has been suggested that formulations used to prepare water-soluble tablets may represent a number of compromises between compression efficiency and water solubility. While magnesium stearate is one of the most widely used lubricants, its hydrophobic properties can retard disintegration and dissolution. To overcome these waterproofing characteristics, sodium lauryl sulfate sometimes is included. One compound found to have the lubricating properties of magnesium stearate without its disadvantages is magnesium lauryl sulfate. Its safety for use in pharmaceuticals has not been established.

Glidants

A glidant is a substance that improves the flow characteristics of a powder mixture. These materials always are added in the dry state just prior to compression (ie, during the lubrication step). Colloidal silicon dioxide Cab-o-sil *(Cabot)* is the most commonly used glidant and generally is used in low concentrations of 1% or less. Talc (asbestos-free) also is used and may serve the dual purpose of lubricant/glidant.

It is especially important to optimize the order of addition and the mixing process for these materials, to maximize their effect and to make sure that their influence on the lubricant(s) is minimized.

Disintegrants

A disintegrant is a substance or a mixture of substances added to a tablet to facilitate its breakup or disintegration after administration. The active ingredient must be released from the tablet matrix as efficiently as possible to allow rapid dissolution. Materials serving as disintegrants have been classified chemically as starches, clays, celluloses, algins, gums, and cross-linked polymers.

The oldest and still the most popular disintegrants are corn and potato starch that have been well dried and powdered. Starch has a great affinity for water and swells when moistened, thus facilitating the rupture of the tablet matrix. However, others have suggested that its disintegrating action in tablets is due to capillary action rather than swelling; the spherical shape of the starch grains increases the porosity of the tablet, thus promoting capillary action. Starch, 5%, is suggested, but if more rapid disintegration is desired, this amount may be increased to 10% or 15%. Although it might be expected that disintegration time would decrease as the percentage of starch in the tablet increased, this does not appear to be the case for tolbutamide tablets. In this instance, there appears to be a critical starch concentration for different granulations of the chemical. When their disintegration effect is desired, starches are added to the powder blends in the dry state.

A group of materials known as *super disintegrants* have gained in popularity as disintegrating agents. The name comes from the low levels (2–4%) at which they are completely effective. Croscarmellose, crospovidone, and sodium starch glycolate represent examples of a cross-linked cellulose, a cross-linked polymer, and a cross-linked starch, respectively.

The development of these disintegrants fostered new theories about the various mechanisms by which disintegrants work. Sodium starch glycolate swells 7- to 12-fold in less than 30 sec. Croscarmellose swells 4- to 8-fold in less than 10 sec. The starch swells equally in all three dimensions, while the cellulose swells only in two dimensions, leaving fiber length essentially the same. Since croscarmellose is the more efficient disintegrating agent, it is postulated that the rate, force, and extent of swelling play an important role in those disintegrants that work by swelling. Cross-linked PVP swells little but returns to its original boundaries quickly after compression. Wicking, or capillary action, also is postulated to be a major factor in the ability of cross-linked PVP to function.[17–19]

In addition to the starches, a large variety of materials have been used and are reported to be effective as disintegrants. This group includes Veegum HV, methylcellulose, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp, and carboxymethylcellulose.[20] Sodium lauryl sulfate in combination with starch also has been demonstrated to be an effective disintegrant. In some cases the apparent effectiveness of surfactants in improving tablet disintegration is postulated as due to an increase in the rate of wetting.

The disintegrating agent usually is mixed with the active ingredients and diluents prior to granulation. In some cases it may be advantageous to divide the starch into two portions: one part is added to the powdered formula prior to granulation, and the remainder is mixed with the lubricant and added prior to compression. Incorporated in this manner, the starch serves a double purpose; the portion added to the lubricant rapidly breaks down the tablet to granules, and the starch mixed with the active ingredients disintegrates the granules into smaller particles. Veegum has been shown to be more effective as a disintegrator in sulfathiazole tablets when most of the quantity is added after granulation and only a small amount before granulation. Likewise, the montmorillonite clays were found to be good tablet disintegrants when added to prepared granulations as powder. They are much less effective as disintegrants when incorporated within the granules.

Factors other than the presence of disintegrants can affect the disintegration time of compressed tablets significantly. The binder, tablet hardness, and the lubricant have been shown to influence the disintegration time. Thus, when the formulator is faced with a problem concerning the disintegration of a compressed tablet, the answer may not lie in the selection and quantity of the disintegrating agent alone.

The evolution of carbon dioxide is also an effective way to cause the disintegration of compressed tablets. Tablets containing a mixture of sodium bicarbonate and an acidulant such as tartaric or citric acid will effervesce when added to water. Sufficient acid is added to produce a neutral or slightly acidic reaction when disintegration in water is rapid and complete. One drawback to the use of the effervescent type of disintegrator is that such tablets must be kept in a dry atmosphere at all times during manufacture, storage, and packaging. Soluble, effervescent tablets provide a popular form for dispensing aspirin and noncaloric sweetening agents.

Coloring Agents

Colors in compressed tablets serve functions other than making the dosage form more esthetic in appearance. Color helps the manufacturer to control the product during its preparation, as well as serving as a means of identification to the user. The wide diversity in the use of colors in solid dosage forms makes it possible to use color as an important category in the identification code developed by the AMA to establish the identity of an unknown compressed tablet in situations arising from poisoning.

All colorants used in pharmaceuticals must be approved and certified by the FDA. For several decades colorants have been subjected to rigid toxicity standards, and as a result, a number of colorants have been removed from an approved list of Food, Drug and Cosmetic Act (FD&C) colors, or *delisted*. Several have

Table 45-1. Colors Approved for Use in the US in Oral Dosage Forms[a,b]

COLOR	OTHER NAMES	COLOR INDEX (CI 1971)	USE RESTRICTION (US)
FD&C Red 40	Allura red	16035	FDA certification on each lot of dye
D&C Red 33	Acid fuchsin D Naphtalone red B	17200	ADI 0–0.76 mg
D&C Red 36			ADI 0–1.0 mg
Canthaxanthinin	Food orange 8	40850	None
D&C Red 22	Eosin Y	45380	FDA certification on each lot of dye
D&C Red 28	Phloxine B	45410	FDA certification on each lot of dye
D&C Red 3	Erythrosine	45430	FDA certification on each lot of dye
Cochineal extract	Natural red 4 Carmine	75470	None
Iron oxide—red	—	77491	ADI 0–5 mg elemental iron
FD&C Yellow 6	Sunset yellow FCF Yellow orange 5	15985	None
FD&C Yellow 5	Tartrazine	19140	Label declaration and FDA certification on each lot of dye
D&C Yellow 10	Quinoline yellow WS	47005	FDA certification on each lot of dye
Beta-carotene	—	40800	
Iron oxide—yellow	—	77492	ADI 0–5 mg elemental iron
FD&C BLue 1	Brilliant blue FCF	42090	FDA certification on each lot of dye
FD&C Blue 2	Indigotine Indigo carmine	73015	None
FD&C Green 3	Fast green FCF	42035	FDA certification on each lot of dye
Iron oxide—black	—	77499	ADI 0–5 mg elemental iron
Caramel	Burnt sugar	—	None
Titanium dioxide	—	77891	None

[a] Abbreviations: ADI, acceptable daily intake (per kg body weight); CI, color index numbers of 1971 (US); D&C, Drug and Cosmetic Dyes (US); FD&C, Food, Drug and Cosmetic Dyes (US); FDA, Food and Drug Administration (US).
[b] As of February, 1988 and subject to revision.

been listed as well. The colorants currently approved in the US are listed in Table 45-1. Each country has its own list of approved colorants, and formulators must consider this in designing products for the international market.[21]

Any of the approved, certified, water-soluble FD&C dyes, mixtures of the same, or their corresponding lakes may be used to color tablets. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal resulting in an insoluble form of the dye. In some instances multiple dyes are used to give a purposefully heterogeneous coloring in the form of speckling to compressed tablets. The dyes available do not meet all the criteria required for the ideal pharmaceutical colorants. The photosensitivity of several of the commonly used colorants and their lakes has been investigated, as well as the protection afforded by a number of glasses used in packaging tablets.

Another approach for improving the photostability of dyes has been in the use of ultraviolet-absorbing chemicals in the tablet formulations with the dyes. The Di-Pac line *(Amstar)* is a series of commercially available colored, direct-compression sugars.

The most common method of adding color to a tablet formulation is to dissolve the dye in the binding solution prior to the granulating process. Another approach is to adsorb the dye on starch or calcium sulfate from its aqueous solution; the resultant powder is dried and blended with the other ingredients. If the insoluble lakes are used, they may be blended with the other dry ingredients. Frequently during drying, colors in wet granulations migrate, resulting in an uneven distribution of the color in the granulation. After compression, the tablets will have a mottled appearance due to the uneven distribution of the color. Migration of colors may be reduced by drying the granulation slowly at low temperatures and stirring the granulation while it is drying. The affinity of several water-soluble, anionic, certified dyes for natural starches has been demonstrated; in these cases this affinity should aid in preventing color migration.

Other additives have been shown to act as dye-migration inhibitors. Tragacanth (1%), acacia (3%), attapulgite (5%), and talc (7%) were effective in inhibiting the migration of FD&C Blue No 1 in lactose. In using dye lakes, the problem of color migration is avoided since the lakes are insoluble. Prevention of mottling can be helped also by the use of lubricants and other additives that have been colored similarly to the granulation prior to their use. The problem of mottling becomes more pronounced as the concentration of colorants increases. Color mottling is an undesirable characteristic common to many commercial tablets.

Flavoring Agents

In addition to the sweetness that may be afforded by the diluent of the chewable tablet, eg, mannitol or lactose, artificial sweetening agents may be included. Formerly, the cyclamates, either alone or in combination with saccharin, were used widely. With the banning of the cyclamates and the indefinite status of saccharin, new natural sweeteners are being sought. Aspartame *(Pfizer),* has found applications in pharmaceutical formulations. Sweeteners other than the sugars have the advantage of reducing the bulk volume, considering the quantity of sucrose required to produce the same degree of sweetness. Being present in small quantities, they do not affect markedly the physical characteristics of the tablet granulation.

POWDER COMPACTION

Compressed tablets became a commercially viable and efficient dosage form with the invention of tablet machines. In 1843 William Brockendon, a British inventor, author, artist, and watchmaker, received British Patent #9977 for *Shaping Pills, Lozenges, and Black Lead by Pressure in Dies.*[22] In over 150 years of tablet manufacture, the basic process has not changed. Surprisingly, improvements have been made only with regards to speed of manufacture and quality control.

The process of compaction has several identifiable phases. As can be seen in Figure 45-3, when powders undergo compression (a reduction in volume), the first process to occur is a consolidation of the powders. During this consolidation phase, the powder particles adopt a more efficient packing order. The second phase of the compaction process is elastic, or reversible de-

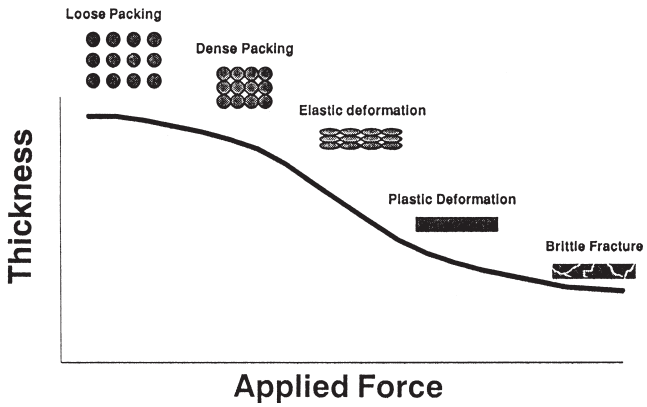


Figure 45-3. The stages of powder compaction.

formation. If the force were to be removed during this phase, the powder would recover completely to the efficiently packed state. For most pharmaceutical powders, this phase is very short in duration and very difficult to identify on most instrumented tablet presses. The third phase of compaction is plastic, or irreversible, deformation of the powder bed. It is this phase of the compaction process that is the most critical in tablet formation. If too much force is applied to the powder, brittle fracture occurs. If the force was applied too quickly, fracture and de-bonding during stress relaxation can occur.

In 1950, Stewart reported on the importance of plastic flow and suggested that if a material has significant plastic flow under compression, it will be more likely to form a compact.[23] David and Augsburger evaluated stress-relaxation data, using the Maxwell model of viscoelastic behavior in an attempt to quantify the rate of plastic deformation of some direct compression excipients.[24] Jones has used the term *contact time* to describe the total time for which a moving punch applies a detectable force to the die contents during the compression and decompression event, excluding ejection.[25]

Rees and Rue evaluated three parameters: stress relation during compaction, effect of contact time on tablet density, and rate of application of diametrical compression on tablet deformation.[26]

Jones[25] outlined numerous techniques to evaluate the compactability of powders. Because of the completeness of his review, these parameters are discussed below.

Tablet Strength—Compression Pressure Profile

Most formulators use tablet *hardness,* or tensile strength, as a measure of the cohesiveness of a tablet. With even the simplest of instrumented tablet presses, it is possible to plot tensile strength versus the force applied to the tablet. Figure 45-4 illustrates such a plot. These plots can be useful in identifying forces that can cause fracture and can lead to a quick, tangible assessment of the compatibility of the formulation. However, there are many limitations to this method, as these plots cannot predict *lamination* or *capping*. In addition, the cohesiveness of a tablet can change upon storage, in either a positive or negative direction.

Tablet Friability

This test is discussed later in the chapter, and there have been many suggestions about how they should be performed. Many formulators believe this is an important indicator of cohesiveness but is of limited value in predicting failure in the field.

Changes in Bed Density during Compression

As applied stress (force) increases, elastic and plastic deformation of the particles occurs, which results in plastic flow and a reduction in inter- and intraparticulate void spaces. This lowers the overall compact density.

For highly cohesive systems, the reduction in void space may yield a compact of sufficient strength for insertion into a capsules shell. However, the inherent cohesiveness for most drugs and excipients is not suitable alone for tablet manufacture.

The Heckel equation is given below; K can be considered equal to the reciprocal of the mean yield pressure, and A is a function of the original compact volume and is related to the densification and particle rearrangement prior to bonding.

$$\text{Log } [1/(1 - D)] = KP + A$$

where D is the relative density at pressure P, and K and A are constants.

Hersey and Rees[28] have classified Heckel plots into two categories. Figure 45-5 shows both types of Heckel plots. Type 2 differs from Type 1 in that above a certain pressure a single linear relationship occurs irrespective of the initial bed density.

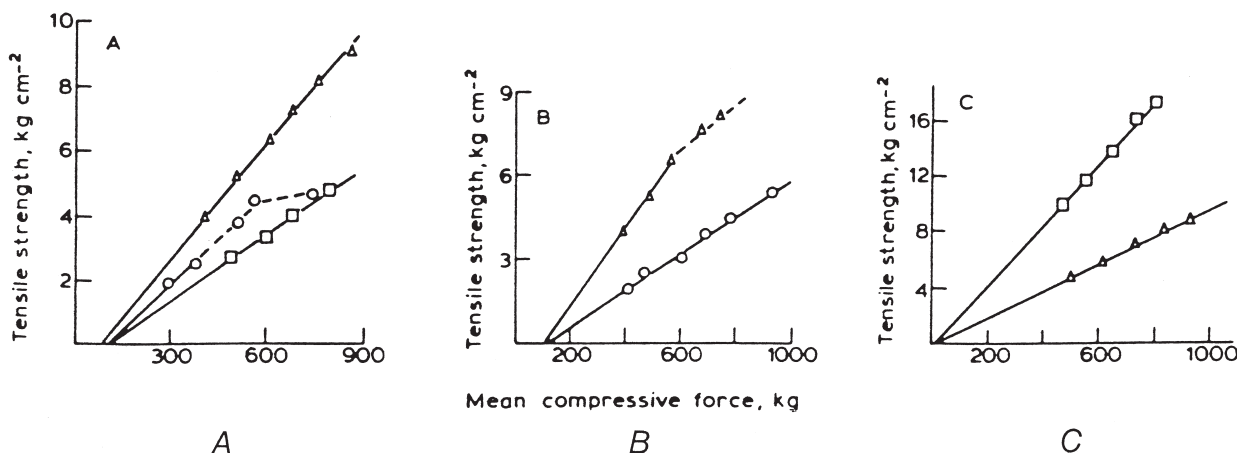


Figure 45-4. Tensile strength of compacts prepared from different crystal forms. *A:* Barbitone (104–152 μm)—○, Form I; □, Form II; △, Form III. *B:* Sulfathiazole (104–152 μm)—○, Form I; △, Form II. *C:* Aspirin (250–353 μm)—△, Form I; □, Form IV. (From Summers MP, Enever RP, Carless JE. *J Pharm Sci* 1977; 66:1172.)

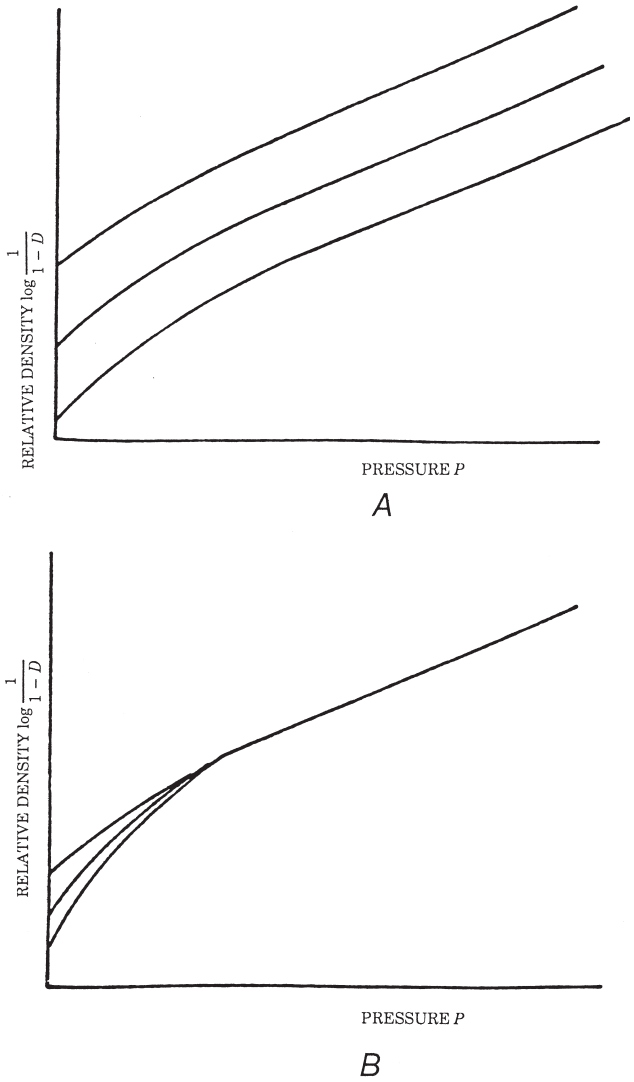


Figure 45-5. Heckel plots. *A:* Type I. *B:* Type II. (From Jones TM. *Acta Pharm Tech* 1978.)

This is independent of particle size and is probable due to fragmentation of particles and their subsequent compaction by plastic deformation. For Type 1 materials, no such fracture occurs, but adjacent particles simply deform plastically.

The pressure at which the plots transition to a linear portion is approximately equal to the minimum pressure required to form a coherent compact.

Changes in Surface Area During Compression

Bulk powders change their state of packing during compaction, and individual particles fracture and/or plastically deform. During this process, the surface area of the powders and the compact in whole, changes. Conventional nitrogen absorption techniques can estimate these changes. Although this can be tedious, these measurements can give a means of examining lamination tendency.

Stress Relaxation

The experimental technique consists of holding the compression process at a point of maximum compression and observing the compression force over various periods of time. By increasing the duration of this period (dwell time), plastic flow is maximized, and tablet strength increases.

Stress Transmissions during Compression

If the stresses in the upper punch, lower punch, and die wall are monitored, as in Figure 45-6, a general plot can be constructed showing the relationship between these forces. The elastic limit is reached at point *A*. At point *B,* the applied force is released, and the transmitted force on the wall of the die falls rapidly. The upper punch ceases to contact the powder/compact at point *C,* where the transmitted force falls rapidly to a residual force, point *D*. The force needed to eject the tablet from the die must be greater than the residual force holding it to the sides of the die. Therefore, residual forces tend to be proportional to ejection forces. In addition, these plots can give a good assessment of the elastic component of the compaction process of a powder.

Work and Compaction

Force-displacement (*F-D*) curves are useful in determining the *work* involved in forming a compact. Curves, such as shown in Figure 45-7,[29] represent the work of the compression process, but all compacts expand somewhat during decompression, and this force is transferred back to the punch. Therefore, by performing a second compression of the compact, the second result can be subtracted from the first for a *corrected F-D curve.* The corrected curve represents the work associated with plastic deformation during powder compaction, as well as a determination of the work of friction of the die wall and the work of elastic deformation.

GRANULATION METHODS

Wet Granulation

The most widely used and most general method of tablet preparation is the wet-granulation method. Its popularity is due to the greater probability that the granulation will meet all the physical requirements for the compression of good tablets. Its chief disadvantages are the number of separate steps involved, as well as the time and labor necessary to carry out the procedure, especially on a large scale. The steps in the wet method are weighing, mixing, granulation, screening the damp mass, drying, dry screening, lubrication, and compression. The equipment involved depends on the quantity or size of the batch. The active ingredient, diluent, and disintegrant are mixed or blended well. For small batches the ingredients may be mixed in stainless steel bowls or mortars. Small-scale blending also

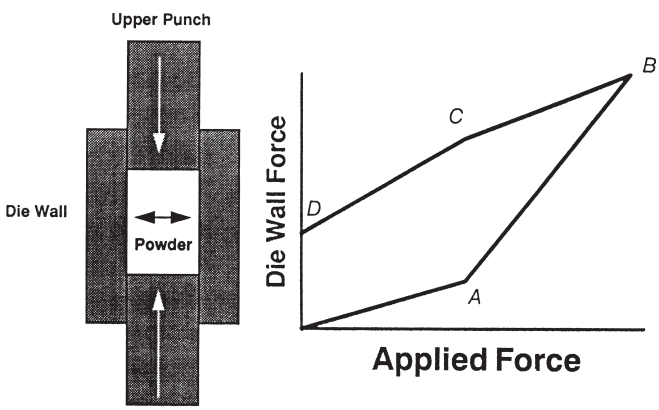
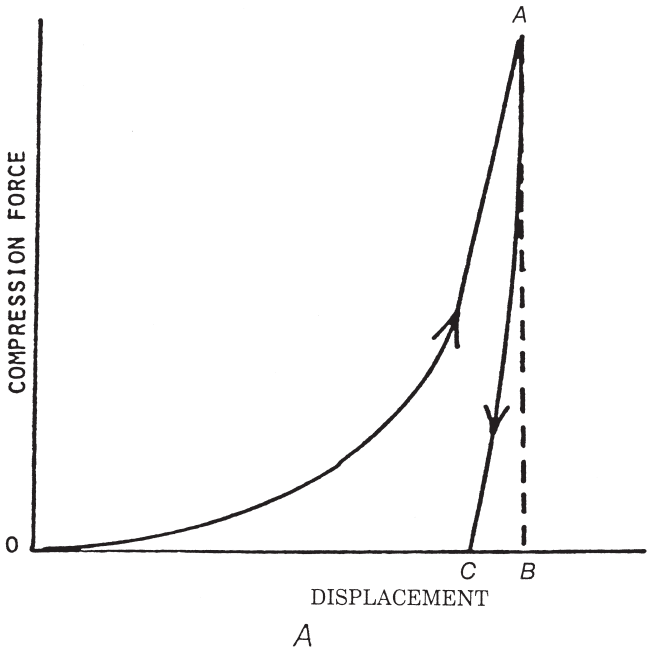


Figure 45-6. Transmitted stresses during tablet compaction.



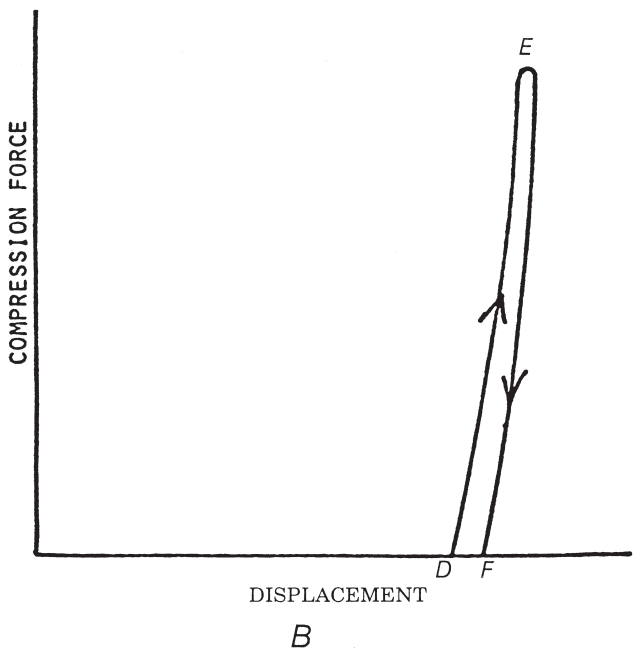


Figure 45-7. Typical forces. *A:* Displacement (F–D) curve; *B:* displacement (F–D), second compression. (From Jones TM. *Acta Pharm Tech* 1978.)

can be carried out on a large piece of paper by holding the opposite edges and tumbling the material back and forth. The powder blend may be sifted through a screen of suitable fineness to remove or break up lumps. This screening also affords additional mixing. The screen selected always should be of the same type of wire or cloth that will not affect the potency of the ingredients through interaction. For example, the stability of ascorbic acid is affected deleteriously by even small amounts of copper, thus care must be taken to avoid contact with copper or copper-containing alloys.

For larger quantities of powder, the Patterson-Kelley twin-shell blender and the double-cone blender offer a means of precision blending and mixing in short periods of time (Fig 45-8). Twin-shell blenders are available in many sizes from laboratory models to large production models. Planetary mixers (eg,

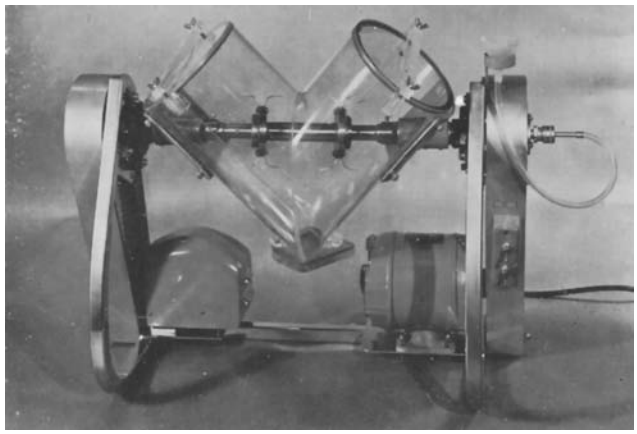


Figure 45-8. Twin-shell blender for solids or liquid-solids blending (courtesy, Patterson-Kelley).

the Glen mixer and the Hobart mixer) have served this function in the pharmaceutical industry for many years (Fig 45-9). On a large scale, ribbon blenders also are employed frequently and may be adapted for continuous-production procedures. Mass mixers of the sigma-blade type have been used widely in the pharmaceutical industry.

Highly popular are the high-speed, high-shear mixers such as the Diosna, Fielder, Lodige/Littleford, and Baker-Perkins. For these mixers a full range of sizes are available. The processing of granulations in these machines is generally faster than in conventional granulators. However, control over the process is critical, and scale-up issues may become extremely important.[30] Fluid-bed granulation (discussed below) also is gaining wide acceptance in the industry. For both of these types of processing, slight modifications to the following procedures are required.

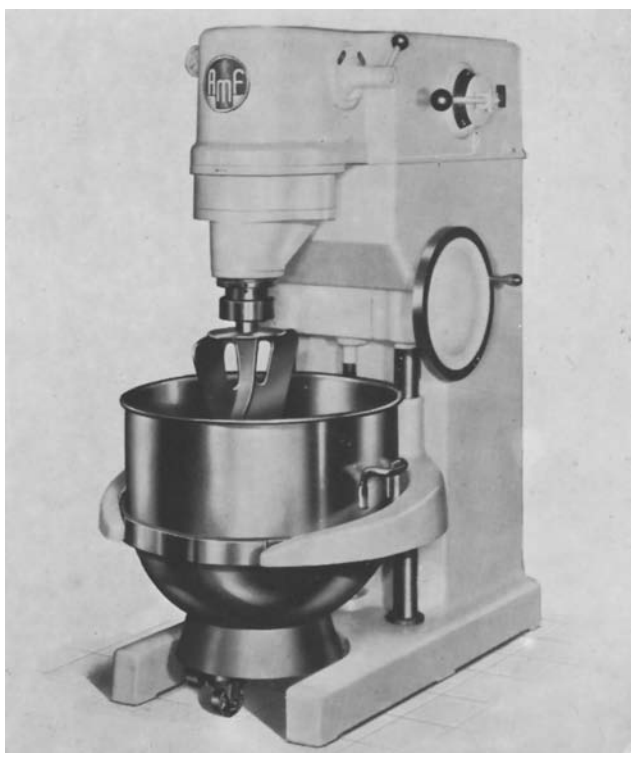


Figure 45-9. The Glen powder mixer (courtesy, Am Machine).

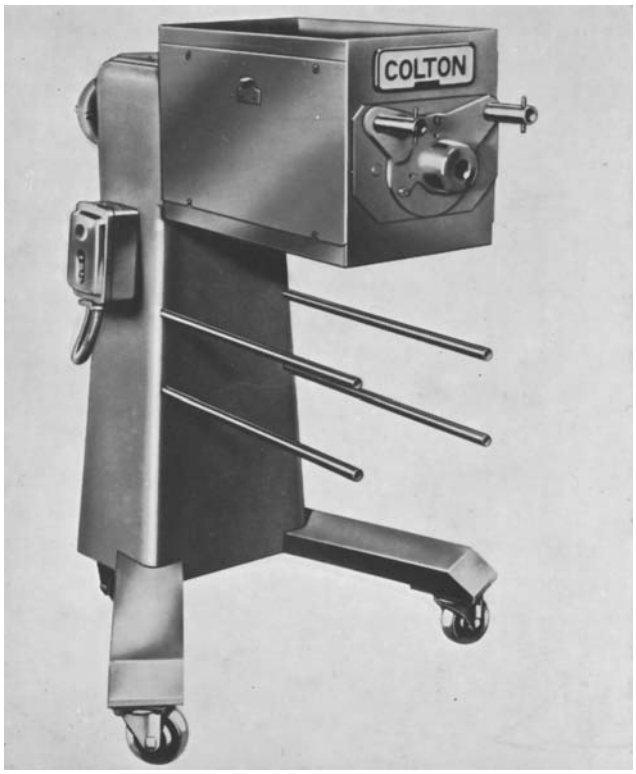


Figure 45-10. Rotary granulator and sifter (courtesy, Vector/Colton).

Solutions of the binding agent are added to the mixed powders with stirring. The powder mass is wetted with the binding solution until the mass has the consistency of damp snow or brown sugar. If the granulation is over-wetted, the granules will be hard, requiring considerable pressure to form the tablets, and the resultant tablets may have a mottled appearance. If the powder mixture is not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication and causing difficulty during compression.

The wet granulation is forced through a 6- or 8-mesh screen. Small batches can be forced through by hand using a manual screen. For larger quantities, one of several comminuting mills suitable for wet screening can be used. These include the Stokes oscillator, Colton rotary granulator, Fitzpatrick comminuting mill, or Stokes tornado mill. See Figure 45-10. In comminuting mills the granulation is forced through the sieving device by rotating hammers, knives, or oscillating bars. Most high-speed mixers are equipped with a chopper blade that operates independently of the main mixing blades and can replace the wet milling step, ie, can obviate the need for a separate operation.

For tablet formulations in which continuous production is justified, extruders such as the Reitz extruder have been adapted for the wet-granulation process. The extruder consists of a screw mixer with a chamber where the powder is mixed with the binding agent, and the wet mass gradually is forced through a perforated screen, forming threads of the wet granulation. The granulation then is dried by conventional methods. A semiautomatic, continuous process using the Reitz extruder has been described for the preparation of the antacid tablet Gelusil *(Warner-Lambert/Pfizer)*.

Moist material from the wet milling step traditionally was placed on large sheets of paper on shallow wire trays and placed in drying cabinets with a circulating air current and thermostatic heat control. See Figure 45-11. While tray drying was the most widely used method of drying tablet granulations in the past, fluid-bed drying is now considered the standard. In drying tablet granulation by fluidization, the material is suspended and agitated in a warm air stream while the granulation is maintained in motion. Drying tests comparing the fluidized bed and a tray dryer for a number of tablet granulations indicated that the former was 15 times faster than the conventional method of tray drying. In addition to the decreased drying time, the fluidization method is claimed to have other advantages such as better control of drying temperatures, decreased handling costs, and the opportunity to blend lubricants and other materials into the dry granulation directly in the fluidized bed. See Figure 45-12.[31]

The application of microwave drying and infrared drying to tablet granulations has been reported as successful for most granulations tried. These methods readily lend themselves to continuous granulation operations. The study of drying methods for tablet granulations led to the development of the Rovac dryer system by Ciba/Novartis pharmacists and engineers. The dryer is similar in appearance to the cone blender except for the heating jacket and vacuum connections. By excluding oxygen and using the lower drying temperatures made possible by drying in a vacuum, opportunities for degradation of the ingredients during the drying cycle are minimized. A greater uniformity of residual moisture content is achieved because of the moving bed, controlled temperature, and controlled time period of the drying cycle. Particle-size distribution can be controlled by varying the speed of rotation and drying temperature as well as by comminuting the granulation to the desired granule size after drying.

In drying granulations it is desirable to maintain a residual amount of moisture in the granulation. This is necessary to maintain the various granulation ingredients, such as gums, in a hydrated state. Also, the residual moisture contributes to the reduction of the static electric charges on the particles. In the selection of any drying process, aneffort is made to obtain a uniform moisture content. In addition to the importance of moisture content of the granulation in its handling during the manufacturing steps, the stability of the products containing moisture-sensitive active ingredients may be related to the moisture content of the products.

Previously it was indicated that water-soluble colorants can migrate toward the surface of the granulation during the drying process, resulting in mottled tablets after compression. This is also true for water-soluble drug substances, resulting in tablets unsatisfactory as to content uniformity. Migration can be reduced by drying the granulation slowly at low temperatures or using a granulation in which the major diluent is present as granules of large particle size. The presence of microcrystalline cellulose in wet granulations also reduces migration tendencies.

After drying, the granulation is reduced in particle size by passing it through a smaller-mesh screen. Following dry screening, the granule size tends to be more uniform. For dry granulations the screen size to be selected depends on the diameter of the punch. The following sizes are suggested:

Tablets up to 3/16 inch diameter, use 20-mesh
Tablets 7/32 to 5/16 inch, use 16-mesh
Tablets 11/32 to 13/32 inch, use 14-mesh
Tablets 7/16 inch and larger, use 12-mesh

For small amounts of granulation, hand screens may be used and the material passed through with the aid of a stainless steel spatula. With larger quantities, any of the comminuting mills

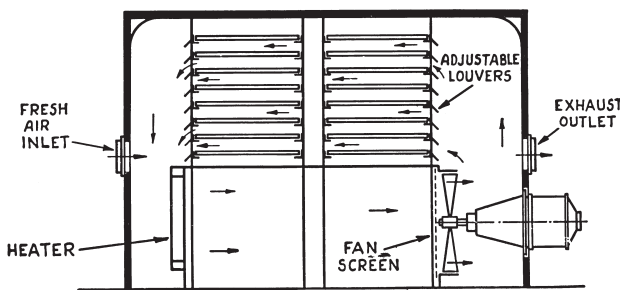


Figure 45-11. Cross-section of tray dryer.

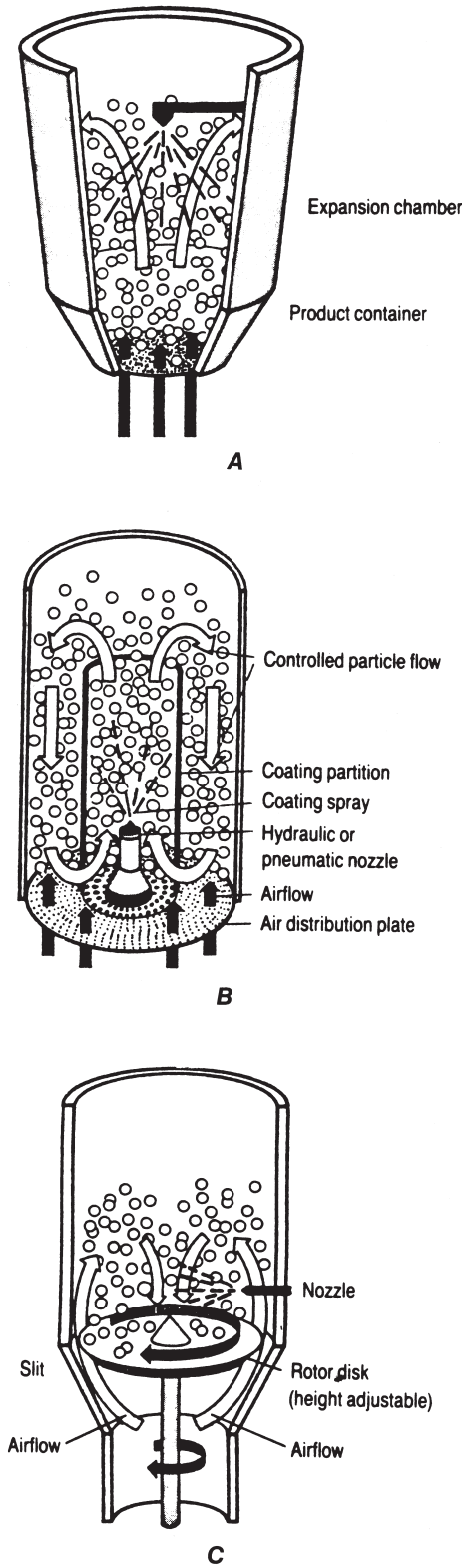


Figure 45-12. Three versions of fluidized-bed granulation and drying. *A:* Top-spray method used in conventional fluid-bed granulation coaters; *B:* bottom-spray method used in Wurster air- suspension columns; *C:* tangential-spray method used in rotary fluid-bed coaters/granulators. (Courtesy, Aster Publ, adapted from Mehta AM. *Pharm Technol* 1988; 12:46.)

with screens corresponding to those just mentioned may be used. Note that the smaller the tablet, the finer the dry granulation to enable more uniform filling of the die cavity; large granules give an irregular fill to a comparatively small die cavity. With compressed tablets of sodium bicarbonate, lactose, and magnesium trisilicate, a relationship has been demonstrated between the particle size of the granulated material and the disintegration time and capping of the resultant tablets. For a sulfathiazole granulation, however, the particle-size distribution did not appear to influence hardness or disintegration.

After dry granulation, the lubricant is added as a fine powder. It usually is screened onto the granulation through 60- or 100-mesh nylon cloth to eliminate small lumps as well as to increase the covering power of the lubricant. As it is desirable for each granule to be covered with the lubricant, the lubricant is blended with the granulation very gently, preferably in a blender using a tumbling action. Gentle action is desired to maintain the uniform granule size resulting from the granulation step. It has been claimed that too much fine powder is not desirable because fine powder may not feed into the die evenly; consequently, variations in weight and density result. Fine powders, commonly designated as *fines,* also blow out around the upper punch and down past the lower punch, making it necessary to clean the machine frequently. Fines, however, at a level of 10–20%, traditionally are sought by the tablet formulator. The presence of some fines is necessary for the proper filling of the die cavity. Now, even higher concentrations of fines are used successfully in tablet manufacture. Most investigators agree that no general limits exist for the amount of fines that can be present in a granulation; it must be determined for each specific formula.

Many formulators once believed (and some still believe) that overblending resulted in an increased amount of fines and, hence, caused air entrapment in the formula. The capping and laminating of tablets associated with overblending lubricants was thought to be caused by these air pockets. Most scientists now recognize that a more plausible explanation has to do with the function of the lubricants themselves. Since the very nature of a lubricant tends to make surfaces less susceptible to adhesion, overblending prevents the intergranular bonding that takes place during compaction.

Fluid-Bed Granulation

A new method for granulating evolved from the fluid-bed drying technology described earlier. The concept was to spray a granulating solution onto the suspended particles, which then would be dried rapidly in the suspending air. The main benefit from this system is the rapid granulation and drying of a batch. The two main firms that developed this technology are *Glatt* and *Aeromatic (now NIRO).* The design of these systems is basically the same with both companies (see Fig 45-12). In this method, particles of an inert material or the active drug are suspended in a vertical column with a rising air stream; while the particles are suspended, the common granulating materials in solution are sprayed into the column. There is a gradual particle buildup under a controlled set of conditions resulting in a tablet granulation that is ready for compression after the addition of the lubricant. An obvious advantage exists, since granulating and drying can take place in a single piece of equipment. It should be noted, however, that many of the mixers discussed previously can be supplied with a steam jacket and vacuum and can provide the same advantage.

In these systems a granulating solution or solvent is sprayed into or onto the bed of suspended particles. The rate of addition of the binder, temperature in the bed of particles, temperature of the air, volume, and moisture of the air all play an important role in the quality and performance of the final product. Many scientists feel that this method is an extension of the wet-granulation method, as it incorporates many of its concepts. However anyone who has developed a formulation in a fluid-bed

system knows that the many operating parameters involved make it somewhat more complex.[31] In addition to its use for the preparation of tablet granulations, this technique also has been proposed for the coating of solid particles as a means of improving the flow properties of small particles. Researchers have observed that, in general, fluid-bed granulation yields a less dense particle than conventional methods, and this can affect subsequent compression behavior. A large-scale fluid-bed granulation process has been described for Tylenol *(McNeil)*. Methods for the preparation of compressed tablets have been reviewed in the literature.[32]

The *Merck* facility at Elkton, VA was the first completely automated tablet production facility in the world. The entire tablet-manufacturing process based on a wet-granulation method was computer-controlled. By means of a computer, the system weighed the ingredients, blended, granulated, dried, and lubricated to prepare a uniform granulation of specified particle size and particle-size distribution. The computer directed the compression of the material into tablets with exacting specifications for thickness, weight, and hardness. After compression, the tablets were coated with a water-based film coating. The computer controlled and monitored all flow of material. The plant represented the first totally automated pharmaceutical manufacturing facility. However, due to shifting market trends and the burdens of process validation and changes to processes, totally automated processes are generally not used today. Instead, many production operations focus on computer-controlled and monitored unit operations, such as seen in various tableting machines and granulators today. See Figure 45-13.

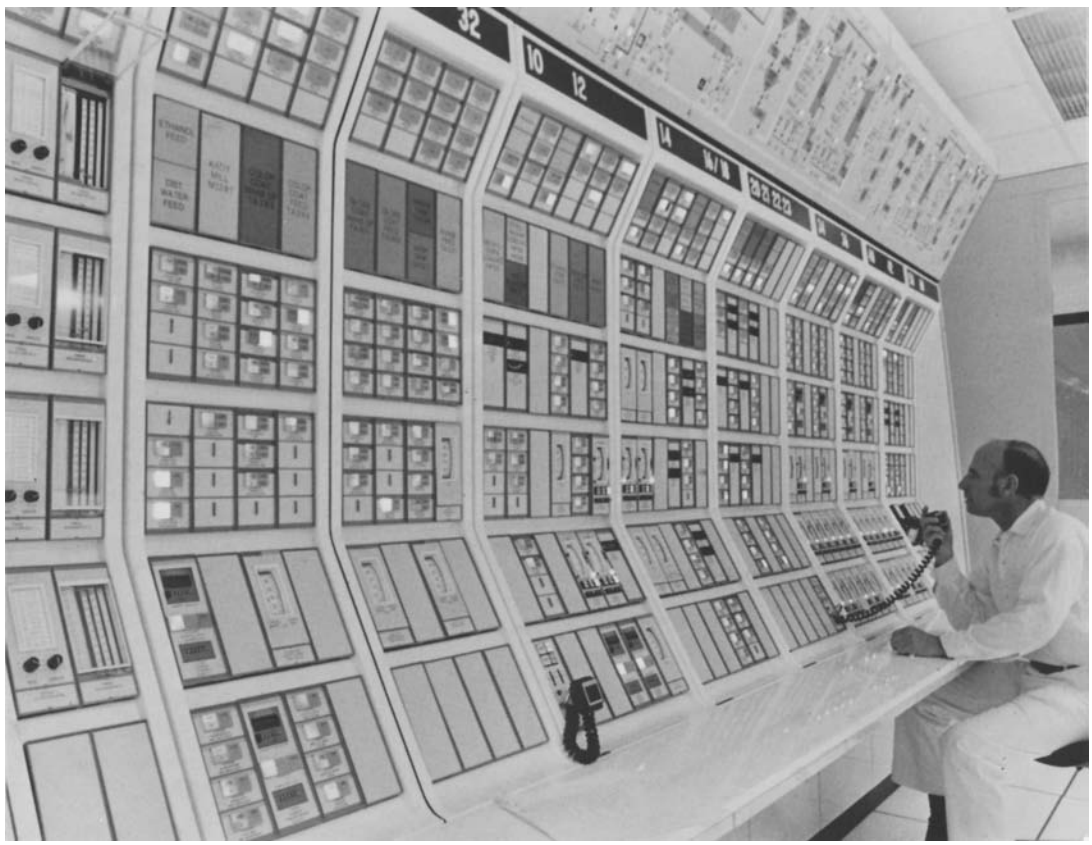
Equipment suppliers work closely with individual pharmaceutical companies in designing specialized and unique systems.

Dry Granulation

When tablet ingredients are sensitive to moisture or are unable to withstand elevated temperatures during drying, and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules. This method is referred to as dry granulation, precompression, or double-compression. It eliminates a number of steps but still includes weighing, mixing, slugging, dry screening, lubrication, and compression. The active ingredient, diluent (if required), and part of the lubricant are blended. One of the constituents, either the active ingredient or the diluent, must have cohesive properties. Powdered material contains a considerable amount of air; under pressure this air is expelled, and a fairly dense piece is formed. The more time allowed for this air to escape, the better the tablet or slug.

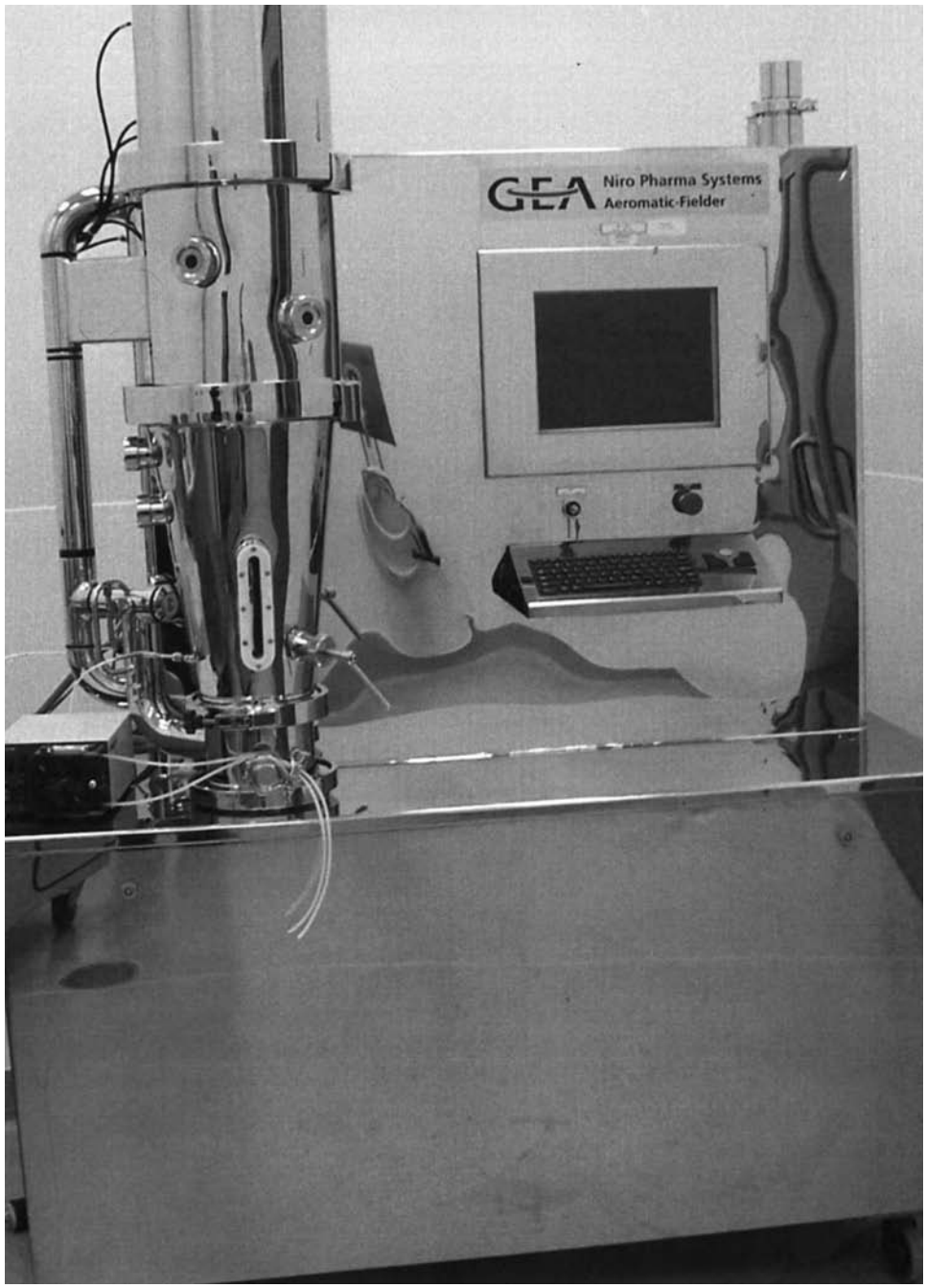
When slugging is used, large tablets are made as slugs because fine powders flow better into large cavities. Also, producing large slugs decreases production time; 7/8 to 1 in are the most practical sizes for slugs. Sometimes, to obtain the pressure that is desired the slug sizes are reduced to 3/4 in. The punches should be flat-faced. The compressed slugs are comminuted through the desirable mesh screen either by hand or, for larger quantities, through the Fitzpatrick or similar comminuting mill. The lubricant remaining is added to the granulation and blended gently, and the material is compressed into tablets. Aspirin is a good example of where slugging is satisfactory. Other materials such as aspirin combinations, acetaminophen, thiamine hydrochloride, ascorbic acid, magnesium hydroxide, and other antacid compounds may be treated similarly.

Results comparable to those accomplished by the slugging process also are obtained with compacting mills. In the com-



A

Figure 45-13. Fixed automated processes in the 1980s have given way to flexible micro-processor controlled unit operations. **a.** Computer control room for the first large-scale computer-controlled tablet manufacturing facility (courtesy, Merck).



B

Figure 45-13. *(continued)* **b.** Computer-controlled/monitored coating.

paction method the powder to be densified passes between high-pressure rollers that compress the powder and remove the air. The densified material is reduced to a uniform granule size and compressed into tablets after the addition of a lubricant. Excessive pressures that may be required to obtain cohesion of certain materials may result in a prolonged dissolution rate. Compaction mills available include the Chilsonator *(Fitzpatrick),* Roller Compactor *(Vector),* and the Compactor Mill *(Allis-Chalmers)*.

Direct Compression

As its name implies, direct compression consists of compressing tablets directly from powdered material without modifying the physical nature of the material itself. Formerly, direct compression as a method of tablet manufacture was reserved for a small group of crystalline chemicals having all the physical characteristics required for the formation of a good tablet. This group includes chemicals such as potassium salts (chlorate, chloride, bromide, iodide, nitrate, permanganate), ammonium chloride, and methenamine. These materials possess cohesive and flow properties that make direct compression possible.

Since the pharmaceutical industry constantly is making efforts to increase the efficiency of tableting operations and reduce costs by using the smallest amount of floor space and labor as possible for a given operation, increasing attention is being given to this method of tablet preparation. Approaches being used to make this method more universally applicable include the introduction of formulation additives capable of im-

C

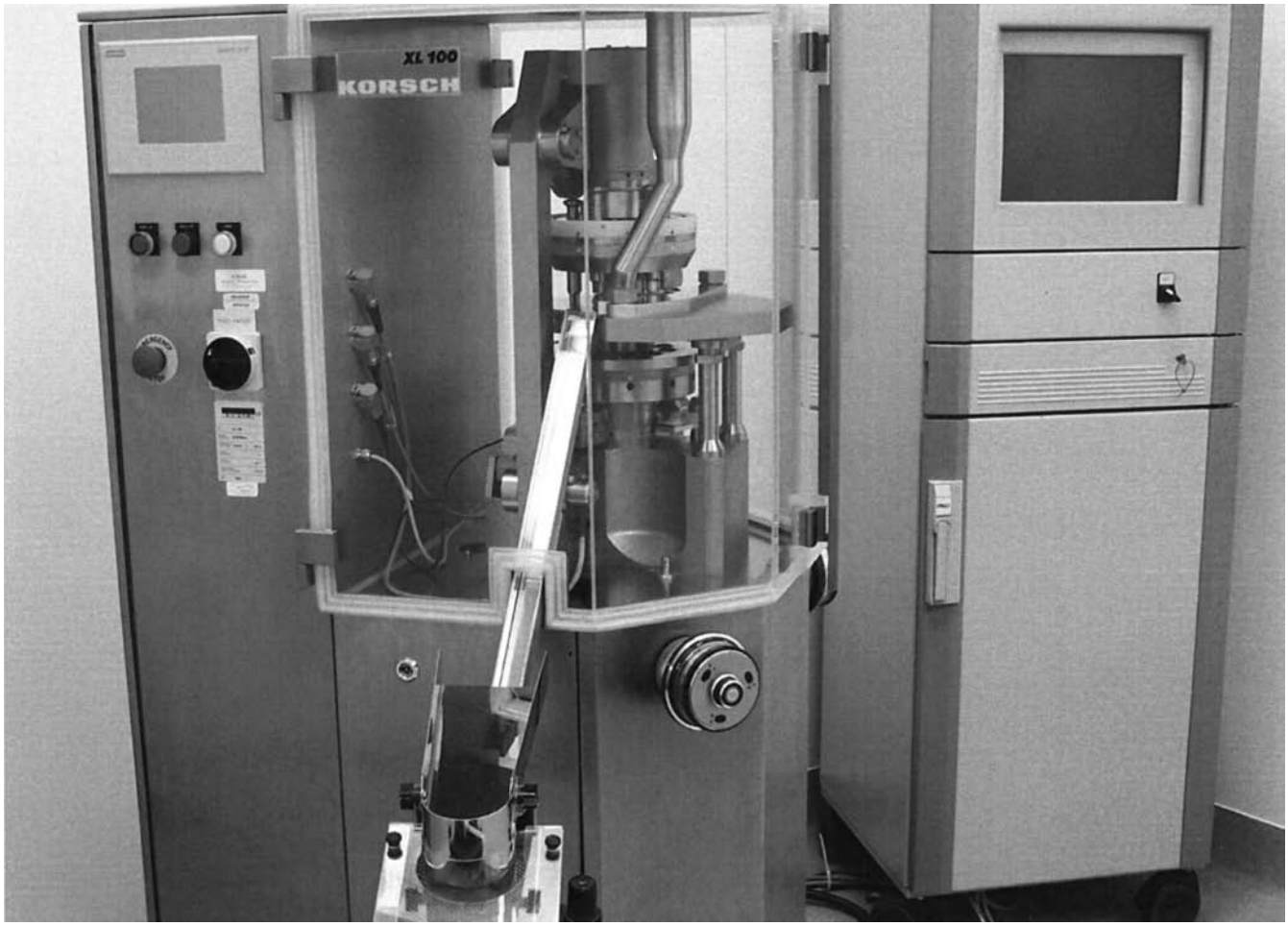
Figure 45-13. *(continued)* **c.** Computer-controlled/monitored granulation.

parting the characteristics required for compression and the use of force-feeding devices to improve the flow of powder blends.

For tablets in which the drug itself constitutes a major portion of the total tablet weight, it is necessary that the drug possess those physical characteristics required for the formulation to be compressed directly. Direct compression for tablets containing 25% or less of drug substances frequently can be used by formulating with a suitable diluent that acts as a carrier or vehicle for the drug.[32–34]

Direct-compression vehicles or carriers must have good flow and compressible characteristics. These properties are imparted to them by a preprocessing step such as wet granulation, slugging, spray drying, spheronization, or crystallization. These vehicles include processed forms of most of the common diluents including dicalcium phosphate dihydrate, tricalcium phosphate, calcium sulfate, anhydrous lactose, spray-dried lactose, pregelatinized starch, compressible sugar, mannitol, and microcrystalline cellulose. These commercially available direct-compression vehicles may contain small quantities of other ingredients (eg, starch) as processing aids. Dicalcium phosphate dihydrate (Di-Tab, *Stauffer*) in its unmilled form has good flow properties and compressibility. It is a white, crystalline agglomerate insoluble in water and alcohol. The chemical is odorless, tasteless, and nonhygroscopic. Since it has no inherent lubricating or disintegrating properties, other additives must be present to prepare a satisfactory formulation.

Compressible sugar consists mainly of sucrose that is processed to have properties suitable for direct compression. It also may contain small quantities of dextrin, starch, or invert sugar. It is a white crystalline powder with a sweet taste and complete water solubility. It requires the incorporation of a suitable lu-



D

Figure 45-13. *(continued)* **d.** Computer-controlled/monitored tableting.

bricant at normal levels for lubricity. The sugar is used widely for chewable vitamin tablets because of its natural sweetness. One commercial source is Di-Pac *(Amstar)* prepared by the cocrystallization of 97% sucrose and 3% dextrins. Some forms of lactose meet the requirements for a direct-compression vehicle. Hydrous lactose does not flow, and its use is limited to tablet formulations prepared by the wet-granulation method. Both anhydrous lactose and spray-dried lactose have good flowability and compressibility and can be used in direct compression provided a suitable disintegrant and lubricant are present. Mannitol is a popular diluent for chewable tablets because of its pleasant taste and mouth feel resulting from its negative heat of solution. In its granular form *(ICI Americas)* it has good flow and compressible qualities. It has a low moisture content and is not hygroscopic.

The excipient that has been studied extensively as a direct compression vehicle is microcrystalline cellulose (Avicel, *FMC*). This nonfibrous form of cellulose is obtained by spray-drying washed, acid-treated cellulose and is available in several grades that range in average particle size from 20 to 100 μm. It is water-insoluble, but the material has the ability to draw fluid into a tablet by capillary action; it swells on contact and thus acts as a disintegrating agent. The material flows well and has a degree of self-lubricating qualities, thus requiring a lower level of lubricant than other excipients.

Forced-flow feeders are mechanical devices, available from pharmaceutical equipment manufacturers, designed to deaerate light and bulky material. Mechanically, they maintain a steady flow of powder moving into the die cavities under moderate pressure. By increasing the density of the powder, higher uniformity in tablet weights is obtained. See Figure 45-14.

Recently, many companies have reversed their optimism for some direct-compression systems. Some formulations made by direct compression were not as *forgiving* as the older wet-granulated products were. As raw material variations occurred, especially with the drug, many companies found themselves with poorly compactable formulations. Interest in direct compression also is stimulating basic research on the flowability of powders with and without additives.

Related Granulation Processes

SPHERONIZATION—Spheronization, a form of pelletization, refers to the formation of spherical particles from wet granulations. Since the particles are round, they have good flow properties when dried. They can be formulated to contain sufficient binder to impart cohesiveness for tableting. Spheronization equipment such as the Marumerizer *(Luwa)* and the CF-Granulator *(Vector)* are commercially available for small-scale manufacture, on up to commercial sized equipment. A wet granulation containing the drug substance, diluent (if required), and binder, is passed first through an extruding machine to form rod-shaped cylindrical segments ranging in diameter from 0.5 to 12 mm. The segment diameter and the size of the final spherical particle depend on the extruder screen size. After extrusion the segments are placed into the Marumerizer where they are shaped into spheres by centrifugal and frictional forces on a rotating plate (see Fig 45-15). The

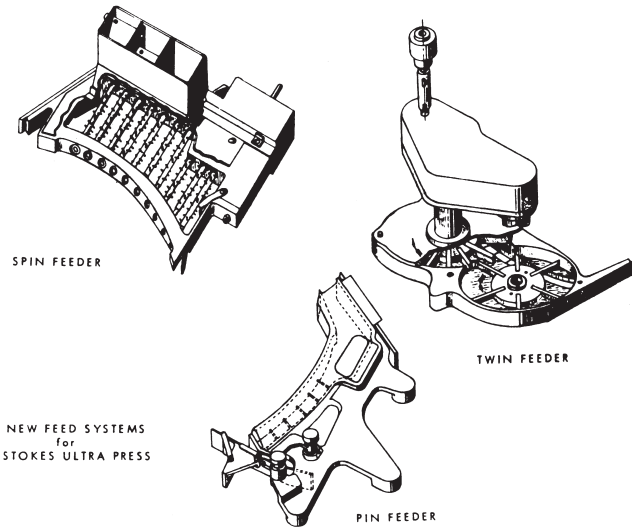


Figure 45-14. Feeding devices designed to promote flow of granulations for high-speed machines (courtesy, Stokes/Pennwalt).

pellets then are dried by conventional methods, mixed with suitable lubricants, and compressed into tablets or used as capsule-fill material. Microcrystalline cellulose has been shown to be an effective diluent and binder in granulations to be spheronized.[35–38] The advantages of the process include the production of granules, regular in shape, size, and surface characteristics; low friability resulting in fewer fines and less dust; and the ability to regulate the size of the spheres within a narrow particle-size distribution.

Spheres also can be produced by fluid-bed granulation techniques and by other specialized equipment such as the CF-Granulator *(Vector)*. These processes, however, must begin with crystals or nonpareil seeds followed by buildup. Exact results, such as sphere density, are different for the various methods and could be important in product performance. These processes can be run as batches or continuously.

SPRAY-DRYING—A number of tableting additives suitable for direct compression have been prepared by the drying process known as spray-drying. The method consists of bringing together a highly dispersed liquid and a sufficient volume of hot air to produce evaporation and drying of the liquid droplets. The feed liquid may be a solution, slurry, emulsion, gel, or paste, provided it is pumpable and capable of being atomized. As shown in Figure 45-16, the feed is sprayed into a current of warm filtered air. The air supplies the heat for evaporation and

Figure 45-15. The inside of a QJ-400 Marumerizer (courtesy, Luwa).

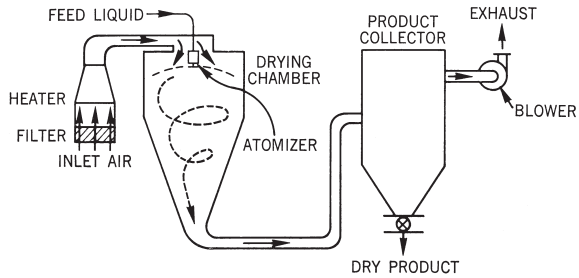


Figure 45-16. Typical spray-drying system (courtesy, Bowen Eng).

conveys the dried product to the collector; the air is then exhausted with the moisture. As the liquid droplets present a large surface area to the warm air, local heat and transfer coefficients are high.

The spray-dried powder particles are homogeneous, approximately spherical in shape, nearly uniform in size, and frequently hollow. The latter characteristic results in low bulk density with a rapid rate of solution. Being uniform in size and spherical, the particles possess good flowability. The design and operation of the spray-dryer can vary many characteristics of the final product, such as particle size and size distribution, bulk and particle densities, porosity, moisture content, flowability, and friability. Among the spray-dried materials available for direct compression formulas are lactose, mannitol, and flour. Another application of the process in tableting is spray-drying the combination of tablet additives as the diluent, disintegrant, and binder. The spray-dried material then is blended with the active ingredient or drug, lubricated, and compressed directly into tablets.

Since atomization of the feed results in a high surface area, the moisture evaporates rapidly. The evaporation keeps the product cool and as a result the method is applicable for drying heat-sensitive materials. Among heat-sensitive pharmaceuticals successfully spray-dried are the amino acids; antibiotics as aureomycin, bacitracin, penicillin, and streptomycin; ascorbic acid; cascara extracts; liver extracts; pepsin and similar enzymes; protein hydrolysates; and thiamine.[39]

Frequently, spray-drying is more economical than other processes, since it produces a dry powder directly from a liquid and eliminates other processing steps as crystallization, precipitation, filtering or drying, particle-size reduction, and particle classifying. By the elimination of these steps, labor, equipment costs, space requirements and possible contamination of the product are reduced. Intrinsic factor concentrate obtained from hog mucosa previously was prepared by *Lederle/American Home Products*, using a salt-precipitation process followed by a freeze-drying. By using spray-drying it was possible to manufacture a high-grade material by a continuous process. The spherical particles of the product facilitated its subsequent blending with vitamin B_{12}. Similar efficiencies have been found in processes producing magnesium trisilicate and dihydroxyaluminum sodium carbonate; both chemicals are used widely in antacid preparations.

Encapsulation of chemicals also can be achieved using spray-drying equipment. The process is useful in coating one material on another to protect the interior substance or to control the rate of its release. The substance to be coated can be either liquid or solid but must be insoluble in a solution of the coating material. The oil-soluble vitamins, A and D, can be coated with a variety of materials such as acacia gum to prevent their deterioration. Flavoring oils and synthetic flavors are coated to give the so-called dry flavors.

SPRAY-CONGEALING—Also called spray-chilling, spray-congealing is a technique similar to spray-drying. It consists of melting solids and reducing them to beads or powder by spraying the molten feed into a stream of air or other gas. The same basic equipment is used as with spray-drying, although

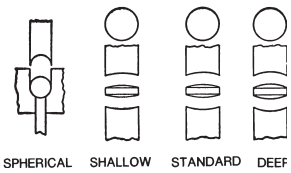


Figure 45-17. Concave punches.

no source of heat is required. Either ambient or cooled air is used, depending on the freezing point of the product. For example, monoglycerides and similar materials are spray-congealed with air at 50°F. A closed-loop system with refrigeration cools and recycles the air. Using this process, drugs can be dissolved or suspended in a molten wax and spray-congealed; the resultant material then can be adapted for a prolonged-release form of the drug.

Among the carbohydrates used in compressed tablets, mannitol is the only one that possesses high heat stability. Mannitol melts at 167° and, either alone or in combination with other carbohydrates, can be fused and spray-congealed. Selected drugs have been shown to be soluble in these fused mixtures, and the resultant spray-congealed material possesses excellent flow and compression characteristics.

TABLET MACHINES

As mentioned previously, the basic mechanical unit in tablet compression involves the operation of two steel punches within a steel die cavity. The tablet is formed by the pressure exerted on the granulation by the punches within the die cavity, or cell. The tablet assumes the size and shape of the punches and die used. See Figures 45-17 and 45-18. While round tablets are used more generally, oval, capsule-form, square, triangular, or other irregular shapes may be used. Likewise, the curvature of the faces of the punches determines the curvature of the tablets. The diameters generally found to be satisfactory and frequently referred to as standard are as follows: 3⁄16, 7⁄32, 1⁄4, 9⁄32, 5⁄16, 11⁄32, 7⁄16, 1⁄2, 9⁄16, 5⁄8, 11⁄16, and 3⁄4 in. Punch faces with ridges are used for compressed tablets scored for breaking into halves or fourths, although it has been indicated that variation among tablet halves is significantly greater than among intact tablets. However, a patented formulation[40] for a tablet scored to form a groove that is one-third to two-thirds the depth of the total tablet thickness is claimed to give equal parts containing substantially equal amounts of the drug substance. Tablets, engraved or embossed with symbols or initials, require punches with faces embossed or engraved with the corresponding designs. See Figures 45-19 and 45-20. The use of the tablet sometimes determines its shape; effervescent tablets are usually large, round, and flat, while vitamin tablets frequently are prepared in capsule-shaped forms. Tablets prepared using deep-cup punches appear to be round and when coated take on the appearance of pills. Veterinary tablets often have a bolus shape and are much larger than those used in medical practice.

The quality-control program for punches and dies, frequently referred to as tooling, instituted by large pharmaceutical companies, emphasizes the importance of their care in modern pharmaceutical production. To produce physically perfect compressed tablets, an efficient punch-and-die program must be set up. Provisions for inspection of tooling, parameters for cost-per-product determination, product identification, and tooling specifications must all be considered. A committee of the Industrial and Pharmaceutical Technology Section of the APhA Academy of Pharmaceutical Sciences established a set of dimensional specifications and tolerances for standard punches and dies.[41]

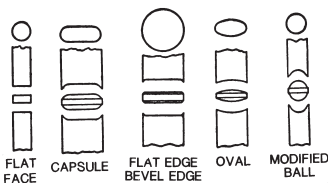


Figure 45-18. Specially shaped punches.

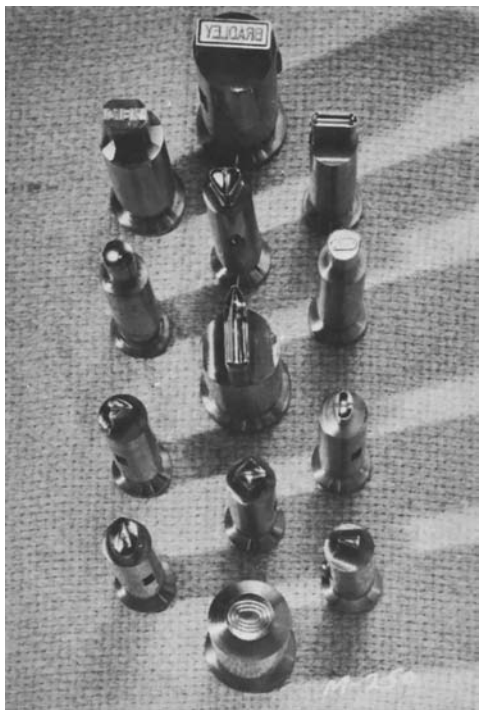


Figure 45-19. Collection of punches (courtesy, Stokes/Pennwalt).

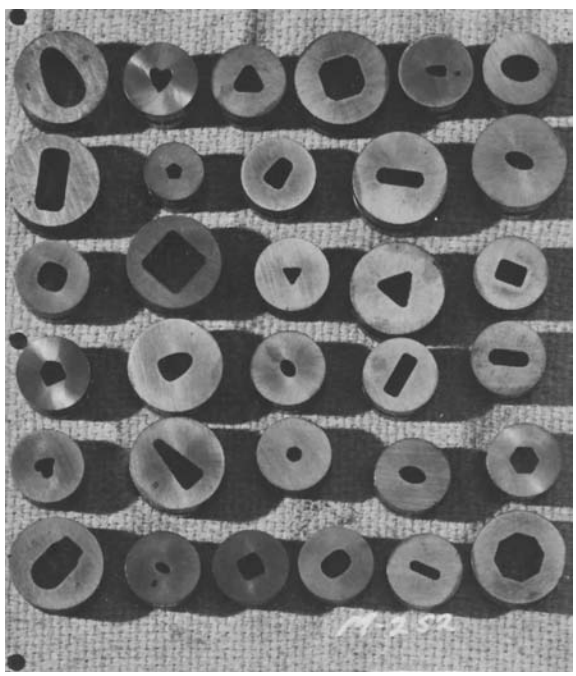


Figure 45-20. Collection of dies (courtesy, Stokes/Pennwalt).

Regardless of the size of the tableting operation, the attention that must be given to the proper care of punches and dies should be noted. They must be highly polished and kept free from rust and imperfections. In cases in which the material pits or abrades the dies, chromium-plated dies have been used. Dropping the punches on hard surfaces will chip their fine edges. When the punches are in the machine, the upper and lower punches should not be allowed to contact each other; otherwise, a curling or flattening of the edges will result that is one of the causes of capping. This is especially necessary to observe in the case of deep-cup punches.

When the punches are removed from the machine, they should be washed thoroughly in warm soapy water and dried well with a clean cloth. A coating of grease or oil should be rubbed over all parts of the dies and punches to protect them from the atmosphere. They should be stored carefully in boxes or paper tubes.

Single-Punch Machines

The simplest tableting machines available are those having the single-punch design. A number of models are available as outlined in Table 45-2. While most of these are power-driven, several hand-operated models are available. Compression is accomplished on a single-punch machine as shown in Figure 45-21. The feed shoe filled with the granulation is positioned over the die cavity, which then fills. The feed shoe retracts and scrapes all excess granulation away from the die cavity. The upper punch lowers to compress the granulation within the die cavity. The upper punch retracts, and the lower punch rises to eject the tablet. As the feed shoe returns to fill the die cavity, it pushes the compressed tablet from the die platform. The weight of the tablet is determined by the volume of the die cavity; the lower punch is adjustable to increase or decrease the volume of granulation, thus increasing or decreasing the weight of the tablet.

For tablets having diameters larger than 1/2 inch, sturdier models are required. This is also true for tablets requiring a high degree of hardness, as in the case of compressed lozenges. The heavier models are capable of much higher pressures and are suitable for slugging.

OPERATION OF SINGLE-PUNCH MACHINES—In installing punches and dies in a single-punch machine, insert the lower punch first by lining up the notched groove on the punch with the lower punch setscrew and slipping it into the smaller bore in the die table; the setscrew is not tightened yet. The lower punch is differentiated from the upper punch in that it has a collar around the punch head. Slip the die over the punch head so that the notched groove (with the widest area at the top) lines up with the die setscrew. Tighten the lower punch setscrew after seating the lower punch by pressing on the punch with the thumb. Tighten the die setscrew, making certain that the surface of the die is flush with the die table. Insert the upper punch, again lining up the grooved notch with the upper punch setscrew. To be certain that the upper punch is seated securely, turn the machine over by hand with a block of soft wood or wad of cloth between the upper and lower punches. When the punch is seated, tighten the upper punch setscrew. Adjust the pressure so that the upper and lower punches will not come in contact with each other when the machine is turned over. Adjust the lower punch so that it is flush with the die table at the ejection point. Install the feed shoe and hopper.

After adding a small amount of granulation to the hopper, turn the machine over by hand and adjust the pressure until a tablet is formed. Adjust the tablet weight until the desired weight is obtained. The pressure will have to be altered concurrently with the weight adjustments. It should be remembered that as the fill is increased the lower punch moves farther away from the upper punch, and more pressure will have to be applied to obtain comparable hardness. Conversely, when the fill is decreased, the pressure will have to be decreased. When all the adjustments have been made, fill the hopper with granulation and turn on the motor. Hardness and weight should be checked immediately, and suitable adjustments made if necessary. Periodic checks should be made on the tablet hardness and weight during the running of the batch, at 15- to 30-min intervals.

When the batch has been run off, turn off the power and remove loose dust and granulation with the vacuum cleaner. Release the pressure from the punches. Remove the feed hopper and the feed shoe. Remove the upper punch, the lower punch, and the die. Clean all surfaces of the tablet machine, and dry well with clean cloth. Cover surfaces with thin coating of grease or oil prior to storage.

As tablets are ejected from the machine after compression, they usually are accompanied by powder and uncompressed granulation. To remove this loose dust, the tablets are passed over a screen, which may be vibrating, and cleaned with a vacuum line.

Table 45-2. Single-Punch Tablet Machines

MACHINE MODEL	MAXIMUM TABLET DIAMETER (INCHES)	PRESS SPEED (TABLETS/MIN)	DEPTH OF FILL (INCHES)
Stokes-Pennwalt equipment[a]			
511-5	½	40–75	7/16
206-4	1¾	10–40	1 1/16
530-1	2	12–48	1⅜
525-2	3	16–48	2
Manesty equipment (Thomas Eng)			
Hand machine	½	100	7/16
Model F3	⅞	85	11/16
Model 35T[a]	3	36	2¼

[a] Widely used for veterinary boluses.

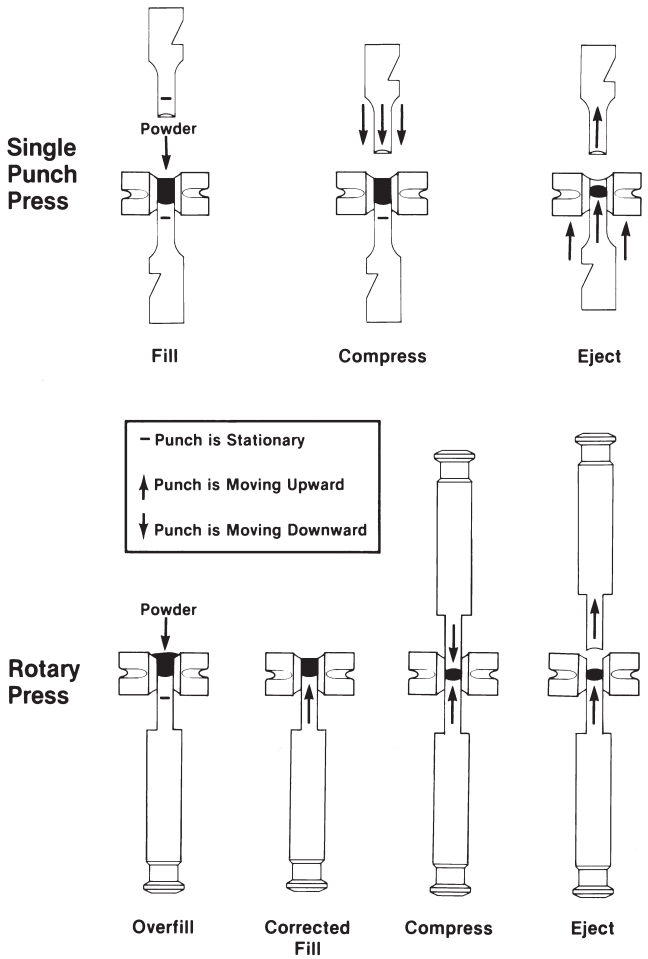


Figure 45-21. The steps associated with single-punch and rotary tablet machines.

Rotary Tablet Machines

For increased production, rotary machines offer great advantages. A head carrying a number of sets of punches and dies revolves continuously while the tablet granulation runs from the

hopper, through a feed frame and into the dies placed in a large, steel plate revolving under it. This method promotes a uniform fill of the die and therefore an accurate weight for the tablet. Compression takes place as the upper and lower punches pass between a pair of rollers, as can be seen in Figure 45-21. This action produces a slow squeezing effect on the material in the die cavity from the top and bottom and so gives a chance for the entrapped air to escape. The lower punch lifts up and ejects the tablet. Adjustments for tablet weight and hardness can be made without the use of tools while the machine is in operation. Figure 45-22 shows a high speed press. Figure 45-23 shows the tooling in a 16-station rotary press in the positions of a complete cycle to produce 1 tablet per set of tooling. One of the factors that contributes to the variation in tablet weight and hardness during compression is the internal flow of the granulation within the feed hopper.

On most rotary machine models there is an excess pressure release that cushions each compression and relieves the machine of all shocks and undue strain. The punches and dies can be removed readily for inspection, cleaning, and inserting different sets to produce a great variety of sizes and shapes. Many older presses have been modernized with protective shields to prevent physical injury and to comply with OSHA standards (Fig 45-24). It is possible to equip the machine with as few punches and dies as the job requires and thus economize on installation costs. For types of rotary machines available, see Table 45-3.

OPERATION OF ROTARY MACHINES—Before inserting punches and dies, make certain that the pressure has been released from the pressure wheel. The die holes should be cleaned thoroughly, making certain that the die seat is completely free of any foreign materials. Back off all die locks, and loosely insert dies into the die holes, then tap each die securely into place with a fiber of soft metal rod through the upper punch holes. After all the dies have been tapped into place, tighten each die lockscrew progressively and securely. As each screw is tightened the die is checked to see that it does not project above the die table. Insert the lower punches through the hole made available by removing the punch head. Turn the machine by hand until the punch bore coincides with the plug hole. Insert each lower punch in its place progressively. Insert the upper punches by dropping them into place in the head. Each punch (upper and lower) should be coated with a thin film of mineral oil before insertion into the machine. Adjust the ejection cam so that the lower punch is flush with the die table at the ejection point.

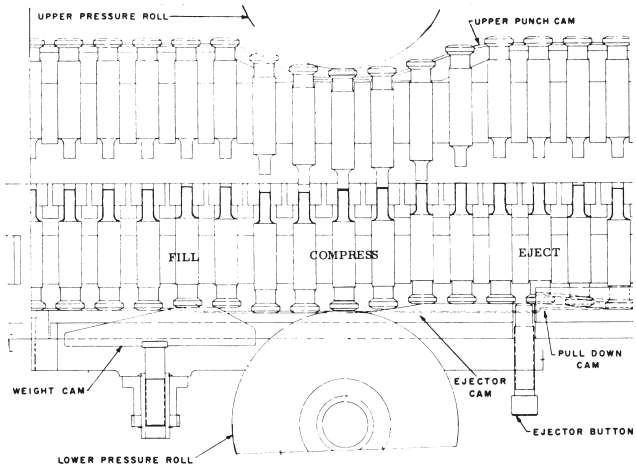


Figure 45-23. Tooling for a 16-station rotary press showing positions of the cycle required to produce one tablet per set of tooling (courtesy, Vector/Colton).

After insertion of the punches and dies, adjust the machine for the tablet weight and hardness. The feed frame should be attached to the machine along with the feed hopper. Add a small amount of the granulation through the hopper and turn over the machine by hand. Increase the pressure by rotating the pressure wheel until a tablet is formed. Check the weight of the tablet and adjust the fill to provide the desired tablet weight. Most likely more than one adjustment of the fill will be necessary before obtaining the acceptable weight. When the fill is decreased, the pressure must be decreased to provide the same hardness in the tablet. Conversely, when the fill is increased, the pressure must be increased to obtain comparable hardness.

Fill the hopper with the granulation and turn on the power. Check tablet weight and hardness immediately after the mechanical operation begins, and make suitable adjustments, if necessary. Check these properties routinely and regularly at 15- to 30-min intervals while the machine is in operation. When the batch has been run, turn off the power. Remove the hopper and feed frame from the machine. Remove loose granulation and dust with a vacuum line. Remove all pressure from the wheel. Remove the punches and dies in the reverse order of that used in setting up the machine. First, remove the upper punches individually,

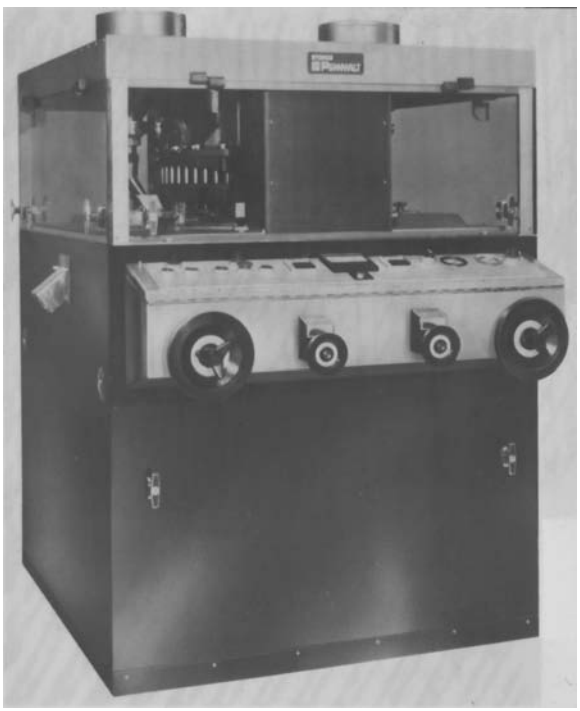


Figure 45-22. Model 747 High Speed Press, double-sided rotary compacting press designed to produce at speeds over 10,000/min (courtesy, Stokes/Pennwalt).

Figure 45-24. Research technicians use an instrumented tablet press to develop processes at Schering-Plough.

Table 45-3. High-Speed Rotary Tablet Machines

MACHINE MODEL	TOOL SETS	MAXIMUM TABLET DIAMETER (INCHES)	PRESS SPEED (TABLETS/MIN)	DEPTH OF FILL (INCHES)
Vector-Colton equipment				
2216	16	5/8	1180	3/4
240	16	7/8	640	13/16
250	12	1 1/4	480	1 1/8
260	25	1 3/16	1450	1 3/8
	31	1	1800	1 3/8
	33	15/16	1910	1 3/8
	43	5/8	2500	1 3/8
270	25	1 3/8	450	2 3/4
Stokes/Pennwalt equipment				
Manesty equipment (Thomas Eng)				
B3B	16	5/8	350–700	11/16
	23	7/16	500–1000	11/16
BB3B	27	5/8	760–1520	11/16
	33	7/16	924–1848	11/16
	35	5/8	1490–2980	11/16
	45	7/16	1913–3826	11/16
D3B	16	1	260–520	13/16
Key equipment				
DC-16	16	15/16	210–510	13/16
BBC	27	5/8	1025–2100	11/16
	35	5/8	1325–2725	11/16
	45	7/16	1700–3500	11/16
Cadpress	37	15/16	850–3500	13/16
	45	5/8	2000–6000	11/16
	55	7/16	2500–7500	11/16
Fette equipment (Raymond Auto)				
		(mm)		(mm)
Perfecta 1000	28	16	2100	18
	33	13	2475	18
Perfecta 2000	29	25	2175	22
	36	16	3600	18
	43	13	4300	18
Courtoy equipment (AC Compact)				
R-100	24	25	285–2260	20
	30	19	356–2850	20
	36	13	550–440	16
Kikusui equipment				
Hercules	18	37	180–540	16
	21	26	210–630	16
	29	25	290–870	16
Virgo	19	16	418–1330	16
	24	11	528–1680	16
Killian equipment				
TX21	21	28	231–1386	20
TX25	25	22	275–2166	20
TX30	30	16	330–3150	20
TX21D	21	25	231–1826	20
TX30A	30	16	330–3150	16
TX40A	40	13	440–4200	16
Korsch equipment				
PH 250/20	20	25	240–1640	22
PH 250/25	25	16	270–2700	18
PH 250/30	30	13	315–3233	18
Elizabeth-Hata equipment				
AP-15-SSU	15	17	300–1050	8–18
AP-18-SSU	18	13	360–1260	8–18
AP-22-SSU	22	11	440–1540	8–18
AP-32-SSU	32	17	640–2240	8–18
AP-38-MSU	38	13	760–2660	8–18
AP-45-MSU	32	11	900–3150	8–18
Vector-Colton equipment				
2247	33	5/8	3480	3/4
	41	7/16	4300	3/4
	49	7/16	5150	3/4
Magna	66	22/32	10,560	3/4
	74	1/2	11,840	3/4
	90	7/16	14,400	3/4
Stokes/Pennwalt equation				
552-2	35	5/8	800–3200	11/16
328-4	45	3/4	1600–4500	1 3/8
610	65	7/16	3500–10,000	11/16
747	65	7/16	3000–10,000	11/16
	53	5/8	2900–8100	11/16
	41	15/16	2150–6150	11/16
Direct Triple Compression Type				
580-1	45	7/16	525–2100	11/16
580-2	35	5/8	400–1600	11/16
610	65	7/16	3500–10,000	11/16
	53	5/8	2900–8100	11/16
Manesty equipment (Thomas Eng)				
Betapress	16	5/8	600–1500	11/16
	23	7/16	860–2160	11/16
Express	20	1	800–2000	13/16
	25	5/8	1000–2500	11/16
	30	7/16	1200–3000	11/16
Unipress	20	1	970–2420	13/16
	27	5/8	1300–3270	11/16
	34	7/16	1640–4120	11/16
Novapress	37	1	760–3700	13/16
	45	5/8	900–4500	11/16
	61	7/16	1220–6100	11/16
BB3B	35	5/8	1490–2980	11/16
BB4	27	5/8	900–2700	11/16
	35	5/8	1167–3500	11/16
	45	7/16	1500–4500	11/16
Rotapress				
Mark IIA	37	1	710–3550	13/16
	45	5/8	1640–8200	11/16
	61	7/16	2200–11,100	11/16
Mark IV	45	1	2090–6000	13/16
	55	5/8	2550–7330	11/16
	75	7/16	3500–10,000	11/16
Fette tool systems				
		(mm)		(mm)
PT 2080	29	25	435–2900	18
	36	16	540–4100	18
	43	16	645–4900	18
PT 2090IC	22	34	1760	18
	29	25	2900	18
	36	16	4140	18
	43	13	5160	18
	47	11	6110	18
PT 3090IC	37	34	5920	18
	49	25	7840	18
	61	16	9760	18
P 3100	37	25	5618	22
	45	16	8100	18
	55	13	9900	18
Courtoy equipment (AC Compact)				
R-200	43	25	750–5833	20
	55	19	916–8500	20
	65	13	1083–10,000	16
Kikusui equipment				
Libra	36	16	900–2520	16
	45	11	1125–3150	16
	49	8	1225–3430	16
Gemini	55	16	2200–7700	16
	67	11	2680–9380	16
	73	8	2920–10,200	16
Elizabeth-Hata equipment				
AP-45-LDU	45	17	1800–6300	8–18
AP-55-LDU	55	13	2200–7700	8–18
AP-65-LDU	65	11	2600–9100	8–18
AP-71-LDU	71	11	2840–9940	8–18
51-XLDU	51	17	2040–7140	8–18
65-XLDU	61	13	2440–8540	8–18

then the lower punches, and finally the dies. Wash each punch and die in alcohol and brush with a soft brush to remove adhering material. Dry them with a clean cloth, and cover them with a thin coating of grease or oil before storing.

High-Speed Rotary Tablet Machines

The rotary tablet machine has evolved gradually into models capable of compressing tablets at high production rates. See Figures 45-22, 45-25, and 45-26. This has been accomplished by increasing the number of stations, ie, sets of punches and dies, in each revolution of the machine head, improving feeding devices, and on some models installing dual compression points. In Figure 45-26, the drawing shows a rotary machine with dual compression points. Rotary machines with dual compression points are referred to as double rotary machines, and those with one compression point, single rotary. In the diagram, half of the tablets are produced 180° from the tablet chute. They travel outside the perimeter and discharge with the second tablet production. While these models are mechanically capable of operating at the production rates shown in Table 45-3, the actual speed still depends on the physical characteristics of the tablet granulation and the rate that is consistent with compressed tablets having satisfactory physical characteristics. The main difficulty in rapid machine operation is ensuring adequate filling of the dies. With rapid filling, dwell time of the die cavity beneath the feed frame is insufficient to ensure the requirements of uniform flow and packing of the dies. Various methods of force-feeding the granulation into the dies have been devised to refill the dies in the very short dwell time permitted on the high-speed machine. These devices are illustrated in Figure 45-14. Presses with triple compression points (see Table 45-3) permit the partial compaction of material before final compaction. This provides for partial deaeration and particle orientation of material before final compression. This helps in the direct compacting of materials and reduces laminating and capping due to entrapped air.

Figure 45-25. Rotapress Mark IIA. Designed for improvements in sound reduction, operator safety, cleanliness, and operational convenience; note the control panel on front of machine (courtesy, Thomas/Manesty).

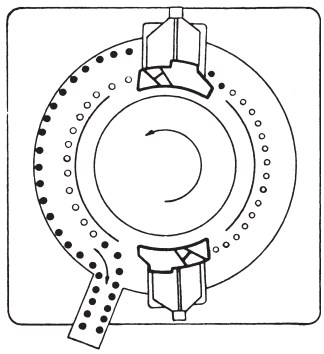


Figure 45-26. The movement of tablets on die table of a double rotary press (courtesy, Vector/Colton).

Multilayer Rotary Tablet Machines

The rotary tablet machines also have been developed into models capable of producing multiple-layer tablets; the machines are able to make 1-, 2-, or 3-layer tablets (Versa Press, *Stokes/Pennwalt*). Stratified tablets offer a number of advantages. Incompatible drugs can be formed into a single tablet by separating the layers containing them with a layer of inert material. It has permitted the formulation of time-delay medication and offers a wide variety of possibilities in developing color combinations that give the products identity.

Originally, the tablets were prepared by a single-compression method. The dies were filled with the different granulations in successive layers, and the tablet was formed by a single compression stroke. The separation lines of the tablets prepared by this method tended to be irregular. In the machines now available for multilayer production the granulation receives a precompression stroke after the first and second fill, which lightly compacts the granulation and maintains a well-defined surface of separation between each layer. The operator is able to eject either precompressed layer with the machine running at any desired speed for periodic weight and analysis checks.

Other multiple-compression presses can receive previously compressed tablets and compress another granulation around the preformed tablet. An example of a press with this capability is the Manesty Drycota *(Thomas/Manesty)*. Pressure-coated tablets can be used to separate incompatible drug substances and also to give an enteric coating to the core tablets.

Capping and Splitting of Tablets

The splitting or capping of tablets is one of great concern and annoyance in tablet making. It is quite difficult to detect while the tablets are being processed but can be detected easily by vigorously shaking a few in the cupped hands. A slightly chipped tablet does not necessarily mean that the tablet will cap or split.

There are many factors that may cause a tablet to cap or split:

Excess *fines* or powder, which traps air in the tablet mixture.

Deep markings on tablet punches. Many designs or *scores* on punches are too broad and deep. Hairline markings are just as appropriate as deep, heavy markings.

Figure 45-27. Courtoy R-100 with computer-controlled operation.

Worn and imperfect punches. Punches should be smooth and buffed. Nicked punches often cause capping. The development of fine feather edges on tablets indicates wear on punches.

Worn dies. Dies should be replaced or reversed. Dies that are chrome-plated or have tungsten carbide inserts wear longer and give better results than ordinary steel dies.

Too much pressure. By reducing the pressure on the machines the condition may be corrected.

Unsuitable formula. It may be necessary to change the formula.

Moist and soft granulation. This type of granulation will not flow freely into the dies, thus giving uneven weights and soft or capped tablets.

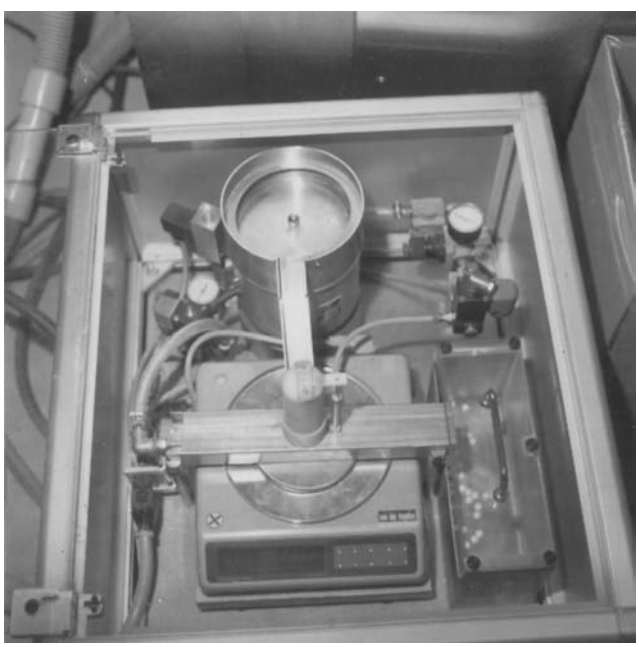


Figure 45-28. Direct weighing of tablets produced gives actual weight feedback for the controller of the Courtoy R-100 (seen in the bottom left of Fig 45-27).

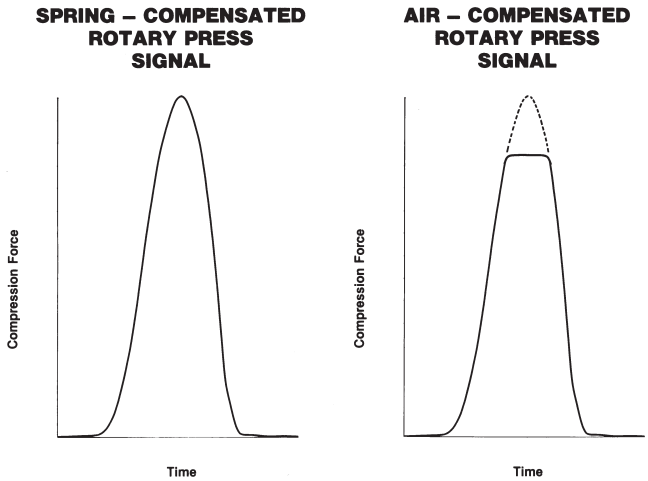


Figure 45-29. Force-time curves for two types of tablet press.

Poorly machined punches. Uneven punches are detrimental to the tablet machine itself and will not produce tablets of accurate weight. One punch out of alignment may cause one tablet to split or cap on every revolution.

Instrumented Tablet Presses

Compressional and ejectional forces involved in tablet compression can be studied by attaching strain gauges to the punches and other press components involved in compression. The electrical output of the gauges has been monitored by telemetry or use of a dual-beam oscilloscope equipped with camera.[42,43] Instrumentation permits a study of the compaction characteristics of granulations, their flowabilities, and the effect of formulation additives, such as lubricants, as well as differences in tablet press design, as shown in Figures 45-27 to 45-30. Physical characteristics of tablets, such as hardness, friability, disintegration time, and dissolution rate, are influenced not only by the nature of the formulation but by the compressional force as well.

As can be seen in Figures 45-29 and 45-30, the rate and duration of compaction forces can be quantified. The rate of force application has a profound effect on powder consolidation within the die and, hence, efficiency of packing and powder compaction. The rate of release of force, or *decompression* has

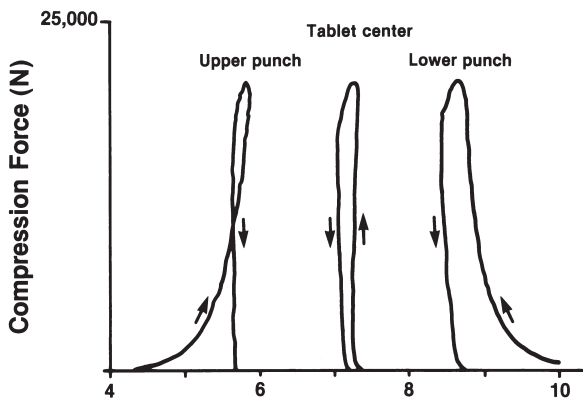


Figure 45-30. Plot showing the upper and lower punch forces as functions of the position of the punch face within the die. A biaxial force/displacement curve also shown is a plot of the position of the tablet center as a function of the compression force.

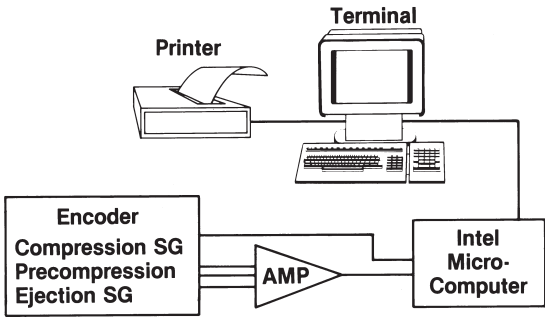


Figure 45-31. Schematic of an instrumentation system using a microcomputer as developed by Schering-Plough.

a direct effect on the ability of the tablet to withstand relaxation. A prominent hypothesis, fostered by Hiestand[44,45] and later Luenberger[46], suggested that capping and laminating of tablets is caused by too-rapid stress relaxation or decompression. This explains why slowing a tablet press and using tapered dies is useful in such situations. Most prominent pharmaceutical scientists have embraced this theory and largely have discounted air entrapment as a cause of capping and laminating.

Figure 45-30 presents an interesting set of plots. Walter and Augsburger reported that as compaction force rises, the steel tooling actually compresses in accommodation to the forces applied. The forces used to produce a tablet are considerable and should be monitored and understood.[47] Therefore, definition of the compressional force and duration of force (dwell time) giving a satisfactory tablet for a formulation provides an in-process control for obtaining both tablet-to-tablet and lot-to-lot uniformity (see Figs 45-24 and 45-31).

Instrumentation has led to the development of on-line, automatic, electromechanical tablet weight-control systems capable of continuously monitoring the weights of tablets as they are produced. Units are available commercially (Thomas Tablet Sentinel *(Thomas Eng);* Fette Compression Force Monitor *(Raymond Auto);* Vali-Tab *(Stokes/Pennwalt)*) and are applicable to single or rotary tablet machines. Most commercial presses today can be delivered with some sort of instrumentation attached. When tablet weights vary from preset limits, the monitor automatically will adjust the weight control mechanism to reestablish weights within acceptable limits. If the difficulty continues, the unit will activate an audible warning signal or an optional shut-down relay on the press (see Figs 45-27 and 45-28). Most production-model tablet presses come equipped with complete instrumentation (optional) and with options for statistical analysis and print out of compression/ejection signals. The techniques and applications of press instrumentation have been reviewed.[48,49]

Contamination Control

While good manufacturing practices used by the pharmaceutical industry for many years have stressed the importance of cleanliness of equipment and facilities for the manufacture of drug products, the penicillin contamination problem resulted in renewed emphasis on this aspect of manufacturing. Penicillin, as either an airborne dust or residual quantities remaining in equipment, is believed to have contaminated unrelated products in sufficient concentrations to cause allergic reactions in individuals hypersensitive to penicillin who received these products. This resulted in the industry spending millions of dollars to change or modify buildings, manufacturing processes, equipment, and standard operating procedures to eliminate penicillin contamination.

With this problem has come renewed emphasis on the dust problem, material handling, and equipment cleaning in dealing with drugs, especially potent chemicals. Any process using chemicals in powder form can be a dusty operation; the preparation of compressed tablets and encapsulation fall in this category. In the design of tablet presses attention is being given to the control and elimination of dust generated in the tableting process. In the Perfecta press shown in Figure 45-32, the pressing compartment is completely sealed off from the outside environment, making cross-contamination nearly impossible. The pressing compartment can be kept dust-free by the air supply and vacuum equipment developed for the machine. It removes airborne dust and granular particles that have not been compressed, thus keeping the circular pressing compartment and the upper and lower punch guides free of dust.

Drug manufacturers have the responsibility to make certain that microorganisms present in finished products are unlikely to cause harm to the patient and will not be deleterious to the product. An outbreak of *Salmonella* infections in Scandinavian countries was traced to thyroid tablets that had been prepared from contaminated thyroid powder. This concern eventually led to the establishment of microbial limits for raw materials of animal or botanical origin, especially those that readily support microbial growth and are not rendered sterile during subsequent processing. Harmful microorganisms when present in oral products include *Salmonella* spp, *Escherichia coli,* certain *Pseudomonas* spp such as *P aeruginosa,* and *Staphylococcus aureus*. The compendia have microbial limits on raw materials such as aluminum hydroxide gel, cornstarch, thyroid, acacia, and gelatin.

These represent examples of the industry's efforts to conform with the intent of current good manufacturing practice as defined by the FDA.

Figure 45-32. Fette Perfecta 3000 high-speed tablet press with pressing compartment completely sealed off from outside environment, making cross-contamination impossible (courtesy, Raymond Auto).

Tablet Formulations

WET GRANULATION

CT Acetaminophen, 300 mg

INGREDIENTS	IN EACH	IN 10,000
Acetaminophen	300 mg	3000 g
Polyvinylpyrrolidone	22.5 mg	225 g
Lactose 61.75 mg 617.5 g		
Alcohol SD3A—200 proof	4.5 mL	45 L
Stearic acid	9 mg	90 g
Talc	13.5 mg	135 g
Cornstarch	43.25 mg	432.5 g

Blend acetaminophen, polyvinylpyrrolidone, and lactose together; pass through a 40-mesh screen. Add the alcohol slowly, and knead well. Screen the wet mass through a 4-mesh screen. Dry the granulation at 50° overnight. Screen the dried granulation through a 20-mesh screen. Bolt the stearic acid, talc, and cornstarch through a 60-mesh screen prior to mixing by tumbling with the granulation. Compress, using 7/16-inch standard concave punch. Ten tablets should weigh 4.5 g (courtesy, *Abbott*).

CT Ascorbic Acid USP, 50 mg

INGREDIENTS	IN EACH	IN 7000
Ascorbic acid USP (powder No. 80)[a]	55 mg	385 g
Lactose	21 mg	147 g
Starch (potato)	13 mg	91 g
Ethylcellulose N 100 (80–105 cps)	16 mg	112 g
Starch (potato)	7 mg	49 g
Talc	6.5 mg	45.5 g
Calcium stearate (impalpable powder)1 mg		7 g
Weight of granulation		836.5 g

[a] Includes 10% in excess of label claim.
Granulate the first three ingredients with ethylcellulose (5%) dissolved in anhydrous ethyl alcohol, adding additional anhydrous alcohol to obtain good, wet granules. Wet-screen through a #8 stainless steel screen and dry at room temperature in an air-conditioned area. Dry-screen through a #20 stainless steel screen and incorporate the remaining three ingredients. Mix thoroughly and compress. Use a flat, beveled, ¼-inch punch. Twenty tablets should weigh 2.39 g.

Chewable Antacid Tablets

INGREDIENTS	IN EACH	IN 10,000
Magnesium trisilicate	500 mg	5000 g
Aluminum hydroxide, dried gel	250 mg	2500 g
Mannitol	300 mg	3000 g
Sodium saccharin	2 mg	20 g
Starch paste, 5%	qs	qs
Oil of peppermint	1 mg	10 g
Magnesium stearate	10 mg	100 g
Cornstarch	10 mg	100 g

Mix the magnesium trisilicate and aluminum hydroxide with the mannitol. Dissolve the sodium saccharin in a small quantity of purified water, then combine this with the starch paste. Granulate the powder blend with the starch paste. Dry at 140°F and screen through 16-mesh screen. Add the flavoring oil, magnesium stearate, and corn starch; mix well. Age the granulation for at least 24 hr and compress, using a ⅝-inch, flat-face, bevel-edge punch (courtesy, *Atlas*).

CT Hexavitamin

INGREDIENTS	IN EACH	IN 7000
Ascorbic acid USP (powder)[a]	82.5 mg	577.5 g
Thiamine mononitrate USP (powder)[a]	2.4 mg	16.8 g
Riboflavin[a]	3.3 mg	23.1 g
Nicotinamide USP (powder)[a]	22 mg	154 g
Starch	13.9 mg	97.4 g
Lactose	5.9 mg	41.2 g
Zein	6.4 mg	45 g
Vitamin A acetate	6250 U	
Vitamin D_2[a] (use Pfizer crystalets medium granules containing 500,000 U vitamin A acetate and 50,000 U vitamin D_2/g)	625 U	87.5 g
Magnesium stearate		7.5 g
Weight of granulation		1050 g

[a] Includes the following in excess of label claim: ascorbic acid 10%, thiamine mononitrate 20%, riboflavin 10%, nicotinamide 10%, and vitamin A acetate–vitamin D_2 crystalets 25%.
Thoroughly mix the first six ingredients and granulate with zein (10% in ethyl alcohol, adding additional alcohol if necessary to obtain good, wet granules). Wet-screen through a #8 stainless steel screen and dry at 110 to 120°F. Dry-screen through a #20 stainless steel screen and add the vitamin crystalets. Mix thoroughly, lubricate, and compress. Ten tablets should weigh 1.50 g. Coat with syrup.

CT Theobromine-Phenobarbital

INGREDIENTS	IN EACH	IN 7000
Theobromine	325 mg	2275 g
Phenobarbital	33 mg	231 g
Starch	39 mg	273 g
Talc	8 mg	56 g
Acacia (powder)	8 mg	56 g
Stearic acid	0.7 mg	4.9 g
Weight of granulation		2895.9 g

Prepare a paste with the acacia and an equal weight of starch. Use this paste for granulating the theobromine and phenobarbital. Dry and put through a 12-mesh screen, add the remainder of the material, mix thoroughly, and compress into tablets, using a 13/32-inch concave punch. Ten tablets should weigh 4.13 g.

FLUID-BED GRANULATION

CT Ascorbic Acid USP, 50 mg

INGREDIENTS	IN EACH	IN 10,000
Ascorbic acid USP (powder no 80)[a]	55 mg	550 g
Lactose	21 mg	210 g
Starch (potato)	13 mg	130 g
Ethylcellulose N100 (80–105 cps)	16 mg	160 g
Starch (potato)	7 mg	70 g
Talc	6.5 mg	65 g
Calcium stearate	1 mg	10 g
Weight of granulation		1195.0 g

[a] Includes 10% in excess of claim.
Add the first three ingredients to the granulator. Mix for 5 to 15 min or until well mixed. Dissolve the ethylcellulose in anhydrous ethanol and spray this solution and any additional ethanol into the fluidized mixture. Cease spraying when good granules are produced. Dry to approximately 3% moisture. Remove the granules and place them in a suitable blender. Sequentially add the remaining three ingredients with mixing steps in between each addition. Compress, using a flat, beveled, 1/4-inch punch. Twenty tablets should weigh 2.39 g.

Sustained-Release (SR) Procainamide Tablets

INGREDIENTS	IN EACH	IN 10,000
Procainamide	500 mg	5000 g
HPMC 2208, USP	300 mg	3000 g
Carnauba wax	60 mg	600 g
HPMC 2910, USP	30 mg	300 g
Magnesium stearate	4 mg	40 g
Stearic acid	11 mg	110 g
Talc	5 mg	50 g
Weight of granulation		9100 g

Place the first three ingredients in the granulator and mix for 5 to 15 min. Dissolve the HPMC in water (mix in hot water, then cool down) and spray into the fluidized mixture. Dry to approximately 5% moisture. Sequentially add the last three ingredients, with mixing steps in between each addition. Compress, using capsule-shaped tooling. Ten tablets should weigh 9.1 g.

DRY GRANULATION

CT Acetylsalicylic Acid

INGREDIENTS	IN EACH	IN 7000
Acetylsalicylic Acid (crystals 20-mesh)	0.325 g	2275 g
Starch		226.8 g
Weight of granulation		2501.8 g

Dry the starch to a moisture content of 10%.Thoroughly mix this with the acetylsalicylic acid. Compress into slugs. Grind the slugs to 14- to 16-mesh size. Recompress into tablets, using a 13/32-inch punch. Ten tablets should weigh 3.575 g.

CT Sodium Phenobarbital

INGREDIENTS	IN EACH	IN 7000
Phenobarbital sodium	65 mg	455 g
Lactose (granular, 12-mesh)	26 mg	182 g
Starch	20 mg	140 g
Talc	20 mg	140 g
Magnesium stearate	0.3 mg	2.1 g
Weight of granulation		919.1 g

Mix all the ingredients thoroughly. Compress into slugs. Grind and screen to 14- to 16-mesh granules. Recompress into tablets, using a 9/32-inch concave punch. Ten tablets should weigh 1.3 g.

CT Vitamin B Complex

INGREDIENTS	IN EACH	IN 10,000
Thiamine mononitrate[a]	0.733 mg	7.33 g
Riboflavin[a]	0.733 mg	7.33 g
Pyridoxine hydrochloride	0.333 mg	3.33 g
Calcium pantothenate[a]	0.4 mg	4 g
Nicotinamide	5 mg	50 g
Lactose (powder)	75.2 mg	752 g
Starch	21.9 mg	219 g
Talc	20 mg	200 g
Stearic acid (powder)	0.701 mg	7.01 g
Weight of granulation		1250 g

[a] Includes 10% in excess of label claim.
Mix all the ingredients thoroughly. Compress into slugs. Grind and screen to 14- to 16-mesh granules. Recompress into tablets, using a ¼-inch concave punch. Ten tablets should weigh 1.25 g.
Sufficient tartaric acid should be used in these tablets to adjust the pH to 4.5.

DIRECT COMPRESSION

APC Tablets

INGREDIENTS	IN EACH	IN 10,000
Aspirin (40-mesh crystal)	224 mg	2240 g
Phenacetin	160 mg	1600 g
Caffeine (anhyd USP gran)	32 mg	320 g
Compressible sugar (Di-Pac[a])	93.4 mg	934 g
Sterotex	7.8 mg	78 g
Silica gel (Syloid 244[b])	2.8 mg	28 g

[a] *Amstar.*
[b] *Davison Chem.*
Blend ingredients in a twin-shell blender for 15 min and compress on a 13/32-inch standard concave punch (courtesy, *Amstar*).

CT Ascorbic Acid USP, 250 mg

INGREDIENTS	IN EACH	IN 10,000
Ascorbic Acid USP (Merck, fine crystals)	255 mg	2550 g
Microcrystalline cellulose[a]	159 mg	1590 g
Stearic acid	9 mg	90 g
Colloidal silica[b]	2 mg	20 g
Weight of granulation		4250 g

[a] Avicel-PH-101.
[b] Cab-O-Sil.
Blend all ingredients in a suitable blender. Compress, using 7/16-inch standard concave punch. Ten tablets should weigh 4.25 g (courtesy, *FMC*).

Breath Freshener Tablets

INGREDIENTS	IN EACH	IN 10,000
Wintergreen oil	0.6 mg	6 g
Menthol	0.85 mg	8.5 g
Peppermint oil	0.3 mg	3 g
Silica gel (Syloid 244[a])	1 mg	10 g
Sodium saccharin	0.3 mg	3 g
Sodium bicarbonate	14 mg	140 g
Mannitol USP (granular)	180.95 mg	1809.5 g
Calcium stearate	2 mg	20 g

[a] *Davison* Chem.
Mix the flavor oils and menthol until liquid. Adsorb onto the silica gel. Add the remaining ingredients. Blend and compress on 5/16-inch, flat-face bevel-edge punch to a thickness of 3.1 mm (courtesy, *Atlas*).

Chewable Antacid Tablets

INGREDIENTS	IN EACH	IN 10,000
Aluminum hydroxide and magnesium carbonate, codried gel[a]	325 mg	3250 g
Mannitol USP (granular)	675 mg	6750 g
Microcrystalline cellulose[b]	75 mg	750 g
Corn starch	30 mg	300 g
Calcium stearate	22 mg	220 g
Flavor	qs	qs

[a] *Reheis F-MA-11.*
[b] *Avicel*
Blend all ingredients in a suitable blender. Compress, using a 5/8-inch, flat-face, bevel-edge punch (courtesy, *Atlas*).

Chewable Multivitamin Tablets

INGREDIENTS	IN EACH	IN 10,000
Vitamin A USP (dry, stabilized form)	5000 USP units	50 million units
Vitamin D dry, stabilized form)	400 USP units	4 million units
Ascorbic Acid USP	60.0 mg	600 g
Thiamine Hydrochloride USP	1 mg	10 g
Riboflavin USP	1.5 mg	15 g
Pyridoxine Hydrochloride USP	1 mg	10 g
Cyanocobalamin USP	2 μg	20 mg
Calcium Pantothenate USP	3 mg	30 g
Niacinamide USP	10 mg	100 g
Mannitol USP (granular)	236.2 mg	2362 g
Cornstarch	16.6 mg	166 g
Sodium saccharin	1.1 mg	11 g
Magnesium stearate	6.6 mg	66 g
Talc USP	10 mg	100 g
Flavor	qs	qs

Blend all ingredients in a suitable blender. Compress, using a ⅜-inch, flat-face, bevel-edge punch (courtesy, *Atlas*).

CT Ferrous Sulfate

INGREDIENTS	IN EACH	IN 7000
Ferrous Sulfate USP (crystalline)	0.325 g	2275 g
Talc		0.975 g
Sterotex		1.95 g
Weight of granulation		2277.93 g

Grind to 12- to 14-mesh, lubricate, and compress. Coat immediately to avoid oxidation to the ferric state with 0.410 gr of tolu balsam (dissolved in alcohol) and 0.060 gr of salol and chalk. Use a deep, concave, 1½₂-inch punch. Ten tablets should weigh 3.25 g.

CT Methenamine

INGREDIENTS	IN EACH	IN 7000
Methenamine (12- to 14-mesh crystals)	0.325 g	2275 g
Weight of granulation		2275 g

Compress directly, using a 7⁄₁₆-inch punch. Ten tablets should weigh 3.25 g.

CT Phenobarbital USP, 30 mg

INGREDIENTS	IN EACH	IN 10,000
Phenobarbital	30.59 mg	305.9 g
Microcrystalline cellulose[a]	30.59 mg	305.9 g
Spray-dried lactose	69.16 mg	691.6 g
Colloidal silica[b]	1.33 mg	13.3 g
Stearic acid	1.33 mg	13.3 g
Weight of granulation		1330 g

[a] Avicel-PH-101.
[b] QUSO F-22.
Screen the phenobarbital to break up lumps and blend with the microcrystalline cellulose. Add spray-dried lactose and blend. Finally, add the stearic acid and colloidal silica; blend to obtain a homogeneous mixture. Compress, using a ⅝₂-inch, shallow, concave punch. Ten tablets should weigh 1.33 g (courtesy, *FMC*).

Molded Tablets or Tablet Triturates (TT)

Tablet triturates are small, discoid masses of molded powders weighing 30 to 250 mg each. The base consists of lactose, β-lactose, mannitol, dextrose, or other rapidly soluble materials. It is desirable in making tablet triturates to prepare a solid dosage form that is rapidly soluble; as a result they are generally softer than compressed tablets.

Figure 45-33. Hand-molding tablet triturates (courtesy, Merck).

This type of dosage form is selected for a number of drugs because of its rapidly dissolving characteristic. Nitroglycerin in many concentrations is prepared in tablet triturate form since the molded tablet rapidly dissolves when administered by placing under the tongue. Potent alkaloids and highly toxic drugs used in small doses are prepared as tablet triturates that can serve as dispensing tablets to be used as the source of the drug in compounding other formulations or solutions. Narcotics in the form of hypodermic tablets originally were made as tablet triturates because they rapidly dissolve in sterile water for injection prior to administration. Today with stable injections of narcotics available, there is no longer any justification for their use in this manner. Although many hypodermic tablets currently are made, they are used primarily for oral administration.

Tablet triturates are made by forcing a moistened blend of the drug and diluent into a mold, extruding the formed mass, which is allowed to dry. This method is essentially the same as it was when introduced by Fuller in 1878. Hand molds may vary in size, but the method of operation is essentially the same. Molds consist of two plates made from polystyrene plastic, hard rubber, nickel-plated brass, or stainless steel. The mold plate contains 50 to 500 carefully polished perforations. The other plate is fitted with a corresponding number of projecting pegs or punches that fit the perforations in the mold plate. The mold plate is placed on a flat surface, the moistened mass is forced into the perforations, and the excess is scraped from the top surface. The mold plate is placed over the plate with the corresponding pegs and lowered. As the plates come together, the pegs force the tablet triturates from the molds. They remain on the tops of the pegs until dry, and they can be handled (see Fig 45-33). In some hand molds, as shown in Figure 45-34, the pegs are forced down onto the plate holding the moist trituration.

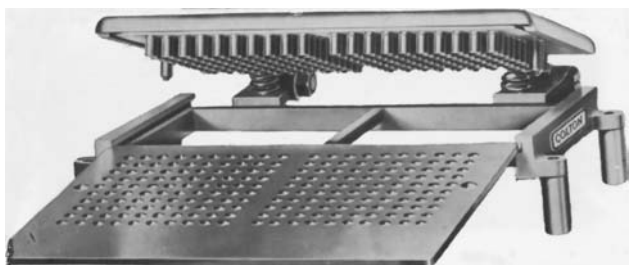


Figure 45-34. Tablet triturate mold (courtesy, Vector/Colton).

FORMULATION

In developing a formula it is essential to know the blank weight of the mold that is to be used. To determine this, the weight of the diluent that exactly fills all the openings in the mold is determined by experiment. This amount of diluent is weighed and placed aside. The total amount of the drug required is determined by multiplying the number of perforations in the plate used in the previous experiment by the amount of drug desired in each tablet. The comparative bulk of this medication is compared with that of an equal volume of diluent and that quantity of diluent is removed and weighed. The drug and the remaining diluent are mixed by trituration, and the resulting triturate is moistened and forced into the openings of the mold. If the perforations are not filled completely, more diluent is added, its weight noted, and the formula written from the results of the experiments.

It is also permissible in the development of the formula to weigh the quantity of medication needed for the number of tablets represented by the number of perforations in the mold, triturate with a weighed portion (more than 1/2) of the diluent, moisten the mixture, and press it into the perforations of the mold. An additional quantity of the diluent is moistened immediately and also forced into the perforations in the plate until they are filled completely. All excess diluent is removed, the trial tablets are forced from the mold, then triturated until uniform, moistened again, if necessary, and remolded. When these tablets are dried thoroughly and weighed, the difference between their total weight and the weight of medication taken will indicate the amount of diluent required and accordingly supply the formula for future use for that particular tablet triturate.

PREPARATION

The mixed powders are moistened with a proper mixture of alcohol and water, although other solvents or moistening agents such as acetone, petroleum benzin, and various combinations of these may be used in specific cases; the agent of choice depends on the solvent action that it will exert on the powder mixture. Often the moistening agent is 50% alcohol, but this concentration may be increased or decreased depending on the constituents of the formula. Care must be used in adding the solvent mixture to the powder. If too much is used, the mass will be soggy and will require a long time to dry, and the finished tablet will be hard and slowly soluble; if the mass is too wet, shrinkage will occur in the molded tablets; finally, a condition known as creeping will be noticed. Creeping is the concentration of the medication on the surface of the tablet caused by capillarity and rapid evaporation of the solvent from the surface. Because molded tablets by their very nature are quite friable, an inaccurate strength in each tablet may result from creeping if powder is lost from the tablet's surface. On the other hand, if an insufficient amount of moistening agent is used, the mass will not have the proper cohesion to make a firm tablet. The correct amount of moistening agent can be determined initially only by experiment.

HAND-MOLDING TABLET TRITURATES

In preparing hand-molded tablets place the mold plate on a glass plate. The properly moistened material is pressed into the perforations of the mold with a broad spatula, exerting uniform pressure over each opening. The excess material is removed by passing the spatula at an oblique angle, with strong hand pressure, over the mold to give a clean, flat surface. The material thus removed should be placed with the remainder of the unmolded material.

The mold with the filled perforations should be reversed and moved to another clean part of the plate where the pressing operation with the spatula is repeated. It may be necessary to add more material to fill the perforations completely and uniformly. The mold should be allowed to stand in a position so that part of the moistening agent will evaporate equally from both faces. While the first plate is drying, another mold can be prepared. As soon as the second mold has been completed, the first mold should be sufficiently surface-dried so that the pegs will press the tablets from the mold with a minimum of sticking.

To remove the tablets from the mold, place the mold over the peg plate so that the pegs and the perforations are in juxtaposition. The tablets are released from the mold by hand pressure, which forces the pegs through the perforations. The ejected tablets are spread evenly in single layers on silk trays and dried in a clean, dust-free chamber with warm, circulating air. If only a small quantity of tablet triturates is made and no warm-air oven is available, the tablet triturates may be dried to constant weight at room temperature.

MACHINE-MOLDING TABLET TRITURATES

Tablet triturates also can be made using mechanical equipment. The automatic tablet triturate machine illustrated in Figure 45-35 makes tablet triturates at a rate of 2500/min. For machine-molding, the powder mass need not be as moist as for plate-molding, since the time interval between forming the tablets and pressing them is considerably shorter. The moistened mass passes through the funnel of the hopper to the feed plates below. In this feed plate are four holes having the same diameter as the mouth of the funnel. The material fills one hole at a time and, when filled, revolves to a position just over the mold plate. When in position the weighted pressure foot lowers and imprisons the powder. At the same time a spreader in the sole of the pressure foot rubs it into the mold cavities and evens it off so that the triturates are smooth on the surface and are of uniform density. When this operation is completed, the mold passes to the next position, where it registers with a nest of punches or pegs that eject the tablets from the mold plate onto a conveyor belt. The conveyor belt sometimes is extended to a length of 8 or 10 ft. under a battery of infrared drying lamps to hasten the setting of the tablets for more rapid handling. This method of drying can be used only if the drug is chemically stable to these drying conditions.

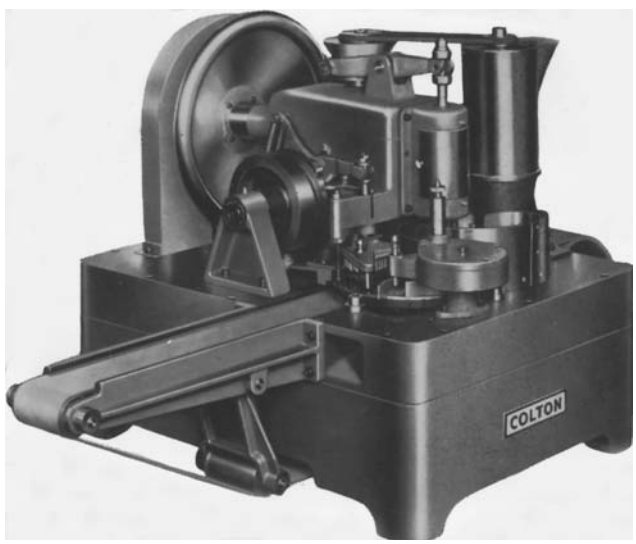


Figure 45-35. Automatic tablet triturate machine (courtesy, Vector-Colton).

COMPRESSED TABLET TRITURATES

Frequently, tablet triturates are prepared on compression tablet machines using flat-face punches. When solubility and a clear solution are required, water-soluble lubricants must be used to prevent sticking to the punches. The granulations are prepared as directed for ordinary compressed tablets; lactose generally is used as the diluent. Generally, tablet triturates prepared by this method are not as satisfactory as the molded type regarding their solubility and solution characteristics.

TABLET CHARACTERISTICS

Compressed tablets may be characterized or described by a number of specifications. These include the diameter size, shape, thickness, weight, hardness, disintegration time, and dissolution characteristics. The diameter and shape depend on the die and the punches selected for the compression of the tablet. Generally, tablets are discoid in shape, although they may be oval, oblong, round, cylindrical, or triangular. Their upper and lower surfaces may be flat, round, concave, or convex to various degrees. The concave punches (used to prepare convex tablets) are referred to as shallow, standard, and deep cup, depending on the degree of concavity (see Figs 45-17 to 45-20). The tablets may be scored in halves or quadrants to facilitate breaking if a smaller dose is desired. The top or lower surface may be embossed or engraved with a symbol or letters that serve as an additional means of identifying the source of the tablets. These characteristics along with the color of the tablets tend to make them distinctive and identifiable with the active ingredient that they contain.

The remaining specifications assure the manufacturer that the tablets do not vary from one production lot to another. In the case of new tablet formulations their therapeutic efficacy is demonstrated through clinical trials, and it is the manufacturer's aim to reproduce the same tablet with the exact characteristics of the tablets that were used in the clinical evaluation of the dosage form. Therefore, from the control viewpoint these specifications are important for reasons other than physical appearance.

Tablet Hardness

The resistance of the tablet to chipping, abrasion, or breakage under conditions of storage, transportation, and handling before usage depends on its hardness. In the past, a rule of thumb described a tablet to be of proper hardness if it was firm enough to break with a sharp snap when it was held between the 2nd and 3rd fingers and using the thumb as the fulcrum, yet didn't break when it fell on the floor. For obvious reasons and control purposes a number of attempts have been made to quantitate the degree of hardness.

A small and portable hardness tester was manufactured and introduced in the mid-1930s by *Monsanto*. It now is distributed by the Stokes Div *(Pennwalt)* and may be designated as either the Monsanto or Stokes hardness tester. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. The force is measured in kilograms and when used in production, a hardness of 4 kg is considered to be minimum for a satisfactory tablet.

The Strong-Cobb hardness tester introduced in 1950 also measures the diametrically applied force required to break the tablet. In this instrument the force is produced by a manually operated air pump. As the pressure is increased, a plunger is forced against the tablet placed on anvil. The final breaking point is indicated on a dial calibrated into 30 arbitrary units. The hardness values of the Stokes and Strong-Cobb instruments are not equivalent. Values obtained with the Strong-Cobb tester have been found to be 1.6 times those of the Stokes tester.

Another instrument is the Pfizer hardness tester, which operates on the same mechanical principle as ordinary pliers. The force required to break the tablet is recorded on a dial and may be expressed in either kilograms or pounds of force. In an experimental comparison of testers the Pfizer and the Stokes testers were found to check each other fairly well. Again the Strong-Cobb tester was found to give values 1.4 to 1.7 times the absolute values on the other instruments.

The most widely used apparatus to measure tablet hardness or crushing strength is the Schleuniger apparatus, also known as the Heberlein, distributed by *Vector*. This and other, newer, electrically operated test equipment eliminate the operator variability inherent in the measurements described above. Newer equipment is also available with printers to provide a record of test results. See Figure 45-36.

Manufacturers, such as *Key, Van Kel, Erweka,* and others, make similar hardness testers.

Hardness (or more appropriately, crushing strength) determinations are made throughout the tablet runs to determine the need for pressure adjustments on the tableting machine. If the tablet is too hard, it may not disintegrate in the required period of time or meet the dissolution specification; if it is too soft, it will not withstand the handling during subsequent processing such as coating or packaging and shipping operations.

A tablet property related to hardness is *friability,* and the measurement is made by use of the Roche friabilator. Rather than a measure of the force required to crush a tablet, the instrument is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling, and shipping. A number of tablets are weighed and placed in the tumbling apparatus where they are exposed to rolling and repeated shocks resulting from freefalls within the apparatus. After a given number of rotations the tablets are weighed, and the loss in weight indicates the ability of the tablets to withstand this type of wear (Fig 45-37).

Recent research has proposed that there are at least three measurable hardness parameters that can give a clue to the compatibility and intrinsic strength of powdered materials. These include bonding strength, internal strain, and brittleness. Hiestand proposed indices to quantify these parameters, and they are listed in Table 45-4 for a number of materials.

The higher the bonding index, the stronger a tablet is likely to be. The higher the strain index, the weaker the tablet. Since the two parameters are opposite in their effect on the tablet, it is possible for a material (such as Avicel) to have a relatively high strain index, but yet have superior compaction properties because of an extraordinary bonding potential. The higher the brittleness index, the more friable the tablet is likely to be. For

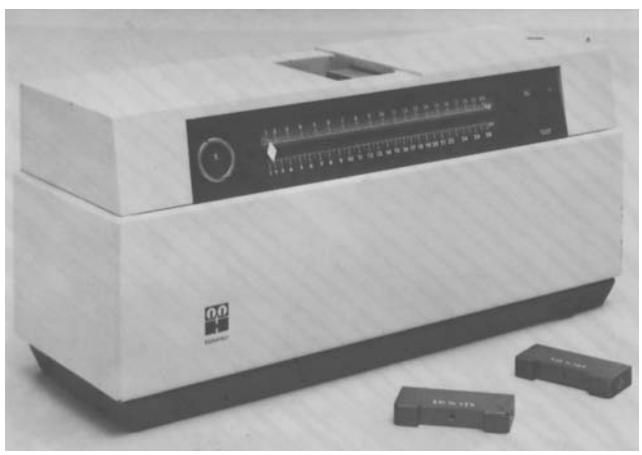


Figure 45-36. The Schleuniger or Heberlein tablet hardness tester shown with calibration blocks (courtesy, Vector).

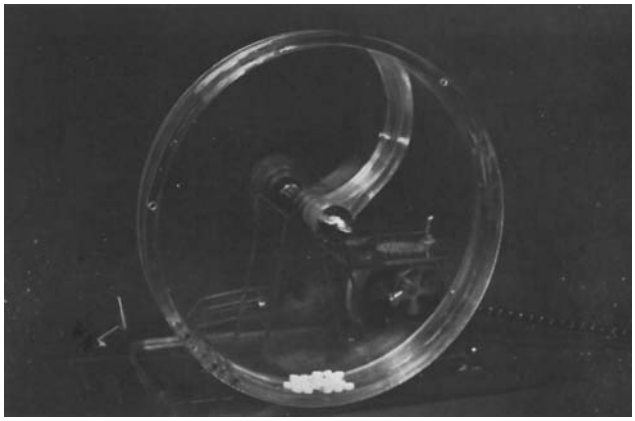


Figure 45-37. The Roche friabilator (courtesy, Hoffmann-LaRoche).

a more detailed discussion of this subject, the reader is directed to References 22, 37, 38.

A similar approach is taken by many manufacturers when they evaluate a new product in the new market package by sending the package to distant points and back using various methods of transportation. This is called a *shipping test*. The condition of the product on its return indicates its ability to withstand transportation handling.

Tablet Thickness

The thickness of the tablet from production-run to production-run is controlled carefully. Thickness can vary with no change in weight because of difference in the density of the granulation and the pressure applied to the tablets, as well as the speed of tablet compression. Not only is the tablet thickness important in reproducing tablets identical in appearance but also to ensure that every production lot will be usable with selected packaging components. If the tablets are thicker than specified, a given number no longer may be contained in the volume of a given size bottle. Tablet thickness also becomes an important characteristic in counting tablets using filling equipment. Some filling equipment uses the uniform thickness of the tablets as a counting mechanism. A column containing a known number of tablets is measured for height; filling is accomplished by continually dropping columns of tablets of the same height into bottles. If thickness varies throughout the lot, the result will be variation in count. Other pieces of filling equipment can malfunction because of variation in tablet thickness, since tablets above specified thickness may cause wedging of tablets in previously adjusted depths of the counting slots. Tablet thickness is determined with a caliper or thickness gauge that measures the thickness in millimeters. Plus or minus 5% may be allowed, depending on the size of the tablet.

Table 45-4. Hiestand Compaction Indices for a Number of Materials

MATERIAL	BONDING INDEX	STRAIN INDEX	BRITTLENESS INDEX
Aspirin	1.5	1.11	0.16
Dicalcium phosphate	1.3	1.13	0.15
Lactose anhydrous	0.8	1.40	0.27
Avicel pH 102	4.3	2.20	0.04
Corn starch	0.4	2.48	0.26
Sucrose NF	1.0	1.45	0.35
Erythromycin dihydrate	1.9	2.13	0.98

Uniformity of Dosage Forms

TABLET WEIGHT—The volumetric fill of the die cavity determines the weight of the compressed tablet. In setting up the tablet machine the fill is adjusted to give the desired tablet weight. The weight of the tablet is the quantity of the granulation that contains the labeled amount of the therapeutic ingredient. After the tablet machine is in operation the weights of the tablets are checked routinely, either manually or electronically, to ensure that proper-weight tablets are being made. This has become rather routine in most manufacturing operations with newer, electronically controlled tablet presses. The USP has provided tolerances for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50 mg or more of the drug substance or when the latter comprises 50% or more, by weight, of the dosage form. Twenty tablets are weighed individually, and the average weight is calculated. The variation from the average weight in the weights of not more than two of the tablets must not differ by more than the percentage listed below; no tablet differs by more than double that percentage. Tablets that are coated are exempt from these requirements but must conform to the test for content uniformity if it is applicable.

AVERAGE WEIGHT	PERCENT DIFFERENCE
130 mg or less	10
More than 130 mg through 324 mg	7.5
More than 324 mg	5

CONTENT UNIFORMITY—To ensure that every tablet contains the amount of drug substance intended, with little variation among tablets within a batch, the USP includes the content uniformity test for certain tablets. Due to the increased awareness of physiological availability, the content uniformity test has been extended to monographs on all coated and uncoated tablets and all capsules intended for oral administration where the range of sizes of the dosage form available includes a 50 mg or smaller size, in which case the test is applicable to all sizes (50 mg and larger and smaller) of that tablet or capsule. The official compendia can be consulted for the details of the test. Tablet monographs with a content uniformity requirement do not have a weight variation requirement.

Tablet Disintegration

It is recognized generally that the *in vitro* tablet disintegration test does not necessarily bear a relationship to the *in vivo* action of a solid dosage form. To be absorbed, a drug substance must be in solution, and the disintegration test is a measure only of the time required under a given set of conditions for a group of tablets to disintegrate into particles. Generally, this test is useful as a quality-assurance tool for conventional (non-sustained-release) dosage forms. In the present disintegration test the particles are those that will pass through a 10-mesh screen. In a comparison of disintegration times and dissolution rates or initial absorption rates of several brands of aspirin tablets, it was found that the faster-absorbed tablets had the longer disintegration time. Regardless of the lack of significance as to *in vivo* action of the tablets, the test provides a means of control in ensuring that a given tablet formula is the same as regards disintegration from one production batch to another. The disintegration test is used as a control for tablets intended to be administered by mouth, except for tablets intended to be chewed before being swallowed or tablets designed to release the drug substance over a period of time.

Exact specifications are given for the test apparatus, inasmuch as a change in the apparatus can cause a change in the results of the test. The apparatus consists of a basket rack holding six plastic tubes, open at the top and bottom; the bottom of the tubes is covered with 10-mesh screen. See Figure 45-38. The basket rack is immersed in a bath of suitable liquid, held at 37°C,

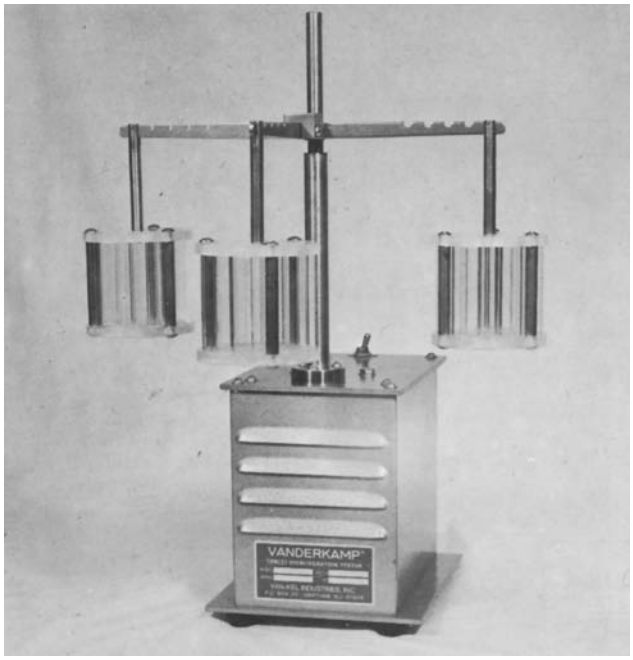


Figure 45-38. Vanderkamp tablet disintegration tester (courtesy, VanKel).

preferably in a 1-L beaker. The rack moves up and down in the fluid at a specified rate. The volume of the fluid is such that on the upward stroke the wire mesh remains at least 2.5 cm below the surface of the fluid and descends to not less than 2.5 cm from the bottom on the downward stroke. Tablets are placed in each of the six cylinders along with a plastic disc over the tablet unless otherwise directed in the monograph. The endpoint of the test is indicated when any residue remaining is a soft mass with no palpably soft core. The plastic discs help to force any soft mass that forms through the screen.

For compressed, uncoated tablets the testing fluid is usually water at 37°, but in some cases the monographs direct that Simulated Gastric Fluid TS be used. If one or two tablets fail to disintegrate, the test is to be repeated using 12 tablets. Of the 18 tablets then tested, 16 must have disintegrated within the given period of time. The conditions of the test are varied somewhat for coated tablets, buccal tablets, and sublingual tablets. Disintegration times are included in the individual tablet monograph. For most uncoated tablets the period is 30 min, although the time for some uncoated tablets varies greatly from this. For coated tablets up to 2 hr may be required, while for sublingual tablets, such as CT Isoproterenol Hydrochloride, the disintegration time is 3 min. For the exact conditions of the test, consult the USP.

Dissolution Test

For certain tablets the monographs direct compliance with limits on dissolution rather than disintegration. Since drug absorption and physiological availability depend on having the drug substance in the dissolved state, suitable dissolution characteristics are an important property of a satisfactory tablet. Like the disintegration test, the dissolution test for measuring the amount of time required for a given percentage of the drug substance in a tablet to go into solution under a specified set of conditions is an *in vitro* test. It is intended to provide a step toward the evaluation of the physiological availability of the drug substance, but as described currently, it is not designed to measure the safety or efficacy of the tablet being tested. Both the safety and effectiveness of a specific dosage form must be demonstrated initially by means of appropriate *in vivo* studies and clinical evaluation. Like the disintegration test, the dissolution test does provide a means of control in ensuring that a given tablet formulation is the same as regards dissolution as the batch of tablets shown initially to be clinically effective. It also provides an *in vitro* control procedure to eliminate variations among production batches. Refer to Chapter 35 for a complete discussion of dissolution testing.

Validation

In this era of increasing regulatory control of the pharmaceutical industry, manufacturing procedures cannot be discussed without the mention of some process-validation activity. By way of documentation, product testing, and perhaps in-process testing as well, manufacturers can demonstrate that their formulas and processes perform in the manner expected and that they do so reproducibly.

Although the justification for requiring validation is found in the regulations relating to *Current Good Manufacturing Practices for Finished Pharmaceuticals* as well as other sources, there is still much room for interpretation, and the process varies from one company to another. General areas of agreement appear to be that

The validation activity must begin in R&D and continue through product introduction.
Documentation is the key.
In general, three batches represent an adequate sample for validation.

The FDA has rejected historical data or *retrospective validation*. They require that new products be validated from beginning to end, a process called *prospective validation*.

CAPSULES

Capsules are solid dosage forms in which the drug substance is enclosed in either a hard or soft, soluble container or shell of a suitable form of gelatin. The soft gelatin capsule was invented by Mothes, a French pharmacist, in 1833. During the following year DuBlanc obtained a patent for his soft gelatin capsules. In 1848 Murdock patented the two-piece hard gelatin capsule. Although development work has been done on the preparation of capsules from methylcellulose, starch and calcium alginate, gelatin, because of its unique properties, remains the primary composition material for the manufacture of capsules. The gelatin used in the manufacture of capsules is obtained from collagenous material by hydrolysis. There are two types of gelatin, Type A, derived mainly from pork skins by acid processing, and Type B, obtained from bones and animal skins by alkaline processing. Blends are used to obtain gelatin solutions with the viscosity and bloom strength characteristics desirable for capsule manufacture.[50]

The encapsulation of medicinal agents remains a popular method for administering drugs. Capsules are tasteless, easily administered, and easily filled either extemporaneously or in large quantities commercially. In prescription practice the use of hard gelatin capsules permits a choice in prescribing a single drug or a combination of drugs at the exact dosage level considered best for the individual patient. This flexibility is an advantage over tablets. Some patients find it easier to swallow capsules than tablets, therefore preferring to take this form when possible. This preference has prompted pharmaceutical manufacturers to market the product in capsule

form, even though the product already has been produced in tablet form. While the industry prepares approximately 75% of its solid dosage forms as compressed tablets, 23% as hard gelatin capsules, and 2% as soft elastic capsules, market surveys have indicated a consumer preference of 44.2% for soft elastic capsules, 39.6% for tablets, and 19.4% for hard gelatin capsules.[51]

HARD GELATIN CAPSULES

The hard gelatin capsule, also referred to as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely surrounding the drug formulation. The classic capsule shape is illustrated in Figure 45-39. These capsules are filled by introducing the powdered material into the longer end or body of the capsule and then slipping on the cap. Hard gelatin capsules are made largely from gelatin, FD&C colorants, and sometimes an opacifying agent such as titanium dioxide; the USP permits the gelatin for this purpose to contain 0.15% sulfur dioxide to prevent decomposition during manufacture. Hard gelatin capsules contain 12–16% water, but the water content can vary depending on the storage conditions. When the humidity is low, the capsules become brittle; if stored at high humidities, the capsules become flaccid and lose their shape. Storage in high-temperature areas also can affect the quality of hard gelatin capsules. Gelatin capsules do not protect hygroscopic materials from atmospheric water vapor, as moisture can diffuse through the gelatin wall.

Companies having equipment for preparing empty hard gelatin capsules include *Lilly, Parke-Davis, Scherer,* and *SmithKline*. The latter's production is mainly for its own use; the others are suppliers to the industry. With this equipment, stainless steel pins, set in plates, are dipped into the gelatin solution, which must be maintained at a uniform temperature and an exact degree of fluidity. If the gelatin solution varies in viscosity, it correspondingly will decrease or increase the thickness of the capsule wall. This is important since a slight variation is sufficient to make either a loose or a tight joint. When the pins have been withdrawn from the gelatin solution, they are rotated while being dried in kilns through which a strong blast of filtered air with controlled humidity is forced. Each capsule is stripped, trimmed to uniform length and joined, the entire process being mechanical. Capsule-making equipment is illustrated in Figures 45-40 and 45-41. These show the stainless steel pins being dipped into the gelatin solutions and then being rotated through the drying kiln.

Capsules are supplied in a variety of sizes. The hard, empty capsules (Fig 45-39) are numbered from 000, the largest size that can be swallowed, to 5, which is the smallest. Larger sizes are available for use in veterinary medicine. The approximate capacity for capsules from 000 to 5 ranges from 600 to 30 mg, although this will vary because of the different densities of powdered drug materials.

Commercially filled capsules have the conventional oblong shape illustrated, with the exception of capsule products by *Lilly* and *SmithKline,* which are of distinctive shape. For Lilly products, capsules are used in which the end of the base is tapered to give the capsule a bullet-like shape; products encapsulated in this form are called *Pulvules*. The *SmithKline* capsules differ in that both ends of the cap and body are angular, rather than round.

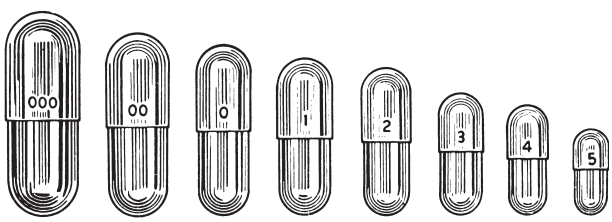


Figure 45-39. Hard gelatin capsules showing relative sizes (courtesy, Parke-Davis).

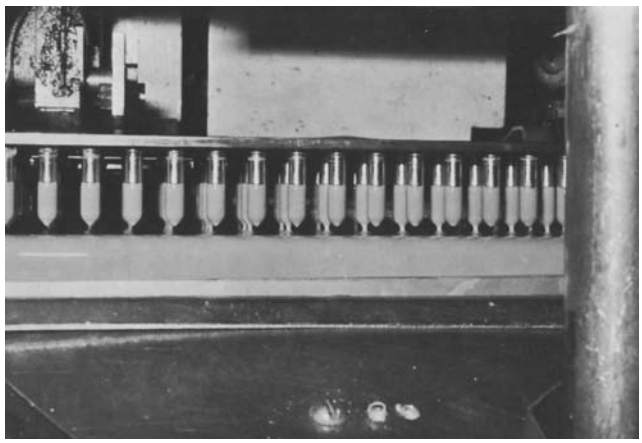


Figure 45-40. Manufacture of hard gelatin capsules by dipping stainless steel pins into gelatin solutions (courtesy, Lilly).

After hard gelatin capsules are filled and the cap applied, there are a number of methods used to ensure that the capsules will not come apart if subjected to vibration or rough handling, as in high-speed counting and packaging equipment. The capsules can be spot-welded by means of a heated metal pin pressed against the cap, fusing it to the body, or they may be banded with molten gelatin laid around the joint in a strip and dried. Colored gelatin bands around capsules have been used for many years as a trademark by *Parke-Davis* for their line of capsule products, *Kapseals*. Another approach was used in the *Snap-Fit* and *Coni-Snap* capsules. A pair of matched locking rings are formed into the cap and body portions of the capsule. Prior to filling, these capsules are slightly longer than regular capsules of the same size. When the locking rings are engaged after filling, their length is equivalent to that of the conventional capsule.

Following several tampering incidents, many pharmaceutical companies now use any number of locking and sealing technologies to manufacture and distribute these very useful dosage forms safely. Unfortunately, tamper-resistant packaging has become standard for capsule products.

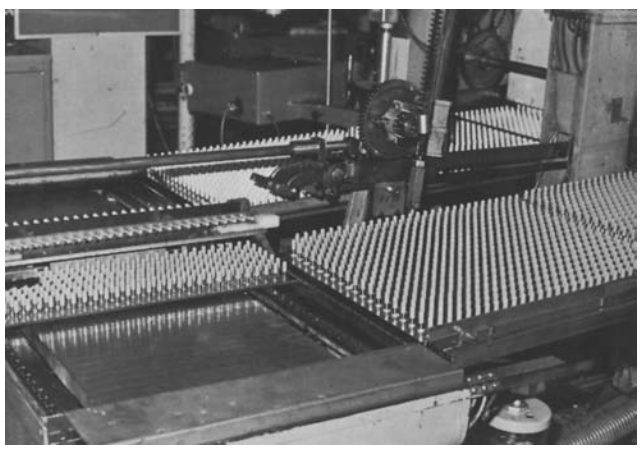


Figure 45-41. Formed capsules being dried by rotating through a drying kiln (courtesy, Lilly).

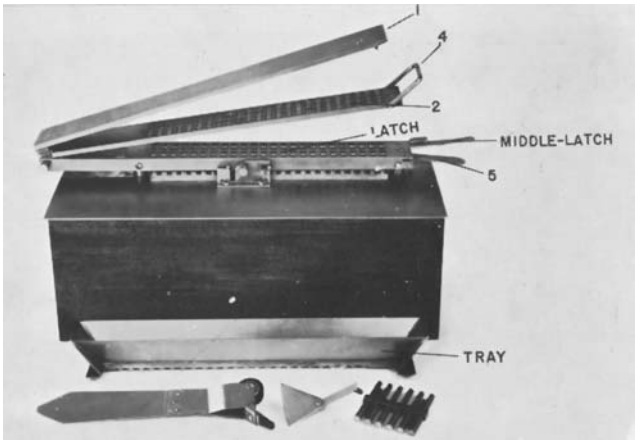


Figure 45-42. Hand-operated capsule machine (courtesy, Chemi-Pharm).

It is usually necessary for the pharmacist to determine the size of the capsule needed for a given prescription through experimentation. The experienced pharmacist, having calculated the weight of material to be held by a single capsule, often will select the correct size immediately. If the material is powdered, the base of the capsule is filled and the top is replaced. If the material in the capsule proves to be too heavy after weighing, a smaller size must be taken and the test repeated. If the filled capsule is light, it is possible that more can be forced into it by increasing the pressure or, if necessary, some of the material may be placed in the cap. This is not desirable as it tends to decrease the accuracy of subdivision and it is much better to select another size, whose base will hold exactly the correct quantity. In prescription filling it is wise to check the weight of each filled capsule.

In addition to the transparent, colorless, hard gelatin capsule, capsules are also available in various transparent colors such as pink, green, reddish brown, blue, yellow, and black. If they are used, it is important to note the color as well as the capsule size on the prescription so that in the case of renewal the refilled prescription will duplicate the original. Colored capsules have been used chiefly by manufacturers to give a specialty product a distinctive appearance. Titanium dioxide is added to the gelatin to form white capsules or to make an opaque, colored capsule. In addition to color contrasts, many commercial products in capsules are given further identification by markings, which may be the company's name, a symbol on the outer shell of the capsule, or banding. Some manufacturers mark capsules with special numbers based on a coded system to permit exact identification by the pharmacist or physician.

Extemporaneous Filling Methods

When filling capsules on prescription, the usual procedure is to mix the ingredients by trituration, reducing them to a fine and uniform powder. The principles and methods for the uniform distribution of an active medicinal agent in a powder mixture are discussed in Chapter 37. Granular powders do not pack readily in capsules, and crystalline materials, especially those that consist of a mass of filament-like crystals such as the quinine salts, are not fitted easily into capsules unless powdered. Eutectic mixtures that tend to liquefy may be dispensed in capsules if a suitable absorbent such as magnesium carbonate is used. Potent drugs given in small doses usually are mixed with an inert diluent such as lactose before filling into capsules. When incompatible materials are prescribed together, it is sometimes possible to place one in a smaller capsule and then enclose it with the second drug in a larger capsule.

Usually, the powder is placed on paper and flattened with a spatula so that the layer of powder is not greater than about ⅓ the length of the capsule that is being filled. This helps to keep both the hands and capsules clean. The cap is removed from the selected capsule and held in the left hand; the body is pressed repeatedly into the powder until it is filled. The cap is replaced and the capsule is weighed. In filling the capsule the spatula is helpful in pushing the last quantity of the material into the capsule. If each capsule has not been weighed, there is likely to be an excess or a shortage of material when the specified number of capsules have been packed. This condition is adjusted before dispensing the prescription.

A number of manual filling machines and automatic capsule machines are available for increasing the speed of the capsule-filling operation. Figure 45-42 illustrates a capsule-filling machine that was known formerly as the Sharp & Dohme machine. This equipment is now available through *ChemiPharm*. Many community pharmacists find this a useful piece of apparatus, and some pharmaceutical manufacturers use it for small-scale production of specialty items. The machine fills 24 capsules at a time with the possible production of 2000 per day. Entire capsules are placed in the machine by hand; the lower plate carries a clamp that holds the capsule bases and makes it possible to remove and replace the caps mechanically. The plate holding the capsule bases is perforated for three sizes of capsules. The powder is packed in the bases; the degree of accuracy depends on the selection of capsule size and the amount of pressure applied in packing. The hand-operated machine (Model 300, *ChemiPharm*) illustrated in Figure 45-43 has a production capacity of 2000 capsules per hour. The machine is made for a single capsule size and cannot be changed over for other sizes. A different machine is required for any additional capsule size. Its principle of operation is similar to that of the Sharp & Dohme machine.

Machine Filling Methods

Large-scale filling equipment for capsules operates on the same principle as the manual machines described above, namely the filling of the base of the capsule. Compared with tablets,

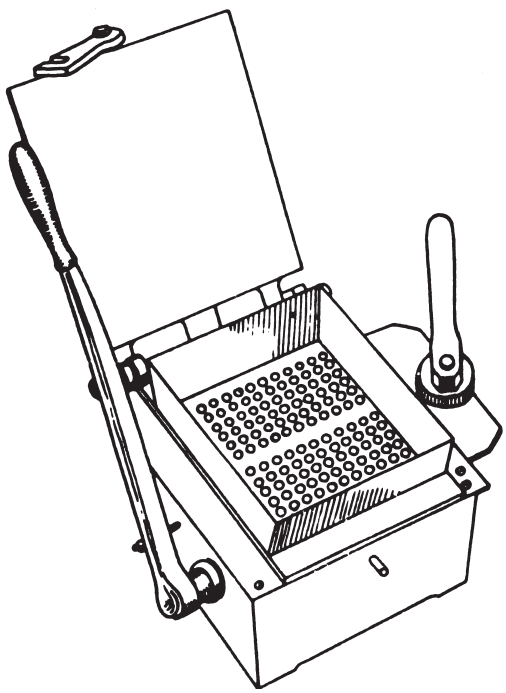


Figure 45-43. Hand-operated capsule machine, Model 300 (courtesy, ChemiPharm).

Table 45-5. Capsule Fill Chart

CAPSULE FILL WEIGHTS (MG) BASED ON SIZE AND DENSITY

POWDER DENSITY (g/ml)	CAPSULE VOLUME (mL) 0.95	0.78	0.68	0.54	0.5	0.37	0.3	0.25	0.21	0.13
	CAPSULE SIZE 00	0el	0	1el	1	2	3	4el	4	5
0.3	285	234	204	162	150	111	90	75	63	39
0.4	380	312	272	216	200	148	120	100	84	52
0.5	475	390	340	270	250	185	150	125	105	65
0.6	570	468	408	324	300	222	180	150	126	78
0.7	665	546	476	378	350	259	210	175	147	91
0.8	760	624	544	432	400	296	240	200	168	104
0.9	855	702	612	486	450	333	270	225	189	117
1.0	950	780	680	540	500	370	300	250	210	130
1.1	1045	858	748	594	550	407	330	275	231	143
1.2	1140	936	816	648	600	444	360	300	252	156
1.3	1235	1014	884	702	650	481	390	325	273	169
1.4	1330	1092	952	756	700	518	420	350	294	182
1.5	1425	1170	1020	810	750	555	450	375	315	195

powders for filling into hard gelatin capsules require a minimum of formulation efforts. The powders usually contain diluents such as lactose, mannitol, calcium carbonate, or magnesium carbonate. Since the flow of material is of great importance in the rapid and accurate filling of the capsule bodies, lubricants such as the stearates also are used frequently.

Because of the absence of numerous additives and manufacturing processing, the capsule form is used frequently to administer new drug substances for evaluation in initial clinical trials. However, it is now realized that the additives present in the capsule formulation, like the compressed tablet, can influence the release of the drug substance from the capsule. Tablets and capsules of a combination product containing triamterene and hydrochlorothiazide in a 2:1 ratio were compared clinically. The tablet caused approximately twice as much excretion of hydrochlorothiazide and three times as much triamterene as the capsule.[52]

Most equipment operates on the principle by which the base of the capsule is filled and the excess is scraped off. Therefore, the active ingredient is mixed with sufficient volume of a diluent, usually lactose or mannitol, to give the desired amount of the drug in the capsule when the base is filled with the powder mixture. The manner of operation of the machine can influence the volume of powder that will be filled into the base of the capsule; therefore, the weights of the capsules must be checked routinely as they are filled. See Table 45-5.

Semiautomatic capsule-filling machines manufactured by *Parke-Davis* and *Lilly* are illustrated in Figures 45-44 and 45-45. The Type 8 capsule-filling machine performs mechanically under the same principle as the hand filling of capsules. This includes separation of the cap from the body, filling the body half, and rejoining the cap and body halves.

Empty capsules are taken from the bottom of the capsule hopper into the magazine. The magazine gauge releases one

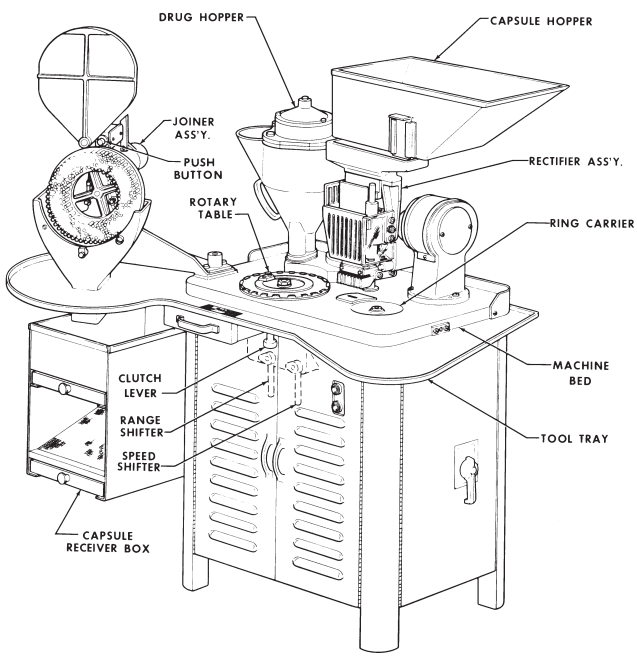


Figure 45-44. Schematic of Type 8 capsule-filling machine (courtesy, Parke-Davis).

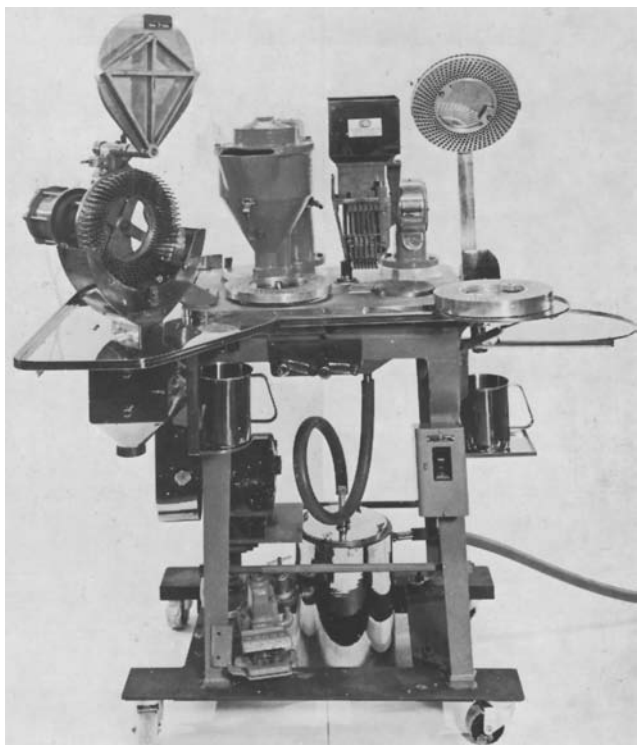


Figure 45-45. Type 8 capsule-filling machine (courtesy, Lilly).

capsule from each tube at the bottom of each stroke of the machine. Leaving the magazine, the capsules drop onto the tracks of the raceway and are pushed forward to the rectifying area with a push blade. The rectifier block descends, turning the capsules in each track, cap up, and drops them into each row of holes in the capsule-holding ring assembly.

As the capsules fall into the holding ring, the cap half has a seat on the counter bore in each hole for the top ring. The body half is pulled by vacuum down into the bottom ring. When all rows in the ring assembly are full, the top ring, filled with caps only, is removed and set aside for later assembly. The body halves now are located in the bottom ring, ready for filling.

The ring holding the body halves is rotated at one of eight speeds on the rotary table. The drug hopper is swung over the rotating ring, and the auger forces drug powder into the open body cavities. When the ring has made a complete revolution and the body halves have been filled, the hopper is swung aside. The cap-holding ring is placed over the body-holding ring and the assembly is ready for joining. The capsule-holding ring assembly is placed on the joiner and the joiner plate is swung down into position to hold the capsules in the ring. The peg ring pins are entered in the holes of the body holding ring and tapped in place by the air cylinder pushing the body halves back into the cap halves.

The holding-ring assembly is now pushed by hand back onto the peg ring away from the joiner plate, thus pushing the capsules out of the holding-ring assembly. The joined capsules then fall through the joiner chute into the capsule receiver box. The capsule receiver box screens the excess powder from the capsules and delivers them to any convenient container.

Many companies use the Type 8 capsule-filling equipment for small-scale manufacture and clinical supplies for investigational use because of its ease of operation, low cost, and extreme flexibility. A Type 8 capsule filling machine will produce approximately 200,000 capsules per day. This, of course, depends upon the operator and the type of material being filled. For this machine, a mathematical model has been developed that describes the effect of selected physical powder properties as well as mechanical operating conditions on the capsule-filling operation. While the Type 8 capsule-filling machine has been in existence for many years, recent modifications have been made to this machine to improve the capsule-filling operations.

There are several pieces of equipment available that are classified as automatic capsule-filling machines. These are automatic in the sense that one operator can handle more than one machine. In this category are the Italian-made Zanasi *(United Machinery)* and MG-2 *(Supermatic)* models, plus the West German–made Hoefliger & Karg models *(Bosch)*.

Automatic capsule machines are capable of filling either powder or granulated products into hard gelatin capsules. With accessory equipment these machines also can fill pellets or place a tablet into the capsule with the powder or pellets. The capsules are fed at random into a large hopper. They are oriented as required and transferred into holders where the two halves are separated by suction. The top-half and bottom-half of the capsules are in separate holders, which at this stage take diverting directions.

A set of filling heads collects the product from the hopper, compresses it into a soft slug, and inserts this into the bottom half of the capsule. After filling, each top-half is returned to the corresponding bottom-half. The filled capsules are ejected, and an air blast at this point separates possible empty capsules from the filled. The machines can be equipped to handle all sizes of capsules. Depending upon the make and model, speeds from 9000 to 150,000 units per hour can be obtained (see Figs 45-46 to 45-48).

All capsules, whether they have been filled by hand or by machine, will require cleaning. Small quantities of capsules may be wiped individually with cloth. Larger quantities are rotated or shaken with crystalline sodium chloride. The capsules then are rolled on a cloth-covered surface.

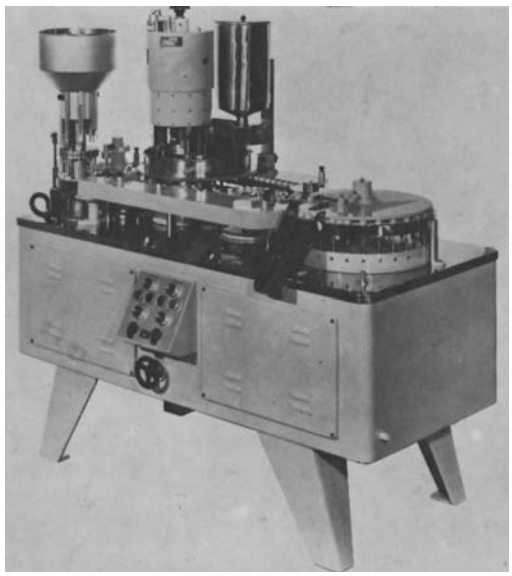


Figure 45-46. MG-2, automatic capsule-filling machine (courtesy, Supermatic).

Uniformity of Dosage Units

The uniformity of dosage forms can be demonstrated by either of two methods, weight variation or content uniformity. Weight variation may be applied when the product is a liquid-filled, soft, elastic capsule or when the hard gelatin capsule contains 50 mg or more of a single active ingredient comprising 50% or more, by weight, of the dosage form. See the official compendia for details.

Disintegration tests usually are not required for capsules unless they have been treated to resist solution in gastric fluid (enteric-coated). In this case they must meet the requirements for disintegration of enteric-coated tablets. For certain capsule dosage forms a dissolution requirement is part of the monograph. Procedures used are similar to those employed in the case of compressed tablets.

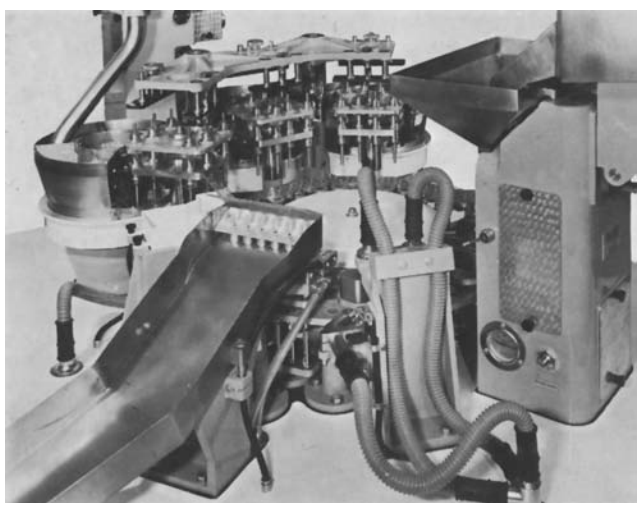


Figure 45-47. Zanasi automatic filling machine, Model AZ-60. The set of filling heads shown at the left collects the powder from the hopper, compresses it into a soft slug, and inserts it into the bottom half of the capsule (courtesy, United Machinery).

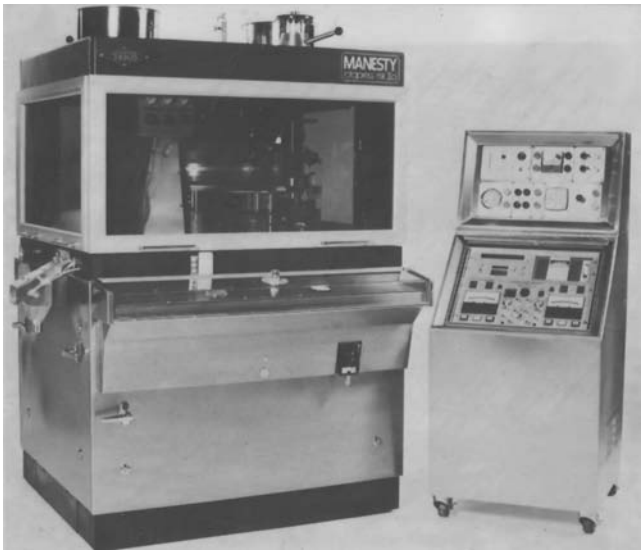


Figure 45-48. Hoefliger & Karg automatic capsule-filling machine, Model GFK 1200 (courtesy, Amaco).

SOFT ELASTIC CAPSULES

The soft elastic capsule (SEC) is a soft, globular, gelatin shell somewhat thicker than that of hard gelatin capsules. The gelation is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of fungi. Commonly used preservatives are methyl- and propylparabens and sorbic acid. When the suspending vehicle or solvent can be an oil, soft gelatin capsules provide a convenient and highly acceptable dosage form. Large-scale production methods generally are required for the preparation and filling of soft gelatin capsules.

Formerly, empty soft gelatin capsules were available to the pharmacist for the extemporaneous compounding of solutions or suspensions in oils. Commercially filled soft gelatin capsules come in a wide choice of sizes and shapes; they may be round, oval, oblong, tubular, or suppository-shaped. Some sugar-coated tablets are quite similar in appearance to soft gelatin capsules. The essential differences are that the soft gelatin capsule has a seam at the point of closure of the two halves, and the contents can be liquid, paste, or powder. The sugar-coated tablet will not have a seam but will have a compressed core.

Oral SEC dosage forms generally are made so that the heat seam of the gelatin shell opens to release its liquid medication into the stomach less than 5 min after ingestion. Its use is being studied for those drugs poorly soluble in water having bioavailability problems. When used as suppositories, it is the moisture present in the body cavity that causes the capsule to come apart at its heat-sealed seam and to release its contents.

Plate Process

In this method a set of molds is used. A warm sheet of prepared gelatin is laid over the lower plate, and the liquid is poured on it. A second sheet of gelatin is carefully put in place, and this is followed by the top plate of the mold. The set is placed under the press where pressure is applied to form the capsules, which are washed off with a volatile solvent to remove any traces of oil from the exterior. This process has been adapted and is used for encapsulation by *Upjohn*. The sheets of gelatin may have the same color or different colors.

Rotary-Die Process

In 1933 the rotary-die process for elastic capsules was perfected by Robert P Scherer.[53] This process made it possible to improve the standards of accuracy and uniformity of elastic gelatin capsules and globules.

The rotary-die machine is a self-contained unit capable of continuously and automatically producing finished capsules from a supply of gelatin mass and filling material, which may be any liquid, semiliquid, or paste that will not dissolve gelatin. Two continuous gelatin ribbons, which the machine forms, are brought into convergence between a pair of revolving dies and an injection wedge. Accurate filling under pressure and sealing of the capsule wall occur as dual and coincident operations; each is delicately timed against the other. Sealing also severs the completed capsule from the net. The principle of operation is shown in Figure 45-49. See also Figure 45-50.

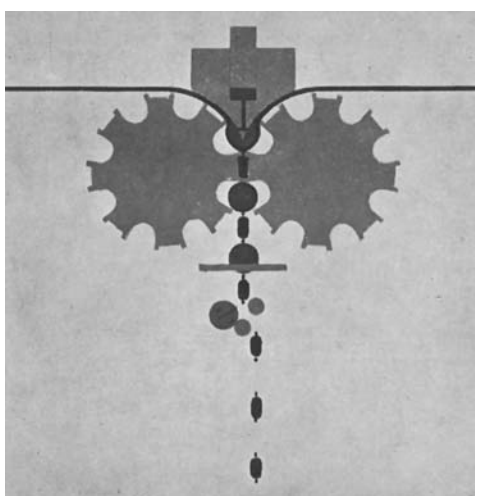


Figure 45-49. Rotary-die elastic capsule filler.

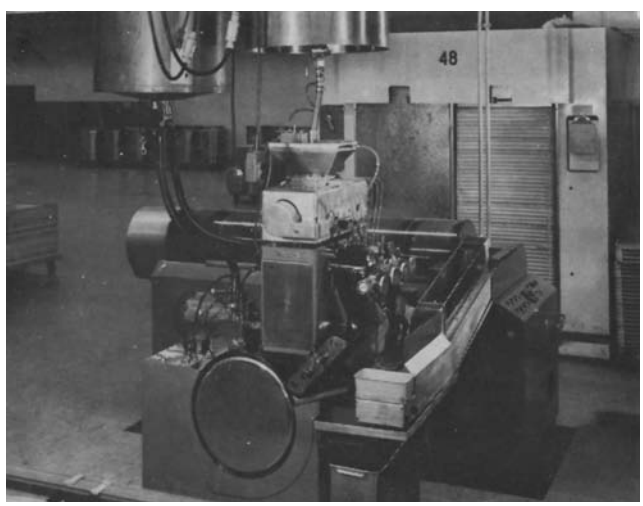


Figure 45-50. Scherer soft elastic capsule machine (courtesy, Scherer).

By this process the content of each capsule is measured individually by a single stroke of a pump so accurately constructed that plunger travel of 0.025 inch will deliver 1 <minim> (apoth). The Scherer machine contains banks of pumps so arranged that many capsules may be formed and filled simultaneously. All pumps are engineered to extremely small mechanical tolerances and to an extremely high degree of precision and similarity. All operations are controlled on a weight basis by actual periodic checks with a group of analytical balances. Individual net-fill weights of capsules resulting from large-scale production vary no more than ±1 to 3% from theory, depending upon the materials used.

The rotary-die process makes it possible to encapsulate heavy materials such as ointments and pastes. In this manner solids can be milled with a vehicle and filled into capsules. When it is desirable to have a high degree of accuracy and a hermetically sealed product, this form of enclosure is suited ideally.

The modern and well-equipped capsule plant is completely air conditioned, a practical necessity for fine capsule production. Its facilities and operations include the availability of carbon dioxide at every exposed point of operation for the protection of oxidizable substances before encapsulation. Special ingredients also have been used in the capsule shell to exclude light wavelengths that are destructive to certain drugs.

Norton Capsule Machine

This machine produces capsules completely automatically by leading two films of gelatin between a set of vertical dies. These dies as they close, open, and close are in effect a continual vertical plate forming row after row of pockets across the gelatin film. These are filled with medicament and, as they progress through the dies, are sealed, shaped, and cut out of the film as capsules, which drop into a cooled solvent bath.

Accogel Capsule Machine

Another means of soft gelatin encapsulation uses the Accogel machine and process which were developed at *Lederle*. The Accogel, or Stern machine, uses a system of rotary dies but is unique in that it is the only machine that successfully can fill dry powder into a soft gelatin capsule. The machine is available to the entire pharmaceutical industry by a lease arrangement and is used in many countries of the world. It is extremely versatile, not only producing capsules with dry powder but also encapsulating liquids and combinations of liquids and powders. By means of an attachment, slugs or compressed tablets may be enclosed in a gelatin film. The capsules can be made in a variety of colors, shapes, and sizes.

Microencapsulation

As a technology, microencapsulation is placed in the section on capsules only because of the relationship in terminology to mechanical encapsulation described above. The topic is also discussed in Chapter 47 (Extended-release and Targeted Drug Delivery Systems) of this text. Essentially, microencapsulation is a process or technique by which thin coatings can be applied reproducibly to small particles of solids, droplets of liquids, or dispersions, thus forming microcapsules. It can be differentiated readily from other coating methods in the size of the particles involved; these range from several tenths of a micrometer to 5000 μm in size.

A number of microencapsulation processes have been disclosed in the literature.[54] Some are based on chemical processes and involve a chemical or phase change; others are mechanical and require special equipment to produce the physical change in the systems required.

A number of coating materials have been used successfully; examples of these include gelatin, polyvinyl alcohol, ethylcellulose, cellulose acetate phthalate, and styrene maleic anhydride. The film thickness can be varied considerably, depending on the surface area of the material to be coated and other physical characteristics of the system. The microcapsules may consist of a single particle or clusters of particles. After isolation from the liquid manufacturing vehicle and drying, the material appears as a free-flowing powder. The powder is suitable for formulation as compressed tablets, hard gelatin capsules, suspensions, and other dosage forms.

The process provides answers for problems such as masking the taste of bitter drugs, a means of formulating prolonged-action dosage forms, a means of separating incompatible materials, a method of protecting chemicals against moisture or oxidation, and a means of modifying a material's physical characteristics for ease of handling in formulation and manufacture.

Among the processes applied to pharmaceutical problems is that developed by the National Cash Register Co (NCR). The NCR process is a chemical operation based on phase separation or coacervation techniques. In colloidal chemistry, coacervation refers to the separation of a liquid precipitate, or phase, when solutions of two hydrophilic colloids are mixed under suitable conditions.

The NCR process, using phase separation or coacervation techniques, consists of three steps:

1. Formation of three immiscible phases: a liquid manufacturing phase, a core material phase, and a coating material phase.
2. Deposition of the liquid polymer coating on the core material.
3. Rigidizing the coating, usually by thermal, cross-linking, or desolvation techniques, to form a microcapsule.

In Step 2, the deposition of the liquid polymer around the core material occurs only if the polymer is absorbed at the interface formed between the core material and the liquid vehicle phase. In many cases physical or chemical changes in the coating polymer solution can be induced so that phase separation (coacervation) of the polymer will occur. Droplets of concentrated polymer solution will form and coalesce to yield a two-phase, liquid-liquid system. In cases in which the coating material is an immiscible polymer or insoluble liquid polymer, it may be added directly. Also monomers can be dissolved in the liquid vehicle phase and, subsequently, polymerized at the interface.

Equipment required for microencapsulation by this method is relatively simple; it consists mainly of jacketed tanks with variable-speed agitators. Figure 45-51 shows a typical flow diagram of a production installation.

Other Oral Solid Dosage Forms

PILLS

Pills are small, round, solid, dosage forms containing a medicinal agent and are intended for oral administration. Pills were formerly the most extensively used oral dosage form, but they have been replaced largely by compressed tablets and capsules. Substances that are bitter or unpleasant to the taste, if not corrosive or deliquescent, can be administered in this form if the dose is not too large.

Formerly, pills were made extemporaneously by the community pharmacist whose skill at pill-making became an art. However, the few pills that are now used in pharmacy are prepared on a large scale with mechanical equipment. The pill formulas of the NF were introduced largely for the purpose of establishing standards of strength for the well-known and currently used pills. Hexylresorcinol Pills consist of hexylresorcinol crystals covered with a rupture-resistant coating that is dispersible in the digestive tract. It should be noted that the official hexylresorcinol pills are prepared not by traditional methods but by a patented process, the gelatin coating being sufficiently tough that it cannot be broken readily, even when chewed. Therefore,

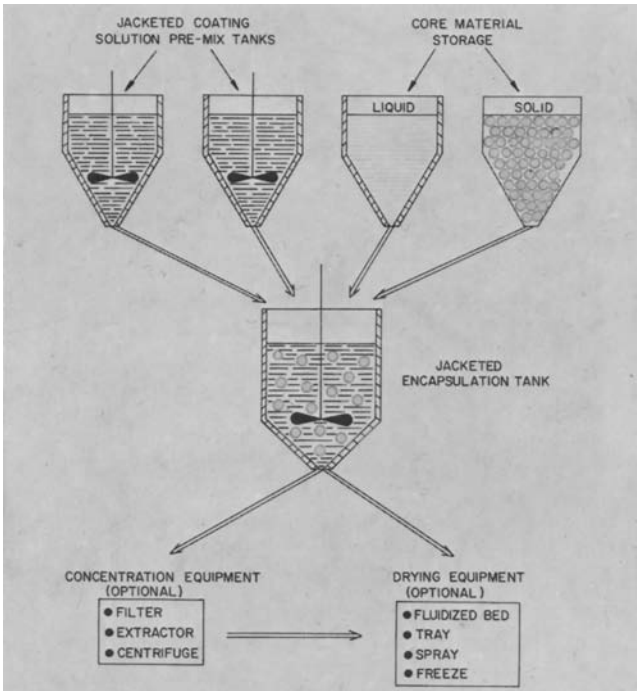


Figure 45-51. Production installation for the microencapsulation process (courtesy, NCR).

the general method for the preparation of pills does not apply to hexylresorcinol pills.

Previous editions of this text should be consulted for methods of pill preparation.

TROCHES

These forms of oral medication, also known as *lozenges* or *pastilles,* are discoid-shaped solids containing the medicinal agent in a suitably flavored base. The base may be a hard sugar candy, glycerinated gelatin, or the combination of sugar with sufficient mucilage to give it form. Troches are placed in the mouth, where they slowly dissolve, liberating the active ingredient. The drug involved can be an antiseptic, local anesthetic, antibiotic, antihistaminic, antitussive, analgesic, or a decongestant.

Formerly, troches were prepared extemporaneously by the pharmacist. The mass is formed by adding water slowly to a mixture of the powdered drug, powdered sugar, and a gum until a pliable mass is formed. Powdered acacia in 7% concentration gives sufficient adhesiveness to the mass. The mass is rolled out and the troche pieces cut out using a cutter, or else the mass is rolled into a cylinder and divided. Each piece is shaped and allowed to dry before dispensing.

If the active ingredient is heat-stable, it may be prepared in a hard candy base. Syrup is concentrated to the point at which it becomes a pliable mass, the active ingredient is added, and the mixture is kneaded while warm to form a homogeneous mass. The mass is worked gradually into a pipe form having the diameter desired for the candy piece, and the lozenges are cut from the pipe and allowed to cool. This is an entirely mechanical operation with equipment designed for this purpose.

If the active ingredient is heat-labile, it may be made into a lozenge preparation by compression. The granulation is prepared in a manner similar to that used for any compressed tablet. The lozenge is made using heavy compression equipment to give a tablet that is harder than usual, as it is desirable for the troche to dissolve or disintegrate slowly in the mouth. In the formulation of the lozenge the ingredients are chosen that will promote its slow-dissolving characteristics. Compression is gaining in popularity as a means of making troches and candy pieces because of the increased speeds of compression equipment. In cases in which holes are to be placed in troches or candy pieces, core-rod tooling is used (Fig 45-52). Core-rod tooling includes a rod centered on the lower punch around which the troche is compressed in the die cavity. The upper punch has an opening in its center for the core rod to enter during compression. It is evident that maximum accuracy is needed to provide alignment as the narrow punches are inserted into the die.

CACHETS

Related to capsules, inasmuch as they provide an edible container for the oral administration of solid drugs, cachets formerly were used in pharmacy. They varied in size from ¾ to ⅛ inch in diameter and consisted of two concave pieces of wafer made of flour and water. After one section was filled with the prescribed quantity of the medicinal agent, they were sealed tightly by moistening the margins and pressing them firmly together. When moistened with water, their character was changed entirely; they became soft, elastic, and slippery. Hence, they could be swallowed easily by floating them on water.

PELLETS

The term pellet is sometimes applied to small, sterile cylinders about 3.2 mm in diameter by 8 mm in length, which are formed by compression from medicated masses.[55] Whenever prolonged and continuous absorption of testosterone, estradiol, or desoxycorticosterone is desired, pellets of these potent hormones may be used by implantation.

MEDICATED CHEWING GUM

Chewing gum has been a widely popular form of confection that has its roots in ancient times. Only recently has its use as a drug delivery system become mainstream. Worldwide, there are commercially available chewing gums for use in smoking cessation, pain relief, and motion sickness. Chewing gum can also offer an advantage for localized delivery of drugs in the mouth, and is now being evaluated for these uses.[56–60]

Gums can be manufactured by a variety of mixing processes that incorporate several components into a sheet of product,

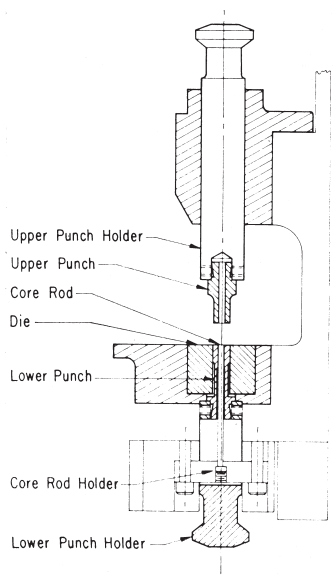


Figure 45-52. Core-rod tooling for compressing troches or candy pieces with hole in center (courtesy, Vector/Colton).

Table 45-6. Formula of a Medicated Chewing Gum

COMPONENT	CONENTRATION (%W/W)
Drug	0–40
Gum Base	20–45
Sweeteners	30–60
Softeners	0–10
Flavor(s)	1–5
Color(s)	0–1

whereby the units are stamped or cut from the rolled out sheet. A typical formulation for a chewing gum might be considered in Table 45-6.

Chewing gums can be made by compression and other processes, but the predominant method in use today is mixing, rolling and stamping of the finished units. After the finished units are completed, they can be film or sugar coated for better mouth feel or taste improvement.

RAPIDLY DISSOLVING TABLETS

Recently, a number of fast-dissolving tablets have been produced to rapidly deliver drugs for a variety of applications. One of the first solid dosage forms, Zydis (RP Scherer) used lyophilized technology to prepare the powder to dissolve quickly on the tongue. Since then, numerous technologies have been developed to give quick dissolution of the active in the mouth. Other technologies such as Lyoc (Farmalyoc), WOW-Tab (Yamanouchi), Flash-Dose (Biovail), Orasolv (CIMA) and DuraSolv (CIMA) have been used in commercialized products. There are some comparable benefits to one technology over the others, but the objective is still the same. These products have had some acceptance, and will have a place in formularies for years to come.

The challenges these dosage forms have had is durability during shipping, and changes to the drug substance that can occur during the lyophilization or manufacturing process. In addition, these products are best suited for drugs where there is a demonstrable benefit from very fast onset of activity of the drug. To date, there have been few clinical studies to show the significance of benefit of these products over standard immediate-release products.

TABLETS MADE BY ELECTROSTATIC DEPOSITION

The most common example of electrostatic deposition takes place every day in the office photocopy machine. The basic principle of electrostatic deposition is well-founded in basic physics: opposite charges attract. Deposition of material occurs when a pattern of charges is established on the substrate where the deposition is desired, and very fine particles with an opposite charge is placed near the substrate. The Sarnoff Research Laboratories developed an electro-static method of depositing and thereby coating solid surfaces with powder in a dry form. This technology was initially developed for phosphorus coating for cathode ray tubes, and was first applied to the manufacture of tablets by Delsys Corporation, now merged with Elan Corporation.[61–65]

Figure 45-53 illustrates this process. A substrate is chosen as the base for the deposit of particles. The charging is done us-

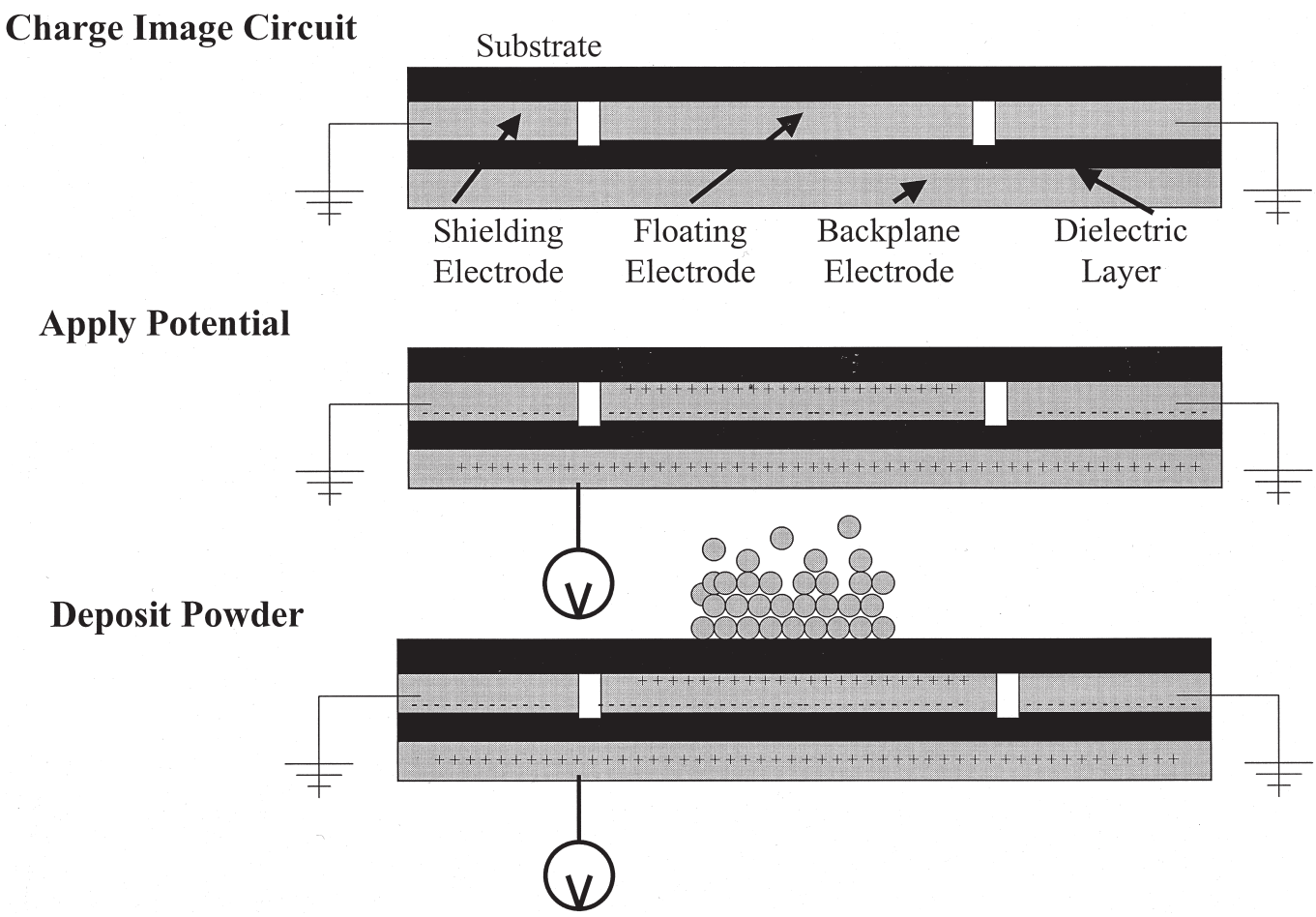


Figure 45-53. Electrostatic powder deposition process.

ing a three-layer structure that has a conducting backplane electrode, an insulating layer and a patterned conducting top electrode. Application of a positive voltage to the backplane electrode establishes a positive surface charge in the electrode. Charges that mirror the backplane charges are induced in the conductive top electrodes. In the floating electrodes, negative mirror charges induced by the backplane electrode leave uncompensated positive charges in the top surface of the floating electrode. By controlling the amount and strength of these positive charges, the rate of deposition and porosity of the resulting solid can be controlled.

The electrostatic process has several potential applications. First, the uniformity of ultra low dose drugs could be precisely achieved. Drugs with significant stability or incompatibility problems could be easily addressed without separate operations. Because little or no excipients are used in this process, the cost, storage and movement of materials in the modern manufacturing facility may be reduced significantly. In addition, it may be possible to have a final formulation designed and finalized much earlier in the development process. Currently, there are no commercial tablets using this technology, but one can imagine the considerable issues associated with the scale-up, validation and implementation of this technology.

THREE-DIMENSIONAL PRINTING OF TABLETS

Another technology that has been adapted for the manufacture of tablets is three-dimensional printing, called 3DP by Therics Corporation, the company to first apply this technology to pharmaceuticals. The technology is quite similar to ink-jet printer technology. It was improved by engineers at the Massachusetts Institute of Technology, and later at Therics.

Figures 45-54 and 45-55 illustrate three-dimensional printing.[66] In Figure 45-54, the basic system is shown. Powder is spread into a tray and binder droplets are precisely sprayed onto a substrate to form virtually any shape or design. A piston holding the unit changes position for each pass of the dispensing module, allowing for a build-up of the tablet. The process is repeated over and over until the desired shape is obtained. Using a tray that can accommodate many hundreds of powder wells, and hundreds of dispensing modules would be required to make this unit suitable for commercial manufacture. To this date, there are no commercial tablets made from this technology. However, it's versatility and complete freedom for design of novel solid dosage forms make this technology fascinating. Figure 45-55 illustrates this point showing a design on the computer screen, with a tablet completed next to it. In the cutaway section can be seen many programmed walls and empty compartments "constructed" within the confines of the tablet.

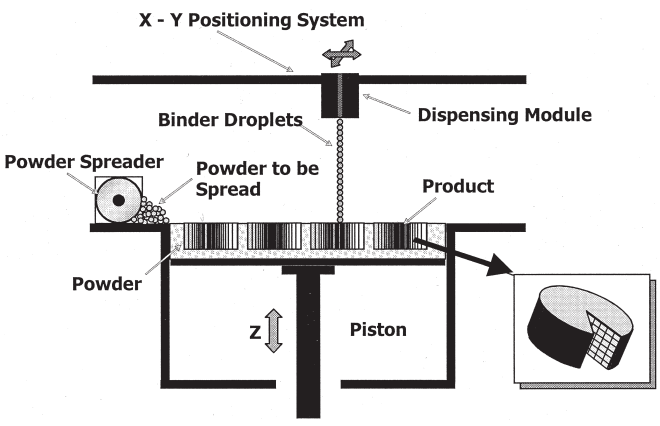


Figure 45-54. Three-dimensional printing process.

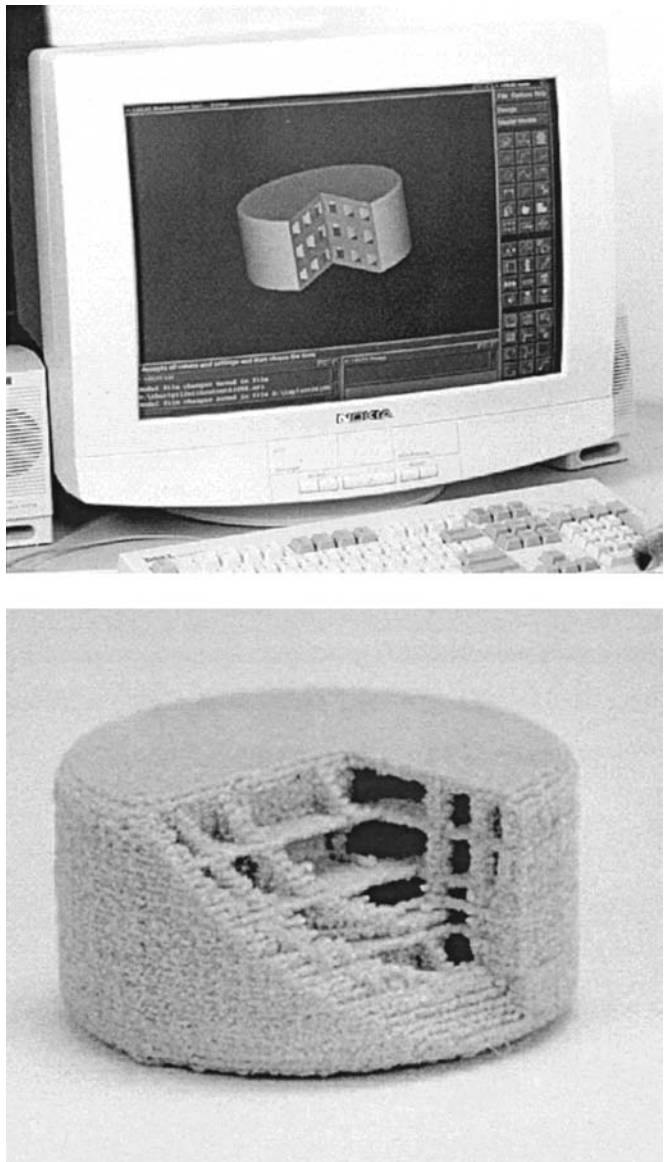


Figure 45-55. Design versatility of three-dimensional printing.

Three-dimensional printing technology has all of the advantages of electrostatic powder deposition, but has many more practical applications.

WEB-COATED SYSTEMS

In the early 1980s, Roche laboratories developed a system whereby sheets of a substrate were coated with drug and binder solution.[62] A number of sheets were then laminated, or glued together to form a complex, multi-layered sheet containing drug and various binder/excipient systems. The final laminate sheet was then punched to produce many dosage forms. This system was quite flexible, and was capable of producing various types of controlled-release, and combination products. However, due to it's impracticality, it was abandoned by Roche in the mid-1980s. It remains an important development, and is instructive from a historical perspective.

HOT-MELT EXTRUSION

Hot-melt extrusion technology has been extensively used as a processing technique in the plastics industry and is currently being investigated in the pharmaceutical arena as a novel tableting method. The process involves the active, suitable polymeric carrier, and other excipients being mixed in the molten state and then extruded through a die. The final product may take the form of a film, pipe, tube, or granule, depending on the shape of the die. A matrix is formed due to the melted polymer acting as a thermal binder. In addition to being anhydrous, this technology offers the advantage of tableting poorly compressible materials and manufacturing sustained-release tablets. The thermal stability of each material must be sufficient to withstand the production process.

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CHAPTER 46

Coating of Pharmaceutical Dosage Forms

Stuart C Porter, PhD

Any introduction to tablet coating must be prefaced by an important question—*Why coat tablets?*—since in many instances, the coating is applied to a dosage form that already is functionally complete. In attempting to answer this question, if one examines the market, it will become apparent that a significant proportion of pharmaceutical solid dosage forms are coated. The reasons for this range from the esthetic to a desire to control the bioavailability of the drug, and include:

1. Protecting the drug from its surrounding environment (particularly air, moisture, and light) in order to improve stability
2. Masking unpleasant taste and odor
3. Making it easier for the patient to swallow the product
4. Improving product identity, from the manufacturing plant, through intermediaries, and to the patient
5. Facilitating handling, particularly in high-speed packaging/filling lines, and automated counters in pharmacies, where the coating minimizes cross-contamination due to dust elimination
6. Improving product appearance, particularly where there are noticeable visible differences in tablet core ingredients from batch to batch
7. Reducing the risk of interaction between incompatible components. This would be achieved by using coated forms of one or more of the offending ingredients (particularly active compounds)
8. Improving product robustness, since coated products generally are more resistant to mishandling (eg, abrasion, attrition)
9. Modifying drug release, as in enteric-coated, repeat-action and sustained-release products.

EVOLUTION OF THE COATING PROCESS—Tablet coating is perhaps one of the oldest pharmaceutical processes still in existence. Historically, the literature cites Rhazes (850–932 AD) as being one of the earliest *tablet coaters,* having used the mucilage of psyllium seeds to coat pills that had an offending taste. Subsequently, Avicenna[1] was reported to have used gold and silver for pill coating. Since then, there have been many references to the different materials used in *tablet coating*. White[2] mentioned the use of finely divided talc in what was at one time popularly known as *pearl coating,* while Kremers and Urdang[3] described the introduction of the gelatin coating of pills by Garot in 1838.

An interesting reference[4] reports the use of waxes to coat poison tablets. These waxes, being insoluble in all parts of the gastrointestinal tract, were intended to prevent accidental poisoning (the contents could be utilized by breaking the tablet prior to use).

While earlier coated products were produced by individuals working in pharmacies, particularly when extemporaneous compounding was the order of the day, that responsibility now has been assumed by the pharmaceutical industry. The earliest attempts to apply coatings to pills yielded variable results and usually required the handling of single pills. Such pills would have been mounted on a needle or held with a pair of forceps and literally dipped into the coating fluid, a procedure that would have to be repeated more than once to ensure that the pill was coated completely. Subsequently, the pills were held at the end of a suction tube, dipped, and then the process repeated for the other side of the pill. Not surprisingly, these techniques often failed to produce a uniformly coated product.[5]

Initially, the first sugar-coated pills seen in the US were imported from France about 1842[5]; while Warner, a Philadelphia pharmacist, became among the first indigenous manufacturers in 1856.[6]

Pharmaceutical pan-coating processes are based on those used in the candy industry, where techniques were highly evolved, even in the Middle Ages. Today most coating pans are fabricated from stainless steel, while early pans were made from copper, because drying was effected by means of an externally applied heat source. Current thinking, even with conventional pans, is to dry the coated tablets with a supply of heated air and remove the moisture and dust-laden air from the vicinity of the pan by means of an air-extraction system.

Pan-coating processes underwent little further change until the late 1940s and early 1950s, with conventional pans being the mainstay of all coating operations up to that time. However, in the last 50 years there have been some significant advances made in coating-process technology, mainly as a result of a steady evolution in pan design and associated ancillary equipment.

Interestingly, in the early years of this development, an entirely new form of technology evolved, namely that of film coating. Recognizing the deficiencies of the sugar-coating process, advocates of film coating were achieving success by using polymer based coatings dissolved in highly volatile organic solvents.

These solvents circumvented the problems often associated with the poor drying capabilities of conventional equipment and enabled production quotas to be met with significant reductions in processing times and materials used. The disadvantage of this approach, however, always has been associated with the fact that the solvents used were often flammable and toxic.

Advances that occurred with equipment design, begun with the development of the Wurster[7] process and continued by the evolution of side-vented pans, have resulted in the gradual emergence of coating processes in which drying efficiency can be maximized. Thus, while film coating began as a process using inefficient drying equipment, relying on highly volatile coating formulations for success, it has evolved into one in which the processing equipment is a major factor in ensuring that rapid drying occurs. Improved drying capabilities have permitted common use of aqueous film-coating formulations.

Advances in equipment design also have benefited the sugar-coating process, where, because of current Good Manufacturing Practices (cGMP) and to maintain product uniformity

and performance, the trend has been toward using fully automated processes. Nonetheless, film coating tends to dominate as the process of choice for tablet coating.

PHARMACEUTICAL COATING PROCESSES

Basically, there are four major techniques for applying coatings to pharmaceutical solid dosage forms: (1) sugar coating, (2) film coating, (3) microencapsulation, and (4) compression coating.

Although it could be argued that the use of mucilage of psyllium seed, gelatin, etc, as already discussed, was an early form of film coating, *sugar coating* is regarded as the oldest method for tablet coating and involves the deposition from aqueous solution of coatings based predominantly on sucrose as a raw material. The large quantities of coating material that are applied and the inherent skill often required of the operators combine to result in a long and tedious process. The introduction of improved formulations and processing techniques has resulted, however, in a significant reduction in processing times (from several days to less than 1 day).

Film coating, the deposition of a thin polymeric film onto the dosage form from solutions that were originally organic-solvent-based, but which now rely much more on water as the prime solvent, has proven to be a popular alternative to sugar coating, to the extent that this latter process has all but been superceded.

Microencapsulation is a modified form of film coating, differing only in the size of the particles to be coated and the methods by which this is accomplished. This process is based on either mechanical methods such as pan coating, air-suspension techniques, multiorifice centrifugal techniques, and modified spray-drying techniques, or physicochemical ones involving coacervation-phase separation, in which the material to be coated is suspended in a solution of the polymer. Phase separation is facilitated by the addition of a nonsolvent, incompatible polymer or inorganic salts or by altering the temperature of the system.

Compression coating involves the use of modified tabletting machines that allow the compaction of a dry coating around a tablet core produced on the same machine. The main advantage of this type of coating process is that it eliminates the use of any solvent, whether aqueous or organic in nature. However, this process is mechanically complex and has not proven popular as a method for coating tablets. Compression technology has, in recent times, been readopted as a means of applying special coatings for novel drug-delivery applications.

Sugar Coating of Compressed Tablets

While the term *sugar* is somewhat generic and lends itself to describing a range of carbohydrate materials, sugar coating relies primarily on the use of sucrose. The main reason is that sucrose is one of the few materials that produces smooth, high-quality coatings that are essentially dry and tack-free at the end of the process. While the popularity of sugar coating has certainly declined, this process is still used by many companies that have invested in the complete modernization of the process. In spite of certain inherent difficulties associated with the sugar-coating process, products that have been expertly sugar coated still remain among the most elegant available.

Since sugar coating is a multistep process, where esthetics of the final coated product is an important goal, it has been, and still is in many companies, highly dependent on the use of skilled manpower. For these reasons, the sugar-coating process is often protracted and tedious. However, processing times have been reduced gradually in the last few decades through process modification, typically involving thin sugar-coating procedures, and by means of automation.

The sugar-coating process can be subdivided into six main steps: (1) sealing, (2) subcoating, (3) smoothing, (4) color coating, (5) polishing, and (6) printing.

SEALING—The sealing coat is applied directly to the tablet core for the purpose of separating tablet ingredients (primarily the drug) from water (which is a major constituent of the coating formulation) in order to achieve good product stability. A secondary function is to strengthen the tablet core. Sealing coats usually consist of alcoholic solutions (approximately 10–30% solids) of resins such as shellac, zein, cellulose acetate phthalate, or polyvinyl acetate phthalate.

Historically, shellac has proven to be the most popular material, although it can cause impaired bioavailability due to a change in resin properties on storage. A solution to this problem has been to use a shellac-based formulation containing a measured quantity of polyvinylpyrrolidone (PVP).[8]

The quantities of material required to be applied as a sealing coat will depend primarily on tablet and batch size. However, another important factor is tablet porosity, since highly porous tablets will tend to soak up the first application of solution, thus preventing it from spreading uniformly across the surface of every tablet in the batch. Thus, one or more further applications of resin solution may be necessary to ensure that the tablet cores are sealed effectively.

Since most sealing coats develop a degree of tack (stickiness) at some time during the drying process, it is usual to apply a dusting powder to prevent tablets from sticking together or to the pan. A common dusting powder is asbestos-free talc. Overzealous use of talc may cause problems, firstly, by imparting a high degree of slip to the tablets, thus preventing them from rolling properly in the pan, and secondly by creating a surface that, at the beginning of the subsequent subcoating stage, is very difficult to wet. Such poor wetting often results in uneven subcoat buildup, particularly on the tablet edges. If there is a tendency for either of these problems to occur, one solution is to replace part or all of the talc with some other material such as terra alba, which will form a slightly rougher surface. Use of talc now is being frowned upon because of its potential carcinogenicity.

If it is necessary to prepare a delayed-release (enteric-coated) product, this can be achieved by making additional applications of the seal-coat solution. Under these circumstances, however, it is more preferable to use sealcoating formulations based on synthetic polymers such as polyvinyl acetate phthalate or cellulose acetate phthalate, rather than shellac.

SUBCOATING—Subcoating is a critical operation in the sugar-coating process that can have a marked effect on ultimate tablet quality. Sugar coating is a process that often leads to a 50 to 100% weight increase, and it is at the subcoating stage that most of the buildup occurs.

Historically, subcoating has been achieved by the application of a gum-based solution to the sealed tablet cores, and once this solution has been distributed uniformly throughout the tablet mass, it is followed by a liberal dusting of powder, which serves to reduce tack and facilitate tablet buildup. This procedure of application of gum solution, spreading, dusting, and drying is continued until the requisite buildup has been achieved. Thus, the subcoating is a sandwich of alternate layers of gum and powder. Some examples of binder solutions are shown in Table 46-1 and those of dusting powder formulations in Table 46-2.

Table 46-1. Binder Solution Formulations for Subcoating

	A, % W/W	B, % W/W
Gelatin	3.3	6.0
Gum acacia (powdered)	8.7	8.0
Sucrose	55.3	45.0
Water	to 100.0	to 100.0

Table 46-2. Dusting Powder Formulations for Subcoating

	A, % W/W	B, % W/W
Calcium carbonate	40.0	—
Titanium dioxide	5.0	1.0
Talc (asbestos-free)	25.0	61.0
Sucrose (powdered)	28.0	38.0
Gum acacia (powdered)	2.0	—

While this approach has proved to be very effective, particularly where there is difficulty in covering edges, if care is not taken, a *lumpy* subcoat will be the result. Also, if the amount of dusting powder applied is not matched to the binding capacity of the gum solution, not only will the ultimate coating be brittle, but also dust will collect in the back of the pan, a factor that may contribute to excessive roughness. An alternative approach, particularly when using an automated dosing system, involves the application of a suspension subcoat formulation. With this type of formulation, the powdered materials responsible for coating buildup are dispersed in the gum-based solution. A typical formulation is shown in Table 46-3. This approach allows the solids loading to be matched more closely to the binding capacity of the base solution and often permits the less-experienced coater to achieve satisfactory results.

SMOOTHING—Depending on how successfully the subcoat was applied, it may be necessary to smooth out the tablet surface further prior to application of the color coating. Smoothing usually can be accomplished by the application of a simple syrup solution (approximately 60–70% sugar solids).

Often, the smoothing syrups contain a low percentage of titanium dioxide (1–5%) as an opacifier. This can be particularly useful when the subsequent color-coating formulation uses water-soluble dyes as colorants, since it makes the surface under the color coating more reflective, resulting in a brighter, cleaner final color.

COLOR COATING—This stage is often the most critical to the successful production of a sugar-coating product and involves the multiple application of syrup solutions (60–70% sugar solids) containing appropriate coloring materials. The types of coloring materials used can be divided into two categories: dyes or pigments. The distinction between the two simply is one of solubility in the coating fluid. Since water-soluble dyes behave entirely differently from water-insoluble pigments, the application procedure used in the color coating of tablets will depend on the type of colorant chosen.

When used by a skilled artisan, water-soluble dyes produce the most elegant sugar-coated tablets, since it is possible to obtain a cleaner, brighter final color. However, since water-soluble dyes are migratory colorants (that is to say, moisture that is removed from the coating on drying will cause migration of the colorant, resulting in a nonuniform appearance), great care must be exercised in their use, particularly when dark color shades are required. Such care can be achieved by applying small quantities of colored syrup that are just sufficient to wet the surface of every tablet in the batch, and then allowing the tablets to dry slowly. It is essential that each application be allowed to dry thoroughly before subsequent applications are made, otherwise moisture may become trapped in the coating and may cause the tablets to *sweat* on standing.

Table 46-3. Typical Suspension Subcoating Formulation

	% W/W
Distilled water	25.0
Sucrose	40.0
Calcium carbonate	20.0
Talc (asbestos-free)	12.0
Gum acacia (powdered)	2.0
Titanium dioxide	1.0

The final color obtained may be the result of up to 60 individual applications of colored syrup. This factor, combined with the need to dry each application slowly and thoroughly, results in very long processing times (eg, assuming 50 applications are made, which can take between 15 and 30 min each, the coloring process can take up to 25 hours to complete). The more recent introduction of preformulated dye-based coloring systems has obviated many of these problems.

Tablet color coating with pigments, as advocated by Tucker et al,[9] offers some significant advantages. First of all, since pigment colors are water-insoluble, they present no problems of migration since the colorant remains where it is deposited. In addition, if the pigment is opaque or is combined with an opacifier such as titanium dioxide, the desired color can be developed much more rapidly, thus resulting in a thinner color coat. Since each color-syrup application now can be dried more rapidly, fewer applications are required, and significant reductions can be made in both processing times and costs.

Although pigment-based color coatings are by no means foolproof, they will permit more abuse than a dye color-coating process and are easier to use by less-skilled coating operators. Pharmaceutically acceptable pigments can be classified either as inorganic pigments (eg, titanium dioxide, iron oxides) or certified lakes. Certified lakes are produced from water-soluble dyes using a process known as *laking,* whereby each dye molecule is bonded to the surface of a suitable insoluble substrate (such as alumina hydrate, a material chemically very similar to the aluminum hydroxide used in many antacid formulations).

Certified lakes, particularly when used in conjunction with an opacifier such as titanium dioxide, provide an excellent means of coloring sugar coatings and permit a wide range of shades to be achieved. However, the incorporation of pigments into the syrup solution is not as easy as with water-soluble dyes, since it is necessary to ensure that the pigment is wetted completely and dispersed uniformly. Thus, the use of pigment color concentrates, which are commercially available, is usually beneficial.

POLISHING—Sugar-coated tablets are, by nature, very dull in appearance, and thus need to be polished to achieve a final elegance. Polishing is achieved by applying mixtures of waxes (beeswax, carnauba wax, candelila wax, or hard paraffin wax) to the tablets in a polishing pan. Such wax mixtures may be applied as powders or as dispersions in various organic solvents.

PRINTING—To identify sugar-coated tablets (in addition to shape, size, and color) often it is necessary to print them, either before or after polishing, using pharmaceutical branding inks, by means of the process of *offset rotogravure.*

SUGAR-COATING PROBLEMS—Various problems may be encountered during the sugar coating of tablets. It must be remembered that any process in which tablets are kept tumbling constantly can cause problems if the tablets are not strong enough to withstand the applied stress. Tablets that are too soft or have a tendency to laminate may break up and the fragments adhere to the surface of otherwise good tablets.

Sugar-coating pans exhibit inherently poor mixing characteristics. If care is not exercised during the application of the various coating fluids, non-uniform distribution of coating material can occur, resulting in an unacceptable range of sizes of finished tablets within the batch.

Overzealous use of dusting powders, particularly during the subcoating stage, may result in a coating being formed in which the quantity of fillers exceeds the binding capacity of the polymer used in the formulation, creating soft coatings or those with increased tendency to crack.

Irregularities in appearance are not uncommon and occur either as the result of color migration during drying when water-soluble dyes are used or of *washing back* when overdosing

of colored syrups causes the previously dried coating layers to be redissolved. Rough tablet surfaces will produce a *marbled* appearance during polishing, since wax buildup occurs in the small depressions in the tablet surface.

Film Coating of Solid Dosage Forms

Film coating is a process that involves the deposition of a thin, but uniform, film onto the surface of the substrate. Unlike sugar coating, film coating is a very flexible process that allows a broad range of products (eg, tablets, powders, granules, nonpareils, capsules) to be coated. Film coatings essentially are typically applied continuously to a moving mass of product, usually by means of a spray technique, although manual application procedures have been used.

Historically, film coating was introduced in the early 1950s to combat the shortcomings of the then predominant sugar-coating process. Film coating has proved successful as a result of the many advantages offered, including

1. Minimal weight increase (typically 2–3% of tablet core weight)
2. Significant reduction in processing times
3. Increased process efficiency and output
4. Increased flexibility in formulations
5. Improved resistance to chipping of the coating

In the early years of film coating, the major process advantages resulted from the greater volatility of the organic solvents used; however, the use of such organic solvents has created many potential problems, including

1. Flammability hazards
2. Toxicity hazards
3. Concerns over environmental pollution
4. Cost (relating either to minimizing items 1 to 3 or to the cost of the solvents themselves)

However, since the initial introduction of film coating, significant advances have been made in process technology and equipment design. The emphasis has changed from a process needing highly volatile organic solvents (in order to facilitate rapid drying) to one where even a relatively slow drying solvent such as water can be accommodated through significant improvements in the drying capabilities of the processing equipment used.

Thus, there has been a transition from conventional pans to side-vented pans and fluid-bed equipment, and consequently from the problematic organic solvent-based process to an aqueous one.

FILM COATING RAW MATERIALS—The major components in any film-coating formulation consist primarily of a polymer, plasticizer, colorant, and solvent (or vehicle).

Ideal properties for the polymer include solubility in a wide range of solvent systems to promote flexibility in formulation, an ability to produce coatings that have suitable mechanical properties, and appropriate solubility in gastrointestinal fluids such that drug bioavailability is not compromised.

Cellulose ethers are often the preferred polymers in film coating, particularly hydroxypropyl methylcellulose. Suitable substitutes are hydroxypropyl cellulose, which may produce slightly tackier coatings, and methylcellulose, although this polymer has been reported to retard drug dissolution.[10] Alternatives to the cellulose ethers are acrylic copolymers (eg, methacrylate and methyl methacrylate copolymers) and vinyl polymers (eg, polyvinyl alcohol).

For most film-coating applications, where there is no intent to modify drug-release characteristics, polymers are typically used as solutions in either water (preferred) or organic solvents.

Many of the commonly used polymers are available in a range of molecular-weight grades, a factor that also must be considered in the selection process. Molecular weight may have an important influence on various properties of the coating system, such as solution viscosity and mechanical strength and flexibility of the resultant film.

The incorporation of a plasticizer into the formulation improves the flexibility of the coating, reduces the risk of the film cracking, and potentially improves adhesion of the film to the substrate. To ensure that these benefits are achieved, the plasticizer must show a high degree of compatibility with the polymer and be retained permanently in the film, if the properties of the coating are to remain consistent on storage. Examples of typical plasticizers include glycerin, propylene glycol, polyethylene glycols, triacetin, acetylated monoglyceride, citrate esters (eg, triethyl citrate), or phthalate esters (eg, diethyl phthalate).

Colorants usually are used to improve the appearance of the product as well as to facilitate product identification. Additionally, certain physical properties of the coating (eg, its performance as a moisture barrier) may be improved. As in the case of sugar coating, colorants can be classified as either water-soluble dyes or insoluble pigments.

The use of water-soluble dyes is precluded with organic solvent-based film coating because of the lack of solubility in the solvent system. Thus, the use of pigments, particularly aluminum lakes, provides the most useful means of coloring film-coating systems. Although it may seem obvious to use water-soluble dyes in aqueous formulations, the use of pigments is preferred, since:

1. They are unlikely to interfere with bioavailability[11] as do some water-soluble dyes.
2. They help to reduce the permeability of the coating to moisture.[12]
3. They serve as bulking agents to increase the overall solids content in the coating dispersion without dramatically increasing viscosity.
4. They tend to be more light stable.

The major solvents used in film coating typically belong to one of these classes: alcohols, ketones, esters, chlorinated hydrocarbons, and water. Solvents perform an important function in the film-coating process, since they aid in the application of the coating to the surface of the substrate. Good interaction between solvent and polymer is necessary to ensure that optimal film properties are obtained when the coating dries. This initial interaction between solvent and polymer will yield maximum polymer chain extension, producing films having the greatest cohesive strength and, thus, the best mechanical properties. An important function of the solvent systems also is to ensure a controlled deposition of the polymer onto the surface of the substrate so that a coherent and adherent film coat is obtained.

Although it is very difficult to give typical examples of film-coating formulations, since these will depend on the properties of the materials used, such formulations usually are based on 5–20% (w/w) coating solids in the requisite vehicle (with the higher concentration range preferred for aqueous formulations), of which 60–70% is polymer, 6–7% is plasticizer, and 20–30% is pigment.

Modified-Release Film Coatings

Film coatings can be applied to pharmaceutical products to modify drug release. The USP describes two types of modified-release dosage forms, namely those that are *delayed release* and those that are *extended release.* Delayed-release products often are designed to prevent drug release in the upper part of the gastrointestinal (GI) tract. Film coatings used to prepare this type of dosage form are commonly called *enteric coatings*. Extended-release products are designed to extend drug release over a period of time, a result that can be achieved by the application of a *sustained-* or *controlled-release* film coating.

ENTERIC COATINGS—Enteric coatings generally remain intact in the stomach but will dissolve and release the contents of the dosage form once it reaches the small intestine. The purpose of an enteric coating is to delay the release of drugs that are inactivated by the stomach contents, (eg, pancreatin, erythromycin, and substituted benzimidazole compounds that are proton pump inhibitors) or may cause nausea or bleeding by irritating the gastric mucosa (eg, aspirin, steroids). In addition, such coatings can be used to give a simple repeat-action effect

in which additional drug that has been applied over the enteric coat is released in the stomach, while the remainder, being protected by the coating, is released further down the gastrointestinal tract.

The action of enteric coatings results from a difference in composition of the respective gastric and intestinal environments in regard to pH and enzymatic properties. Although there have been repeated attempts to produce coatings that are subject to intestinal enzyme breakdown, this approach is not popular, since enzymatic decomposition of the film is rather slow. Thus, most currently used enteric coatings are weak acids that remain undissociated in the low pH environment of the stomach but readily ionize when the pH rises to about 5. The most effective enteric polymers are polyacids having a pK_a of 3 to 5. Coatings that respond to enzymatic breakdown are now being considered as protective coatings suitable for the colonic delivery of polypeptide drugs.

Historically, the earliest enteric coatings used formalin-treated gelatin, but this approach was unreliable, since the polymerization of gelatin could not be controlled accurately and often resulted in failure to release the drug, even in the lower intestinal tract. Another early candidate was shellac, but again the main disadvantage resulted from further polymerization that occurred on storage, often resulting in failure to release the active contents. Pharmaceutical formulators now prefer to use synthetic polymers to prepare more effective enteric coatings.

One of the oldest synthetic polymers used for enteric coating is cellulose acetate phthalate (CAP). However, a pH greater than 6 usually is required to allow the coating to dissolve, and thus a significant delay in drug release may ensue. It also is relatively permeable to moisture and gastric fluid compared with most enteric polymers. Additionally, this polymer is very susceptible to hydrolytic decomposition in which phthalic and acetic acids are split off, resulting in a change in polymer properties, and thus enteric coating performance.

Other useful polymers include polyvinyl acetate phthalate (PVAP, which is less permeable to moisture and gastric fluid, more stable to hydrolysis, and able to ionize at a lower pH); hydroxypropyl methylcellulose phthalate (HPMCP, which has properties similar to PVAP); acrylic copolymers, such as methacrylic acid–methacrylic acid ester copolymers (some of which have a high dissociation constant[13]); cellulose acetate trimellitate (CAT, which has properties similar to CAP); carboxymethyl ethylcellulose (CMEC); and hydroxypropyl methylcellulose acetate succinate (HPMCAS).

In recent years, acrylic copolymers have evolved as the most preferred (in terms of performance and global acceptability) materials for designing enteric coating formulations.

Since enteric coating polymers are, by nature, insoluble in water (except at high pH), their use in aqueous coating systems has required the adaptation of so-called latex technology that has resulted in the creation of either liquid polymer dispersions or dry powder coating systems that can readily be dispersed in water prior to use.

SUSTAINED-RELEASE COATINGS—The concept of sustained release formulations was developed to eliminate the need for multiple dosage regimens, particularly for those drugs requiring reasonably constant blood levels over a long period of time. In addition, it also has been adopted for those drugs that need to be administered in high doses, but where too rapid a release is likely to cause undesirable side effects (eg, the ulceration that occurs when potassium chloride is released rapidly in the gastrointestinal tract).

Formulation methods used to obtain the desired drug release rate from sustained-action dosage forms include

1. Increasing the particle size of the drug
2. Embedding the drug in a matrix
3. Coating the drug or dosage form containing the drug
4. Forming complexes of the drug with materials such as ion-exchange resins

Only those methods that involve some form of coating fall within the scope of this chapter. A discussion of other controlled release drug delivery systems can be found in Chapter 47 (Extended-Release and Targeted Drug Delivery Systems). The mechanisms of drug release from film-coated products are also provided.

Materials that have been found suitable for producing sustained-release coatings include

1. Mixtures of waxes (eg, beeswax, carnauba wax) with glyceryl monostearate, stearic acid, palmitic acid, glyceryl monopalmitate, and cetyl alcohol. These provide coatings that are dissolved slowly or broken down in the GI tract.
2. Shellac and zein. These polymers remain intact until the pH of gastrointestinal contents becomes less acidic.
3. Ethylcellulose, which provides a membrane around the dosage form and remains intact throughout the gastrointestinal tract. However, it does permit water to permeate the film, dissolve the drug, and diffuse out again.
4. Acrylic resins, which behave similarly to ethylcellulose as a diffusion-controlled drug-release coating material
5. Cellulose acetate (diacetate and triacetate)
6. Silicone elastomers

As with enteric coatings, many of the synthetic polymers suitable for sustained-release film-coating applications are available as aqueous polymer dispersions (often called latexes or pseudolatexes) that can be used in aqueous coating processes.[14]

Various methods have been used to prepare sustained- release products using film-coating techniques. Examples include the application of suitable film coatings to:

1. Dried granules (either irregular or spheronized)
2. Drug-loaded beads (or nonpareils)
3. Drug crystals
4. Drug/ion-exchange-resin complexes
5. Tablets (including mini tablets[15])

In the first four examples, the final coated particles can be either filled into two-piece hard-gelatin capsules or compacted into tablets. Additionally, coated drug/ion-exchange-resin complexes may be dispersed in viscous liquids to create liquid suspensions. A comprehensive overview of the coating of multiparticulate dosage forms has been given by Ghebre-Sellassie.[16]

An interesting application of the film-coated, sustained-release tablet is the elementary osmotic pump. In this device, a tablet core (formulated to contain osmotically active ingredients) is film coated with a semi-permeable membrane. This membrane is subsequently *pierced* with a laser to create a delivery orifice. Once such a device is ingested, the infusion of water generates an osmotic pressure within the coated tablet that *pumps* the drug out through the orifice.

With sustained-release products, one must remain aware constantly of the fact that the final dosage forms typically contain drug loadings that are sufficiently high to cause problems if the entire dose is released quickly. This phenomenon, commonly called *dose-dumping,* can be avoided only if:

1. The film coating is mechanically sound and will resist rupture on ingestion of the dosage form.
2. Sufficient coating is applied uniformly across the surface of the material that is to be coated.
3. The dosage form is not chewed or crushed prior to ingestion.

FILM-COATING PROBLEMS

As with sugar coating, problems may occur during, or subsequent to, the film-coating process. The tablets being coated may not be sufficiently robust or may have a tendency to *laminate* while being coated. Since film coats are relatively thin, their ability to hide defects is significantly less than that of sugar coating. Hence, tablets that have poor resistance to abrasion (ie, they exhibit high friability characteristics) can be problematic, since imperfections may readily be apparent after coating. It is very important to identify tablets with suspect properties, whether mechanical or performance related (eg, poor dissolution), prior to a coating process, since subsequent recovery or reworking of tablets may be extremely difficult after a coating has been applied.

Various process-related problems can occur during the application of a film coating. One example is *picking,* which is a consequence of the fluid delivery rate exceeding the drying capacity of the process, causing tablets to stick together and subsequently break apart. Another example, *orange peel* or *roughness,* is usually the result of premature drying of atomized droplets of solution, or it may be a consequence of spraying too viscous a coating solution such that effective atomization is difficult.

Mottling, or lack of color uniformity, can result from uneven distribution of color in the coating, a problem often related to the use of soluble dyes in aqueous film coating, when color migration can occur, either by evolution of residual solvent in the film or by migration of plasticizer in which the colorant may be soluble. The use of pigments in the film-coating process minimizes the incidence of this latter objection considerably. However, uneven color also can result from inadequate dispersion of the pigments in the coating solution.

Finally, some major problems occur as the result of internal stresses that develop within the film as it dries. One example is *cracking,* which occurs when these stresses exceed the tensile strength of the film. This problem may be compounded by the existence of post compaction strain relaxation (a phenomenon that can occur with certain types of tablet formulations, such as those containing ibuprofen, after ejection from the die during the tabletting process), which causes tablets to expand. Another example is *logo-bridging* (ie, bridging of monograms present in the surface of the tablet core), which occurs when the internal stresses are able to overcome the adhesive bonds formed between the coating and the tablet surface, causing the film to pull away so that legibility of the monogram is lost. An understanding of the properties of the various ingredients used in the film-coating formulation and how these ingredients interact with one another can allow the formulator to avoid many of these internal-stress-related problems.[17]

COATING PROCEDURES AND EQUIPMENT

COATING PANS—Sugar coating historically has involved the ladling of the various coating fluids onto a cascading bed of tablets in a conventional coating pan (Fig 46-1) fitted with a means of supplying drying air to the tablets and an exhaust to remove moisture and dust-laden air from the pan.

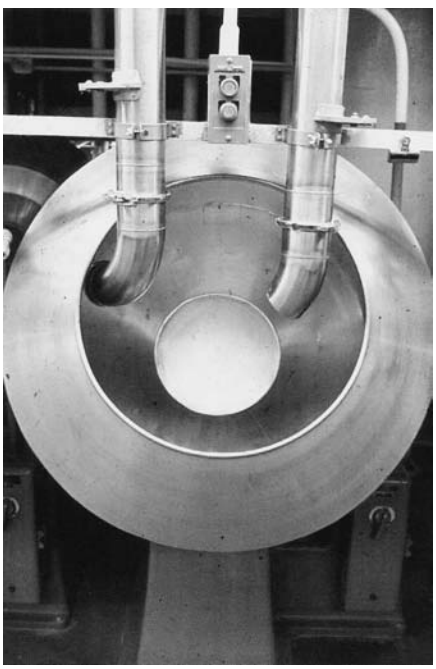

Figure 46-1. Typical equipment set-up for conventional sugar coating.

Typically, after the requisite volume of liquid has been applied, some time is allowed for the tablets to mix and the liquid to be dispersed fully throughout the batch. To facilitate the uniform transfer of liquid, the tablets often are *stirred* by hand, or in larger pans, by means of a rake, to overcome mixing problems often associated with *dead spots,* an inherent problem seen with conventional pans. Finally, tablets are dried by blowing air onto the surface of the tablet bed. Thus, sugar coating is a sequential process consisting of consecutive cycles of liquid application, mixing, and drying.

During the early history of film coating, the equipment used was adapted essentially from that already employed for sugar coating. Although ladling of coating liquids during the film-coating process has been practiced, usually the liquid is applied using a spray technique. Spray equipment used is essentially of two types:

1. Airless (or hydraulic) spray, where the coating liquid is pumped under pressure to a spray nozzle with a small orifice and atomization of the liquid occurs as it expands rapidly on emerging from the nozzle. This is analogous to the effect achieved when one places one's finger over the end of a garden hose.
2. Air spray, where liquid is pumped, under little or no pressure, to the nozzle and is subsequently atomized by means of a blast of compressed air that makes contact with the stream of liquid as it passes through the nozzle aperture.

Airless-spray techniques typically are used in large-scale film-coating operations employing organic solvents, while air-spray techniques are more effective in either a small-scale laboratory set-up or aqueous film-coating operations.

Spray application enables finely atomized droplets of the coating solution to be delivered across the surface of the moving tablet mass in a manner that achieves uniform coverage while preventing adjacent tablets from sticking together as the coating solution is rapidly dried. While all the events that take place during the spray application process occur continuously and concurrently, the overall picture can be more simply represented as shown in Figure 46-2.

The spray process can be operated either intermittently or continuously. In the early years of film coating, the lack of adequate drying conditions inside the coating apparatus, together with the preference for using airless coating techniques (with their inherently higher delivery rates) with organic solvent-based formulations typically required the use of intermittent spray procedures. This technique allowed excess solvent to be removed during the nonspray part of the cycle and thus reduced the risk of *picking* and the tendency for tablets to stick together. However, in later years, improvements in drying capabilities have resulted in the preferred use of continuous spray procedures, as this permits uniform coatings to be applied in a shorter process.

As indicated previously, pan equipment initially was completely conventional in design and, with the exception of the addition of spray-application equipment, was similar to that used in sugar coating. Fortunately, film-coating formulations were based on relatively volatile organic solvents, which enabled acceptable processing times to be achieved in spite of the relative deficiencies of the air-handling systems. However, such equipment did not produce a completely enclosed system, a fact that

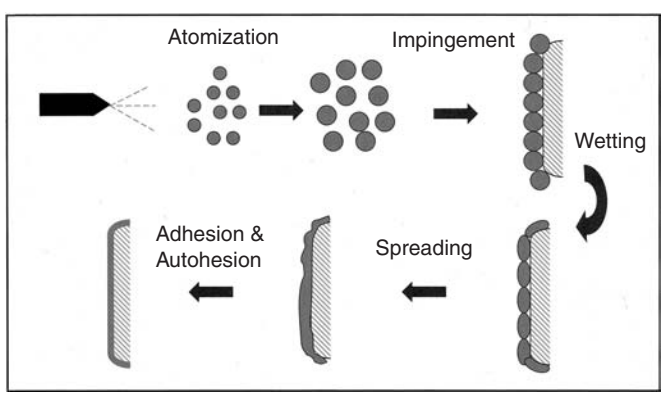

Figure 46-2. The film-coating process.

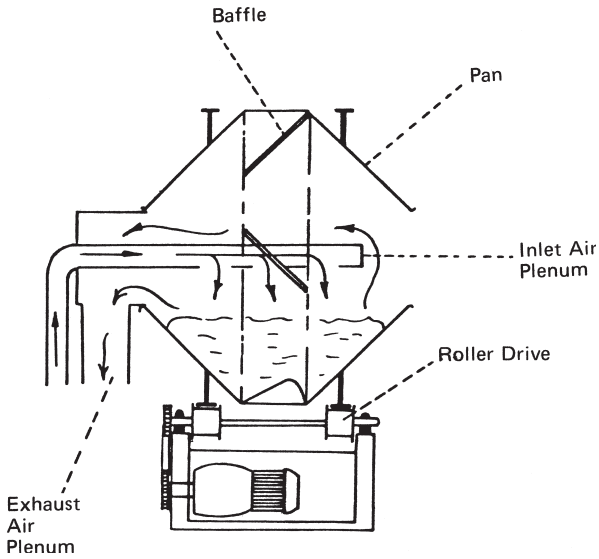

Figure 46-3. A Pellegrini coating pan.

made effective solvent containment extremely difficult to achieve. Although conventional pans possessed acceptable properties with regard to mixing of the tablet mass in the sugar-coating process (particularly as this could be augmented by manual stirring of the tablets during processing), they were less suited to meet the more rigorous demands of the film-coating process, even when some simple baffle system was installed.

The introduction of aqueous film coating in the latter part of the twentieth century presented a more serious challenge to the continued use of conventional processing equipment. Limitations in both drying and mixing capabilities potentially signified a dramatic increase in processing times while substantially compromising product quality and long-term stability. Fortunately, these problems have been eliminated as coating-pan design has evolved and improved.

Although considerable experimentation has taken place with the geometric design of conventional equipment, a substantial change came with the introduction of the Pellegrini coating pan (Fig 46-3), a somewhat angular pan that rotates on a horizontal axis. Pan design, and installation of an integral baffle system, ensures that more uniform mixing is achieved. Additionally, since the services are introduced through the rear opening, the front can potentially be closed off to produce an enclosed coating system. Although drying air is still applied only to the surface of the tablet bed, the other advantages derived from the basic overall design ensure that the Pellegrini pan is more suitable for film coating than the conventional equipment previously discussed. Pellegrini pans are available with capacities ranging from the 10-kg laboratory scale-up to 1000 kg for high-output production.

Considering the drying inefficiencies in pan where most of the drying takes place only on the surface of the tablet bed, se veral attempts have been made to improve air exchange, particularly within the tablet bed. The schematic shown in Figure 46-4 conceptually describes the basis for equipment designed to improve the drying capabilities exhibited by more conventional coating equipment.

Two such types of equipment, both based on the Pellegrini style of coating pan, are supplied by GS and Nicomac. In both cases, an air plenum fitted with a perforated *boot* is immersed into the cascading bed of product being coated. A second air plenum is also led inside the coating pan. With this type of design, either a *direct* or a *reverse airflow* plan can be used.

A major advance in pan coating technology was the introduction of the side-vented pan concept, an innovation developed by Eli Lilly. This concept, formally designated as the Accela-cota, has formed the basis for a wide range of *side-vented*

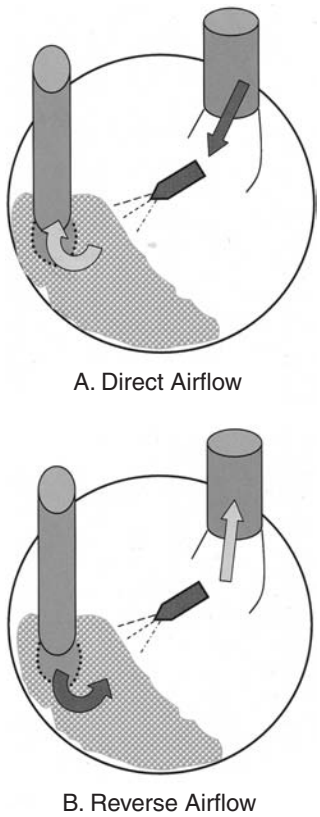

Figure 46-4. Upgraded conventional coating pans. **A.** Direct airflow. **B.** Reverse airflow.

coating pan designs, a schematic of which is shown in Figure 46-5. The salient features of side-vented coating pans are:

1. An angular pan (fitted with an integral baffle system) that rotates on a horizontal axis.
2. A coating system that is completely enclosed.

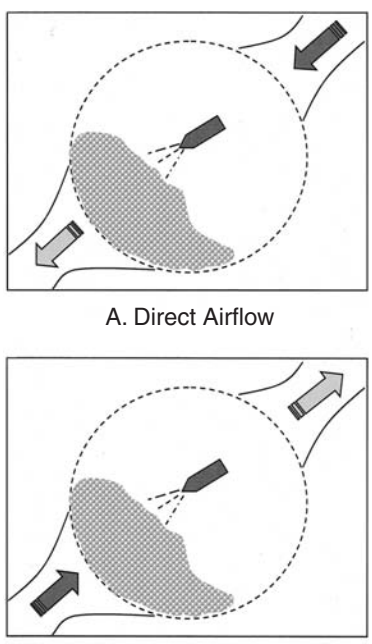

Figure 46-5. Side-vented coating pans. **A.** Direct airflow. **B.** Reverse airflow.

3. A perforated pan that allows drying air to be pulled through a cascading bed of tablets while the coating liquid is applied to the tablet surface using a spray-atomization technique.

Side-vented coating pans exhibit dramatically improved drying characteristics, a feature that facilitated the successful adoption of aqueous film-coating technology. Manufacturers of side-vented coating pans include Thomas Engineering, BWI Manesty, O'Hara, Glatt, Dumoulin, Vector Freund, and Driam.

Ongoing trends with side-vented coating pans have produced:

1. Designs that permit multidirectional air flow.
2. Fully automated, computerized coating processes (especially for production-scale coating purposes).
3. Effective clean-in-place (CIP) systems that facilitate compliance with GMPs.
4. Laboratory-scale coating equipment provided with interchangeable coating pans representing batch capacities in the range of 3–40 kg (depending on product density).
5. Coating pans designed to permit continuous processing (where the product is constantly introduced into one end and flows, fully coated, out the other).

Although improvements in coating-pan design have predominately occurred to improve the aqueous film-coating process, they have also benefited the sugar-coating process.

FLUIDIZED-BED COATING EQUIPMENT—Fluid-bed processing technology has long been used in the pharmaceutical industry. While several attempts have been made to apply this technology to the film-coating process, a major success came with the introduction of the Wurster concept (a schematic of which is shown in Figure 46-6) in the 1950s.

At a time when organic-solvent-based coating formulations were still primarily used, the Wurster process was extremely popular for coating a variety of pharmaceutical dosage forms, especially tablets. Although fluid-bed processing inarguably exhibits the most effective drying characteristics of any film-coating process, the introduction of aqueous coating formulations initially created waning interest in using the Wurster process for coating tablets. A major factor in this trend undoubtedly was related to the increased potential (compared with use of coating pans) for tablet breakage in the fluid-bed process. During the last 30 years, however, resurgent interest in the Wurster process has occurred as a result of the growing demand for applying film coatings to pellets, granules, and powders (so-called *multiparticulates*) when producing modified-release dosage forms.

The suitability of the fluid-bed process for film coating multiparticulates also has generated interest in processes other than the Wurster for this application. In particular, modifications of the spray granulation process (often termed the *top-spray coating process*) and a rotary process (often called the *tangential spray process*) have both been used for the film coating of multiparticulates. Schematics for all these processes also are shown in Figure 46-6.

Three major manufacturers of fluid-bed processing equipment (Glatt Air Techniques, Vector Corporation, and GEA) all have adopted a principle in which a basic processing unit is designed to accept modular inserts for each of the three fluid-bed coating processes shown in Figure 46-6. Selection of a particular type of insert often is determined by the nature and intended functionality of the coating applied; for example

1. Granulator Top-Spray Process—preferred when a taste-masking coating is being applied; additionally suitable for the application of hot-melt coatings.
2. Wurster, Bottom-Spray Process—preferred for the application of modified-release coatings to a wide variety of multiparticulates; also suitable for drug layering when the drug dose is in the low-to-medium range.
3. Rotor, Tangential-Spray Process—suitable for the application of modified-release film coatings to a wide range of multiparticulate products; ideal for drug layering when the dose is medium to high; also useful as a spheronizing process for producing spheres from powders.

While the general trend has been to use equipment employing this modular concept, an innovative approach to fluid-bed film coating was introduced by Hüttlin, who created a design known as the Kugel coater.[18]

POTENTIAL FOR TOTALLY AUTOMATED COATING SYSTEMS—Over the course of time, the pharmaceutical industry has witnessed a general transition away from manually operated sugar-coating processes, requiring total operator involvement, to film-coating ones where operator intervention is infrequent. Increasing familiarity with, and understanding of, tablet coating as a unit process, and a desire to ensure compliance with GMPs, ultimately have increased the desire to achieve reproducible and consistent conformity to design specifications for every batch of product made. Achievement of such an objective is clearly compromised if the idiosyncrasies of individual operators are allowed to have a major impact on final product quality (in its broadest sense).

Total automation of a well designed and validated process can provide a solution to these problems. Automation involves the development of a process in which all the important variables (and requisite constraints) are predetermined. These variables, once adequately defined, can then be used as the ba-

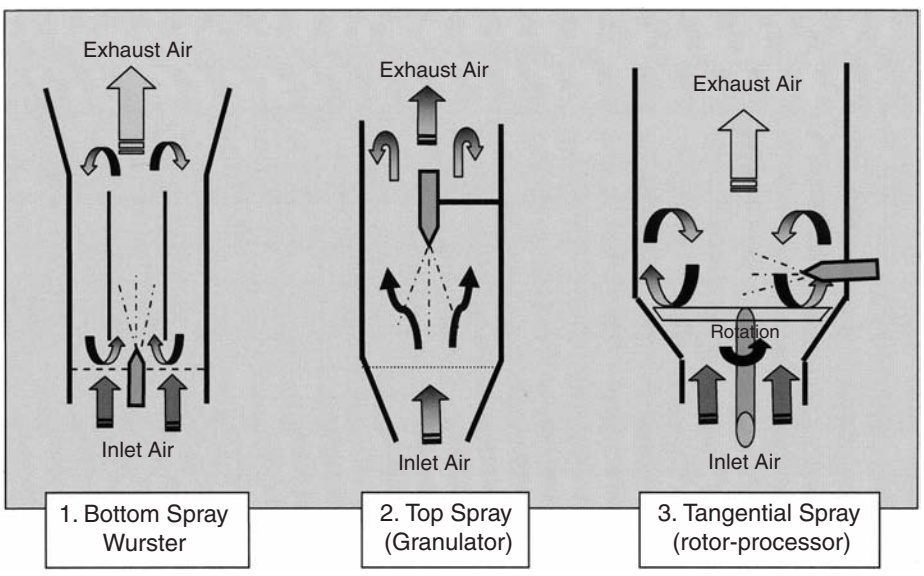

Figure 46-6. Three basic processes used for fluid-bed film coating.

sis for creating a process where ultimate control and monitoring of each critical process parameter can be accomplished through use of either a microprocessor or a central computer system. However, such a system will only be as good as those peripheral devices used to detect critical process conditions (eg, such as air flow, temperature, humidity, application volumes, or delivery rates), and the rate at which the control systems can respond to changes so that the process can be maintained within defined process limits.

Since a sugar-coating process always has been highly operator dependent, removal of much of the operator intervention could be achieved by automation. Automation has, however, been complex because of the various sequences that occur and the variety of coating fluids used in a single sugar-coating process. That it has been accomplished is evidenced by the number of commercially available systems that have been introduced.[19] The technology for automated control of both sugar- and film-coating processes has become very refined, and most major equipment suppliers are able to offer a coating process that is automated to various degrees (depending on end-user preferences).

QUALITY CONTROL OF COATED TABLETS

The most important aspects of coated tablets that must be assessed from a quality-control standpoint are appearance characteristics and drug availability. From the appearance standpoint, coated tablets must be shown to conform, where applicable, to some color standard, otherwise the dispenser and the consumer may assume that differences have occurred from previous lots, signifying a changed or substandard product. In addition, because of the physical abuse that tablets, both in their uncoated and coated forms, receive during the coating process, it is essential to check for defects such as chipped edges, picking, etc, and ensure that they do not exceed predetermined limits.

Often, to identify the products, coated tablets may be imprinted (particularly with sugar-coated tablets) or bear a monogram (commonly seen with tablets that are film-coated). The clarity and quality of such identifying features must be assessed. The failure of a batch of coated tablets to comply with such preset standards may result in 100% inspection being required or the need for the batch to be reworked.

Batch-to-batch reproducibility for drug availability is of paramount importance; consequently each batch of product should be submitted to some meaningful test such as a dissolution test. Depending on the characteristics of the tablet core to be coated, tablet coatings can modify the drug release profile, even when not intended (unlike the case of enteric- or controlled-release products). Since this behavior may vary with each batch coated (being dependent, for example, on differences in processing conditions or variability in raw materials used), it is essential that this parameter be assessed, particularly in products that are typically borderline (refer to Chapter 45 *Oral Solid Dosage Forms*).

STABILITY TESTING OF COATED PRODUCTS

The stability-testing program for coated products will vary depending on the dosage form and its composition. Many stability-testing programs are based on studies that have disclosed the conditions a product may encounter prior to end use. Such conditions usually are referred to as normal and include ranges in temperature, humidity, light, and handling conditions. The conditions to be employed in modern stability-testing programs often conform to the guidelines established by the International Committee on Harmonization (ICH). A more detailed discussion on the stability of pharmaceutical products may be found in Chapter 52.

Limits of acceptability are established for each product for qualities such as color, appearance, availability of drug for absorption, and drug content. The time over which the product retains specified properties, when tested at normal conditions, may be defined as the *shelf life*. The container for the product may be designed to improve the shelf life. For example, if the color in the coating is light-sensitive, the product may be packaged in an amber bottle and/or protected from light by using a paper carton. When the coating is friable, resilient material such as cotton may be incorporated in both the top and bottom of the container, and if the product is affected adversely by moisture, a moisture-resistant closure may be used and/or a desiccant may be placed in the package. The shelf life of the product is determined in the commercial package tested under normal conditions.

The stability of the product also may be tested under exaggerated conditions. This usually is done for the purpose of accelerating changes so that an extrapolation can be made early, concerning the shelf life of the product. Although useful, highly exaggerated conditions of storage can supply misleading data for coated dosage forms. Any change in drug release from the dosage form is measured *in vitro,* but an *in vivo* measurement should be used to confirm that drug availability remains within specified limits over its stated shelf life. This confirmation can be obtained by testing the product initially for *in vivo* availability and then repeating at intervals during storage at normal conditions for its estimated shelf life (or longer).

Interpretation of stability data for coated, modified-release products should be undertaken with extreme care, since the diffusion characteristics of polymeric films can change significantly under exaggerated temperature conditions. This change may be confounding when trying to predict their diffusion characteristics under more moderate conditions and thus can prove misleading when predicting shelf life.

When elevated-temperature stability studies are conducted on products coated with aqueous polymeric dispersions (latexes or pseudolatexes), the data obtained might be more indicative of morphological changes that have occurred in the film. Such changes may result from partial destruction of the film when coated material adheres together in the container and subsequently is broken apart; additionally, these changes might result from further coalescence of the coating (which can occur when the coating is not coalesced completely during the coating process).

Stability tests usually are conducted on a product at the time of development, during the pilot phase and on representative lots of the commercial product. Stability testing must continue for the commercial product as long as it remains on the market because subtle changes in a manufacturing process and/or a raw material can have an impact on the shelf life of a product.

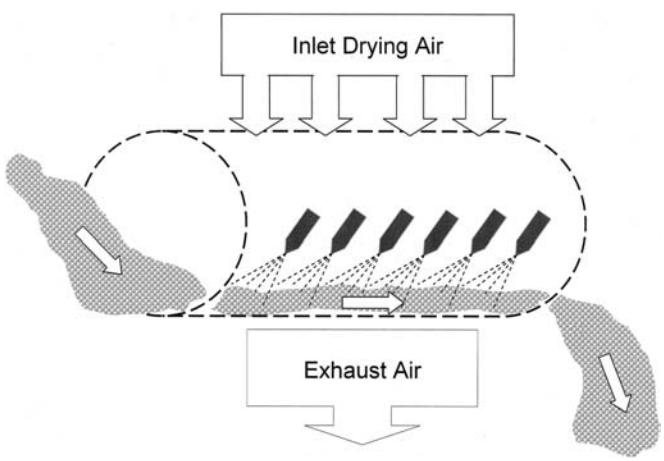

Figure 46-7. Continuous film-coating process.

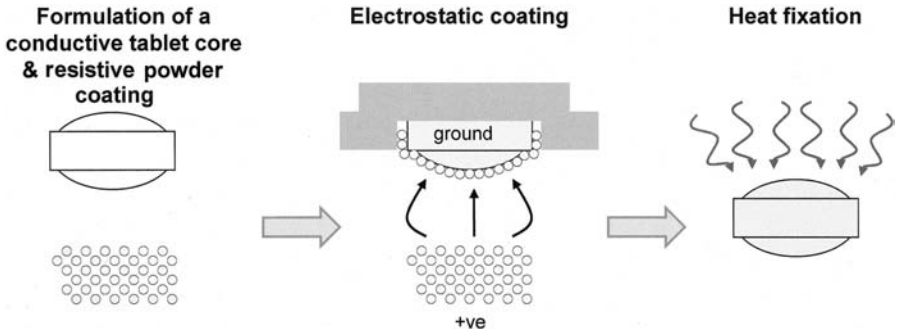

Figure 46-8. Electrostatic powder coating process.

RECENT TRENDS IN PHARMACEUTICAL COATING TECHNOLOGY

There is an inherent conservatism expressed by pharmaceutical manufacturers towards accepting major changes in raw materials (ie, non-active ingredients) and processing technologies. Thus, change tends to be evolutionary rather than revolutionary. Still, some interesting events have occurred over the last decade.

Of particular note is the growing interest in *Process Analytical Technology*. This has resulted in bringing many analytical procedures out of the laboratory and closer to the manufacturing process with which they may be associated. The desire here is to introduce, ideally as an on-line control function, specific analytical techniques that can be used to enhance the quality of the final coated products. One example is the use of near infrared techniques that can be used to analyze coated product in such a way that, for example, product moisture contents, drug contents, amount of coating applied, and even, to some extent, drug release rates can be predicted before that product is discharged from the coating process.

Another advance involves the increasing acceptance of continuous film coating processes, as described by Mancoff [20] and Pentecost. [21] Current continuous processes are based on the concept of a stretched side-vented coating pan, where uncoated product is introduced at one end, passes by a whole bank of spray guns, and emerges from the other end fully coated (Fig 46-7). The advantages of this type of process include:

1. Increasing output (typical outputs are in the range of 500 to 1000 kg h^{-1}), compared to common batch processes which might coat a 250 kg batch in one to two hours, while a 500kg batch might be coated in three to four hours.
2. Reducing residence time in a process where product is typically exposed to stressful conditions (attrition, high humidities and temperatures) from several hours to about 15 minutes.
3. Improving uniformity of distribution of coating materials.

Continuous coating processes of this type are usually reserved for coating large-volume products where desired applied coating levels are in the range of 3–4% (based on the tablet core weight).

Currently, most coating processes involve the spray application of liquid coating systems where solidification of the coating is achieved through solvent removal (ie, drying), and distribution of coating materials is facilitated through constant motion of the material being coated. A more revolutionary approach to film coating, also based on a continuous process, involves the electrostatic deposition of powder coating systems to the surface of tablets (and fusing the coating through application of heat) using principles that are based on electrophotography (photocopying). In this process, described by Staniforth et al [22] and illustrated in Figure 46-8, tablets are coated individually one side at a time. The advantages of this type of process are:

1. No solvents (aqueous or organic) are used.
2. The coating is deposited onto tablets in a much more precise manner than can be achieved with any other existing pharmaceutical coating process.
3. Novel imaging can be achieved.
4. Tablet surfaces can be only partially coated, thus facilitating applications involving novel drug delivery.

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CHAPTER 47

Extended-Release and Targeted Drug Delivery Systems

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Adam WG Alani, M Sc
Joseph R Robinson, PhD

The goal of any drug delivery system is to provide a therapeutic amount of drug to a proper site in the body so that the desired drug concentration can be achieved promptly and then maintained. That is, the drug-delivery system should deliver drug at a rate dictated by the needs of the body over a specified period of time. This idealized objective points to the two aspects most important to drug delivery, namely, *spatial placement* and *temporal delivery*. Spatial placement relates to targeting drugs to specific organs, tissues, cells, or even subcellular compartments; whereas temporal delivery refers to controlling the rate of drug delivery to the target site. An appropriately designed controlled drug delivery system can be a major advance toward solving these two problems. It is for this reason that the science and technology responsible for development of controlled drug delivery has been, and continues to be, the focus of a great deal of attention in both industrial and academic laboratories. The history of controlled delivery technology can be divided roughly into three time periods. From 1950 to 1970 is the period of extended drug release. A number of systems containing hydrophobic polymers and waxes were fabricated with drugs into dosage forms with the aim of maintaining drug levels and, hence, drug action for an extended period of time. However, a lack of understanding of anatomic and physiologic barriers impeded the development of efficient delivery systems. From 1970 to 1990, research mainly focused on determining the needs in controlled drug delivery and on understanding the barriers for various routes of administration. Zero-order release was emphasized in controlled drug delivery. Interest in drug targeting accelerated during this period as well. The rapid progress in biotechnology and molecular biology promoted drug delivery research in the 1980s and early 1990s. Post 1990, the modern era of controlled drug delivery technology, represents the period in which an attempt at drug optimization was emphasized. In the past two decades, considerable effort has been expended on developing novel polymeric carriers, biomacromolecule delivery systems, etc.[1] Currently, numerous products formulated for various routes of administration and claiming sustained or controlled drug delivery, exist on the market. The bulk of research has been directed toward oral dosage forms that satisfy the temporal aspect of drug delivery. In addition, some of the newer approaches under investigation may allow for spatial placement as well.

CONVENTIONAL DRUG THERAPY

To gain an appreciation for the value of controlled drug therapy, it is useful to review some fundamental aspects of conventional drug delivery. Consider single dosing of a hypothetical drug that follows a simple one-compartment pharmacokinetic model for disposition. Depending on the route of administration, a conventional dosage form of the drug can produce a drug blood level versus time profile similar to that shown in Figure 47-1. The term *drug blood level* refers to the concentration of drug in blood or plasma, but the concentration in any tissue could be plotted on the ordinate. It can be seen from this figure that administration of a drug by either intravenous injection or an extravascular route (eg, orally, intramuscularly, or rectally) does not maintain drug blood levels within the therapeutic range for an extended period of time. The short duration of action is due to the inability of conventional dosage forms to control temporal delivery. If an attempt is made to maintain drug blood levels in the therapeutic range for longer periods by, for example, increasing the initial dose of an intravenous injection, as shown by the dotted line in Figure 47-1, toxic levels may be produced at early time points. Obviously, this approach is undesirable and unsuitable. An alternative approach is to administer the drug repetitively using a constant dosing interval, as in a multiple-dose therapy. This is shown in Figure 47-2 for the oral route. In this case the therapeutic drug blood level reached and the time required to reach that level depend on the dose and the dosing interval.

There are several potential problems inherent in multiple-dose therapy:

1. If the dosing interval is not appropriate for the biological half-life of the drug, large peaks and valleys in the drug blood level may result. For example, drugs with short half-lives require frequent dosing to maintain constant therapeutic levels.
2. The drug blood level may not be within the therapeutic range at sufficiently early time points, an important consideration for certain disease states.
3. Patient noncompliance with the multiple-dosing regimen can result in failure of this approach.

In many instances, potential problems associated with conventional drug therapy can be overcome. When this is the case, drugs given in conventional dosage forms by multiple dosing can produce the desired drug blood level for extended periods of time. Frequently, however, these problems are significant enough to make drug therapy with conventional dosage forms less desirable than modified-release drug therapy. This fact, coupled with the intrinsic inability of conventional dosage forms to achieve spatial placement, is a compelling stimulus for development of controlled drug delivery systems.

MODIFIED-RELEASE DRUG THERAPY

Terminology

Currently, most modified-release delivery systems fall into the following four categories:

1. Delayed-release
2. Extended-release

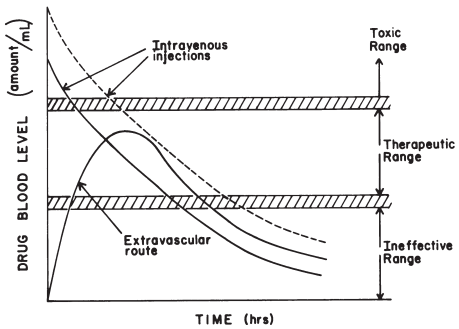

Figure 47-1. Typical drug blood level versus time profiles for intravenous injection or an extravascular route of administration.

3. Site-specific targeting
4. Receptor targeting

Delayed-release systems are either those that use repetitive, intermittent dosing of a drug from one or more immediate-release units incorporated into a single dosage form, or an enteric delayed release system. Examples of delayed-release systems include repeat-action tablets and capsules, and enteric-coated tablets where timed release is achieved by a barrier coating.

Extended-release systems include any dosage form that maintains therapeutic blood or tissue levels of the drug for a prolonged period. If the system can provide some actual therapeutic control, whether this is temporal or spatial or both, of drug release in the body, it is considered a controlled delivery system. This explains why extended-release is not equivalent to controlled-release.

Site-specific and *receptor targeting* refer to targeting a drug directly to a certain biological location. In the case of site-specific release, the target is adjacent to or in the diseased organ or tissue; for receptor release, the target is the particular drug receptor within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery requirement and are also considered controlled drug delivery systems.

Controlled drug delivery can be defined as delivery of the drug at a predetermined rate and/or to a location according to the needs of the body and disease states for a definite time period. A controlled delivery system must fulfill one or several of the following requirements[2]:

1. *Extend drug action at a predetermined rate* by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects that may be associated with a sawtooth kinetic pattern of conventional release.
2. *Localize drug action* by placing a controlled delivery system (usually rate-controlled) adjacent to or in a diseased tissue or organ.
3. *Target drug action* by using carriers or chemical derivatives to deliver a drug to a particular target cell type.
4. *Provide a physiologically/therapeutically based drug release system*. In other words, the amount and the rate of drug release are determined by the physiological/therapeutic needs of the body.

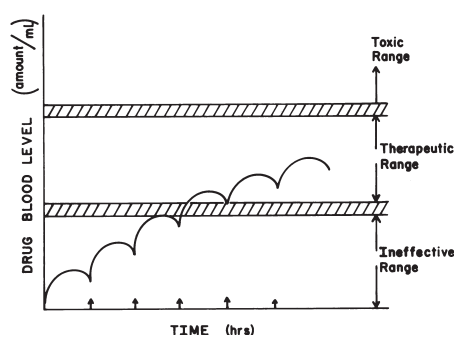

Figure 47-2. Typical drug blood level versus time profile following oral multiple-dose therapy.

Recently, a novel modification of drug delivery systems has emerged from the pharmaceutical industry. A *fast-dissolve drug delivery system* consists of a solid dosage form that dissolves or disintegrates in the oral cavity without the need of water or chewing. Among commercial products, fast dissolution or disintegration is achieved by forming an open matrix network containing the active ingredient (Zydis, *Eli Lilly*), by incorporating saliva-activated effervescent agents (OraSolv, *Cima*), or by using a mixture of a disintegrating agent and a swelling agent (Flashtab, *Prographarm*).[3]

Potential Advantages

All modified-release products share the common goal of improving drug therapy over that achieved with their conventional counterparts. There are several potential advantages of modified-release systems over conventional dosage forms, as shown in Table 47-1.

Patient compliance has been recognized as a necessary and important component in the success of all self-administered drug therapies. Minimizing or eliminating patient compliance is an obvious advantage of extended-release therapy. Because of the nature of its release kinetics, an extended-release system should be able to use less total drug over the time course of therapy than a conventional preparation. The advantages of this are a decrease or elimination of both local and systemic side effects, less potentiation or reduction in drug activity with chronic use, and minimization of drug accumulation in body tissues with chronic dosing.

The most important reason for modified-release drug therapy is improved efficiency in treatment (ie, optimized therapy). By obtaining constant or some other pattern of drug blood levels from an extended-release system, the desired therapeutic effect can be obtained promptly and maintained for a prolonged period of time. Reducing or eliminating fluctuations in the drug blood level allows better disease state management. In addition, the method by which extended release is achieved can improve the bioavailability of some drugs. For example, drugs susceptible to enzymatic inactivation or bacterial decomposition can be protected by encapsulation in polymeric systems suitable for extended release. For drugs that have a specific window for absorption, increased bioavailability can be achieved by localizing the extended-release delivery system in certain regions of the gastrointestinal tract. Improved efficiency in treatment also can take the form of a special therapeutic effect not possible with a conventional dosage form.

The last potential advantage listed in Table 47-1 (ie, economic savings) can be examined from two points of view. Although the initial unit cost of most extended-release delivery systems usually is greater than that of conventional dosage forms because of the special nature of these products, the average cost of treatment over an extended time period may be

Table 47-1. Potential Advantages of Modified-Release Drug Therapy

1. Avoid patient compliance problems
2. Employ less total drug
   a. Minimize or eliminate local side effects
   b. Minimize or eliminate systemic side effects
   c. Obtain less potentiation or reduction in drug activity with chronic use
   d. Minimize drug accumulation with chronic dosing
3. Improve efficiency in treatment
   a. Cure or control condition more promptly
   b. Improve control of condition (ie, reduce fluctuation in drug level)
   c. Improve bioavailability of some drugs
   d. Make use of special effects (eg, sustained-release aspirin for morning relief of arthritis by dosing before bedtime)
4. Economic savings

lower. Economic savings also may result from a decrease in nursing time/hospitalization, less lost work time, etc.

DRUG PROPERTIES RELEVANT TO EXTENDED-RELEASE FORMULATION

The design of extended-release delivery systems is subject to several variables of considerable importance. Among these are the route of drug administration, the type of delivery system, the disease being treated, the patient, the length of therapy, and the properties of the drug. Each of these variables is interrelated, which imposes additional constraints upon the design of the delivery system. Of particular interest to the scientist designing the system are the constraints imposed by the properties of the drug. It is these properties that have the greatest effect on the behavior of the drug in the delivery system and in the body. The properties of a drug are conveniently described as being either physicochemical or biological. Obviously, there is no clear-cut distinction between these two categories, since the biological properties of a drug are a function of its physicochemical properties. For this discussion, however, those attributes that can be determined from *in vitro* experiments will be considered physicochemical properties. Biological properties resulting from typical pharmacokinetic studies on the absorption, distribution, metabolism, and elimination (ADME) characteristics of a drug and from pharmacodynamic studies will be covered in the next section.

Among all the physicochemical properties, solubility and membrane permeability are recognized as fundamental parameters controlling the rate and extent of drug absorption. A *Biopharmaceutic Drug Classification,* proposed by Amidon et al,[4] defines four cases of oral therapeutic products based on these two attributes:

1. High solubility-high permeability drugs.
2. Low solubility-high permeability drugs.
3. High solubility-low permeability drugs.
4. Low solubility-low permeability drugs.

Solubility and permeability play an influential role in the performance of conventional products; their role is even greater in extended-release systems.

Aqueous Solubility and pKa

It is well known that for a drug to be absorbed, it must dissolve in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane. The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration in solution and, hence, the driving force for diffusion across membranes. Dissolution rate is related to aqueous solubility, as shown by the *Noyes-Whitney equation* that, under sink conditions, is

$$dC/dt = k_D A C_s \quad (1)$$

where dC/dt is the dissolution rate, k_D is the dissolution rate constant, A is the total surface area of the drug particles, and C_s is the aqueous saturation solubility of the drug. The dissolution rate is constant only if A remains constant, but the important point to note is that the initial rate is directly proportional to C_s. Therefore, the aqueous solubility of a drug can be used as a first approximation of its dissolution rate. Drugs with low aqueous solubility have low dissolution rates and usually suffer oral bioavailability problems.

The aqueous solubility of weak acids or bases is governed by the pKa of the compound and the pH of the medium. For a weak acid

$$S_t = S_0 (1 + Ka/[H^+]) = S_0 (1 + 10^{\,\mathrm{pH-pKa}}) \quad (2)$$

where S_t is the total solubility (both the ionized and unionized forms) of the weak acid, S_0 is the solubility of the unionized form, Ka is the acid dissociation constant, and $[H^+]$ is the hydrogen ion concentration in the medium. Similarly, for a weak base

$$S_t = S_0 (1 + [H^+]/Ka) = S_0 (1 + 10^{\,\mathrm{pKa-pH}}) \quad (3)$$

where S_t is the total solubility (both the conjugate acid and free-base forms) of the weak base, S_0 is the solubility of the free-base form, and Ka is the acid dissociation constant of the conjugate acid. Equations 2 and 3 predict that the total solubility of a weak acid or base with a given pK_a can be affected by the pH of the medium.

Considering the pH-partition hypothesis, the importance of Equations 2 and 3 relative to drug absorption is evident. The pH-partition hypothesis simply states that the unionized form of a drug will be absorbed preferentially, in a passive manner, through membranes. Since weakly acidic drugs exist primarily in the unionized form in the stomach (pH = 1 to 2), their absorption will be excellent in such an acidic environment. On the other hand, weakly basic drugs exist primarily in the ionized form (conjugate acid) at the same site, and their absorption will be poor. In the upper portion of the small intestine, the pH is more basic (pH = 5 to 7), and the reverse will be expected for weak acids and bases. The ratio of Equation 2 or 3 written for either the pH of the gastric or intestinal fluid and the pH of blood is indicative of the driving force for absorption based on pH gradient. For example, consider the ratio of the total solubility of aspirin in the blood and gastric fluid

$$R = (1 + 10^{\,\mathrm{pHb-pKa}})/(1 + 10^{\,\mathrm{pHg-pKa}}) \quad (4)$$

where pH_b is the pH of blood (pH 7.4), pH_g is the pH of the gastric fluid (pH 2), and the pKa of aspirin is about 3.4. Substituting these values into Equation 4 gives a value for R of $10^{3.8}$, indicating that aspirin is readily absorbed within the stomach. The same calculation for intestinal pH (about 7) yields a ratio close to 1, indicating less driving force for aspirin absorption within the small intestine. Ideally, the release of an ionizable drug from an extended-release system should be programmed in accordance with the variation in pH of the different segments of the gastrointestinal tract so that the amount of preferentially absorbed forms, and thus the plasma level of the drug, will be approximately constant throughout the time course of drug action.

In general, extremes in aqueous solubility of a drug are undesirable for formulation into an extended-release product. A drug with very low solubility and a slow dissolution rate will exhibit dissolution-limited absorption and yield an inherently sustained blood level. In most instances, formulation of such a drug into an extended-release system may not provide considerable benefits over conventional dosage forms. Even if a poorly soluble drug were considered a candidate for formulation into an extended-release system, a constraint would be placed on the type of delivery system that could be used. For example, any system relying on diffusion of the drug through a polymer as the rate-limiting step in release would be unsuitable for a poorly soluble drug, since the driving force for diffusion is drug concentration in the polymer or solution, and this concentration would be low. For a drug with very high solubility and a rapid dissolution rate, it is often quite difficult to decrease its dissolution rate and slow its absorption. Preparing a slightly soluble form of a drug with normally high solubility is one possible method for producing extended-release dosage forms.

Partition Coefficient

Between the time when a drug is administered and when it is eliminated from the body, it must diffuse through a variety of biological membranes that act primarily as lipid-like barriers. A major criterion in evaluation of the ability of a drug to penetrate these lipid membranes (ie, its membrane permeability) is its apparent oil/water partition coefficient, defined as

$$K = C_O/C_W \quad (5)$$

where C_O is the equilibrium concentration of all forms of the

drug in an organic phase at equilibrium, and C_W is the equilibrium concentration of all forms in an aqueous phase. A frequently used solvent for the organic phase is 1-octanol. In general, drugs with extremely large values of K are very oil-soluble and will partition into membranes quite readily. The relationship between tissue permeation and partition coefficient for the drug generally is defined by the *Hansch correlation,* which describes a parabolic relationship between the logarithm of the activity of a drug or its ability to be absorbed and the logarithm of its partition coefficient, as shown in Figure 47-3. The explanation for this relationship is that the activity of a drug is a function of its ability to cross membranes and interact with the receptor. As a first approximation, the more effectively a drug crosses membranes, the greater its activity. There is also an optimum partition coefficient for a drug in which it most effectively permeates membranes and thus shows greatest activity. Values of the partition coefficient below this optimum result in decreased lipid solubility, and the drug will remain localized in the first aqueous phase it contacts. Values larger than the optimum result in poorer aqueous solubility but enhanced lipid solubility, and the drug will not partition out of the lipid membrane once it gets in. The value of K at which optimum activity is observed is approximately 1000/1 in n-octanol/water. Drugs with a partition coefficient that is higher or lower than the optimum are, in general, poorer candidates for formulation into extended-release dosage forms.

Drug Stability

Of importance for oral dosage forms is the loss of drug through acid hydrolysis and/or metabolism in the gastrointestinal tract. Since a drug in the solid state undergoes degradation at a much slower rate than a drug in suspension or solution form, it would seem possible to improve significantly the relative bioavailability of a drug that is unstable in the gastrointestinal tract by placing it in a slowly available extended-release form. For those drugs that are unstable in the stomach, the most appropriate controlling unit would be one that releases its contents only in the intestine. The reverse is the case for those drugs that are unstable in the environment of the intestine; the most appropriate controlling unit in such a case would be one that releases its contents only in the stomach. However, it is very difficult for a delivery system to release its contents in a specific region of the gastrointestinal tract. Thus, drugs with significant stability problems in any particular area of the gastrointestinal tract are less suitable for formulation into extended-release systems that deliver their contents uniformly over the length of the gastrointestinal tract. Delivery systems that remain localized in a certain area of the gastrointestinal tract (eg, a bioadhesive drug-delivery system) and act as reservoirs for drug release are preferred for drugs that not only suffer from stability problems but have other bioavailability problems. Under some circumstances, extended-release drug delivery systems may provide benefits for highly unstable drugs. As mentioned earlier, the drug may be protected from enzymatic degradation by incorporation into an enteric-coated dosage form.

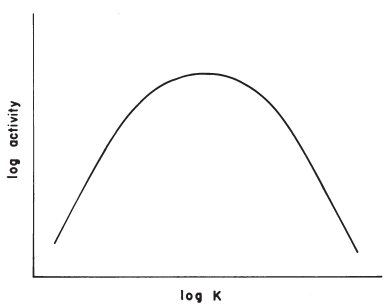

Figure 47-3. Typical relationship between drug activity and partition coefficient, *K,* generally known as the Hansch correlationship.

The presence of metabolizing enzymes at the site of absorption is not necessarily a negative factor in extended-release formulation. Indeed, the prodrug approach to drug delivery takes advantage of the presence of these enzymes to regenerate the parent molecule of an inactive drug derivative.

Molecular Size and Diffusivity

As previously discussed, a drug must diffuse through a variety of biological membranes during its time course in the body. In addition to diffusion through these biological membranes, drugs in many extended-release systems must diffuse through a rate-controlling polymeric membrane or matrix. The ability of a drug to diffuse in polymers, its so-called diffusivity (diffusion coefficient D), is a function of its molecular size (or molecular weight). For most polymers, it is possible to relate log D empirically to some function of molecular size as

$$\log D = -s_v \log v + k_v = -s_M \log M + k_m \qquad (6)$$

where v is molecular volume, M is molecular weight, s_v, s_M, k_v, and k_m are constants. The value of D thus is related to the size and shape of the cavities as well as size and shape of drugs. Generally, values of the diffusion coefficient for intermediate-molecular-weight drugs (ie, 150 to 400 Da) through flexible polymers range from 10^{-6} to 10^{-9} cm^2/sec, with values on the order of 10^{-8} being most common.[5] A value of approximately 10^{-6} is typical for these drugs through water as the medium. For drugs with a molecular weight greater than 500 Da, their diffusion coefficients in many polymers frequently are so small that they are difficult to quantify (ie, less than 10^{-12} cm^2/sec). Thus, high-molecular-weight drugs should be expected to display very slow release kinetics in extended-release devices using diffusion through polymeric membranes or matrices as the releasing mechanism.

Protein Binding

Distribution of the drug into the extravascular space is governed by the equilibrium process of dissociation of the drug from the bound plasma proteins (eg, albumin). The drug-protein complex can serve as a reservoir in the vascular space for extended drug release to extravascular tissues, but only for those drugs that exhibit a high degree of binding. Thus, the protein-binding characteristics of a drug can play a significant role in its therapeutic effect, regardless of the type of dosage form. Extensive binding to plasma proteins may result in a long half-life of elimination for the drug; such drugs generally do not require an extended-release dosage form. On the other hand, drugs that exhibit a high degree of binding to plasma proteins also might bind to biopolymers in the gastrointestinal tract, which could have an influence on drug delivery.

The main attractive forces responsible for binding are van der Waals forces, hydrogen bonding, and electrostatic forces. In general, charged compounds have a greater tendency to bind a protein than uncharged compounds because of electrostatic effects. The presence of a hydrophobic moiety on the drug molecule also increases its binding potential. Some drugs that exhibit greater than 95% protein binding at therapeutic levels are amitriptyline, bishydroxycoumarin, diazepam, diazoxide, dicumarol, and novobiocin.

PHARMACOKINETIC AND PHARMACODYNAMIC CONSIDERATIONS

Release Rate and Dose[6]

Conventional dosage forms include solutions, suspensions, capsules, tablets, emulsions, aerosols, foams, ointments, and suppositories. For purposes of this discussion, these dosage forms

can be considered to release their active ingredients into an absorption pool immediately. This is illustrated by the following simple kinetic scheme:

$$\text{Dosage Form} \xrightarrow[\text{drug release}]{k_r} \text{Absorption Pool} \xrightarrow[\text{absorption}]{k_a} \text{Target Area} \xrightarrow[\text{elimination}]{k_e}$$

The absorption pool represents a solution of the drug at the site of absorption, and the terms k_r, k_a, and k_e are first-order rate constants for drug release, absorption, and overall elimination, respectively. Immediate release from a conventional dosage form implies that $k_r >>> k_a$ or, alternatively, that absorption of drug across a biological membrane, such as the intestinal epithelium, is the rate-limiting step in delivery of the drug to its target area. For nonimmediate-release dosage forms, $k_r <<< k_a$, that is, release of drug from the dosage form is the rate-limiting step. This causes the above kinetic scheme to reduce to

$$\text{Dosage Form} \xrightarrow[\text{drug release}]{k_r} \text{Target Area} \xrightarrow[\text{elimination}]{k_e}$$

Essentially, the absorptive phase of the kinetic scheme becomes insignificant compared with the drug release phase. Thus, the effort to develop a nonimmediate-release delivery system must be directed primarily to altering the release rate by affecting the value of k_r. This has been attempted in many ways, as discussed later in this chapter.

Although it is not necessary or desirable to maintain a constant level of drug in the blood or target tissue for all therapeutic cases, this is the ideal starting goal of an extended-release delivery system. In fact, in some cases optimum therapy is achieved by providing oscillating, rather than constant, drug levels. An example of this is antibiotic therapy, where the activity of the drug is required only during the growth phase of the microorganism.

The ideal goal in designing an extended-release system is to deliver drug to the desired site at a rate according to the needs of the body (ie, a self-regulated system based on feedback control). However, this is a difficult assignment. Although some attempts have been made to achieve this goal, such as with the self-regulating insulin pump, there is no commercial product representing this type of system as yet. In the absence of feedback control, we are left with a simple extending effect. The pivotal question is at what rate a drug should be delivered to maintain a constant blood drug level. This constant rate should be the same as that achieved by continuous intravenous infusion where a drug is provided to the patient at a constant rate just equal to its rate of elimination. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. That is, release from the dosage form should follow zero-order kinetics, as shown by

$$k_r^0 = \text{Rate In} = \text{Rate Out} = k_e \cdot C_d \cdot V_d \tag{7}$$

where k_r^0 is the zero-order rate constant for drug release (amount/time), k_e is the first-order rate constant for overall drug elimination (time^{-1}), C_d is the desired drug level in the body (amount/volume), and V_d is the volume of the space in which the drug is distributed. The values of k_e, C_d, and V_d needed to calculate $k_r{}^0$ are obtained from appropriately designed single-dose pharmacokinetic studies. Equation 7 provides the method to calculate the zero-order release rate constant necessary to maintain a constant drug blood or tissue level for the simplest case, where drug is eliminated by first-order kinetics. For many drugs, however, more complex elimination kinetics and other factors affecting their disposition are involved. This in turn affects the nature of the release kinetics necessary to maintain a constant drug blood level. It is important to recognize that while zero-order release may be desirable theoretically, non-zero-order release may be equivalent clinically to constant release in many cases. Aside from the extent of intra- and intersubject variation is the observation that for many drugs, modest changes in drug tissue levels do not result in an improvement in clinical performance. Thus, a nonconstant drug level may be indistinguishable clinically from a constant drug level.

To achieve a therapeutic level promptly and sustain the level for a given period of time, the dosage form generally consists of two parts: an initial priming dose, D_i, that releases drug immediately, and a maintenance or sustaining dose, D_m. The total dose, W, thus required for the system is

$$W = D_i + D_m \tag{8}$$

For a system in which the maintenance dose releases drug by a zero-order process for a specified period of time, the total dose is

$$W = D_i + k_r^0 T_d \tag{9}$$

where T_d is the total time required for extended release from one dose. If the maintenance dose begins release of drug at the time of dosing ($t = 0$), it will add to that which is provided by the initial dose, thus increasing the initial drug level. In this case a correction factor is needed to account for the added drug from the maintenance dose

$$W = D_i + k_r^0 T_d - k_r^0 T_p \tag{10}$$

The correction factor $k_r^0 T_p$ is the amount of drug provided during the period from $t = 0$ to the time of the peak drug level, T_p. No correction factor is needed if the dosage form is constructed in such a fashion that the maintenance dose does not begin to release drug until time T_p.

It already has been mentioned that a perfectly invariant drug blood or tissue level versus time profile is the ideal starting goal of an extended-release system. The way to achieve this, in the simplest case, is use of a maintenance dose that releases its drug by zero-order kinetics. However, satisfactory approximations of a constant drug level can be obtained by suitable combinations of the initial dose and a maintenance dose that releases its drug by a first-order process. The total dose for such a system is

$$W = D_i + (k_e C_d / k_r) V_d \tag{11}$$

where k_r is the first-order rate constant for drug release (time^{-1}), and k_e, C_d, and V_d are as defined previously. If the maintenance dose begins releasing drug at $t = 0$, a correction factor is required just as in the zero-order case. The correct expression in this case is

$$W = D_i + (k_e C_d / k_r) V_d - D_m k_e T_p \tag{12}$$

To maintain drug blood levels within the therapeutic range over the entire time course of therapy, most extended-release drug delivery systems are, like conventional dosage forms, administered as multiple rather than single doses. For an ideal extended-release system that releases drug by zero-order kinetics, the multiple dosing regimen is analogous to that used for a constant intravenous infusion. For those extended-release systems having release kinetics other than zero-order, the multiple dosing regimen is more complex, and its analysis is beyond the scope of this chapter; Welling and Dobrinska[7] provide a more detailed discussion about this subject.

Since an extended-release system is designed to alleviate repetitive dosing, it naturally will contain a greater amount of drug than a corresponding conventional form. The typical administered dose of a drug in a conventional dosage form will give some indication of the total amount of drug needed in an extended-release preparation. For those drugs requiring large conventional doses, the volume of the sustained dose may be too large to be practical or acceptable, depending on the route of administration. The same may be true of drugs that require a large release rate from the extended-release system (eg, drugs with short half-lives). For the oral route, the volume of the product is limited by patient acceptance. For the intramuscular, intravenous, or subcutaneous routes, the limitation is tolerance of the drug at the injection site. For very potent drugs, incorporation of large amounts of drug is potentially dangerous if the system fails to control drug release.

Absorption

The rate, extent, and uniformity of absorption of a drug are important factors when considering its formulation into an extended-release system. Since the rate-limiting step in drug delivery from an extended-release system is its release from a dosage form, rather than absorption, a rapid rate of drug absorption relative to its release is essential if the system is to be successful. As stated previously, $k_r <<< k_a$. This becomes most critical in the case of oral administration. Assuming that the transit time of a drug through the absorptive area of the gastrointestinal tract is between 9 and 12 hr, the maximum absorption half-life should be 3 to 4 hr.[8] This corresponds to a minimum absorption rate constant k_a value of 0.17 to 0.23 hr^{-1} necessary for about 80–95% absorption over a 9- to 12-hr transit time. For a drug with a very slow rate of absorption (ie, $k_a << 0.17\ hr^{-1}$), the above discussion implies that a first-order release rate constant k_r less than 0.17 hr^{-1} is likely to result in unacceptably poor bioavailability in many patients. Therefore, slowly absorbed drugs will be difficult to be formulated into extended-release systems where the criterion $k_r <<< k_a$ must be met.

The extent and uniformity of the absorption of a drug, as reflected by its bioavailability and the fraction of the total dose absorbed, may be quite low for a variety of reasons. This is usually not a prohibitive factor in its formulation into an extended-release system. Some possible reasons for a low extent of absorption are poor water solubility, low partition coefficient, acid hydrolysis and metabolism, or site-specific absorption. The last reason is also responsible for nonuniformity of absorption. Many of these problems can be overcome by an appropriately designed extended-release system, as exemplified by the discussion under *Potential Advantages of Modified-Release Drug Therapy*.

Distribution

When designing extended-release systems, it is desirable to have as much information as possible regarding drug disposition. In actual practice, decisions usually are based on only a few pharmacokinetic parameters, one of which is the volume of distribution (V_d) as given in Equation 7. The distribution of a drug into vascular and extravascular spaces in the body is an important factor in its overall elimination kinetics. This, in turn, influences the formulation of that drug into an extended-release system, primarily by restricting the magnitude of the release rate and the dose size that can be employed.[6] At present, calculation of these quantities is based primarily on one-compartment pharmacokinetic models. A description of estimation of these quantities based on multicompartment models is beyond the scope of this chapter. However, the main considerations that need to be dealt with will be presented if a two-compartment model is operative.

Two parameters that are used to describe the distribution characteristics of a drug are its apparent volume of distribution and the ratio of drug concentration in tissue to that in plasma at steady state, the so-called T/P ratio. The apparent volume of distribution is merely a proportionality constant that relates drug concentration in the blood or plasma to the total amount of drug in the body. The magnitude of the apparent volume of distribution can be used as a guide for additional studies and as a predictor for a drug-dosing regimen and hence the need to employ an extended-release system. For drugs that obey a one-compartment model, the apparent volume of distribution is

$$V = \text{dose}/C_0 \tag{13}$$

where C_0 is the initial drug concentration immediately after an intravenous bolus injection, but before any drug has been eliminated. The application of this equation is based on the assumption that the distribution of a drug between plasma and tissues takes place instantaneously. This is rarely a good assumption, and it is usually necessary to invoke multi-compartment models to account for the finite time required for the drug to distribute fully throughout the available body space. In the case of a two-compartment model, it has been shown that the best estimate of total volume of drug distribution is given by the apparent volume of distribution at steady state[9]:

$$V_{ss} = (1 + k_{12}/k_{21})V_1 \tag{14}$$

where V_1 is the volume of the central compartment, k_{12} is the rate constant for distribution of drug from the central to the peripheral compartment, and k_{21} is that from the peripheral to the central compartment. As its name implies, V_{ss} relates drug concentration in the blood or plasma at steady state to the total amount of drug in the body during repetitive dosing or constant-rate infusion. The use of Equation 14 is limited to those instances where a steady-state drug concentration in both compartments has been reached; at any other time, it tends to overestimate or underestimate the total amount of drug in the body.

To avoid the ambiguity inherent in the apparent volume of distribution as an estimator of the amount of drug in the body, the T/P ratio also can be used. If the amount of drug in the central compartment, P, is known, the amount of drug in the peripheral compartment, T, and hence the total amount of drug in the body can be calculated by

$$T/P = k_{12}(k_{21} - \beta) \tag{15}$$

Here, β is the slow disposition rate constant. The important point to note is that the T/P ratio estimates the relative distribution of drug between compartments, whereas V_{ss} estimates the extent of distribution in the body. Both parameters contribute to an estimation of the distribution characteristics of a drug, but their relative importance in this respect is open to debate.

Metabolism

The metabolic conversion of a drug to another chemical form usually can be considered in the design of an extended-release system for that drug. As long as the location, rate, and extent of metabolism are known and the rate constant(s) for the process(es) are not too large, successful extended-release products can be developed.

There are two factors associated with the metabolism of some drugs, however, which present problems for their use in extended-release systems. One is the ability of the drug to induce or inhibit enzyme synthesis, which may result in a fluctuating drug blood level with chronic dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through hepatic first-pass effect. Examples of drugs that are subject to intestinal metabolism upon oral dosing are hydralazine, salicylamide, nitroglycerin, isoproterenol, chlorpromazine, and levodopa. Examples of drugs that undergo extensive first-pass hepatic metabolism are propoxyphene, nortriptyline, phenacetin, propranolol, and lidocaine.

Elimination and Biological Half-Life

The rate of elimination of a drug is described quantitatively by its biological half-life, $t_{1/2}$, which is related to its apparent volume of distribution (V) and its systemic clearance (Cl):

$$t_{1/2} = 0.693V/Cl = 0.693V \cdot AUC/dose \tag{16}$$

Cl is equal to the ratio of an intravenously administered dose to the total area under the drug blood level versus time curve (AUC).

To achieve extended-release drug delivery, it is desirable to have zero-order drug input. Under steady state, rate in = rate out, then

$$R_0 = C_{ss}Cl \tag{17}$$

This equation shows that the input rate of an extended-release system is determined solely by steady-state concentration C_{ss} and systemic clearance. Half-life, a common pharmacokinetic parameter, is not directly needed to determine the input rate.

Similarly, volume of distribution is also not a major consideration in designing extended-release delivery systems, although a larger volume of distribution often requires a higher drug load to achieve a therapeutic blood level. However, half-life does play a role in determining the benefits of formulating a drug into an extended-release dosage form. A drug with a short half-life requires frequent dosing, and this makes it a desirable candidate for an extended-release formulation. On the other hand, a drug with a long half-life is dosed at greater time intervals, and thus there is less need for an extended-release system. Practically, it is difficult to define precise upper and lower limits for the value of half-life of a drug that best suits extended-release formulation. In general, a drug with a half-life of less than 2 hr probably should not be used, since such systems will require unacceptably large release rates and large doses. At the other extreme, drugs with half-lives longer than 8 hours are usually not suitable candidates for extended-release dosage forms because they do not provide benefits over conventional dosage forms. In addition, half-life may be useful in determining the dosing interval of an extended-release dosage form. Some examples of drugs with half-lives less than 2 hr are ampicillin, cephalexin, cloxacillin, furosemide, levodopa, penicillin G, and propylthiouracil. Examples of those with half-lives greater than 8 hr are dicumarol, diazepam, digitoxin, digoxin, guanethidine, phenytoin, and warfarin.

Efficacy and Safety

There may not exist a direct correlation between the pharmacokinetics (PK) and pharmacodynamics (PD) of a drug. In other words, it may be difficult to predict the effect of a drug based only on pharmacokinetic data. As a result, a PK/PD model may be required to obtain a rational design of an extended-release dosage form. Typically, a graded response can be represented by

$$E = PC + E_0 \tag{18}$$

where P is a proportionality constant, C is the plasma concentration, and E_0 is the baseline effect. In some cases, a more satisfactory relationship is obtained by using

$$E = P \log C + E_0 \tag{19}$$

In fact, in most cases, the relationship is much more complex than a simple linear one, and sometimes it can be represented only by an expression closely related to enzyme kinetics.

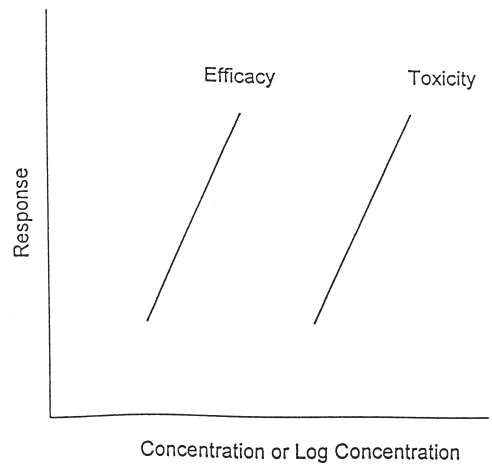

Figure 47-4. Relationship between pharmacological and toxicological responses and concentration. The relative distance between efficacy and toxicity is the therapeutic index of the drug substance. (From Park K, ed. *Controlled Drug Delivery: Challenges and Strategies.* Washington DC: American Chemical Society, 1997, p 589.)

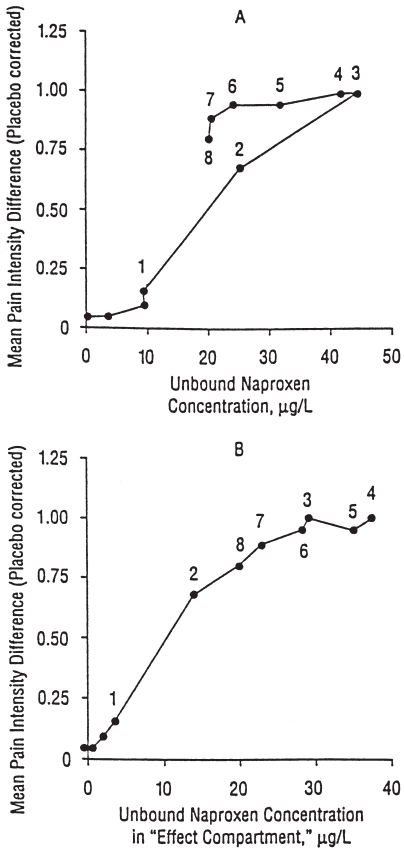

Figure 47-5. Relationship between the mean pain index and concentration of the analgesic index. Obviously, there is a hysteresis in A. However, this clockwise hysteresis is removed when an effect compartment is introduced. (From Rowland M, Tozer TN. *Clinical Pharmacokinetics: Concepts and Applications,* 3rd ed. Baltimore: Lippincott Williams & Wilkins, 1995, p 360.)

$$E = E_0 + (E_{max}C^n)/(E_{50}{}^n + C^n) \tag{20}$$

where E_{max} is the maximal effect, E_{50} is the drug concentration to produce 50% of a maximal effect, and n is a constant. This equation is sometimes subject to variability. Patients differ widely in their values of E_{50} and n for a given drug. Figure 47-4[10] shows a typical response-concentration relationship. Hysteresis may often be found in response-concentration relationships when there is a delayed response due to a slow distribution phase. In this case, an effect compartment model may be useful to correlate the response and concentration (Fig 47-5*A* and *B*[11]). A constant blood level by zero-order release does not necessarily produce a constant pharmacological effect. Nitroglycerin is a good example for illustrative purposes. A constant level of nitroglycerin can lead to tolerance and result in a decreased pharmacological response. Hence, an "off" period is required for adequate nitroglycerin therapy. To conclude, it is necessary to have a thorough knowledge of the relationship between concentration and effect and its dependence on disease and time profile of drug input to have a more rational design of extended-release delivery systems.

There are very few drugs whose specific therapeutic concentrations are known. Instead, a therapeutic concentration range is listed, with increasing toxic effects expected above this range and a falloff in desired therapeutic response observed below the range. For some drugs, the incidence of side effects, in addition to toxicity, is believed to be a function of plasma concentration.[12] An extended-release system can, at times, minimize side effects for a particular drug by controlling its plasma concentration and using less total drug over the time course of therapy.

The most widely used measure of the margin of safety of a drug is its therapeutic index, *TI*, defined as

$$TI = TD_{50}/\mathrm{ED}_{50} \quad (21)$$

where TD_{50} is the median toxic dose and ED_{50} is the median effective dose. The value of *TI* varies from as little as unity, where the effective dose is also producing toxic symptoms, to several thousand. For very potent drugs, whose therapeutic concentration range is narrow, the value of *TI* is small. In general, the larger the value of *TI*, the safer the drug. Drugs with very small values of *TI* usually are poor candidates for formulation into extended-release products, primarily because of technological limitations of precise control over release rates. A drug is considered to be relatively safe if its *TI* value exceeds 10. Examples of drugs with values of $TI < 10$ are some barbiturates and cardiac glycosides.

RATE-CONTROLLED DELIVERY SYSTEMS

Rate-controlled release systems deliver a drug at a predetermined rate for a specific time period. The delivery can be either systemically or locally. In contrast to numerous commercial products claiming controlled drug release from delivery systems, there are only a small number of mechanisms by which the release rate is controlled, although one product may combine two or more mechanisms to achieve optimal control. In this section, the commonly used methods are discussed.

Diffusion Systems

In these systems, the release rate of drug is determined by its diffusion through an inert membrane barrier, usually an insoluble polymer. There are basically two types of diffusion devices: *reservoir devices*, in which a core of drug is surrounded by a polymeric membrane, and *matrix devices*, in which dissolved or dispersed drug is distributed uniformly in an inert polymeric matrix.

RESERVOIR DEVICES—The release of drug from a reservoir device is governed by *Fick's first law of diffusion*

$$J = -DdC_m/dx \quad (22)$$

where *J* is the flux of drug across a membrane in the direction of decreasing concentration (amount/area-time), *D* is the diffusion coefficient of the drug in the membrane (area/time), and dC_m/dx is the change in concentration of drug in the membrane over a distance *x*. If it is assumed that the drug on either side of the membrane is in equilibrium with the respective surface layer of the membrane, as shown in Figure 47-6[13], then the concentration just inside the membrane surface can be related to the concentration in the adjacent region by the expressions:

$$K = C_{m(0)}/C_{(0)} \text{ at } x = 0 \quad (23)$$

$$K = C_{m(l)}/C_{(l)} \text{ at } x = l \quad (24)$$

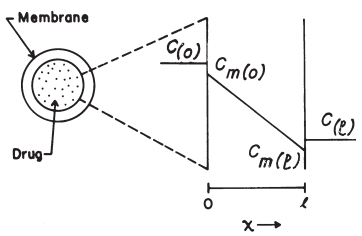

Figure 47-6. Reservoir diffusion device. $C_{m(0)}$ and $C_{m(l)}$ represent concentrations of drug at the inside surfaces of the membrane and $C_{(0)}$ and $C_{(l)}$ represent concentrations in the adjacent regions. (From Langer R, Wise D, eds. *Medical Applications of Controlled Release Technology.* Boca Raton, FL: CRC Press, 1985, p 171.)

Table 47-2. Reservoir Diffusion Products

PRODUCTS	ACTIVE INGREDIENT(S)	MANUFACTURER
Nico-400	Nicotinic acid	Jones
Nitro-Bid	Nitroglycerin	Hoechst Marion Roussel
Cerespan capsules	Papaverine HCl	Rorer
Nitrospan capsules	Nitroglycerin	Rorer
Measurin tablets	Acetylsalicylic acid	Sanofi-Winthrop
Bronkodyl S-R capsules	Theophylline	Sanofi-Winthrop

where *K* is the partition coefficient. Assuming that *D* and *K* are constant, Equation 22 can be integrated to give

$$J = DK\Delta C/l \quad (25)$$

where ΔC is the concentration difference across the membrane.

If the activity of the drug inside the reservoir is maintained constant and the value of *K* is less than unity, zero-order release can be achieved. This is the case when the drug is present as a solid (ie, its activity is unity). Depending on the shape of the device, the equation describing drug release will vary. Only the simplest geometry, that of a rectangular slab or sandwich, is presented here. For the slab geometry, the equation describing release is

$$dM_t/dt = ADK\Delta C/l \quad (26)$$

where M_t is the mass of drug released at time *t*, dM_t/dt is the steady-state release rate at time *t*, *A* is the surface area of the device. Similar equations can be written for cylindrical or spherical geometric devices. To obtain a constant drug-release rate, it is necessary to maintain constant area, diffusion path length, concentration, and diffusion coefficient. In other words, all the terms on the right hand side of Equation 26 are held constant. This is often not the case in actual practice because one or more of the above terms will change in the product. Swelling or contraction of the polymer membrane causes a change in the diffusion length and diffusion coefficient of the drug through the membrane.

Diffusion reservoir devices have been some of the widely used and most successful oral systems. Common methods used to develop reservoir-type devices include microencapsulation of drug particles and film coating of tablets (see Chapter 46, *Coating of Pharmaceutical Dosage Forms*). In most cases, particles coated by microencapsulation form a system in which the drug is contained in the coating film as well as in the core of the microcapsule. Drug release usually involves a combination of dissolution and diffusion, with dissolution being the process that controls the release rate. If the encapsulating material is selected properly, diffusion will be the controlling process. Some materials used as the membrane barrier coat, alone or in combination, are hardened gelatin, methyl- or ethylcelluloses, polyhydroxymethacrylate, hydroxypropylcellulose, polyvinylacetate, and various waxes. Examples of some marketed orally dosed products using an encapsulated reservoir of drug are shown in Table 47-2. Drug release from these products probably is based primarily on diffusion, but dissolution may occur as well.

Diffusion-controlled reservoir devices are also used in other routes: parental (Norplant subdermal levonorgestrel implant, *Wyeth-Ayerst*), ocular (Vitrasert ganciclovir implant, *Chiron*), transdermal (Transderm-Scop scopolamine patch, *Novartis*), and vaginal (Estring estradiol vaginal ring, *Pharmacia*).

MATRIX DEVICES—The rate of release of a drug dispersed as a solid in an inert matrix has been described by Higuchi.[14,15] Figure 47-7 depicts the physical model for a planar slab. In this model, it is assumed that the solid drug dissolves from the surface layer of the device first; when this layer becomes exhausted of drug, the next layer begins to be depleted by dissolution and diffusion through the matrix to the external

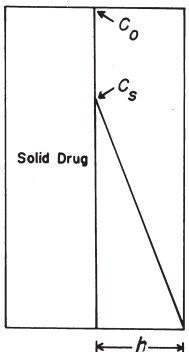

Figure 47-7. Physical model used for a planar-slab matrix-diffusion device.

solution. In this fashion, the interface between the region containing dissolved drug and that containing dispersed drug moves into the interior as a front. The assumptions made in deriving the mathematical model are

1. A pseudo-steady state is maintained during release.
2. The total amount of drug present per unit volume in the matrix, C_0, is substantially greater than the saturation solubility of the drug per unit volume in the matrix, C_s (ie, excess solute is present).
3. The release medium is a perfect sink at all times.
4. Drug particles are much smaller in diameter than the average distance of diffusion.
5. The diffusion coefficient remains constant.
6. No interaction occurs between the drug and the matrix.

Based on Figure 47-7, the change in the amount of drug released per unit area, dM, with a change in the depleted zone thickness, dh, is

$$dM = C_0\,dh - (C_s/2)dh \tag{27}$$

However, based on Fick's first law

$$dM = (D_m C_s/h)dt \tag{28}$$

where D_m is the diffusion coefficient in the matrix. If Equations 27 and 28 are equated, solved for h, and that value of h substituted back into the integrated form of Equation 28, an equation for M is obtained

$$M = [C_s\,D_m\,(2C_0 - C_s)t]^{1/2} \tag{29}$$

Similarly, a drug released from a porous or granular matrix is described by

$$M = [C_a\,D_s\,(\varepsilon/T)(2C_0 - \varepsilon C_a)t]^{1/2} \tag{30}$$

where ε is porosity of the matrix, T is tortuosity, C_a is the solubility of the drug in the release medium, and D_s is the diffusion coefficient of drug in the release medium. In this system, drug is leached from the matrix through channels or pores.

For purposes of data treatment, Equations 29 and 30 are conveniently reduced to

$$M = kt^{1/2} \tag{31}$$

where k is a constant, so that a plot of the amount of drug released versus the square root of time should be linear if release of the drug from the matrix is diffusion-controlled. The release rate of drug from such a device is not zero-order, since it decreases with time, but as previously mentioned, this may be clinically equivalent to constant release for many drugs.

The three major types of materials used in the preparation of matrix devices are insoluble plastics, hydrophilic polymers, and fatty compounds. Plastic matrices that have been investigated include methyl acrylate–methyl methacrylate, polyvinyl chloride, and polyethylene. The Gradumet tablet *(Abbott)* was an example of a dosage form using a plastic matrix. Hydrophilic polymers include methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and carbopol 934. Fatty compounds include various waxes such as carnauba wax and glyceryl tristearate.

The most common method of preparation is to mix the drug with the matrix material and then compress the mixture into tablets. In the case of wax matrices, the drug generally is dispersed in molten wax, which is then congealed, granulated, and compressed into cores. In any extended-release system, it is necessary for a portion of the drug to be available immediately as a priming dose and the remainder to be released in a sustained fashion. This is accomplished in a matrix tablet by placing the priming dose in a coat of the tablet. The coat can be applied by press coating or by conventional pan or air suspension coating. Some marketed matrix diffusion products for oral dosing are listed in Table 47-3. Similar to reservoir devices, matrix devices are also used to deliver drugs in other routes: parental (Compudose subdermal estradiol implant, *Elanco*) and transdermal (Deponit nitroglycerin patch, *Schwarz Pharma*).

DIFFUSION-CONTROLLED IMPLANTS—Implants are most commonly used for parental administration over a significantly prolonged period of time (days to years). Norplant (*Wyeth-Ayerst*) is a commercially available levonorgestrel implant system, indicated for the prevention of pregnancy for as long as 5 yr. Although implants possess such evident advantages as convenience and compliance, concerns over body responses to a foreign material often raise biocompatibility and safety issues. Application of biocompatible polymers to the construction of implants for achieving better control over the duration of drug activity and precision of dosing actually started with the discovery of the silicone elastomer. The rate of drug release was found to be controlled by the thickness and surface area of the membrane as well as polarity of the penetrant. Toward the end of the 1960s, a concentrated effort was made to expand the silicone elastomer-based implantable therapeutic system technology to other biocompatible polymers, in an attempt to control the release of water-soluble molecules. Some of these systems include a microporous membrane made from an ethylene/vinyl acetate copolymer for the ocular delivery of pilocarpine, a biodegradable (lactic/glycolic acid) copolymer for subcutaneous and intramuscular controlled administration of narcotic antagonists, a bioerodible polysaccharide polymer for delivery of anti-inflammatory steroids, hydrogel for subcutaneous controlled administration of estrus-synchronizing agents, or implantable therapeutic systems activated by osmotic pressure, vapor pressure, magnetism, etc.

In both types of implants made of nondegradable polymer (ie, reservoir devices and matrix devices), drug release is governed by diffusion.

In reservoir devices, the drug is encapsulated within a compartment that is enclosed by a rate-limiting polymeric membrane. The drug reservoir may contain either solid drug particles or a dispersion of solid drug in a liquid- or solid-type dispersing medium. The polymeric membrane may be fabricated from a homogeneous or a heterogeneous nonporous polymeric material or a microporous or semipermeable membrane.

Table 47-3. Matrix Diffusion Products

PRODUCTS	ACTIVE INGREDIENT(S)	MANUFACTURER
Gradumet tablets		Abbott
Desoxyn	Methamphetamine	
Ferro-Gradumet	Ferrous sulfate	
Tral	Hexocyclium methylsulfate, Phenobarbital	
Lontab tablets		
PBZ-SR	Tripelennamide HCl	Novartis
Procan SR	Procainamide HCl	Pfizer
Choledyl SA	Oxtriphylline	Pfizer

Drug encapsulation may be accomplished by molding, encapsulation, microencapsulation, or other techniques.

The drug release *(dQ/dt)* from this type of implantable therapeutic systems is defined by

$$dQ/dt = C_R\,(1/P_m + 1/P_d) \tag{32}$$

where C_R is the drug concentration in the reservoir compartment; P_m and P_d are the permeability coefficients of the rate-controlling membrane and of the hydrodynamic diffusion layer existing on the surface of the membrane, respectively. P_m and P_d are defined as

$$P_m = (K_{m/r}\,D_m)/\delta_m \tag{33}$$

$$P_d = (K_{a/m}\,D_a)/\delta_d \tag{34}$$

where $K_{m/r}$ and $K_{a/m}$ are the partition coefficients for the interfacial partitioning of drug molecules from the reservoir to the membrane and from the membrane to the aqueous diffusion layer, respectively; D_m and D_a are the diffusion coefficients in the membrane and in the aqueous diffusion layer, respectively; and δ_m and δ_d are the thickness of the membrane and of the aqueous diffusion layer, respectively.

Substituting Equation 33 and Equation 34 for P_m and P_d in Equation 32 and then integrating gives

$$Q/t = [(K_{m/r}\,K_{a/m}\,D_a\,D_m)C_R\,]/[(K_{m/r}\,D_m\,\delta_d) + (K_{a/m}\,D_a\,\delta_m)] \tag{35}$$

that defines the rate of drug release at steady state from a membrane permeation-type extended-release drug delivery device. Since the drug reservoir consists of solid drug particles or a solid drug suspension, C_R in the system remains constant. Hence, the release rate from reservoir-type diffusion-controlled implant does not vary with time (zero-order release kinetics). Examples of this type of implantable therapeutic systems are Alza's Progestasert IUD and Ocusert.[16]

In matrix diffusion-type extended-release drug delivery, drug particles are homogeneously dispersed throughout a lipophilic or hydrophilic polymer matrix. The dispersion may be accomplished by blending the drug with a viscous liquid polymer or a semisolid polymer at room temperature, followed by cross-linking of the polymer or by mixing drug particles with a melted polymer at an elevated temperature. Dispersion also can be achieved by dissolving the drug particles and/or the polymer in an organic solvent followed by mixing and evaporation of the solvent in a mold at an elevated temperature or under vacuum.

The rate of drug release from this type of delivery device is not constant and is defined by

$$dQ/dt = [(AC_p\,D_p)/2t]^{1/2} \tag{36}$$

where A is the initial drug loading dose dispersed in the polymer matrix; C_p and D_p are the solubility and diffusivity of the drug molecules in the polymer, respectively. Integration of Equation 36 gives

$$Q/t^{1/2} = (2AC_p\,D_p)^{1/2} \tag{37}$$

that defines the flux of drug release at steady state from a matrix diffusion-type drug-delivery device. Thus a matrix system provides decreasing release with time (square root of time-release kinetics). Examples of this type of implantable therapeutic system are the contraceptive vaginal ring[17] and Compudose implant (*Elanco*).[18]

Drug release kinetic of a matrix system can be improved by using reservoir/matrix hybrid-type polymeric implants so that release approximates the constant release from a reservoir system. Examples of this hybrid system are Syncro-Mate-C implant (*Sanofi-CEVA*) and Implanon (*Organon*).[19] In the former, an estradiol valerate suspension is dispersed in millions of individually sealed microreservoirs; then the mixture of microreservoirs is placed in a silicone polymer tube for *in situ* polymerization and molding. Drug molecules initially diffuse through the microreservoir membrane and then through the silicone polymer coating membrane. In the latter, 3-ketodesogestrel is dispersed in a polymer matrix; this polymer matrix is then coated with another rate-limiting polymeric membrane.

Implants typically are placed subcutaneously to control drug release via various mechanisms. Both nonbiodegradable polymers, such as silicone elastomer (polydimethylsiloxane), and biodegradable polymers, such as poly(caprolactone), poly(lactic acid) (PLA), or poly(glycolic acid), can be used. An ideal implantable therapeutic system should be biostable, biocompatible with minimal tissue-implant interactions, nontoxic, noncarcinogenic, and removable if required. Also, the system should release drug at a constant, programmed rate for a predetermined duration of medication.

TRANSDERMAL PATCHES—The transdermal route offers several advantages over other methods of delivery. Although the skin, particularly the stratum corneum, presents a barrier to most drug absorption, it provides a large (1–2 m^2) and accessible surface area for drug diffusion. Additionally, transdermal administration, as compared to other routes, is fairly noninvasive. Patients are quite willing to accept the use of a simple-looking "patch" as it can be conveniently applied and removed. Over the past two decades, the challenge of transdermal drug delivery has been acknowledged by pharmaceutical scientists. The intensity of interest in the potential biomedical applications of transdermal controlled drug administration is demonstrated by increasing research activity in the development of various types of transdermal therapeutic systems for long-term continuous infusion of therapeutic agents, including antihypertensive, antianginal, analgesic, steroidal, and contraceptive drugs. Although transdermal delivery is currently limited to relatively few drugs, it has achieved considerable commercial success. Success in developing these drugs (ie, nitroglycerin, scopolamine, estradiol, testosterone, nicotine, clonidine, fentanyl, and the estrogen-progestin combination) into transdermal products lies in the fact that all these drugs are very potent and require no more than 20mg/day for effective therapy. A discussion of the fundamental aspects of transdermal drug absorption can be found in Chapter 44, *Medicated Topicals*.

Current transdermal patches can be classified into four types:

1. Membrane-modulated system represented by Transderm-Scop (Scopolamine, *Novartis*).
2. Adhesive dispersion-type system represented by Deponit (nitroglycerin, *Schwarz Pharma*).
3. Matrix dispersion-type system represented by Nitrodur (nitroglycerin, *Schering*).
4. Microreservoir system represented by Nitrodisc (nitroglycerin, *Roberts*).

In a *membrane-modulated system*, the drug reservoir is totally encapsulated in a shallow compartment molded from a drug-impermeable backing and a rate-controlling polymeric membrane. The drug molecules are released only through the rate-controlling polymeric membrane. The rate-limiting membrane can be microporous or nonporous. On the external surface of the membrane, a thin layer of drug-compatible, hypoallergenic, adhesive polymer (eg, silicone or polyacrylate adhesive) may be applied to achieve intimate contact of the transdermal system with the skin. The rate of drug release from this type of drug-delivery system can be tailored by varying the polymer composition, permeability coefficient, or thickness of the rate-limiting membrane and adhesive. A representation of these systems is shown in Figure 47-8.

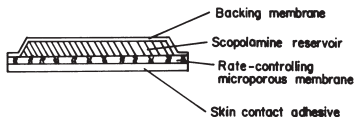

Figure 47-8. Transdermal device for delivery of scopolamine.

An *adhesive dispersion-type system* lacks the permeation-controlling membrane. In this system the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive, by solvent casting, onto a flat sheet of drug-impermeable backing membrane to form a thin drug-reservoir layer. On top of the drug-reservoir layer, layers of nonmedicated, rate-controlling adhesive polymer of constant thickness are applied to produce an adhesive diffusion-controlled drug delivery system.

In a *matrix dispersion-type system*, the drug reservoir is formed by homogeneously dispersing the drug in a hydrophilic or lipophilic polymer matrix, and then the medicated polymer is molded into a medicated disc with a defined surface area and controlled thickness. The disc is then glued onto an occlusive baseplate in a compartment fabricated from a drug-impermeable backing. The adhesive polymer is spread along the circumference to form a strip of adhesive rim around the medicated disc. Release rate is controlled by diffusion from the matrix.

In a *microreservoir system*, the drug reservoir is formed by first suspending the drug particles in an aqueous solution of water-soluble polymer and then dispersing it homogeneously in a lipophilic polymer by high-shear mechanical force to form a large number of unleachable, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer *in situ,* which produces a medicated polymer disc with a constant surface area and a fixed thickness. This medicated disc is positioned at the center and surrounded by an adhesive rim. Release of the drug from this type of drug-delivery device follows either an interfacial partition or a matrix diffusion-controlled process.

Dissolution Systems

As mentioned earlier in this chapter, a drug with a slow dissolution rate will yield an inherently sustained blood level. In principle, then, it would seem possible to prepare extended-release products by controlling the dissolution rate of drugs that are highly water-soluble. This can be done by preparing an appropriate salt or derivative, by coating the drug with a slowly soluble material, or by incorporating it into a tablet with a slowly soluble carrier. Ideally, the surface area available for dissolution must remain constant to achieve a constant release rate. This is, however, difficult in practice.

The dissolution process can be considered diffusion-layer-controlled, where the rate of diffusion from the solid surface to the bulk solution through an unstirred liquid film is the rate-determining step. In this case the dissolution process at steady state is described by the Noyes-Whitney equation

$$dC/dt = k_D A(C_s - C) = (D/h)A(C_s - C) \qquad (38)$$

where dC/dt is the dissolution rate, k_D is the dissolution rate constant, A is the total surface area, C_s is the saturation solubility of the solid, and C is the concentration of solute in the bulk solution. The dissolution-rate constant, k_D, is equal to the diffusion coefficient, D, divided by the thickness of the diffusion layer, h. The above equation predicts a constant dissolution rate if the surface area, diffusion coefficient, diffusion layer thickness, and concentration difference are kept constant. However, as dissolution proceeds, all of these parameters may change, especially surface area. For spherical particles, the change in area can be related to the weight of the particle; under the assumption of sink conditions, Equation 38 becomes the cube-root dissolution equation

$$w_0^{1/3} - w^{1/3} = k_D' t \qquad (39)$$

where k_D' is the cube-root dissolution-rate constant, and w_0 and w are initial weight and weight of the amount remaining at time t, respectively.

Two common formulations relying on dissolution to determine release rate of drug are shown in Figure 47-9. Most products fall into two categories: *encapsulated/reservoir dissolution systems* and *matrix dissolution systems*.

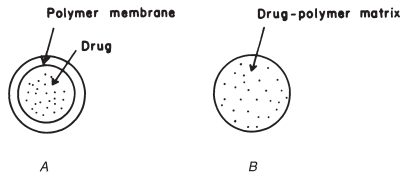

Figure 47-9. Systems using dissolution. **A.** Encapsulated formulation in which drug release is determined by thickness and dissolution rate of the polymer membrane. **B.** Matrix formulation in which drug release is determined by dissolution rate of the polymer.

Encapsulated dissolution systems can be prepared either by coating particles or granules of drug with slowly soluble polymers whose thicknesses vary or by microencapsulation. Microencapsulation can be accomplished by using phase separation, interfacial polymerization, heat-fusion, or solvent-evaporation. The coating materials may be selected from a wide variety of natural and synthetic polymers, depending on the drug to be coated and the release characteristics desired. The most commonly used coating materials include gelatin, carnauba wax, shellac, cellulose acetate phthalate, and cellulose acetate butyrate. Drug release from microcapsules is a mass-transport phenomenon and can be controlled by adjusting the size of microcapsules, thickness of coating materials, and the diffusivity of core materials. The thickness can be varied from less than 1 μm to 200 μm by changing the amount of coating material from 3% to 30% of the total weight. If only a few different thicknesses are used, usually three or four, drugs will be released at different, predetermined times to give a delayed-release effect (ie, repeat-action). If a spectrum of different thicknesses is employed, a zero-order release of the drug can be obtained from the dosage form as a whole. Microcapsules commonly are filled into capsules and rarely tableted as their coatings tend to disrupt during compression. A partial list of some marketed products relying primarily on encapsulated dissolution is shown in Table 47-4.

A matrix dissolution device is prepared by compressing the drug with a slowly soluble polymer carrier into a tablet form. There are two general methods of preparing drug-wax particles: congealing and aqueous dispersion. In the congealing method, drug is mixed with a wax material and either spray-congealed or congealed and screened. In the aqueous dispersion method, the drug-wax mixture is simply sprayed or placed in water, and the resulting particles are collected. Matrix tablets are also made by direct compression of a mixture of drug, polymer, and excipients. Examples of marketed orally administered products relying primarily on matrix dissolution are listed in Table 47-5. In a matrix dissolution device, the decrease in drug release due to decreased size of the matrix can be partially offset by constructing a nonlinear concentration profile in the polymer matrix (eg, the core of the dissolution matrix contains more drug than the outer layer [Adalat nifedipine tablet, *Bayer*]).[20] Matrix dissolution devices are also widely used in parenteral therapy (eg, Zoladex subcutaneous implant for delivery of goserelin [*AstraZeneca*]).

Table 47-4. Encapsulated Dissolution Products

PRODUCTS	ACTIVE INGREDIENT(S)	MANUFACTURER
Spansule capsules		GlaxoSmithKline
Dexedrine	Dextroamphetamine sulfate	
Hispril	Diphenylpyraline HCl	
Thorazine	Chlorpromazine HCl	
Sequel capsules		
Artane	Trihexyphenidyl	Lederle
Diamox	Acetazolamide	Wyeth-Ayerst
Ferro-sequels	Ferrous fumarate, Docusate sodium	Lederle

Table 47-5. Matrix Dissolution Products

PRODUCTS	ACTIVE INGREDIENT(S)	MANUFACTURER
Extentab tablets		Whitehall-Robins
Dimetane	Brompheniramine maleate	
Quinidex	Quinidine sulfate	
Timespan tablets		
Mestinon	Pyridostigmine bromide	ICN
Repetab tablets		Schering-Plough
Chlor-Trimeton	Chlorpheniramine maleate	
Demazin	Dexchlorpheniramine maleate, Pseudoephedrine HCl	
Trilafon	Perphenazine	

Osmotic Systems

Osmotic pressure can be employed as the driving force to generate a constant release of drug, provided a constant osmotic pressure is maintained and a few other features of the physical system are constrained. A tablet consists of a core of an osmotically active drug, or a core of an osmotically inactive drug, in combination with an osmotically active salt surrounded by a semipermeable membrane containing a small orifice, as shown in Figure 47-10*A*.[21] The membrane allows free diffusion of water but not drug. When the tablet is exposed to water or any fluid in the body, water will flow into the tablet because of the osmotic pressure difference, and the volume flow rate, dV/dt, of water into the tablet is

$$dV/dt = (kA/h)(\Delta\pi - \Delta P) \quad (40)$$

where k, A, and h are the membrane permeability, area, and thickness, respectively, $\Delta\pi$ is the osmotic pressure difference, and ΔP is the hydrostatic pressure difference. If the orifice is sufficiently large, the hydrostatic pressure difference is small compared with the osmotic pressure difference, and Equation 40 becomes

$$dV/dt = (kA/h)\Delta\pi \quad (41)$$

Thus, the volume flow rate of water into the tablet is determined by permeability, area, and thickness of the membrane. The drug will be pumped out of the tablet through the orifice at a controlled rate, dM/dt, equal to the volume flow rate of water into the tablet multiplied by the drug concentration, C_s:

$$dM/dt = (dV/dt)C_s \quad (42)$$

The release rate will be constant until the concentration of drug inside the tablet falls below saturation.

Several modifications of the osmotic pressure-controlled drug delivery system have been developed. A layer of bioerodible polymer can be applied to the external surface of the semipermeable membrane. As a result, the system consists of two compartments separated by a movable piston, as shown in Figure 47-10*B*[22]. For a system that does not have an orifice, hydraulic pressure is built up inside as the gastrointestinal fluid is imbibed, until the wall ruptures and the contents are released to the environment.

The advantage of the osmotic system is that it only requires osmotic pressure to be effective and is essentially independent of the environment. The drug release rate can be predetermined precisely regardless of pH changes through the gastrointestinal tract. Some materials used as the semipermeable membrane include polyvinyl alcohol, polyurethane, cellulose acetate, ethylcellulose, and polyvinyl chloride. Drugs that have demonstrated successful release from an osmotic system *in vivo* after oral dosing are potassium chloride and acetazolamide. Osmosis is also successfully used to consistently release drug from an implant, such as *Alza*'s Alzet miniosmotic pump and Duros pump.

Mechanical Systems[19]

Mechanically driven pumps are commonly used to precisely control the infusion rate of a drug in the clinics. Externally programmable pumps can facilitate zero-order and intermittent drug release. Pumps made of biocompatible and long-lasting titanium also can be implanted intraperitoneally, even intraarterially or intrathecally with proper surgical procedures.

The Infusaid pump is a fixed-rate (nonprogrammable) implantable infusion pump using vapor pressure activation theory, in which the vapor chamber contains a fluid that vaporizes at body temperature and creates a vapor pressure. Under the vapor pressure, a bellows moves upward and forces release of the drug.

The SynchroMed implantable pump allows the infusion rate of drug solution to be programmed by a portable computer with special software that transmits instructions to the pump. The pump is driven by a step motor, controlled by signals from the microprocessor, and is capable of delivering infusate at varying rates. The programmer even provides delivery patterns that are characteristic of various doses at different times. The SynchroMed pump is approved for a variety of uses including chemotherapy, management of cancer pain, osteomyelitis and spasticity. The MiniMed pump delivers insulin intraperitoneally. Insulin infused into the peritoneum is absorbed faster and more completely than by subcutaneous injection. In this pump, a solenoid-motor controlled piston drives insulin through a delivery catheter. The pumping rate can be programmed to deliver the desired insulin dose.

Swelling Systems

In these systems, drug is dispersed throughout the polymer and has difficulty in diffusing out of the polymer matrix. *In vivo*, biological fluid diffuses into the matrix and causes its outer polymer region to swell, allowing release of the drug entrapped inside the polymer at a predictable rate. This release mechanism and osmosis-induced drug release are summarized as solvent activation by Langer.[23]

Hydrogel-constructed swelling systems are attractive because they can achieve spatial placement of a dosage form in the gastrointestinal tract as well as extended release. Gastric emptying is a size-dependent process. Particles greater than 10

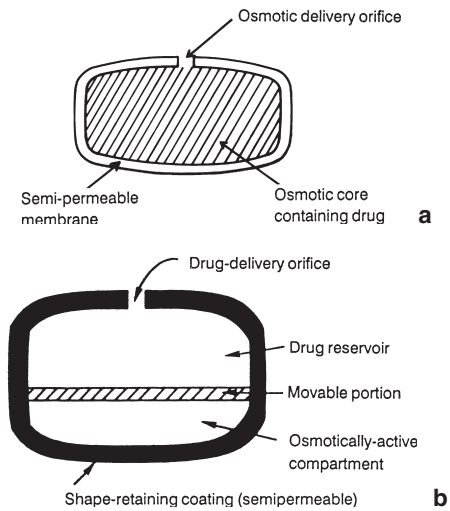

Figure 47-10. Osmotic pressure-controlled drug-delivery systems **A.** An osmotic tablet. (From Robinson JR, ed. *Sustained and Controlled Release Drug Delivery Systems.* New York: Dekker, 1978, p 557.) **B.** A system with two compartments separated by movable partition. (From Robinson JR, Lee VHL, eds. *Controlled Drug Delivery,* 2nd ed. New York: Dekker, 1987, p 373.)

mm are unable to be released into the duodenum and thus retained in the stomach. Hence, a dosage form with a larger size may be beneficial in prolonging retention time in the stomach. However, a dosage form with too big a size is difficult for patients to swallow and, more importantly, the dosage form must dissolve/degrade to be discharged. Hydrogel can absorb up to 100 times its dry weight of water. Thus it is retained because of its large size caused by swelling and expanding. In addition, the adhesive property of swollen hydrogel can further increase residence time of the dosage form.

Erosion-Controlled Systems

In these systems, drug is dispersed throughout the polymer, and the rate of drug release depends on the erosion rate of the polymer. However, some diffusion of the drug from the polymer may also occur. Degradation of the polymer *in vivo* makes long-term accumulation impossible. Therefore an implant made of degradable polymers does not require surgical removal. However, the surface area over which drug release occurs changes as a function of time, which makes zero-order release unlikely.

To maximize control over release, it is often desirable for a system to degrade only from its surface. Poly(lactic-co-glycolic acid) (PLGA), the most commonly used degradable polymer, however, displays bulk erosion with significant degradation in the matrix interior. In a surface-eroding system, the drug release rate is proportional to the polymer erosion rate and can be controlled by changing system thickness and total drug content. Surface erosion eliminates the possibility of dose dumping, thus improving device safety. Surface erosion can be achieved when the degradation rate of the polymer matrix surface is much faster than the rate of water penetration into the matrix bulk. Theoretically, the polymer should be hydrophobic with water-labile linkages connecting monomers. One example is the safe and successful local delivery of nitrosoureas by intracerebrally implanting polyanhydride disks containing the drug.[23]

Controlled Release by Stimulation

MAGNETISM-ACTIVATED IMPLANTS—In this system, drug and small magnetic beads are dispersed throughout a polymer matrix. Upon exposure to biological fluid, drug is released slowly by diffusion. When the system is under the influence of an external magnetic field, drug is released at a much higher rate. This is probably due to movement of the dispersed magnetic beads that squeeze out the drug through pores on the polymer surface. Rate of drug release from these systems can be changed by manipulating the orientation and the strength of the magnetic field or by modifying the mechanical properties of the polymer matrix. Kost and Langer [24] showed that insulin release from poly(ethylene-co-vinyl acetate) matrix bearing magnetic beads could be triggered by using an oscillating magnetic field. This device demonstrated a significant reduction in glucose level when implanted in diabetic rats.

ELECTRICITY-MODULATED SYSTEMS—*Iontophoresis*, primarily used in transdermal delivery, is the facilitated movement of ions across a membrane under the influence of an externally applied electric field. The mechanism of iontophoresis is based on the physical phenomenon "like charges repel and opposite charges attract." Figure 47-11[25] gives a schematic description of an iontophoretic system. Positively charged drugs are placed at the positive pole, while negatively charged peptides are placed at the negative pole. Repulsion of "like charges" and attraction of opposite charges push the drug across the membrane. Iontophoretic delivery of ionic species can be described by the following equation[26]:

$$J^{isp} = J^p + J^e + J^c \qquad (43)$$

where J^p, J^e, J^c represent the passive skin permeation flux, the electrically driven skin permeation flux, and the convective flow-driven skin permeation flux, respectively. Because of the presence of J_p and J_c, facilitation of delivery of neutral molecules is also possible using iontophoresis.

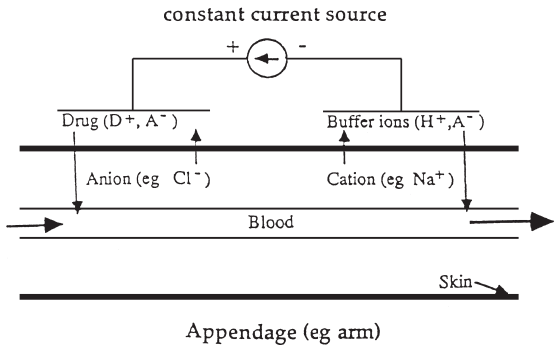

Figure 47-11. An iontophoretic system. (From Singh P, Maibach HI. *Crit Rev Ther Drug Carrier Sys* 1994; 11:161.)

Figure 47-12[27] gives a schematic representation of an iontophoretic transdermal patch. Generally speaking, an iontophoretic patch consists of three components:

1. An aqueous *drug reservoir* that is usually a biocompatible gel or adsorbent-pad material.
2. A *return reservoir* that completes the circuit. Typically, this circuit is a saline formulation.
3. An *electronic controller* that is programmable to give a complicated dosing pattern.

There are two profiles of applying electric current: continuous and pulsatile. Pulsatile application is more efficient in facilitating peptide delivery.[28] An electric field with direct current applied continuously to the stratum corneum causes electrochemical polarization, which operates against the applied field and results in a decrease in the magnitude of the effective current across the skin. This greatly decreases the efficiency of iontophoretic drug delivery. When the current is applied periodically (on and off), it presents an opportunity for the skin to depolarize during the "off" state. Each cycle starts in a state with no residual polarization. Pulsatile profile also enables the skin to tolerate much higher voltage and stronger current.

Iontophoresis carries a number of advantages. It is simple and noninvasive so that patients are willing to accept it. Moreover, electronically controlled patches allow complex dosing regimens according to the individual need of the patients. While most delivery systems are limited to small, nonpolar, lipophilic molecules, iontophoresis can facilitate transport of charged and high-molecular-weight drugs (eg, protein and peptide drugs). As a versatile technique, iontophoresis may be useful for local drug delivery in several areas of medicine other than dermatology, such as dentistry, ophthalmology, and otolaryngology. Local irritation and erythema are two common adverse effects of iontophoresis. Generally, the side effects are

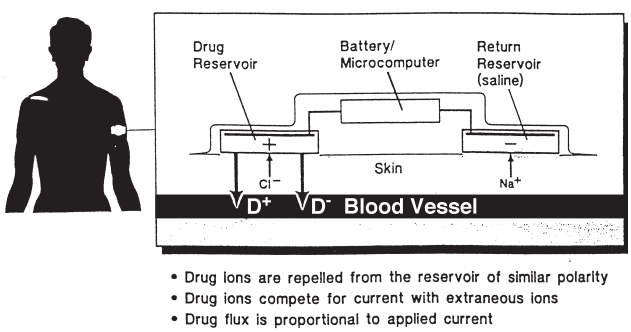

Figure 47-12. The components of an iontophoretic patch. (From Green PG. *J Controlled Release* 1996; 41:33.)

mild; however, iontophoresis may not be useful in emergency situations as there is a lag time between drug administration and its appearance in the bloodstream.

Short-term (micro- or milliseconds) exposure to brief, high-intensity electrical pulses increases permeability of the skin, presumably creating aqueous pores in the lipid network of the stratum corneum, which is the mechanism of enhanced transdermal delivery by *electroporation*.[29] Furthermore, the size of the newly created pores is increased as long as the electric field is applied. Erythma, edema, and petechiae are common but presumably transient side effects. Electroporation was initially used by molecular biologists to enhance the uptake of biomacromolecules (eg, plasmid DNA) by bacterial cells. Intramuscular electroporation gene delivery has found potential in treating various diseases including tumors, renal diseases and anemia.[30]

Electricity also can be used to modulate drug release from polymeric delivery systems by mechanisms such as solubilization of a polymer complex and modification of polymer swelling/deswelling. The small solute release can be enhanced during deswelling by a squeezing mechanism, whereas large molecule release can be increased during the swelling process. Kwon et al[31] reported a novel polymeric system. Reacting to a small electric current, the system changed from a solid state to solution by distintegrating the insoluble polymer complex into the two water-soluble composite polymers: polyethyloxazoline and poly(methacrylic acid) (PMAA). The insoluble polymer complex formed by intermolecular hydrogen bonding between carboxyl and oxazoline groups below pH 5, but dissociated above pH 5.4. The disintegration of the polymer complex was attributed to unionization and ionization of the carboxyl group of PMAA at different pHs. A pulsatile pH change induced by a step function of electric current could facilitate the disintegration, resulting in modulated release of such drugs as insulin.

ULTRASOUND-MODULATED SYSTEMS—In general, ultrasound-controlled polymeric delivery systems are simple devices designed for subcutaneous implantation. Miyazaki et al[32] studied the releases of bovine insulin from ethylenevinyl alcohol copolymer matrices and reservoir-type drug delivery systems. When the devices implanted in diabetic rats were exposed to ultrasound (1W/cm^2 for 30 min), a sharp drop in blood glucose levels was observed, indicating a rapid release of insulin from the implants. Drug carrier matrices can be made of either erodible or nonerodible polymers. Kost et al[33] observed that both polymer erosion and drug release were increased when the systems were exposed to ultrasound. Ultrasound can enhance permeation of water into the degradable polymer matrix, leading to exposure of labile linkage for hydrolysis and mechanical shear stress caused by the micro liquid jet produced by cavitation phenomenon.[34] Drug release was also enhanced in nonerodible systems where the release was diffusion dependent. However, the mechanism is not fully understood yet.

Phonophoresis is ultrasound-activated migration of drug molecules through the skin. Its enhancement mechanism is not clear; however, a combination of thermal, mechanical, or cavitational effects are thought to be involved in this process.[35,36] The efficacy and safety of phonophoresis may depend on several parameters: the frequency and intensity of applied ultrasonic energy, the media between the ultrasonic applicator and the skin, and the length of exposure time.[37–39] Ultrasound with low intensity and low frequency appears to be safe for use. However, high-intensity ultrasound may result in burns due to localized heating of the skin. Phonophoresis has also been explored to promote ocular drug delivery by transient modification of the corneal epithelium, whose permeability is comparable to that of the stratum corneum of the skin.[40]

PHOTOIRRADIATION-ACTIVATED SYSTEMS[41]**—**Photoresponsive polymers can be prepared by incorporation of photosensitive compounds such as azobenzene, stilbene, spiropyren, and rhodopsin into a polymeric backbone. These polymers are used for photochemical control of permeation of various solutes, such as metal salts, proteins, amino acids, etc. Modulation of protein permeation was achieved by UV irradiation.[42] Cross-linked random copolymers of hydroxyethyl methacrylate with a monomer containing azobenzene groups in the side chain slightly changed swelling levels by cis-trans isomerization of the azobenzene group to effectively control permeation of large molecules.

THERMORESPONSIVE DELIVERY SYSTEMS—These systems are constructed from thermosensitive hydrogels that exhibit phase transition when temperature is raised to a critical value called the *lower critical solution temperature (LCST).* The phase transition is characterized by a dramatic change in polymer volume accompanied by a significant change in the release rate of the drug formulated into the polymeric system. Thermosensitivity of hydrogels originates from polymer-water interactions, especially hydrophobic-hydrophilic balancing effects and the configuration of side groups; and/or polymer-polymer interaction. Poly[N-isopropylacrylamide (NIPAAm)] hydrates below its LCST (32°C) and dehydrates above the LCST. Thermosensitive polymers composed of NIPAAm and various comonomers with different hydrophilicity have been synthesized. A study on the effect of comonomers on the LCST of the polymers revealed that the anionic acrylic acid caused the highest LCST elevation, followed by the cationic N,N-dimethylaminoethyl methacrylate, and nonionic acrylamide comonomers; while the hydrophobic butylmethacrylate (BMA) led to decreased LCST.[43] When such a swollen hydrogel loaded with drug is transferred to a medium kept at T > LCST, it delivers the drug because the gel collapses on warming through its LCST. Initially, the temperature gradient across the gel causes a burst of surface drug, with formation of a skin and buildup of hydrostatic pressure inside the gel. This pressure will squeeze the fluid containing the drug since a collapsing or desorbing polymer gel matrix/swollen gel front moves rapidly into the interior of the gel. There are two different consequences associated with thermosensitive hydrogels when temperature is raised to the LCST. In the case of the copolymers of NIPPAm with more hydrophobic comonomers, such as BMA, increased temperature over the LCST hinders delivery of the drug due to formation of a dense skin layer.[44,45] This may be advantageous in sustaining drug action, since the hydrogel has adhesive properties and can be retained at the absorption site for an extended period of time. Moreover, slowing of drug release, because of the dense skin layer, provides an extended-release property. On the contrary, an increase in temperature over the LCST can lead to increased delivery. In this case, the drug is squeezed out of the gel with shrinking and the release rate is accelerated. This system has potential application in the control of inflammatory or hyperpyretic reactions. These situations are usually associated with an increase in body temperature. When the temperature is over the LCST, the increased delivery of the anti-inflammatory drug from the gel can alleviate the symptoms promptly.

Recently, Kim's research group[46] synthesized a series of thermosensitive, biodegradable hydrogels composed of poly(ethyleneoxide) and poly(L-lactic acid) block copolymer. An aqueous solution of these copolymers exhibits temperature-dependent reversible gel-sol transitions. The hydrogel can be loaded with bioactive molecules in the aqueous phase at an elevated temperature (around 45°C), where they form a solution. In this form, the polymer is injectable. On subcutaneous injection and subsequent rapid cooling to body temperature, the loaded copolymer forms a gel that can act as an extended-release matrix for the drug.

pH-SENSITIVE DELIVERY SYSTEMS—pH sensitive polymers have either weakly acidic or basic groups covalently attached to a polymer backbone; therefore the charge density of the polymer depends on pH and ionic composition of the environment. Changing the pH of the environment will cause swelling or deswelling of the polymer, which affects the drug release rate from devices or matrices made of these polymers. pH-sensitive polymers containing free carboxyl groups, eg, hydroxypropylmethyl cellulose phthalate and poly(methyl

methacrylate), have been employed in developing enteric coating in conventional oral dosage forms. They are impermeable at low pH, but disintegrate at neutral pH. Polymers composed of hydroxyethyl methacrylate and dimethylaminoethyl methacrylate are involved in controlled delivery of insulin from a reservoir containing a saturated solution of insulin.[47] The membrane consists of a hydrogel polymer with a pendant amine group entrapped with glucose oxidase. In the presence of glucose, the following reaction can take place:

$$\text{Glucose} + H_2O + O_2 \rightarrow \text{Gluconate} + H_2O + H^+$$

The hydrogen ions decrease the pH and lead to protonation of the amine groups. The charged amine groups repel each other, which results in increased swelling and subsequently release of insulin. Permeability of the membrane to insulin is controlled by the insulin level. A pH-sensitive bioerodible polymer such as poly(orthoester) is based on the same principle.[48] Insulin is trapped in the polymer matrix rather than surrounded by a membrane. Protonation of the amine group, triggered by the glucose/glucose oxidase reaction, results in an increase in erosion, with concomitant release of insulin.

SELF-REGULATED DELIVERY SYSTEMS[49]—Self-regulated or feedback-controlled systems should be capable of adjusting drug release according to physiological needs or feedback information (eg, insulin delivery in response to blood glucose level of the patient). Self-regulated delivery systems can be divided into two types: *modulated devices* and *triggered devices*. A modulated device releases a drug continuously at a rate controlled by the concentration of a specific external chemical (eg, hydrogen ion, glucose). A triggered device does not have basal drug release. The drug is only released at a preprogrammed rate when the system is activated by a specific external moiety (eg, metal ion, antibody).

One example of modulated devices for insulin delivery is the pH-sensitive polymeric system utilizing glucose oxidase reaction, which has been described earlier. The solubility of trilysyl insulin is a function of pH.[50] There is a large change in its solubility between pH 5 and 7. The glucose oxidase reaction can alter the pH of the local environment, which leads to increased solubility and dissolution rate. This forms the basis for *solubility-controlled delivery of insulin*.

Lectin-Glycosylated Insulin-Controlled Device is based on competitive binding between glycosylated insulin and glucose to a saccharide-binding substrate, concanavalin A (Con-A). The glycosylated insulin complexed with Con-A can be displaced from the complex in direct proportion to glucose levels. This forms a controlled delivery system for insulin. Due to immunogenicity, Con-A can be cross-linked to minimize its leakage from the device into the plasma. Because the delayed "off" response could lead to hypoglycemia, microspheres were prepared to accelerate the response process since their large surface areas allow rapid diffusion of insulin and glucose.[51]

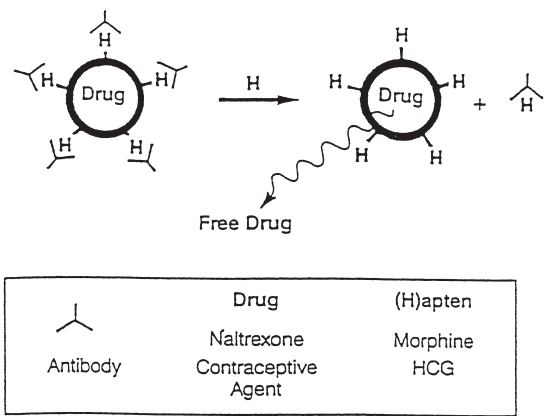

Figure 47-13. Hapten-antibody device. (From Pitt CG, et al. *J Controlled Release* 1985; 2:363.)

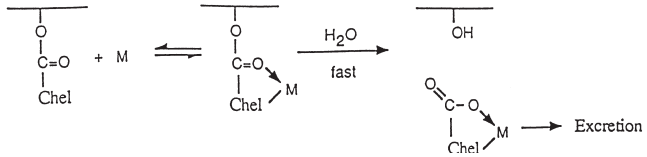

Figure 47-14. Chelation-enhanced hydrolysis device. (From Pitt CG, et al. *J Controlled Release* 1984; 1:3.)

Some hydrogels such as copolymers of acrylamide and allyl glucose can undergo a phase transition in response to glucose concentration.[52] At physiological pH, Con-A exists as a tetramer with four binding sites for glucose. The glucose-containing polymer chains are physically cross-linked by Con-A to form a gel. Free glucose can compete against polymer-bound glucose for the binding sites on Con-A. This competitive binding may result in loosening the network structure and transformation from a gel to a solution. This transition can control the release rate of insulin.

Triggered devices were developed based on hapten-antibody interactions and chelation-enhanced hydrolysis. In the system involving the former mechanism, the drug was enclosed in a membrane that bore haptens conjugated with antibodies (Fig 47-13[53]). The antibodies blocked access of esterase to the polymer, preventing enzyme-induced polymer erosion and concomitant release of the drug. Drug release, accompanying polymer erosion, was triggered by displacement of antibodies from the membrane in the presence of free haptens. Systems using the latter mechanism may be useful in delivery of chelating agents. Metal ions can accelerate hydrolysis of carboxylic esters, phosphate esters, and amides. This enhancement results from complexation of the metal to the ester carbonyl group as shown in Figure 47-14[54]. Release rate of the chelating agent is influenced by the concentration of target metal.

TARGETED DELIVERY SYSTEMS

Targeted drug delivery implies selective and effective localization of drug into the target(s) at therapeutic concentrations with limited access to nontarget sites. A targeted drug delivery system is preferred in the following situations[55]:

1. Pharmaceutical: drug instability, low solubility.
2. Pharmacokinetic: short half-life, large volume of distribution, poor absorption.
3. Pharmacodynamic: low specificity, low therapeutic index.

Targeted drug delivery may provide maximum therapeutic activity by preventing drug degradation or inactivation during transit to the target sites. Meanwhile, it can protect the body from adverse effects because of inappropriate disposition, and minimize toxicity of potent drugs by reducing dose. An ideal targeted delivery system should be nontoxic, biocompatible, biodegradable, and physicochemically stable *in vivo* and *in vitro*. The preparation of the delivery system must be reasonably simple, reproducible, and cost-effective.[56]

Colloidal Drug Carriers

Colloidal drug-delivery systems include micro- and nanoparticles, macromolecular complexes (eg, lipoproteins), liposomes, and niosomes. In many cases, colloidal carriers are used to improve stability of the drug either in biological fluids or in the formulation, to develop extended-release systems with targeting features, and/or to enhance the therapeutic efficacy and reduce drug toxicity by modifying the distribution and controlling the disposition of the drug. Colloidal particles larger than 1 μm are microparticles. Although they are considered as carriers of an earlier generation that can deliver the active agent to the target, because of their size and thus tendency to occlude nee-

dles and capillaries, microparticles are not suitable for administration by general routes, such as intravenous injection. Lipoproteins have been suggested as potential drug carriers for several reasons [56]: (a) they are natural and thus nonimmunogenic; (b) they are not rapidly cleared by the reticuloendothelial system (RES), but endocytosed by a variety of cells expressing lipoprotein receptors on the surface; (c) they are capable of solubilizing lipophilic drugs in their apolar inner core, and carrying amphilic drugs in the outer phospholipid coat; and (d) drugs in the core appear not to affect the binding of surface ligands to various cells. However, the involvement of lipoproteins, especially low-density lipoprotein (LDL), in the pathogenesis of certain cardiovascular disorders makes them less desirable drug carriers. Niosomes are vesicles made of nonionic surfactants (eg, polyglycerol alkylethers, glucosyl dialkylthers, and polyoxyethylene alkylethers). Niosomes can be prepared by similar techniques as those used for liposomes. Their *in vivo* behavior is also similar to that of liposomes: prolonging the circulation of entrapped drug and increasing local concentration at the target site. Niosomes have demonstrated their potential as carriers of the cytotoxic agent doxorubicin.[57]

NANOPARTICLES—A nanoparticle is a submicroscopic solid particle with a size ranging from 10 nm to 1 μm. The size of a nanoparticle allows it to be administered intravenously with little risk of embolism. Materials used in the preparation of nanoparticles are sterilizable, nontoxic, and biodegradable; examples are albumin, ethylcellulose, casein, gelatin, polyesters, polyanhydrides, and polyalkyl cyanoacrylates. They can be prepared from emulsion, micelles, interfacial polymerization, preformed polymers, and coacervation.

Nanoparticles have been successfully applied to medical diagnostics by taking advantage of their rapid uptake by the RES and sequestration by liver Kupffer's cells. For example, nanoparticles loaded with radioisotopic technetium-99m can be used to image hepatic pathologies.[58] The RES consists of phagocytic cells designed to cleanse the bloodstream of bacteria, viruses, cell debris, and other unwanted foreign particles. Such specific cellular processing of nanoparticles points to the possibility of using nanoparticles to target drugs to the liver and phagocytic cells. "Macrophage-evading" or long-circulating nanoparticles may find more applications in experimental and clinical medicine. One expectation is to provide a long-circulating drug reservoir where controlled release of the drug into the vascular compartment can be achieved. To prolong the circulation, nanoparticles should be small enough (≤200 nm) or deformable to escape the simple filtration in the spleen; whereas long-circulating rigid large particles can find the application as splenotropic agents.[59] Besides size, the surface of nanoparticles can be modified to avoid opsonization. Opsonization is the adsorption of protein capable of interacting with specific surface receptors on phagocytic cells. *PEGylation* (ie, attaching polyethylene glycol [PEG] to the particles) is perhaps the most explored approach to avoiding protein adsorption. PEG can be adsorbed or covalently linked to the surface of particles. The PEG chains exposed on the particle surfaces confer hydrophilicity to the particles and thus effectively suppress the binding of opsonins through hydrophobic interaction. PEG is also believed to sterically hinder opsonins from interaction. However, the current technology is not yet sophisticated enough to effectively circumvent rapid clearance of nanoparticles by the RES. The complex processes of gradual nanoparticle degradation within the vasculature and drug release into the circulation have not been well understood. At present, few nanoparticles exist as extended-release systems for delivery of the entrapped drug over a period of days. Much more research focuses on long-circulating nanoparticles as targeted drug delivery systems. Capillary permeability of nanoparticles is found to increase when the endothelial integrity is perturbed during inflammation and in certain cancers. The permeable vascular endothelia in lymph nodes and bone marrow are also capable of removing small-sized particles from the circulation.[60,61] Hence, nanoparticles can promise targeted delivery to inflammation sites such as arthritic joints, to solid tumors, and to hematological malignancies simply because of size exclusion/permeation effect. Attachment of specific ligands that are recognized by nonphagocytic cells through ligand-receptor interaction onto the surface of macrophage-evading particle, expands the targeting spectrum of nanoparticles within the vasculature. Ligand-mediated drug targeting is discussed later in this section.

Block copolymer micelles are among the newest nanoparticles currently under investigation. Copolymers are polymers composed of several different monomeric units. Block copolymers are defined as polymers composed of terminally connected structures. Unlike random polymers, functions can be distinctly designed for each monomeric segment that forms a domain in block copolymer micelles. The features of each monomeric segment can be modified without affecting the others because of separation from other monomeric units. Block copolymers are subdivided into three types, AB-type, ABA type, and $(AB)_n$ multisegments. AB-type copolymers are the most appropriate candidates for the formation of polymeric micelle drug carriers in terms of size, aggregation number, and micelle stability. Usually, the AB-type block copolymers are composed of both hydrophilic poly(ethylene oxide) (PEO) and hydrophobic blocks such as poly(propylene oxide) (PPO), which allows the polymers to self-assemble as micelles in an aqueous media with hydrophobic cores and highly hydrated outer shells. Therefore, a key function of copolymer micelles is to solubilize hydrophobic drugs, such as taxol.[62] Hydrophobic drugs can be incorporated into the hydrophobic core by covalent or noncovalent interaction. The structure of drug-loaded polymeric micelles is shown in Figure 47-15.[63] The polymeric micelle has a diameter of about 20 to 40 nm based on atomic force microscopy, dynamic light scattering measurement, and transmission electron microscopy.[64–66] This

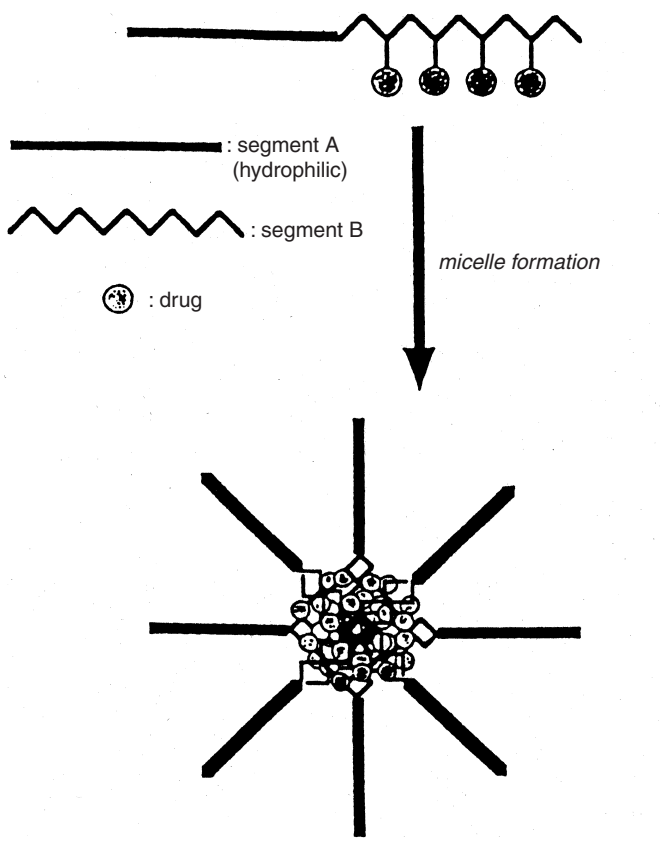

Figure 47-15. Design of micelle-forming polymeric drug. (From Yokoyama M. *Crit Rev Ther Drug Carrier Sys* 1992; 9:213.)

size is very important for the micelle to escape clearance because it is believed that the RES recognition and elimination is lower for particles under 100 nm. Hence, polymeric micelles could be long-circulating in the blood because of their small size as well as hydrophilic shell. Prolonged circulation allows polymeric micelles to accumulate at solid tumors as a result of the so-called enhanced permeability and retention (EPR) effect.[67] Micelles based on PEO-block-PLA or PEO-block-PLGA can gradually release drugs.[68–70] Release of the drug from PEO-block-PLA micelles may be controlled by degradation of PLA.[69] The stability of micelle, micelle core hydrophobicity, and the spacer groups used in binding the drugs to polymer backbones all can play roles in controlling drug release. In other words, a drug-independent delivery system can be designed with its release rate or pattern dictated by the carrier. Other promising biological properties have been discovered with block copolymer micelles, including inhibition of P-glycoprotein responsible for multidrug resistance in cancer cells by PEO-block-PPO-block-PEO micelles,[71] enhancement of drug transport across the blood-brain barrier by the same block micelles,[72] and reduction of self-aggregation and toxicity of amphotericin B by PEO-block-poly(beta-benzyl-l-aspartate) micelles.[73]

LIPOSOMES—When phospholipids are dispersed gently in an aqueous medium, they swell, hydrate, and spontaneously form multilamellar, concentric, bilayer vesicles with layers of aqueous media separating the lipid bilayers. These systems commonly are referred to as multilamellar liposomes, or multilamellar vesicles (MLVs), and can have diameters as large as 4 μm. Sonication or solvent dilution of MLVs results in the formation of small unilamellar vesicles (SUVs) with diameters below 80-100 nm, containing an aqueous solution in the core. Liposomes bear many resemblances to cellular membranes and have been widely used to study membrane behavior and membrane-mediated processes. It probably remains the most extensively studied class of carrier systems as well because of the advantages listed in Table 47-6.[56]

The drug-loading capacity varies among different types of liposomes. For example, MLVs are moderately efficient at trapping solutes, but SUVs are extremely inefficient. However, SUVs offer the advantage of homogeneity and reproducibility in size distribution. A compromise between size and trapping efficiency is offered by large unilamellar vesicles (LUVs). In addition to liposome characteristics, drug entrapment is also dependent on the physicochemical properties of the drug itself, the phospholipids, and other additives used. Polar drugs are trapped in the aqueous space, and nonpolar drugs bind to the lipid bilayer of the vesicle. Polar drugs are released when the bilayer is broken or by permeation, but nonpolar drugs remain affiliated with the bilayer unless it is disrupted by temperature or exposure to lipoproteins. Loading of cationic (or anionic) drugs can be significantly improved by using liposomes containing anionic (or cationic) lipids. Macromolecules such as proteins, polysaccharides, and nucleic acids also can be incorporated into liposomes. More recent studies of liposomal drug delivery have focused on their potential for cellular delivery of biomacromolecules.

Table 47-6. Advantages of Liposomes as Drug Carriers

1. Biologically inert and completely biodegradable
2. Nontoxic, nonantigenic, and nonpyrogenic
3. Producible with various sizes, compositions, and surface properties
4. Entrap a wide variety of hydrophilic and lipophilic drugs
5. Protect entrapped drugs from enzymatic degradation or deactivation from the external media
6. Offer new possibilities of drug targeting by releasing drugs at the site of liposome destruction

Liposomes can interact with cells by four different mechanisms[74]:

1. Endocytosis by phagocytic cells of the RES.
2. Adsorption to the cell surface either by nonspecific hydrophobic or electrostatic forces or by specific interactions with cell-surface components.
3. Fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane, with simultaneous release of liposomal content into the cytoplasm.
4. Transfer of liposomal lipids to cellular or subcellular membranes, or vice versa, without any association of the liposome contents.

Often it is difficult to determine what mechanism is operative, and more than one may operate at the same time.

The fate and disposition of intravenously injected liposomes depend on their physical properties, such as size, fluidity, and surface charges. They may persist in tissues for hours or days, depending on their composition, and their half-lives in the blood range from minutes to several hours. Because of their size, liposomes can exit only in places where large openings or pores exist in the capillary endothelia, such as the sinusoids of the liver or the spleen. Thus, these organs are the predominate sites of uptake. In general, this *in vivo* behavior limits the potential targeting of liposomes to only those organs and tissues accessible to their large size. These include the blood, liver, spleen, bone marrow, and lymphoid organs. Liposomes also can accumulate within leaky vasculature of solid tumors, which encourages many researchers to explore liposomal delivery of chemotherapeutics to tumors. Similar to polymeric nanoparticles, long-circulating PEGylated liposomes that can evade the rapid uptake by the RES are usually more successful than unprotected liposomes in this task.[75–77] Active targeting with drug-entrapped liposomes can be achieved by appending ligands to the carrier systems. For example, immunoliposomes are constructed by attaching antibodies to the drug-loaded liposome surface. Such delivery systems can be directed to groups of cells that express specific antigenic receptors. LDL, folate, and carbohydrate determinants, whose receptors are often overexpressed on the surface of certain malignant cells, also appear on the lists for construction of ligand-conjugated liposomes.

Numerous books, book chapters, and review articles have been dedicated to liposomal drug delivery. The interested reader can go to *Liposome Technology*, edited by Gregoriadis,[78] for preparation, analysis, drug loading, and biological properties of liposomes. *Medical Applications of Liposomes*, edited by Lasic and Papahadjopoulos,[79] summarizes the most important and promising usages of liposomes in medicine.

Ligand-Mediated Targeting

Ligand-mediated targeting has emerged as a novel approach to targeting vascular compartment (first-order), cellular (second-order), or intracellular (third-order) levels.

The ligands explored so far to selectively deliver carrier systems or drugs to cells include antibodies, complements, interleukins, lectins, lipoproteins, polypeptides (eg, insulin, growth factors), transferrin, folate, CAM (cell adhesion molecules), viral proteins, etc. These molecules specifically bind to antigens, carrier molecules, or receptors on the cell surfaces. Appropriate targets expressing these surface recognition molecules for ligand-mediated interactions are immune cells (lymphocytes, leukocytes, macrophages and other phagocytic cells including Kupffer's cells of liver, microglia of brain, Langerhans' cells of skin), endothelial cells, epithelia of the gastrointestinal tract, hepatocytes, certain malignant cells, etc. Thus, ligand-conjugated delivery systems can macroscopically target a variety of organs and specific compartments: vasculature, lymphatics, liver, gastrointestinal tract, brain, and solid tumors.

Ligands are often covalently or noncovalently associated with the drug or the surface of the carrier. Labeling macromolecules with gold particles could stimulate nonspecific interactions involved in the noncovalent association of ligand to

macromolecular drugs or carrier systems.[80] One of the most popular methods of noncovalent conjugation is utilizing natural strong binding of avidin or streptividin to biotin (association constant 10^{15} M^{-1}). Biotinylated ligands can be associated with avidin- or streptividin-attached carrier systems to construct a targeted delivery system. Most studies of ligand-drug/carrier conjugates have employed covalent conjugation. Chemical cross-linking agents are used commonly to attach a drug/carrier to a ligand by reacting with appropriate groups (eg, amine, carbonyl, or sulfhydryl) available on both species. Among the cross-linking agents used are carbodiimide, glutaraldehyde, bisazobenzidine, cyanuric chloride, diethylmalonimidate, and various mixed anhydrides.

Cellular uptake of drugs bound to ligands mostly relies on receptor-mediated endocytosis. Binding of ligand to receptor on the cell surface leads to subsequent internalization of receptor-ligand complex. Upon arrival into the endosome, a specific intracellular compartment to store and process ligand-receptor complex, ligand-drug conjugates may dissociate from the receptors and are directed to the lysosome for degradation. In some cases, ligand-drug conjugates are transported through the cell with the receptors, and the conjugates are released by exocytosis at a different surface locus of the cell from where they originate (transcytosis). A successful ligand-mediated targeted delivery system would be efficiently transported to the target cells, rapidly internalized, processed in the acidic endosomes and lysosomes, and eventually diffuse into the cytosol or specific action sites, such as the nucleus, with functional integrity. The lysosomal membrane is a natural barrier to macromolecular ligands and sizable ligand-drug conjugates, and only low-molecular-weight degradation products are liberated to the cytosol. To avoid the degradation from lysosomes, endosomolytic agents (eg, chloroquine) can be used to break the endosomes containing the conjugates and liberating their contents directly into the cytosol. Or the conjugate could be engineered to become an "artificial virus" whose coat proteins undergo a conformational change at low pH and expose their fusogenic components to fuse with the wall of the endosomes, releasing their contents into the cytosol. Lysosomal degradation may be reduced by neutralizing the acidic pH necessary for hydrolase activity (eg, ammonium chloride, monensin), or directly inhibiting hydrolases with leupeptin. However, all these approaches are usually inappropriate for *in vivo* applications.

Although targeted delivery, with probably the highest specificity at cellular and subcellular levels, can be achieved through ligand-receptor interaction, receptor targeting does have several limitations as suggested by Feener and King.[81] First, the competition of endogenous ligands against exogenously delivered ligands for the same receptor binding sites may substantially reduce the availability of cell-surface receptors to the delivered conjugates. Drug targeting via an antireceptor antibody may eliminate the competition as the antibody may occupy a different site. Second, exogenous ligands, typically a hormone, a growth factor or a transporter protein, may interfere with normal physiological processes and/or elicit undesirable biological and immunological responses. This problem can be encountered when delivering drugs across the blood brain barrier with insulin or transferrin as a ligand. Systemic delivery of insulin puts nondiabetic patients at risk of hypoglycemia. This potential can be overcome by using a proteolytic fragment of insulin maintaining high affinity for receptor binding yet possessing minimal effect on glucose homeostasis.[82] Exogenous supply of transferrin may disturb transport of ferrous ions into the central nervous system. Transferrin receptor antibody could be a solution to this problem. Third, certain natural ligands may exhibit relatively low specificity by binding multiple receptor types that are differentially expressed in various cells. Antireceptor antibodies provide a means to specifically target certain types of receptors.

Among all the ligands discussed above, antibodies are probably the most outstanding candidates due to their excellent binding affinity and specificity. Antibodies have been extensively explored as carriers in cancer diagnosis and therapy when certain specificities expressed on tumor cells, referred to as membrane-bound tumor-associated antigens (TAAs), are discovered and characterized. Currently, monoclonal antibodies of defined class and antigenic specificity can be obtained in a highly purified form from hybridoma cells, which renders construction of antibody-chemotherapeutic conjugates and immunotoxins accomplishable. To improve specificity of action and to aid cellular penetration, antibody fragments rather than the whole antibody molecule are used for drug targeting. Consequently, the molecular size decreases from 150 kD for an entire IgG molecule, to 50 kD for a Fab' fragment, or to 27 kD for a single-chain Fv protein.[83] Fragments of small size, such as Fv protein, can be readily fused with therapeutic entities to construct recombinant proteins with inherent targeting functionality.

A novel strategy to deliver cytotoxic drugs to tumor cells is known as ADEPT (antibody directed enzyme prodrug therapy). In such a system, the enzyme β-glucuronidase is covalently immobilized or coupled to the surface of antibody-attached liposomes; then, when the nontoxic and pharmacologically inactive prodrug epirubicin glucuronide is administered simultaneously, it is converted by the enzyme to the potent antitumor reagent epirubicinin at the vicinity of tumor cells.[84] GDEPT (Gene-directed EPT) differs from ADEPT in that the gene encoding the prodrug-activating enzyme rather than the enzyme itself is delivered into the target cells, which actually makes the tumor or virus-infected cells themselves manufacture the enzyme *in situ*. One apparent advantage of this approach over conventional antibody-drug conjugation is that the formation of active derivatives in close proximity of the target cells could result in higher cellular but lower systemic level of active drugs and thus further reduce systemic toxicity.

As another novel approach, bispecific antibodies have been proposed for cancer or HIV immunotherapy. A bispecific protein, made of a chimeric combination of an antitumor or an anti-gp120 (a glycoprotein expressed on the surface of HIV-infected cells) antibody with an anti-lymphocyte antibody, could redirect T-lymphocytes to lyse tumor cells or HIV-infected cells.[85] One drawback of antibody (and possibly its fragment) targeting is immunogenicity.

Folate, in principle, offers several advantages over antibodies as a targeting ligand. As a vitamin necessary to cell growth and metabolism, folate is presumably nonimmunogenic. It has good stability as well. Furthermore, it is highly specific for tumors as the elevated expression of folate receptor has frequently been identified in various types of human cancers.[86] The interested reader is directed to the exhaustive review by Reddy and Low[87] about folate-mediated tumor targeting.

Another group of macromolecules that can serve in tumor targeting is carbohydrate determinants. Carbohydrate determinants are glycoprotein or glycolipid cell-surface components that are critical in cell-cell recognition, interaction, and adhesion. These markers are often upregulated on the surface of tumor-associated endothelial cells and play an important role in angiogenesis and metastasis of cancers.

Resealed Erythrocytes

The mature erythrocytes serve only as hemoglobin carriers in the blood circulation. It was thought that if therapeutic agents could be entrapped and replace hemoglobin in the viable erythrocytes, the cells may turn into efficient drug delivery systems. Several methods have been employed to incorporate drugs into erythrocytes, including hypoosmotic lysis, electrical breakdown, endocytosis, membrane perturbation with amphotericin B, and lipid fusion.[88] Hypoosmotic lysis is the most commonly used. In this process, erythrocytes first swell to about one and a half times their normal size in a hypotonic medium and the membrane ruptures, resulting in the formation of pores with diameters of 20 to 50 nm. The pores allow equilibration of the intracellular and extracellular solutions. If the ionic

strength of the medium then is adjusted to isotonicity and the cells are incubated at 37°C, the pores will close and cause the erythrocyte to "reseal." Using this technique with a drug present in the extracellular solution, it is possible to entrap up to 40% of the drug inside the resealed erythrocyte and to use this system for targeted delivery via intravenous injection. A variety of biomacromolecules ranging in size from 5000 to 600,000 Da, such as I-asparaginase, insulin, heparin, can be entrapped in erythrocytes.[56] Drug may release from erythrocyte carriers by phagocytosis, diffusion through the cell membrane, or by a specific transport system.[89] Considerable control of drug release can be achieved by modifying polar or charged substituents of the entrapped molecules. The rate of diffusion decreases with increased polarity of entrapped molecules. Prolonged release is possible by entrapment of potent transporter protein inhibitor with the drug.[90] The advantages of using resealed erythrocytes as drug carriers are that they are biodegradable, fully biocompatible, and nonimmunogenic; they exhibit flexibility in circulation time depending on their physicochemical properties; the entrapped drug is shielded from immunological detection; and chemical modification of drug is not required.

The assessment of resealed erythrocytes for use in targeted delivery has been facilitated by studies on the behavior of normal and modified reinfused erythrocytes. They are removed from the circulation by the RES, especially by cells in the spleen and the liver. In general, normal aging erythrocytes, slightly damaged erythrocytes (eg, treated with low concentrations of gluteraldehyde), and those coated lightly with antibodies are recognized by the spleen after intravenous reinfusion, but heavily damaged or modified erythrocytes are removed from the circulation by the liver. This suggests that resealed erythrocytes can be targeted selectively to either the liver or the spleen, depending on their membrane characteristics. In addition to coating with antibodies, removal of portions of cell-surface carbohydrates reduces the circulating half-life. The ability of resealed erythrocytes to deliver drug to the liver or the spleen can be viewed as a disadvantage in that other organs and tissues are inaccessible. Thus the application of this system to targeted delivery may be limited mainly to diseases of these organs and hematological disorders, including tumors, Leishmaniasis, leukemia, thromboembolism, etc. Resealed erythrocytes are also suitable for carrying drugs whose action sites are on these organs; insulin is one example of this case.

Bioadhesives

The success of drug delivery to various mucosal tissues of the body, for either local action or systemic absorption, largely depends on the degree of contact between the drug delivery system and the tissue surface and residence time. Residence time for most musosal routes is less than an hour and typically of the order of minutes, unless some form of adhesive is incorporated in the delivery system.

A bioadhesive can be defined as a substance that can adhere to a biological substrate and remain there for an extended period of time. If the biological substrate is mucus, then the bioadhesive is referred to as a mucoadhesive. Basically, a bioadhesive is used to localize a delivery system to a specific area for local action or to increase contact time at the absorption site so that bioavailability can be improved. Typical increases in residence time by using bioadhesives are given in Table 47-7[91].

Bioadhesion can be regarded as a two-step process.[92] The first step involves establishment of intimate contact that is governed by surface characteristics, composition of the mucoadhesive, mucin, and the applied force or pressure. The second step involves formation of secondary bonds between the adhesive and the mucin-epithelial surfaces. Secondary bonding includes hydrogen bonding as well as electrostatic and hydrophobic interactions. Mucin consists of a protein backbone with pendant sugar groups at appropriate locations. Many of these sugar groups terminate in a sialic or sulfonic acid residue. They carry anionic charges as a result. Mucin can be regarded as a polyelectrolyte with a high charge density holding a large amount of water. The expanded nature of mucin and polymer allows interpenetration that results in an increase in contact area and establishment of physical entanglement between mucin and the mucoadhesive polymer. Physical entanglement can strengthen the network and increase contact area that in turn increases the formation of secondary bonds. Usually, bioadhesive polymers contain a number of hydrophilic groups such as carboxyl, hydroxyl, amide, and sulfate. These groups interact with mucin or epithelial tissues primarily through hydrogen bonding and to a lesser extent through hydrophobic and electrostatic interactions. These groups also allow the polymers to swell after absorbing water and thus maximize the number of adhesion sites. Polycarbophil with thiol groups is able to form disulfide bonds with mucin and thus exhibits significantly stronger adhesive property. When a delivery system containing such modified polycarbophil and carboxymethyl cellulose was used to administer insulin orally to mice, the hypoglycemic effect lasted up to 80 hours.[93] Typically, bonding between the polymer and mucin is strong enough to prevent detachment, so removal is mainly through mucin turnover. It is believed that water-insoluble polymers with light cross-linking are preferred because they are not removed from the site of application by dissolution.

Table 47-7. Approximate Clearance Time of Applied Suspensions for Selected Areas of the Body

ROUTE	RESIDENCE TIME WITHOUT BIOADHESIVE	RESIDENCE TIME WITH BIOADHESIVE
Ocular (human)	1–2 min	12–15 hr
Nasal (human)	2–60 min	6–12 hr
Buccal (human)	2–30 min	6–10 hr
Intestine (dog)	1–3 hr	6–10 hr
Vaginal (human)	30–90 min	3–4 days

There are a number of limitations associated with bioadhesive polymers: fouling of the bioadhesive sites of the polymer before reaching the desired target and rapid mucus turnover making long-term secure adhesion impossible. Eichman and Robinson[94] showed that effervescence possessing mucus-stripping effect may potentially improve the performance of bioadhesives.

Bioadhesive delivery systems have been tried in various routes of administration. Some measure of success has been achieved in vaginal delivery. *Columbia Laboratories* introduced Crinone and Advantage-*S* to the market using a gel containing the bioadhesive polycabophil developed by Robinson et al.[95] The gel adheres to the vaginal tissue for 3 to 4 days and hence serves as a platform for delivery of progesterone or spermicide nonoxynol-9. The major obstacle for ocular drug delivery is the rapid loss of drug because of tear turnover, making the eye a target for bioadhesive systems in order to prolong the residence time. One drawback of these systems, especially gel-like formulations, is that they spread on the cornea surface, causing blurred vision. Bioadhesive microparticles may be attractive for intranasal delivery of peptides and vaccines, especially when combined with penetration enhancers.[96] However, for the buccal route, because of low mucosal permeability, coadministration of bioadhesives and penetration enhancers is recommended for protein and peptide delivery.

The bioadhesive properties of a broad spectrum of polymers in rat and human gastrointestinal tracts have been studied.[97,98] These polymers showed good bioadhesion *in vivo* and *in vitro* in rats, but unfortunately the results in human were disappointing and there is no clear explanation at this time. Second-generation bioadhesives take advantage of specific receptor-mediated interaction between various lectins, bacterial fimbriae and the sugar groups in the mucus or on the epithelial surface. Lectins or fimbriae can be attached to the surfaces of drug-loaded micro- or nanoparticles to provide a bioadhesive

system. One concern with these exogenous biological macromolecules is immunogenicity and toxicity. Safe adhesive delivery systems may be developed using nontoxic tomato lectin.

Prodrugs

A prodrug is a compound formed by chemical modification of a biologically active compound that will liberate the active compound *in vivo* by enzymatic or chemical processes. The primary purposes for designing prodrugs are improving physicochemical properties of drugs to overcome formulation problems, and altering biological properties to enhance their efficacy and to reduce their toxicity. To be useful in targeted delivery, a prodrug must be activated by enzyme or chemical agents near the target site to provide a sufficient supply of parent drug *in situ*. Furthermore, the active parent drug must remain at the target site and not sneak into the systemic circulation, which could cause adverse effects. However, chemically activated prodrugs frequently experience conversion before reaching the target site, which makes them unsuitable for targeted delivery.

Brain targeting remains one of the greatest challenges because the blood-brain barrier is highly impermeable to numerous polar drugs. The most famous prodrug for targeted delivery to the brain is L-3,4-dihydroxyphenylalanine (L-dopa) for Parkinson's disease, a degenerative brain disorder. In this case, L-dopa is transported into the brain, where it is converted to the active drug dopamine by aromatic amino acid decarboxylase. With more and more potent therapeutics identified to treat various brain disorders, effective delivery systems that can accommodate many drugs are desperately needed. A prodrug carrier system developed by Bodor and Simpkins[99] is based on the observation that certain dihydropyridines can easily enter the brain, where they are oxidized to the pyridinium ion whose permeation through the blood-brain barrier is very low. The ionic species formed in the peripheral tissues are rapidly cleared by kidney or biliary secretion. Chemical or enzymatic cleavage of the ester bond on the pyridinium ion slowly releases the conjugated drug in the brain. More lipophilic prodrugs also can be developed to conquer the comparably impermeable stratum corneum of the skin and corneal epithelia of the eye.[100,101]

Prodrugs for oral administration are designed primarily to increase intestinal absorption or to reduce such local side effects as gastric irritation by aspirin. Azo-prodrugs, such as sulphasalazine, olsalazine and balsalazide, have long been used in managing inflammatory disorders of the colon. After entry into the large intestine, the active species, 5-ASA, is released from the prodrug after the cleavage of the azo-linkage. More recently, a number of prodrugs have been developed to target steroid anti-inflammatory agents to the colon. The colonic activation of these prodrugs is based on the colonic microflora producing a wide array of glycosidases.[102] These glycosidases are capable of hydrolyzing glycosides and polysaccharides. The glucoside prodrug of dexamethasone has demonstrated comparable efficacy and reduced side effects with lower doses in experimental animals.[103,104]

In most cases, the prodrug approach is attempted for site-specific drug delivery. However, prodrugs can be used to control the drug release in a limited sense. Consider a water-soluble drug that is modified to a water-insoluble prodrug. The prodrug will have a slower dissolution rate in an aqueous medium than the parent drug, and thus the appearance of the parent drug in plasma will be delayed. This is observed with theophylline prodrug, 7,7′-succinylditheophylline.

DELIVERY OF BIOTECHNOLOGY PRODUCTS

Being charged macromolecules, proteins and nucleic acids exhibit similar biological properties: limited diffusion from the site of administration, rapid clearance from the circulation by enzymatic degradation, inability to penetrate biological membranes, etc. An extensive search for efficient delivery of these two major biotechnology products is encouraged for several reasons. Proteins and peptides continue to be the most potent therapeutics with high specificity. Their sophisticated functions are derived from their complex structures, thus satisfactory "mimicry" with small molecules is no easy to achieve if possible at all. Unlike conventional treatments, most of which provide symptomatic alleviation, gene therapy eliminates genetic defects that cause a variety of diseases including genetic disorders, cancers and cardiovascular diseases, that is, gene therapy promises "cure" in a sense.

Protein and Peptide Drug Delivery

Despite the enormous success of synthetic peptides and biotechnology products to date, much effort continues to be exerted on controlled delivery of peptide drugs via convenient and noninvasive routes of administration.

Basically, low bioavailability of protein and peptide drugs can be attributed to:

1. *Low permeability of absorbing tissue to the drug*. There are two transport pathways for protein and peptide absorption across the mucosal membrane: transcellular (across cells) and paracellular (between cells). Proteins and peptides are charged molecules that cannot penetrate the lipophilic plasma membrane easily (transcellular transport). Meanwhile, paracellular transport through the tight junctions is also fairly limited because of their large molecular sizes (> 500 Da).
2. *Physicochemical instability caused by enzymatic degradation, molecular interaction*. Enzymatic degradation not only affects the fraction absorbed but also half-lives of peptides in the body. The exopeptidases (ie, aminopeptidase and carboxypeptidase) cleave the peptide bond either at the amino or carboxyl terminus of a peptide chain. The endopeptidases (eg, trypsin, chymotrypsin) function within the peptide chains and maintain certain substrate selectivity. Proteins tend to aggregate themselves or interact with various components in the biological milieu, which dramatically affect their biological activity, absorption and biodistribution.
3. *Short residence time of the dosage form at the absorption site*. In most cases, contact time of the delivery system with the absorbing surface is too short to allow therapeutic levels to be maintained over an extended period of time. Short residence time leads to incomplete absorption and failure to maintain sustained drug action.

Table 47-8[105] gives some general methods for enhancing protein delivery. All these methods are essentially based on conquest of the enzymatic and permeation barrier to peptide absorption.

Table 47-8. General Methods for Enhancing Protein Delivery

Increasing absorption
1. Use of prodrugs
2. Chemical modification of the primary structure
3. Incorporation into liposomes or other encapsulation material
4. Coadministration with chemical enhancers
5. Use of physical methods such as iontophoresis and phonophoresis
6. Targeting to specific tissues

Minimizing metabolism
1. Chemical modification of the primary structure
2. Covalent attachment to a polymer
3. Incorporation into liposomes of other encapsulation material
4. Coadministration with an enzyme inhibitor
5. Targeting to specific tissues

Prolonging half-life
1. Protection with polymers, liposomes
2. Use of bioadhesives
3. Targeting to specific tissues

From Wearley LL. *Crit Rev Ther Drug Carrier Sys* 1991; 8:331.

PENETRATION ENHANCEMENT—Penetration of peptides into biological membranes can be enhanced by physical methods or with the assistance of penetration enhancers. The physical approaches proposed for peptide drug delivery (ie, ionophoresis and phonophoresis) are used mainly in transdermal delivery and have been discussed in a previous section. Penetration enhancers are chemical entities that facilitate transport of coadministered substances across biological membranes. The classification of penetration enhancers is shown in Table 47-9.[106] Basically, penetration enhancers adopt one or more of the following mechanisms to improve membrane permeability to peptides:

1. Enhancing transcellular transport by extracting membrane components or increasing its fluidity.
2. Enhancing paracellular transport.
   a. Chelating calcium ions to open tight junctions.
   b. Inducing high osmotic pressure that transiently opens tight junctions.
   c. Introducing agents to disrupt the biochemical structure of tight junctions.
3. Altering mucus structure and rheology to facilitate drug diffusion.
4. Modifying the physical properties of the drug-enhancer entity, eg, forming ion pairs with charged molecules, reducing aggregation of peptides.

The major concern with penetration enhancers to facilitate transport of peptides is their toxicity because most of them act by nonspecific membrane-disrupting mechanisms. For example, some surfactants and bile salts, such as sodium dodecyl sulfate and deoxycholate, can alter brush border membrane and change intestinal permeability and intestinal secretion.[107] In fact, few penetration enhancers have been approved by the FDA because of the safety issue. A good penetration enhancer should only inflict minimal, localized, transient, and rapidly reversible damage to the absorbing tissue. A series of amino acid derivatives with low molecular weight, developed by *Emisphere Technologies*, exhibited their ability to dramatically enhance oral absorption of various peptide drugs, including human growth hormone and insulin, without obvious toxicity.[108,109] The exact mechanism adopted by these compounds has not yet been elucidated. It is speculated that they may modify the conformation of these peptides and thus make the peptides more lipophilic and absorbable.[108] A common complaint associated with penetration enhancers is irritation, especially for transdermal and nasal routes.[110,111] However, irritation is a very complicated phenomenon that may result from the interaction among vehicle, penetration enhancers, buffers, etc. Also, this response is very subjective and varies among individuals.

Table 47-9. Classification of Penetration Enhancers

1. *Surfactants*
   Ionic
   - Sodium lauryl sulfate
   - Sodium laurate
   - Polyoxyethylene-20-cetylether
   - Laureth-9
   - Sodium dodecylsulfate (SDS)
   - Dioctyl sodium sulfosuccinate

   Nonionic
   - Polyoxyethylene-9-lauryl ether (PLE)
   - Tween 80
   - Nonylphenoxypoly-oxyethylene(NP-POE)
   - Polysorbates

2. *Bile salts and derivatives*
   - Sodium glycocholate
   - Sodium deoxycholate
   - Sodium taurocholate
   - Sodium taurodihydro-fusidate (STDHF)
   - Sodium glycodihydro-fusidate

3. *Fatty acids and derivatives*
   - Oleic acid
   - Caprylic acid
   - Mono(di)glycerides
   - Lauric acids
   - Acylcholines
   - Caprylic acids
   - Acylcarnitines
   - Sodium caprate

4. *Chelating agents*
   - EDTA
   - Citric acid
   - Salicylates

5. *Sulfoxides*
   - Dimethyl sulfoxide (DMSO)
   - Decylmethyl sulfoxide

6. *Polyols*
   - Propylene glycol
   - Polyethylene glycol
   - Glycerol
   - Propanediol

7. *Monohydric alcohols*
   - Ethanol
   - 2-Propanol (isopropyl alcohol)

8. *Others (Nonsurfactants)*
   - Urea and its derivatives
   - Unsaturated cyclic ureas
   - Azone (1-dodecylazacycloheptan-2-one) (laurocapram)
   - Cyclodextrin
   - Enamine derivatives
   - Terpenes
   - Liposomes
   - Acyl carnitines and cholines

From Swarbrick J, Boylan JC, eds. *Encyclopedia of Pharmaceutical Technology*, New York, Dekker, 1999, p 1.

Table 47-10. Peptidase Inhibitors

INHIBITOR	PEPTIDASE(S) INHIBITED
Antipain	Cathepsin A, B, papain, trypsin
Leupeptin	Cathepsin B, papain, serine proteinases
Chymostatin	Chymotrypsin (and cysteine proteinases)
Pepstatin	Carboxypeptidases, pepsin, renin, cathepsin B
Bestatin	Leucine aminopeptidase, aminopeptidase B
Amastatin	Aminopeptidase A
PHPFHLFVF	Renin
Alpha-1-antitrypsin	Neutrophil elastase

PROTEASE INHIBITORS—Protease inhibitors are employed, hopefully, to overcome the enzymatic degradation. Some of the proteases and their inhibitors are shown in Table 47-10.[112,113] However, proteins and peptides are subject to multiple routes of degradation. Coadministration of a single enzyme inhibitor does not necessarily result in improved bioavailability. It is necessary to have a thorough understanding of the enzymatic degradation pathway and distribution of the responsible enzymes before this approach can be used successfully in designing a delivery system for proteins and peptides. In addition, the extent of improvement of delivery with this approach largely depends on the relative contribution of enzymatic degradation to the overall barriers. If mucosal permeability and/or short residence time are the major limitations, enzyme inhibitors alone may not necessarily improve the delivery. Rather, a combination of protease inhibitors and penetration enhancers or a protease inhibitor possessing penetration enhancement function (eg, bestatin) may be more useful.

CHEMICAL MODIFICATION— Chemical modification of the primary structure of a peptide could lead to improvement on enzymatic stability and/or mucosal penetration. One example is desmopressin (DDAVP tablets, *Aventis*) for neural diabetes insipidus. It differs structurally from the natural vasopressin in two positions: β-mercaptopropionic acid instead of hemicystine in position 1 and D-arginine in place of L-arginine in position 8. It was found that the cyclic structure accounted for metabolic stability and high membrane permeability of cyclosporin. Cyclization using "chemical linkers" was proposed to stabilize oligopeptides and improve their lipophilicity by reducing their charges and hydrogen bonding potential.[114,115] The linkers were designed to be susceptible to esterase metabolism, leading to release of the peptides. The apparent drawback of this approach is requiring the synthesis of a new chemical entity, which may lead to altered efficacy and/or toxicity. Additionally, modification becomes much more difficult with large peptides. The cyclic prodrug was predicted to be possible for peptides with up to 8 or 9 amino acids.

Chemical modification of peptide drugs is also explored for the purpose of improving their pharmacokinetic profiles and/or reducing their immunogenicity. PEG modification seemingly is able to increase the plasma half-life of protein and reduce the immunogenicity dramatically.[116] A possible mechanism is that the PEGylated protein is too large for glomerular filtration.

PEG may also sterically hinder the protein's interaction with cellular receptors required for metabolism and elimination. PEGylated adenosine deaminase (PEG-ADA) was the first such product approved for use in ADA-deficiency.

BIOADHESIVES—Bioadhesives allow close contact of peptides to the mucous lining, while at the same time minimizing transit so that a high concentration gradient across the membrane can be maintained for an extended period of time. Moreover, localizing the delivery system to a small area permits penetration enhancers and enzyme inhibitors to be used at lower concentrations. This may lessen toxicity and irritation. Harris and Robinson[98] demonstrated that bioadhesives could enhance peptide delivery in ocular and nasal routes because their major barrier was short residence time. When mucosal permeability and/or enzymatic degradation are major limitations, such as the gastrointestinal route, bioadhesives possessing inherent penetration-enhancing effects and/or protease inhibition may be beneficial. Polycarbophil and other polyacrylic acid-based polymers are able to chelate calcium ions in physiological buffers.[117] This may lead to opening of tight junctions that are calcium dependent, with an associated increase in paracellular transport. Moreover, polyacrylate is proposed to chelate bivalent cations that are essential to normal enzyme activity. Nevertheless, this inhibitory effect may be still too weak to protect peptides from enzymatic degradation. Recently, multifunctional matrices have been proposed as a promising strategy for oral peptide delivery.[118] These matrices are based on polymers that possess bioadhesive properties, penetration-enhancing effect, enzyme-inhibiting ability, and/or high buffer capacity. Polyacrylates, cellulose derivatives, and chitosans can be chemically modified to improve certain properties and subsequently serve as the construct materials of the matrices. For example, bioadhesive and penetration-enhancing properties can be improved by the covalent attachment of thiol moieties to these polymers. Conjugation of protease inhibitors enables the matrices to protect peptide drugs against enzymatic degradation. Consequently, multifunctional matrices are capable of overcoming almost all the barriers to the peptide drug absorption simultaneously, leading to substantial improvement of bioavailability.

NANO(MICRO)PARTICLES—Encapsulation can protect a peptide against enzymatic degradation and achieve controlled release as well. There are two subtypes of nano(micro)particles. Nano(Micro)capsules are vesicular systems in which drug molecules are surrounded by a membrane. Nano(Micro)spheres are matrix systems in which drug molecules are dispersed throughout the particle. There are a number of methods for preparing nano(micro)particles such as solvent evaporation, organic phase separation, interfacial polymerization, emulsion polymerization, and spray drying. The choice of methods depends on the physicochemical characteristics and stability of the proteins and peptides.

Among numerous biodegradable or bioerodible polymers used for nano(micro)particles, PLGA-based microspheres have proved useful for controlled delivery of several peptides and proteins. The injectable PLGA microsphere of leuprolide acetate, used for prostate cancer, provides controlled release of the peptide over 30 days.[23] Since diffusivity of a protein or peptide is commonly very low, biodegradation of the polymer allows release of peptides from the nano(micro)particles. The possible mechanisms for release of proteins and peptides are[119]:

1. Polymer erosion or degradation
2. Self-diffusion through pores
3. Release from the polymer surface
4. Pulsed delivery initiated by stimulation, such as application of an oscillating magnetic or sonic field

Mechanism 2 is not as important as 1 because usually the drug-loading efficiency is low, which means the concentration gradient is not high enough for the peptide to be released by passive diffusion. Mechanisms 1 and 3 are the most important processes. An initial burst is frequently observed because of solubilization of free drug near the surface that is followed by disintegration of the matrix. In other words, the release pattern is biphasic, with an initial high release rate followed by a quiescent period and then a period of significant release due to degradation of the polymer. Mechanism 4 has been applied to control the release rate of insulin. The release pattern is controlled by a magnetic field that alters the structure of polymer chains, resulting in increased drug release.[120] Release rates are subject to protein particle size and loading, protein solubility and molecular weight, polymer composition and molecular weight, and dimensions and shape of the matrix.[121–124] One persistent problem of this approach is that, when encapsulated proteins remain in the body for a long time, they tend to denature or aggregate as a result of exposure to moisture at 37°C. This can cause a loss of biological activity and/or changes in immunogenicity.

GENE DELIVERY

It suffices to say that the success of gene therapy largely relies on an efficient and safe delivery system. Currently, gene delivery can be divided into two categories: viral and nonviral. Viral infection involves highly specific processes for targeting the virus to cells in the body and trafficking viral DNA into the nucleus. In a viral delivery system, the gene encoding viral functions are replaced by that encoding therapeutic function within infectious viral particles. The ability of the virus to infect the target cell and direct gene expression is kept intact. The major concern with viral gene delivery is immunogenicity. The residual viral elements can be immunogenic, cytopathic, and/or recombinogenic.

In the nonviral approach, the genetic materials are considered as chemical entities or pharmaceutical products and particulate carriers are used in their delivery. In general, a nonviral gene delivery system comprises plasmid DNA complexed and condensed by a polycationic agent. The polycation can be a cationic lipid, a liposome composed of cationic lipids, a cationic polymer (eg, polylysine, polyethyleneimine), or a positively charged protein (eg, histones). Viral vectors are superior to nonviral systems in terms of transfection efficiency. Although nonviral systems can protect DNA from nuclease degradation, the lesser ability to overcome various systemic barriers listed in Table 47-11[125] presents substantial challenges to their use in gene delivery. Additionally, the ionic interaction of positively surface-charged plasmid/polycation complex with plasma proteins can result in particle destabilization, characterized by aggregation of particles and/or premature release of DNA.

CATIONIC LIPIDS—Liposomes are the most classic and traditional nonviral carriers in gene delivery because they are biodegradable, and ligands can be incorporated for cell-specific targeting. Cationic liposomes are typically composed of charged and neutral lipids. DOPE and cholesterol are the most frequently used neutral lipids. Nucleic acids can be complexed with cationic liposomes by charge interaction. Freeze fracture[126] and cryoelectron microscopy[127] studies established that complexes resemble aggregated spherical particles surrounded by interwound DNA. Complexes with optimal activity usually contain a slight excess of net positive charge that is capable of

Table 47-11. Biological Barriers to Plasmid/Polycation Particles

1. Particle instability in the blood circulation
2. Particle opsonization and rapid clearance by the RES
3. Extravasation, particularly in organs with continuous endothelia
4. Poor cellular internalization
5. Endosomal entrapment and subsequent delivery to lysosomes for degradation
6. Poor uncoupling of DNA and carrier in the cytoplasm
7. Inefficient uptake into the nucleus

efficient binding with the negatively charged cell surface. The complexes are then internalized by endocytosis, and induce a "flip-flop" of anionic lipids normally present on the cytoplasmic face of the membrane bilayer. The oligonucleotides are displaced from the cationic lipid by the anionic lipid that diffuses into the monolayer and subsequently released into the cytoplasm.[128] However, electron microscope studies[129] showed that plasmids complexed with DMRIE liposomes were endocytosed and remained in vesicles or endosomes. No plasmids were found free in the cytosol. Furthermore, the perinuclear endosomes or vesicles fused to generate large aggregates without releasing their contents. pH-sensitive liposomes have been shown to enhance gene delivery efficiency because they are able to fuse with lipid membranes in the acidic environment of the endosomes, thus facilitating the endosomal release of encapsulated gene-expression systems into the cytoplasm of transfected cells.[130] Proteoliposomes, also known as virosomes or chimerasomes, contain reconstituted viral envelope protein that can facilitate the cellular entry and fusion with the endosomal membranes.[131]

Cationic lipids are capable of interacting electrostatically with the negatively charged phosphate backbone of DNA, neutralizing the charge, and promoting condensation of DNA into a compact structure. The complexes usually are formed in combination of DOPE or cholesterol. This complex is not a liposome, but rather a condensed nanoparticle formed by ionic interaction between the negatively charged DNA and cationic lipids and subsequent hydrophobic interactions between the lipids. The mechanism of gene transfer is hypothesized as fusion of the complex with the plasma membrane followed by entry into the cell. It is not clear whether endocytosis is involved in the process. The complex is then fused with an endosome. Endosomal disruption induced by neutral lipids results in release of DNA into the cytoplasm followed by transport of DNA into the nucleus.[132,133]

POLYMERS—Formulations of plasmid DNA with polymers such as polyvinylpyrrolidone (PVP) and polyvinyl alcohol show enhanced stability, retention, and dispersion of DNA. It has been shown that PVP derivatives facilitate dispersion of DNA in muscles.[134] They also protect DNA against degradation by forming hydrogen bonds followed by creating a hydrophobic coating of DNA that improves stability. Moreover, the enhanced cellular uptake of DNA, probably through hydrophobic interaction with the cell membrane, is also evident.

Although DNA can be condensed by neutral polymers, cationic polymers usually provide more efficient gene delivery. Starburst polyamidoamine dentrimer is a highly branched spherical polymer whose surface has a uniform positive charge. Dendrimers can condense plasmids through electrostatic interactions of their terminal primary amines with the DNA phosphate groups. It can allow very efficient gene delivery with a reduced cytotoxicity (compared to polylysine) to a variety of cell types *in vitro*.[135] Polethylenimine (PEI) can also give very high transfection efficiency *in vitro*. PEI may enhance the intracellular trafficking of plasmids by buffering the endosomal compartments, thus preventing degradation of DNA and facilitating release of plasmids via osmotic swelling and rupture. Chitosan is a biodegradable polysaccharide and able to interact with the phosphate groups of DNA. In general, the cationic polymers are capable of forming more homogeneously small and stable complexes, but these complexes show lower levels of transgene expression than lipid-DNA complexes.

Recently, a number of targeted gene delivery systems have been developed by conjugating various ligands to cationic polymers or lipids. The targeting ligands include antibodies, asialoglycoprotein, transferrin, insulin, growth factors, folate, and integrin peptides containing RGD (arginine-glycine-aspartate) motif.[136]

PEPTIDE-BASED GENE DELIVERY[137]—Positively charged synthetic peptides such as poly-L-lysine (PLL) can form small stable complexes with plasmids; however, a PLL/plasmid complex exhibits low transfection efficiency. Peptide-based delivery systems are designed to improve the bioavailability of the therapeutic gene to the target cells. Their major components are:

1. A condensing function mediated by a cationic peptide, such as PLL, histones, protamine, or poly-L-ornithine
2. A receptor-binding function mediated by a peptide or polysaccharide, glycolipid ligand
3. An endosomolytic peptide (eg, synthetic analog of influenza hemaglutinin protein active moiety[138]) or an amphiphilic membrane associating peptide JTS-1[139]
4. A nuclear localization signal peptide to enhance nuclear entry of the plasmid

All these features could make such a peptide-based delivery construct as efficient as viruses but without their limitations.

NOVEL DELIVERY SYSTEMS

Tissue Engineered Delivery Systems[140,141]

Extended-release implants have direct applications to tissue engineering. For instance, a biocompatible polymer matrix or microsphere loaded with growth factors can be implanted at a desired tissue site, where it releases the soluble factors directly into the interstitial space of the tissue. The diffusible agent can affect the survival or function of damaged cells within the local tissue, or provide a signal that elicits cell proliferation or migration within the tissue. Controlled growth factor delivery systems also can be conjugated with biocompatible matrices or porous scaffolds that provide morphological guides for the assembly of regeneration tissue. These matrices are typically implanted at a specific anatomic location where they serve multiple roles. The matrix functions to create and maintain a space *in vivo*. It also serves as a scaffold to support migration, proliferation, and differentiation of healthy cells from the surrounding tissues. As cells invade the matrix, they encounter the growth factor that is either released from or entrapped within the matrix. Saltzman et al[142] have developed a similar system that uses nerve growth factor-loaded PLGA microparticles to prevent the degradation of cholinergic neurons in the brain.

By physically entrapping a plasmid carrying the gene for an active fragment of human parathyroid hormone within a bovine collagen matrix, Bonadio et al[143] created a moldable three-dimensional porous sponge called a gene activated matrix (GAM) to enhance regeneration of bone tissue in dogs after defect injuries. Here, the collagen carrier serves as a scaffold that holds the plasmid *in situ*. After the endogenous fibroblasts arrive at the scaffold, the cells start the process of tissue repair and regeneration. Therefore, by taking advantage of the natural tendency of fibroblasts to grow into the wound, GAM allows for physical targeting of these cells for direct *in vivo* plasmid gene transfer.

Stent implantation has emerged as a new standard angioplasty procedure. The major limitation of coronary stenting is in-stent restenosis. Optimization of stent characteristics could provide improvement to a very limited extent. Preventive or therapeutic agents given systemically may not reach sufficient levels in injured arteries to impact significantly on the restenosis process. Local delivery of drugs from drug-eluting stents allows for drug application at the precise site in a timely manner. Restenosis therapeutics are usually incorporated into eluting polymeric matrices that are subsequently used to coat the stents. Polymers used for such drug delivery vehicles include PVP/cellulose esters, PVP/polyurethane, polymethylidenemaloleate, PLA-co-PLGA, PEG, polyethylenevinyl alcohol, polydimethylsiloxane, etc. Rapamycin-coated *Bx* Velocity stent (*Cordis*), coated with a 50:50 mixture of polyethylenevinyl acetate and polybutylmethacrylate containing 30% rapamycin by weight, have appeared to be very effective in preventing restenosis. A stent also can be used as a platform for cell-based gene transfer, which would provide a significant advantage in terms of site-specific gene expression in the vasculature.

Panetta et al[144] presented a stable *in vivo* transgene expression in the vasculature for over 4 weeks, using a mesh-stent coated with fibronectin as an excellent platform for adherent porcine smooth muscle cells.

ENCAPSULATED CELLS

The principle of cell encapsulation is to develop a capsule with sufficient permeability to nutrient and oxygen for the transplanted cells as well as proteins, polypeptides, hormones, or neurotransmitters secreted by the entrapped cells (insulin in the case of islet cells); at the same time, the capsule shall effectively restrict the entry of immune cells and antibodies that would cause rejection. Various polymers have been used for such a semipermeable capsule. These include polyelectrolyte complexes of cellulose sulphate, photo-crosslinked PEG hydrogels, agarose, copolymers and terpolymers of 2-hydroxyethyl methacrylate, methyl methacrylate and dimethylaminoethyl methacrylate, alginate-poly(L-lysine)-alginate complex, and N-isopropylacrylamide (NIPAAm)-based copolymers. As diabetes continues to be a worldwide medical concern, encapsulated islet cells are regarded as the most promising treatment of the disease. Different immunoisolated cell capsules can be classified as vascular and extravascular. In a vascular device, a tubular membrane enveloping islet cells is grafted directly to the vasculature, mimicking the natural islet environment. Its disadvantages include thrombosis at anastomosis sites and the surgical risk associated with device implantation and retrieval. Extravascular devices can be further classified as microcapsule and macrocapsule. The former involves the envelopment of a single or a small number of islets into a microsphere. The latter is often referred to as an *artificial pancreas*. Compared to microencapsulation, macroencapsulation may better simulate the natural environment of the cells as well as more efficiently protect them from rejection. The macrocapsule is also easier to reseed or remove, and more stable. However, larger transplant volume, longer diffusion distances, limited specific surface area, and the aggregation of the entrapped islet cells may impede diffusion of nutrients and oxygen to the central portion of the islets, thus causing necrosis and malfunction of implanted islets.

The refillable biohybrid artificial pancreas, being developed by Bae's group,[145] has several unique features: a thermally reversible extracellular matrix made of NIPAAm hydrogel copolymers; a long-term biocompatible immunoprotective membrane with improved chemical, mechanical and transport stability; and oxygen carriers and biospecific stimulant polymers added to the extracellular matrix. The extracellular matrix primarily serves to immobilize the cells to prevent their aggregation and necrosis and to provide an acceptable physicochemical environment for cell adherence and growth. To replace and refill the device, the polymer matrix can be cooled and redissolved below its gelation temperature. The used solution is withdrawn and a fresh islet/polymer suspension is injected into the device. At body temperature, the polymer forms a gel to immobilize the cells. Oxygen carriers are added to improve the function and viability of immunoisolated islets. Sulfonylurea grafted polymers can stimulate insulin secretion through interaction with its receptors on the islet cell membrane, so the number of islets can be reduced, resulting in reduced volume of the artificial pancreas.

Based on the same principle, cellular implants have attracted interest in extended-release drug delivery to the central nervous system. Examples are encapsulated dopamine-producing cells and glial cell line-derived neurotrophic factor (GDNF)-producing cells implanted in the striatum and the nigra substantia, respectively for Parkinson's disease, encapsulated trophic factor-producing cells for Alzheimer's disease, Huntington's disease, and amylotropic lateral sclerosis.[146]

MICROCHIP DELIVERY SYSTEMS[147]

Microchips can provide controlled release of single or multiple chemical substances on demand. A representation of microchip

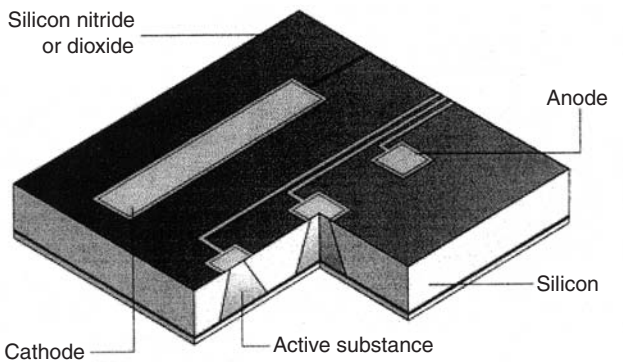

Figure 47-16. Multi-reservoir drug-delivery microchip. (From La Van DA, et al. *Nature Rev Drug Discovery* 2002; 1:77.)

delivery systems is shown Figure 47-16.[148] The system consists of a substrate containing multiple reservoirs capable of holding chemicals in a solid, liquid, or gel form. Each reservoir is capped with a conductive membrane (eg, gold) and wired with the final circuitry controlled by a microprocessor. The central processor controls the exact time and amount of the drug release by controlling the dissolution of the gold membrane. A microchip as small as 2 mm by 2 mm could accommodate over 1000 reservoirs.

Microchip delivery systems have a number of advantages: simplicity of release mechanism, accuracy, complex release patterns, potential for local delivery, stability enhancement, storage and release of multiple chemicals. Microchips are biocompatible and small enough for implantation. The release time could be extended for years depending on the number of reservoirs in the microchip.

The silicone chip is made of non-degradable materials; therefore the chip has to be retrieved at the end of the treatment. The chip is brittle and unfixable, which could cause injuries and aggravation. For some reason the device may fail to operate, requiring surgical intervention to correct. The usage of the chip as a self-regulating release device is limited by biosensors because a specific biosensor is required for an individual disease.

MICROFABRICATED MICRONEEDLES

As mentioned earlier, transdermal administration is fairly restrictive to a majority of therapeutic agents due to extreme impermeability of the stratum corneum. Microfabricated microneedles have the potential to significantly promote transdermal delivery of a large variety of drugs. A microneedle array patch (Fig 47-17[148]) consists of hollow microneedles, which are long and strong enough to penetrate the stratum corneum, but short enough not to stimulate nerves in deeper tissues. Once a drug molecule crosses the stratum corneum, it can rapidly diffuse through the deeper tissue and be taken up by the underlying blood capillaries. Such a patch can dramatically enhance the transdermal delivery without causing pain.[149]

POWDERED DRUG DELIVERY[150]

Dermal and oral powdered drug delivery systems (*PowderJect Technologies*) use the energy from a transient helium gas jet to accelerate and deliver particulate ("powdered") drugs into the skin and mucosal sites, respectively. In the dermal PowderJect, drug particles entrained within a supersonic flow of gas reach velocities sufficient for penetrating the stratum corneum. High-velocity powder injection provides needle- and pain-free delivery of small and large molecules. This technology delivers limited dose (approximately 6 mg), although usually it is adequate

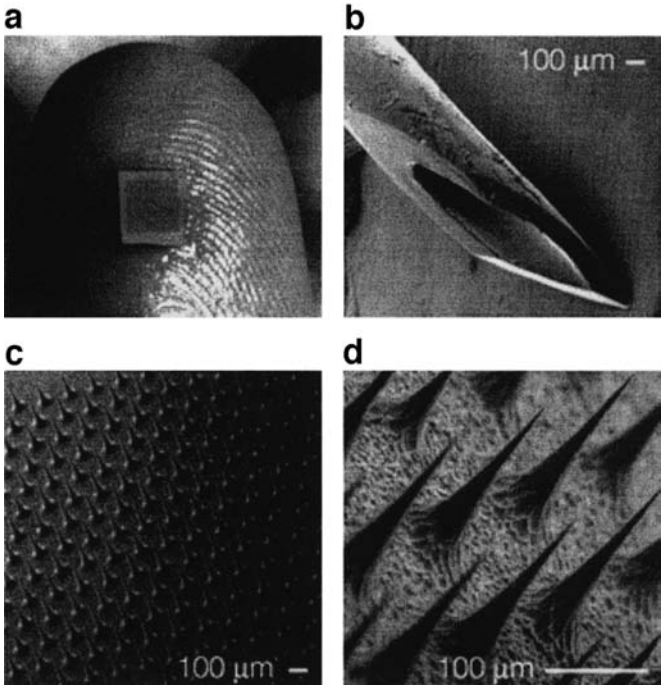

Figure 47-17. Micromachined needles and needle arrays. These images show the design of a needle array for painless transdermal drug delivery. For scale, a conventional hypodermic needle (panel B) is also shown. (From La Van DA, et al. *Nature Rev Drug Discovery* 2002; 1:77.)

to potent drugs. The physical requirements of powders for injection are unique, including particle size range, maximum density and inherent particle strength. Therefore, formulation and methods of characterization and processing are different from those for conventional products.

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CHAPTER 48

The New Drug Approval Process and Clinical Trial Design

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The research and development efforts needed to ensure the safety and efficacy of new drugs are complex, time consuming, and financially risky. Thousands of compounds undergo extensive testing for every one new chemical that receives marketing approval.[1] Research and development costs for each new drug product are estimated to be over $800 million.[2] It has been reported that only 30% of drugs that reach the marketplace generate sufficient revenue to recover the average cost of its development.[3] This chapter discusses the various stages of new drug development and approval in the United States with a focus on clinical trial design and methodology. Readers are encouraged to refer to specific FDA guidance documents for more detailed information (www.fda.gov/cder/guidance/index.htm).

FOOD AND DRUG ADMINISTRATION

The Food and Drug Administration (FDA) oversees the new drug approval process in the United States. Other countries have similar regulatory bodies. The FDA was created as the result of multiple deaths associated with a diethylene glycol-based sulfanilamide product. This solvent was used to enhance the aqueous solubility of the antibiotic. Diethylene glycol, however, is a highly toxic agent used in antifreeze solutions, and numerous deaths resulted from the ingestion of the product. Based on these tragic events, Congress passed the Food, Drug, and Cosmetic Act of 1938, which established FDA as the regulatory authority overseeing the development of new drug products.[4] The Act required disclosure of the ingredients and formulation, assay methods, manufacturing processes, and all animal and human testing to the FDA prior to distribution of the product.

While the Act of 1938 required new drug products to be safe, efficacy standards were not established until another tragedy in the early 1960s. Thalidomide, a synthetic sedative/tranquilizer, had been sold in Europe at that time without a prescription and was viewed as a possible alternative to the more toxic barbiturates.[5] Prior to approval of thalidomide by the FDA, several incidences of toxicity in Europe were reported. Severe birth defects were noted when the drug was administered to pregnant women, the most common being phocomelia or arrested limb development. These events brought about the Kefauver-Harris Amendments of 1962, which strengthened existing laws and emphasized the need for the safety of approved drugs.[6] These Amendments required manufacturers to establish both safety and efficacy of new drug products prior to approval and required investigators to file Investigational New Drug Applications (INDs) prior to testing all drugs in humans. As a side note, thalidomide is currently approved in the United States for the treatment and prevention of painful skin lesions associated with erythema nodosum leprosum. Other potential uses of this drug under investigation include several types of cancer, Crohn's disease, and autoimmune deficiency-associated diseases.[5,7]

The role of the FDA is to promote and protect the health of Americans. A multidisciplinary staff consisting of pharmacists, physicians, pharmacologists, chemists, statisticians, attorneys, and other scientists as well as administrative personnel is employed at the FDA to achieve this goal. The FDA consists of several Centers, each designated with specific responsibilities. The Center for Food Safety and Applied Nutrition oversees food and cosmetic products. The Center for Veterinary Medicine is responsible for animal feed and drugs. The safety and efficacy of medical devices are covered under the Center for Devices and Radiological Health. This Center also oversees radiation-emitting devices such as cellular telephones. The Center for Biologics Evaluation and Research (CBER) supervises biologics. Finally, the Center for Drug Evaluation and Research (CDER) is responsible for drugs and drug products. In addition to reviewing the safety and efficacy of all prescription and over-the-counter drug products prior to marketing, CDER is responsible for monitoring drug safety after initial market approval and has the authority to withdraw from the market drugs posing significant health risks. CDER provides health care professionals and consumers with drug-related information and screens television, radio, and print ads for truthfulness and balance.

OVERVIEW OF THE DRUG APPROVAL PROCESS

As mentioned previously, drug discovery and development is a complex and expensive endeavor. The next several sections of this chapter discuss the various phases of the new drug development and approval process in the United States. While focused specifically on CDER and new drugs/drug products, similar requirements exist for biologics and medical devices. The development process is divided into two sections: (1) preclinical testing (lead compound selection and animal testing of new chemicals) and (2) clinical testing (administration of new chemicals to humans). A schematic of these steps is shown in Figure 48-1.

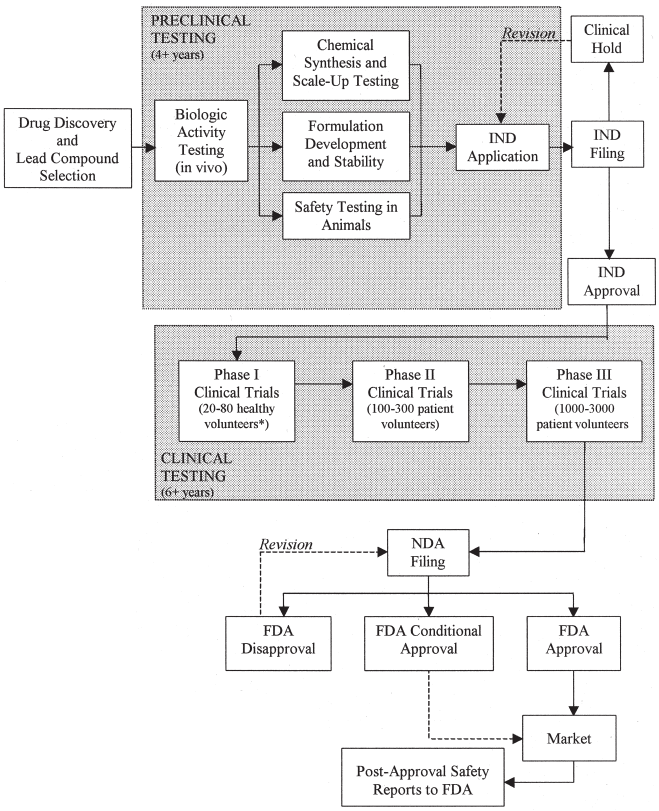

Figure 48-1. The new drug approval process in the United States. *For life-threatening illnesses such as cancer, patients enrolled in Phase I studies may suffer from the disease.

Drug Discovery and Lead Compound Selection

Pharmaceutical companies generally begin the discovery process by targeting a broad disease category (ie, cancer or cardiovascular disease) or a specific disease state (breast cancer or hypertension). A chemical with potential therapeutic benefit(s), known as a lead compound, must first be identified and researchers use various high-throughput assay techniques to rapidly screen large numbers of chemicals for biological activity.

Random screening, as the name implies, requires biological testing of a large variety of diverse compounds from existing chemical libraries. While less up-front financial investment is needed, thousands of compounds may be screened and tested before one agent with significant biochemical activity is identified. A more mechanism-based drug design is targeted synthesis, where researchers focus on one step in a disease process as the target for drug intervention. While an extensive knowledge of the disease state is required, this more directed approach increases the likelihood of successfully identifying a lead compound. In combinatorial chemistry, one compound is used as a base chemical and various functional groups are randomly added to enhance biological activity. This technique is a more expensive, more complex method of identifying potential lead agents. Another method to enhance biological activity is drug modeling, where computers are used to manipulate virtual structures and calculate protein binding capabilities. Although initial costs are significant, drug modeling techniques show a great deal of promise for future drug discovery as more research is conducted to identify biochemical pathways. Generally, combinations of these discovery techniques are used to identify lead compounds. Future discovery techniques will likely rely on the field of functional proteomics and identification of the biological roles of proteins coded by various genes.[8]

Preclinical Testing

A multidisciplinary team of researchers works to determine many of the lead compound's critical properties. This team may continue to work with the compound throughout the entire development process or the development responsibilities may be transferred to another group of scientists during the clinical testing phase. Preclinical testing includes:

- Discovery testing to ensure biological activity in vivo
- Chemical synthesis and scale-up to ensure adequate quantities of high purity can be made
- Formulation development and stability testing to characterize various chemical properties, develop the initial drug delivery system, and determine the stability of the compound (see Chapter 38, *Property-based Design and Preformulation*)
- Animal safety testing to ensure limited toxicities of the lead agent

At this stage of the development process, good laboratory practices (GLPs) are followed. These regulations, set forth in Title 21 of the Code of Federal Regulations (CFR) Section 58, provide standards for the design and conduct of preclinical studies. Qualifications of personnel are specified and requirements for standard operating procedures are established.

During discovery testing, the specifics of the compound's properties, such as the mechanism of action in animal models, compound specificity, duration of action, and structure-activity relationships, are determined. Adequate quantities of the new chemical compound must be produced at a high level of purity. Impurities present at concentrations greater than 0.1% must be characterized and tested for toxicity. The physicochemical properties of the active compound are determined, and the drug delivery system to be used in human testing begins to be developed during this preclinical testing phase. Animal testing provides initial data regarding the absorption, distribution, metabolism, and excretion (ADME) in a living system. Possible side effects and toxicities are noted. Toxicity studies of at least the same duration as the proposed human testing and a minimum of 2 weeks must be completed. Active and inactive metabolites must be characterized. Often times the most appropriate animal model to predict human response is not known, thus toxicity studies are conducted in at least two animal species, one rodent and one nonrodent, to obtain a comprehensive view of the potential toxicity. Early ADME or toxicity problems may be corrected by slight modifications in the new chemical entity.

Animals should be given the new drug product by the same route as intended for humans. Certain dosage forms, such as aerosol, nasal, or buccal delivery systems, may be difficult to administer to animals. In these circumstances, alternative drug delivery routes may be used, and the selected route of administration should ensure sufficient exposure to the new chemical entity. During animal safety testing, dosing studies are conducted, and the highest no-effect dose is determined. In addition to dose, plasma concentrations of the drug are followed, and noted toxicities are correlated to dose and/or blood concentration.

Generally, once discovery testing shows therapeutic promise, the chemical synthesis, formulation development, and animal safety testing occur concurrently (see Fig 48-1). While resources may be wasted on earlier failures, successful candidates will be ready for human testing earlier. The administration of drugs in humans at the earliest time possible ultimately saves valuable resources, as highly toxic compounds can be eliminated while lead agents and alternative compounds are developed.

Additional preclinical studies are conducted during clinical testing to support larger trials and eventually the marketing of the drug product. Formulation development continues throughout the development process and the data gained from both animal and human testing allow for optimization of the drug delivery system. It is imperative to identify and resolve formulation problems early in the development process, as unresolved problems will surely re-emerge later, costing the com-

pany both time and money as clinical testing is delayed. More chronic animal exposure experiments are generally conducted to support further clinical testing.

PRE-IND MEETINGS

Pre-IND meetings may be held prior to submission of an Investigational New Drug application (IND) and at the request of the sponsor during these early stages of product development to discuss testing plans and data requirements. These meetings are generally useful when a drug has been developed overseas, and a great deal of preclinical and clinical data is readily available. During pre-IND meetings, the sponsor and FDA should agree on the acceptable phase of the initial clinical investigation. Clinical data from other countries may eliminate the need for Phase I human safety testing. FDA guidance documents provide an overview of procedures for requesting formal meetings. These meetings are not intended to replace informal discussions with the FDA.

Investigational New Drug Application (IND)

An Investigational New Drug application (IND) must be filed with the FDA and approved prior to administering new drug products to humans. In 21 CFR Section 312, the guidelines for preapproval of all clinical testing are specified. The name and chemical description of the active, a list of active and inactive components, and the manufacturers of these components must be provided. The method of preparation and the dosage form to be administered must be specified. The IND includes all preclinical animal data and the names and locations of the investigators who will be performing the planned clinical trials. Data from clinical trials conducted in other countries should also be included if available. The FDA has 30 days from receipt of the IND to decide if the proposed clinical trial should proceed. The protocol(s) conducted under the IND must be approved by each facility's Institutional Review Board (IRB, described more fully in a subsequent section of this chapter).

Upon receipt, the IND is assigned to one of the various divisions of CDER and the application thoroughly reviewed. If the investigator is not contacted within 30 days, the trial may proceed. Reviewers at FDA may place a clinical hold on the clinical trials at any time. A clinical hold effectively prevents human testing under the IND, until FDA concerns have been adequately addressed. Reasons for placing an IND under a clinical hold include unreasonable or significant risk of illness or injury to trial subjects, insufficient information to assess patient risks, inadequate qualifications of the clinical investigators, or a misleading, erroneous, or incomplete Investigator's Brochure (a document that contains all relevant information about the drug). Revisions to clinical protocols, as well as new protocols or substudies are submitted to the FDA as amendments to the IND. In addition, progress reports regarding the trial must also be provided annually.

It should be noted that not all clinical trials require an IND. A sponsor proposing a trial with a commercially available, FDA-approved drug product is exempt from these IND requirements if the trial (1) is not intended to be submitted to the FDA to support labeling changes or a new indication; (2) is not intended to support a major change in advertising; and (3) does not involve a route of administration, dose, or patient population that significantly increases the risk of the drug. An IND is not required if the trial is exempt according to the above criteria regardless of whether a placebo (inert or inactive treatment) is employed as a control group. Independent investigators rather than pharmaceutical companies often conduct these types of clinical trials.

Clinical Investigations

Clinical investigations involve the administration of a drug to humans. This segment of the drug development process requires substantial financial and time commitments.[9] Figure 48-2 shows the considerable increase in development costs associated with the initiation of clinical trials. Human testing is divided into four phases, each phase having specific objectives. The following sections discuss the various phases of clinical testing.

PHASE I CLINICAL TRIALS

The first series of experiments performed in humans occurs during Phase I clinical testing. A small number of generally healthy volunteers (approximately 20-80 people) are exposed to the new drug product in closely monitored trials, primarily to assess the compound's safety. For the investigation of drugs to treat life-threatening diseases, such as cancer or Acquired Immune Deficiency Syndrome (AIDS), patients afflicted with the disease may be enrolled.[10] In Phase I trials, the starting dose is generally low, often 1/10 of the highest no-effect dose in the animal models. After the initial treatment is completed, additional subjects may be recruited and administered higher doses to determine the maximum dose tolerated without significant side effects. During this phase of testing, preliminary ADME data of the parent drug and all metabolites should be evaluated. Sufficient data regarding pharmacokinetic and pharmacological effects are also obtained to be used in designing future Phase II trials.

PHASE II CLINICAL TRIALS

Phase II clinical testing shifts the focus of the trials from safety to efficacy. In comparison to Phase I trials, a larger number of people (100-300 patients) are enrolled in the trial and the majority of these participants suffer from the target illness. Side effects from the new drug product are also investigated. These clinical trials are closely monitored and well-controlled (see Clinical Trial Planning and Design section). Failure during Phase II testing is common, as the human body is more complex than the test tube. Clinical protocols for Phase II trials must be sent to the FDA as amendments to the IND prior to beginning the trials.

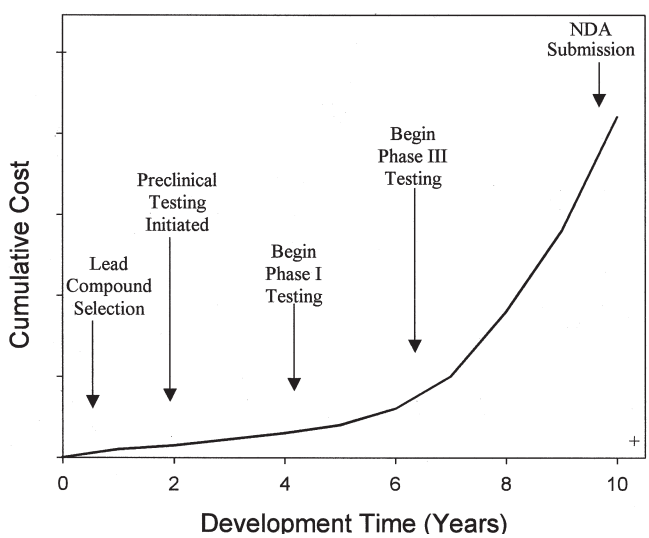

Figure 48-2. Relationship between the time devoted to new drug development and dollars invested. Adapted from Lakings DB. Nonclinical drug development: Pharmacology, drug metabolism, and toxicology. In: Guarino RA, ed. *New Drug Approval Process*. 2000, New York: Marcel Dekker, 2002; pp 17–54.

PHASE III CLINICAL TRIALS

At the end of Phase II testing, sponsors are encouraged to meet with the FDA. These meetings generally involve review of the acceptability of past trials, the design of future trials, and the general drug development plan. Scientists at the FDA carefully review preclinical and clinical data in evaluating proposed Phase III protocols. Specific areas of the proposed Phase III trials that are scrutinized include the inclusion/exclusion criteria, dosing regimens, methods and timing of data collection, duration of treatment and follow-up assessment, blinding of the drug products and plans for maintaining the blind, plans to assess compliance with protocol, identification of primary outcome variables, and methods to account for dropouts. Addressing these key areas of proposed Phase III protocols is expected to limit the bias of trial results. The overall goal of the meeting is a good-faith agreement between the sponsor and FDA regarding data required for submission of a New Drug Application (NDA).

Phase III clinical trials are the longest, most comprehensive trials regarding efficacy and safety of new compounds. Significantly larger numbers (1000-3000) of patients who are afflicted with the target illness are tested. Patients are often recruited, tested, and monitored by several major hospitals and clinics throughout the country. Phase III trials may also be conducted internationally. In addition to determining efficacy, these trials monitor adverse reactions. The new drug may be compared to existing therapeutic regimens (ie, comparator products) or to placebo. The final market formulation for the drug product should be optimized prior to the start of these Phase III trials. Compounds that successfully complete Phase III testing have a 95% chance of being approved by the FDA.[10]

Prior to the completion of Phase III testing and NDA submission, sponsors are encouraged to meet again with the appropriate review division of the FDA. These meetings help establish the appropriate format of the submission so that the review proceeds smoothly and determine if additional animal or human trials are necessary. The meeting should be held sufficiently in advance of the tentative NDA filing date to allow ample time to incorporate recommended changes or perform additional trials.

PHASE IV CLINICAL TESTING

Phase IV trials are post-approval clinical trials designed for one of several reasons. The FDA may mandate Phase IV testing in a specific patient population to further assess efficacy and side effects. Companies may also choose to conduct additional clinical tests to more fully understand how their product compares to other commercially available therapeutic regimens. Since duration of exposure is often limited during Phase III testing, Phase IV trials may be required to assess long-term safety of the drug.

The New Drug Application

Once the Phase III trials have been completed, all preclinical and clinical data are compiled and submitted to the FDA for review. The NDA process is the last hurdle prior to approval and marketing. A NDA document is typically hundreds of thousands of pages containing highly detailed information. The FDA also reviews the proposed product labeling and package insert. Regulation guidelines including the information required for an NDA are provided in 21 CFR 314 Subpart B. Primary items include (1) safety and efficacy of the drug treatment(s); (2) components of drug product(s); (3) description of methods and controls used in manufacturing the active ingredient and the drug delivery system and its packaging; and (4) proposed labeling. According to CDER, the time for a NDA review has been reduced from a median of 22 months in 1992 to approximately 15 months in 2000 (www.fda.gov/cder/reports/reviewtimes/default.htm). The faster review times have been attributed to the Prescription Drug User Fee Act (PDUFA) of 1992 (www.fda.gov/cder/pdufa/default.htm). In 2002, 78 NDAs were approved by the FDA, including 17 new chemical entities.[11]

When a NDA is submitted, relevant sections of the document are distributed to the appropriate reviewers and evaluated first for completeness. If the document is sufficiently complete, the NDA is accepted for review and assigned a priority status. NDAs for new chemical entities are classified as either 'P' for priority review or 'S' for standard review. A 'P' rating is given to new drug products with improved therapeutic effects, safety, and/or side effects in comparison to currently marketed drugs. NDAs assigned a 'P' rating are expected to be reviewed in a more timely manner than those assigned an 'S' rating. If the NDA is deemed too incomplete to review, it is not filed. The decision to accept the NDA is made within 60 days of the date of submission.

Once the NDA is accepted, detailed evaluation continues and the FDA has 180 days from submission to complete the review. Each reviewer submits written comments of his assigned section and makes a recommendation. The NDA may also be presented to an Advisory Committee for comment. All documents are then compiled and ultimately submitted to the Director of the Office of Drug Evaluation. The FDA may approve the product for market, approve with specific conditions attached (Conditional Approval), or disapprove the drug product. Primary reasons for disapproval include lack of demonstrated safety and efficacy, issues with the manufacturing/processing procedures, or false/misleading labeling. If not approved, a letter is sent to the sponsor detailing deficiencies in the application. If the NDA is approved, an approval letter along with a draft of the product labeling is sent to the sponsor. The label is generally a combination of the draft submitted by the sponsor and revisions provided by the reviewing section of the FDA. Standardized labeling requirements are provided in 21 CFR Section 201.57.

Prior to NDA approval, the FDA conducts an inspection of the sponsor's facilities to ensure compliance with current Good Manufacturing Practices (cGMPs) as set forth in 21 CRF Parts 210 and 211. These cGMPs are minimal industry standards and procedures established to ensure consistent quality of manufactured drug products. Pre-approval inspections are conducted within 45 days of the NDA acceptance. If deficiencies are noted during an inspection, a letter (FDA Form 483) is sent to the sponsor delineating the problems. Once the deficiencies are resolved, the company must provide written certification and the FDA will clear the application within 45 days if the corrections are adequate. As this step is often critical in the approval process, companies often hold mock pre-approval audits.

Abbreviated New Drug Application (ANDA)

In addition to approving new drug products for the United States, the FDA is charged with the approval of generic drug products (21 CFR Part 314). This work is accomplished through CDER's Office of Generic Drugs. A generic drug product must be bioequivalent in comparison to an approved proprietary drug product. The review process for generic drugs is specifically focused on bioequivalence testing rather than safety and efficacy. Thus, conventional clinical testing is not required. To be considered bioequivalent, both the rate and extent of drug absorption must be within established parameters in comparison to the reference drug. In vivo (within a biological system) bioequivalence testing is required for most tablet and capsule dosage forms. Applicants may request a waiver from performing in vivo bioequivalence studies for certain drug products where bioavailability may be established by submitting (1) a formulation comparison for products whose bioavailability is evident (eg, oral solutions, injectables) or (2) comparative dissolution. The FDA provides guidance on establishing bioequiv-

alency and Chapter 53 (*Bioavailability and Bioequivalency Testing*) discusses bioequivalency in greater detail. If any portion of the application is not acceptable, a letter of deficiency is issued which details the insufficiencies and requests additional information and data to resolve these concerns. A tentative approval letter delaying the marketing of the generic product may be issued if approval of the generic occurs prior to the expiration date of patents or exclusivities of the reference drug product.

Rapid Access to New Drug Products

As a result of the demand for more rapid access to new drug products, the FDA has written several regulations and policies specifically designed for drugs intended to treat severely debilitating or life-threatening illnesses. Subpart E (21 CFR 312.80-.88) regulations expedite the development and approval process. Subpart H (21 CFR 314.500-.550) allows the FDA to approve a new drug based on a surrogate endpoint (laboratory finding or physical sign that may not be a direct measure of patient response, yet is considered likely to predict therapeutic benefit). Treatment INDs (21 CFR 312.34) are intended to make drugs that are relatively far along in the development process available to seriously ill patients and are typically made available during Phase III clinical trials. The parallel track is an FDA policy focused on patients with clinically significant illnesses related to human immunodeficiency virus (HIV) diseases who cannot be enrolled in ongoing treatments trials (ie, do not meet inclusion criteria, are too severely ill, enrollment is completed, etc). These patients may receive treatment in an open-label design before safety and efficacy have been established.

ORPHAN DRUG APPROVAL

Orphan drugs are defined as drugs used to treat rare diseases or conditions that affect less than 200,000 people in the United States. Orphan drugs go through the same FDA review process previously described. However, the review is generally expedited through FD&C Act Subpart E, as the majority of orphan drugs are used in the treatment of serious or life-threatening disease. The process by which a company can file an application for orphan drug designation is described in 21 CFR Section 316.20. Due to the substantial drug development costs, this class of drugs provides limited opportunities for companies to recoup their investments. The United States federal government through the Orphan Drug Act of 1983 established tax incentives, reduced user fees, and exclusivity agreements to encourage research in the orphan diseases.[12] Grants are also available through the FDA to support clinical research and annual requests for applications may be found in the Federal Register. From 1983 to 1995, 121 drugs have been brought to market in the US under the Act.[12]

Over-The-Counter Drug Approval

The approval process for over-the-counter (OTC) drugs is considerably different from prescription medications and the review is not held to the same standards as a NDA. The first phase of the approval process involves an advisory panel consisting of a multidisciplinary group of scientists that review data provided by manufacturers and other previously published research. The findings are submitted to the FDA and these reports are subsequently summarized in the Federal Register. Interested parties are given an opportunity to comment. Next, the FDA reviews all statements and publishes a tentative final monograph. The FDA also publishes the nature of comments received and provides further opportunity for feedback. Then, the final monograph is published in the Federal Register and goes into effect one year after publication. The monographs establish conditions under which OTC drugs are generally recognized as safe and effective and are not misbranded. By following a monograph, a company can then market an OTC drug without additional FDA approval. For any unsubstantiated claims that a company wishes to make (ie, claims not approved in the monograph), data must be presented to the FDA to justify revision of the monograph or the sponsor may submit a NDA.

POST-APPROVAL ACTIVITIES

Safety Monitoring

After a NDA has been granted and marketing of the drug product is initiated, drug safety is still monitored. Sponsors of the NDA must submit reports of adverse events periodically. For newly approved drugs, these reports are filed quarterly for the first three years then annually. For adverse events that are considered serious and unexpected (ie, fatal or life-threatening, permanently disabling, or requiring or prolonging hospitalization), the sponsor must provide a written report to the FDA within 15 days of receipt of the information. The FDA's MedWatch program encourages health-care providers to directly report serious adverse reactions to drugs to the FDA (www.fda.gov/medwatch). The program also provides alerts to practitioners regarding actions and recommendations by the FDA. Serious adverse events may require minor labeling changes or the addition of warning or precaution statements. If serious safety concerns arise, FDA may withdraw approval of the NDA. Often times an FDA Advisory Committee reviews the NDA in light of the new data prior to an official NDA withdrawal. In some instances, manufacturers have withdrawn drug products prior to FDA action.[13] Periodic, random inspections of drug production facilities are conducted by FDA to ensure conformance with regulations and current Good Manufacturing Practices (see 21 CFR Sections 210 and 211).

Changes to an Approved Product

Any change made to an FDA-approved drug product, including component or composition, chemical synthesis, analytical methods, manufacturing site, manufacturing process, batch size, or labeling, must be submitted to the FDA. Some of the so-called scale-up and post approval changes (SUPAC) require FDA approval prior to the implementation of the change. Depending on the type of change made and the impact the change may have on the quality of the drug product, notification to the FDA may be done through annual reports or supplemental new drug applications (SNDA).

CLINICAL TRIAL PLANNING AND DESIGN

Once pre-clinical testing has been completed, the company will determine whether to pursue further development of the drug, often based on the attractiveness and competitiveness of the pharmaceutical.[14] First, the pharmacological profile must be such that the product will be equal to or better than existing competitors in regards to therapeutic effect. Second, the drug should address an unmet medical need or improve therapy in a population of individuals. The incidence of morbidity and mortality associated with the illness impacts medical need. Third, the market potential must be sufficient to sustain profitability. The number of patients who might change from other therapies to the new therapy is considered. Fourth, risk factors for drug development are assessed. Potential risk is impacted by the pharmacological profile, specifically the efficacy and toxicity of the drug. Fifth, the potential expenses associated with activities required to continue development of the drug are considered. Sixth, the success in the marketplace

is estimated. Success is determined by the number of competitors, whether the drug is the first in its class, and the potential for patients to change from other competing products. Once the pharmaceutical company determines that the product has good potential for success, clinical trials are planned and conducted to move the product forward. The remaining sections of this chapter discuss the clinical trial process for pharmaceutical development and subsequent therapeutic research of marketed products.

Selecting Trial Objectives

The trial objectives vary depending upon the phase of the trial. Objectives for Phase I trials are limited to determining toxicity at a range of dosages. Phase I trials of treatments for terminal illnesses such as cancer chemotherapy or human immunosuppressive virus may also involve efficacy assessment. Objectives of Phase II and III trials are usually based upon clinical efficacy of the product in an increasingly large sample of patients, respectively. Phase IV trials generally assess efficacy and side effects in specific patient populations.

A statement of trial objectives should include, at minimum, the approach of the trial (eg, to compare, assess, evaluate), the specific disease, the types of patients, drug therapy(ies) and dosages being studied, the purpose (eg, safety, efficacy, pharmacokinetic properties) and the clinical endpoints to be measured (eg, biologic measure, rate of cure, cost effectiveness).[15] Clinical trial objectives drive the entire project, from determination of sample size, to recruitment, to measurement of effects of the drug. They also determine feasibility of the trial, because trial duration and costs are directly impacted by the objective under consideration. Objectives involving ultimate outcomes such as mortality or hospitalizations can require durations of several years as well as large sample sizes and multiple trial sites. Trial objectives limited to pharmacokinetic or clinical measurements may be conducted over a shorter time period, at a single site, and with a small number of patients. Generally, broader objectives have more generalizability and, thus, greater clinical implications.

Often several trial objectives are of interest. When this is the case, the clinical question that is most crucial becomes the primary objective and the others become secondary objectives. Selecting the primary objective is important because determination of sample size and data analyses techniques is based upon it. Although secondary objectives should be assessed in regards to sample size, it is understood that sample size may be inadequate to address all of them. Data collection procedures and statistical analyses are established from the trial objectives during planning.

Occasionally results indicate no significant difference in the primary objective, yet the secondary objectives are significant. An example is the DIG trial, where no significant differences in the primary objective of all-cause mortality were found between the digoxin versus placebo treatments, but there were significant differences in rates of and days of hospitalization, and quality of life.[16] Thus, secondary objectives can be very important and should be well-described prior to the conduct of the trial.

Trial Designs

Various designs are used in clinical trials, and the most suitable may be related to the testing phase of the research trial. During Phase I trials, all patients receive the drug, thus an unblinded, open label trial is suitable. In Phase II through III trials, clinical efficacy trial objectives usually dictate that the drug is compared to placebo (inactive treatment) or an alternative therapy. Usually patients receive one of the treatments during the entire course of the trial. This is referred to as a parallel design. Depending upon the objectives of the trial, the treatments may vary by drug, combinations of drug therapy, or dosage levels. In some parallel trials the same patients may receive various dosages of a drug therapy over time. A factorial design is a type of parallel design used to compare different types and combinations of drug therapy. It allows comparisons between single drug therapies and the combination of the two drugs combined. Factorial designs answer several clinical questions with one trial but are complex and must include sufficient sample sizes to detect differences between all treatment options. An example is the Veterans Affairs Cooperative Studies Program trial of terazosin, an alpha blocker, and finasteride, an anti-androgen, for benign prostatic hypertrophy.[17] The research question included comparisons between each drug and each drug versus placebo plus the combination of both drugs versus the other three therapies.

Another type of trial is the crossover design. Crossover designs allow for patients to receive more than one drug treatment or dosage level during the course of the trial. The assumption with a crossover design is that the drug therapy does not have a carry-over effect between the different treatment periods. Usually there is a "washout" period between drug treatment periods, where patients receive a placebo or no medication. The length of time for the "washout" period is dependent upon the duration of action or rate of elimination of the trial drug(s). A key issue to be addressed in crossover designs is whether the washout period is sufficient to eliminate potential carryover effects of the drug(s). If a drug may have long-term effects after it is discontinued, the crossover design is inappropriate. In crossover designs, the type or dosage of therapy may be randomly assigned to allow for detection of crossover effects (Table 48-1). During the washout period, trial data and clinical measures are collected to assess impact of the previous treatments. These measures are considered baseline data for subsequent treatments. Crossover designs are efficient in regards to numbers of patients required to collect a great deal of scientific data. Repeated measures statistical analyses are used to account for the potential impact of collecting data in the same patients over time and different treatments.

In postmarketing surveillance (Phase IV) trials, nonexperimental (observational) designs are used. These include epidemiologic designs such as case-control or cohort studies in which drug therapy is not assigned by the researcher.[18]

Controlling for Bias

A critical component of a clinical trial is control of the intervention being studied. Control occurs primarily at three levels: assignment of patients to the interventions, application of the intervention, and measurement of the trial outcomes.

Table 48-1. Patient Treatment Regimens in a Crossover Design with Three Treatments and Washout Periods

PATIENT	FIRST TREATMENT	WASHOUT PERIOD	SECOND TREATMENT	WASHOUT PERIOD	THIRD TREATMENT
1	A	Placebo or no treatment	B	Placebo or no treatment	C
2	A		C		B
3	B		C		A
4	B		A		C
5	C		B		A
6	C		A		B

ASSIGNMENT OF INTERVENTION

Ability to control assignment is important because cause and effect relationships between drug therapy and clinical outcomes can then be established. Unless the assignment is controlled, confounding variables may affect the outcomes measured in the trial. Control of assignment of interventions is usually accomplished through randomization, whereby patients are assigned to treatment groups by chance. A randomization scheme generated by a computer program or from random numbers lists is often used to assure that assignment to treatment intervention is unbiased.

In most trials, patients have an equal chance of receiving each treatment. However, some trials are designed to have imbalance in treatment assignment. For example, if previous clinical research indicates one treatment is likely to be superior, more patients may be randomly assigned to that treatment (for example 2:1 or 3:1). Specific statistical analysis techniques are used to adjust for the differences in sample size.

Stratified randomization is used to adjust for potential differences in response between specific patient groups or trial sites. The characteristic of concern (eg, type or severity of disease, gender, age, race, or study site) is determined, and then patients are randomized within their stratification group. This assures that equal numbers of patients with these characteristics are assigned to each trial treatment. For example, after stratified randomization, equal proportions of patients in each treatment group would be male or over age 65, etc.

Block randomization is also used in clinical trials. The sample size for a specific number of patients is established so that, as randomization occurs, at regular intervals equal numbers of patients are assigned to each treatment group. This procedure avoids an imbalance in enrollment between the treatment groups as the trial progresses. Often, the sizes of the blocks of trial patients are randomly varied (eg, 8, 4, 16, 12), to help prevent site personnel from guessing patient treatment assignment.

APPLICATION OF INTERVENTIONS

The protocol is used to control the application of the intervention during a clinical trial. Unless the interventions are provided similarly to all patients between and within each treatment group, variations in outcomes may be due to differences in how the intervention was administered. Protocols are designed to address most potential contingencies that occur during the trial, including requirements for dosage adjustments associated with varying patient conditions. Protocol adherence is monitored throughout the trial. Deviations from the protocol are documented and discussed by individuals administering the trial. Clinical site personnel may need to be retrained regarding the protocol or, if deviations are common, the protocol may need revision. In multi-center trials, repeated deviations by a particular site may result in disciplinary action such as removal from participation in the trial.

MEASUREMENT OF TRIAL OUTCOMES

Control of the measurement of trial outcomes is also critical to decrease bias. This is accomplished in several manners. If a special type of measurement tool or instrument is used to measure outcomes, training of all trial personnel regarding use of the instrument is performed prior to trial start-up. Training usually includes an assessment tool to determine whether personnel are using the instrument(s) uniformly. To eliminate the impact of different laboratory procedures, a centralized laboratory for analysis of specimens is often used. Another method is to have a centralized group review and analyze assessments conducted at the trial site(s). When the determination of a trial outcome (endpoint) involves medical judgment, a centralized endpoints committee is used. The endpoints committee reviews the data and determines whether the outcome assessment has been correctly identified and attributed to treatment. The endpoints committee is composed of specialists in the medical subject of the research.

Selecting the Trial Population

Patients are selected for clinical trials using inclusion and exclusion criteria. For Phase I trials, healthy volunteers are generally enrolled (with the exception of drug trials for the treatment of life-threatening diseases). In contrast, patients with the disease are enrolled in Phase II and III trials, and the goal is to select patients to participate in the trial who will likely benefit from the treatment. Inclusion criteria are also used to identify patient groups specified by the trial objectives. Exclusion criteria are used to eliminate patients who might be harmed by treatment, who are unlikely to survive the entire trial period due to nonrelated health problems, or those who should not receive the drug treatment due to allergy, concomitant illness, or a contraindication.

Sample Size

Determination of sample size is a critical aspect of clinical trial design. Sample size is based upon four factors: the expected difference in clinical outcomes between the treatments, the level of error in measurement of clinical outcomes, the alpha level, and the power desired for the trial. Table 48-2 depicts the interrelationships between these four concepts and sample size in clinical trials.

The size of the difference between treatments is predicted based upon the difference that is considered "clinically important" and results of previous research. The question to consider is: How great a difference in the outcome is needed for a clinician to consider changing from standard (or placebo) therapy to the new treatment? Medical specialists are consulted to answer this question. If the intervention is unlikely to achieve this difference in outcomes, then the trial is infeasible. If the difference selected is so small that it is unlikely to change clinical practice, the trial will be inefficient or superfluous.

The "clinically important" difference is adjusted by the level of inherent error in measurement of the outcome. For clinical outcomes that are parametric measures, which have a definite 0 and are mathematically uniform across the scale of measurements, this is expressed as standard deviation, or the inter-related terms, variance or standard error. The "clinically important" difference in outcomes is divided by the amount of inherent error in measurement of outcomes to determine effect size of the treatment expected.

The statistical alpha level is also incorporated into sample size analysis. Alpha is equivalent to Type I error which is defined as the chance of accepting the conclusion that treatments are different when the two treatments are equal. Generally, an alpha level of 0.05 is accepted for medical research. This is equivalent to 5 chances in 100 of making the wrong conclusion that there is a difference between the treatments.

Table 48-2. Interrelationships Between Factors Used to Determine Sample Size in Clinical Trials

	IMPACT ON SAMPLE SIZE	
FACTOR IN CALCULATING SAMPLE SIZE	INCREASE IN FACTOR	DECREASE IN FACTOR
Clinically-important difference between treatments	↓	↑
Inherent error in measurement of outcome	↑	↓
Statistical alpha level	↓	↑
Desired power level	↑	↓

Beta level is known as the chance of a Type II error. Type II error is the chance of concluding that no difference exists between the treatments, when one truly exists. In medical research, beta levels of 0.1 or 0.2 are generally acceptable. This can be interpreted as 10 to 20 chances in 100 that no difference is found by the trial when one truly exists. Power of the trial is 1.00 − beta. The concept of power can be interpreted as: the likelihood of finding a difference when one truly exists. Thus, power levels between 80% and 90% are usually considered sufficient in medical research.

Sample size estimation requires consideration of several scientific aspects of the trial. Since all four factors must be balanced in this calculation, there are usually several potential alternative sample size scenarios developed before a decision regarding sample size is reached. Planning the appropriate sample size is critical to the success of the trial. An inadequate sample size may cause the trial to have insufficient power to detect a significant difference. An excessive sample size results in unnecessary costs and additional risks for patients exposed to ineffective treatment.

Feasibility of Conducting the Trial

Feasibility is dependent upon the trial purpose, the intended application of trial results, and access to trial sites and patients. Generally, the question of feasibility comes down to overall trial cost and timeline, which are intertwined with the primary objective and the sample size required to complete the trial. If the trial purpose is extensive and the results are intended to be generalizable across a broad population, the sample size will be large. Prevention of disease events may require long observation periods, significantly lengthening trial duration and, thus, costs. If the trial population is transient, it may be difficult to perform sufficient patient follow-up over long time periods.

Another aspect of trial purpose that impacts feasibility is the type of outcome. Outcomes of mortality often require lengthy observation periods, depending upon the baseline mortality rate of the trial population. Furthermore, outcomes that are intended to be generalizable across a wide range of patients need to have broad inclusion criteria and few exclusion criteria, to assure that all relevant types of patients are represented in the trial. Lastly, the trial outcome measurements directly affect the type and quantity of data required, as well as additional testing requirements specific for the trial.

Access to trial patients impacts feasibility of conducting the clinical trial. Prior to trial initiation, the number of available patients in a health system is estimated, along with the percentage likely to meet inclusion criteria and enroll. These values are used to determine the number of patients required for recruitment. The rate of estimated enrollment is frequently much greater that actual enrollment.[19] Increasing the number of trial sites can enhance access, but with substantial cost. Many pharmaceutical companies outsource this portion of the drug development process to contract research organizations (CROs). CROs can help identify and provide access to patients. Proper management of outsourcing projects can provide a cost-efficient method for new drug development, saving a pharmaceutical company time, space, and manpower.

Drug Product Design and Blinding

Blinding involves the disguising of drug therapy to the patient and health professionals to minimize the introduction of bias into the trial. It is often an essential characteristic of a controlled trial. Blinding is categorized as single, double, or triple. Single blinding indicates that only the patient is unaware of which treatment group they are assigned. Double blinding indicates that both the patient and the health professional evaluating the effect and collecting data are unaware of trial drug assignment. Triple blinding indicates additional blinding of the biostatistician and Data Safety and Monitoring Board, who assess the comparative safety and efficacy of the treatments during the trial.

Blinding is achieved by developing dosage forms of active and placebo (inert ingredients only) that are indistinguishable in regards to size, shape, color, odor, weight, and other characteristics. Blinding generally requires some type of manipulation of the dosage form, and common techniques and considerations for blinding drug products are displayed in Table 48-3.[20] Ideally, the manufacturer produces a matching placebo (or active comparator) for each drug using a similar formulation, but without the active ingredient. However, it may not be economical or timely for the pharmaceutical company to do so. In these cases the researcher may need to develop matching drug products. Irrespective of the technique used, blinding must not significantly alter the drug release characteristics, the physical stability of the dosage form, or the chemical stability of the active component.[21] In vitro tests for dissolution and potency may be needed to ensure the blinding technique does not affect the performance of the dosage form. In addition, labeling is used to assure that different drugs or dosages used in the trial are indistinguishable.

When factorial designs are used, blinding of each drug product is required. Although it is sometimes possible to make matching dosage forms with each study drug, it is more common to use a "double dummy" approach. This method involves the preparation of a separate matching placebo for each drug product used in the trial. For example, a patient may take two placebo products, an active and placebo combination, or two active drug products. A disadvantage of the double dummy method is that, for drugs used in multiple daily doses, patients must take a large number of dosage forms each day, which can affect patient adherence with the therapeutic regimen.

Trial Drug Packaging

Packaging trial drugs involves creativity as well as consideration of the scientific aspects of the trial. Drugs are packaged to (1) meet trial design requirements, (2) maintain the blinding, (3) minimize the chances for dosing errors, (4) enhance patient adherence to the therapeutic regimen, and (5) maintain drug potency/stability. Package sizes (eg, count per bottle and number of bottles per kit) are designed to meet trial requirements of dosage adjustments, clinical visit periods, visit windows, and dosing frequency. For example, in the DIG trial[16] patients were dosed from 0.125 mg to 0.5 mg (1 to 4 tablets) per day, depending upon clinical response. Patient clinic visits were scheduled for every 4 months ± 14 days. Patients taking 1 or 2 tablets daily were dispensed 1 bottle of 270 dosage units (0.125 mg digoxin or matching placebo tablets) whereas 2 bottles were dispensed to patients taking 3 or 4 tablets per day. Therefore, the package size of 270 tablets was sufficient to meet the requirements of all dosage levels used in the trial for the maximum 134-day visit window.

Clinical trial drug packaging helps to maintain the blinding of the drug through assuring that package style and labeling are exactly equivalent between the different drugs and their matching placebos. Each package is labeled with unique bottle numbers or patient therapy numbers to assure that the therapy matches the treatment assignment. A database is maintained which provides the correspondence between the bottle or therapy number and treatment assignment. Bottle or therapy number assignments can be provided to clinical trial personnel through pre-determined lists or through real-time methods such as telephone assignment systems or web-based programs.

Complicated dosage regimens must occasionally be accommodated in trial drug packaging designs. For example, a patient may receive induction (ramp-up) dosing, taper dosing, or individualized dosing with multiple dosage adjustments during a trial. For oral dosage forms, blister cards can accommodate

Table 48-3. Techniques and Considerations for Blinding of Drug Products

TYPE OF ORIGINAL DOSAGE FORM	TECHNIQUE	CONSIDERATIONS
Tablet	Removal of markings	• Time consuming and manually intensive • Still must match size/shape/color of tablet • Process may alter release properties of a film coating
	Over-encapsulation	• Time consuming and manually intensive • Patients may open capsule and discover original dosage form
	Grinding and re-tableting	• Properties of new dosage form may be different from original form, affecting patient response • Complexity in developing new formulation
	Grinding and encapsulating	• Properties of new dosage form may be different from original, potentially affecting patient response. • Assuring blend uniformity of grinded dosage form while encapsulating • Manually intensive, unless automated encapsulating equipment is available
	Tablet overcoating	• Tablets are developed to match original dosage form • Preserves original dosage form • Pharmaceutical testing (ie,. dissolution) can help verify similarity to original dosage • Cannot be used for embossed tablets
Capsules	Removal of markings	• Time consuming and manually intensive • Still must match size/shape/color of capsule
	Over-encapsulating	• Same as above tablets
	Grinding and re-encapsulating	• Capsule shells from original dosage form may be visible in manufactured product
	Removing ingredients from capsule shells and encapsulating	• Manually intensive • Time consuming • Most capsules are difficult to open
Oral solutions	Matching solution without active ingredient	• Taste and odor may be unique to active ingredient • Discoloration of active ingredient over time may occur and cause unblinding
Injectables	Matching solution without active ingredient	• May be difficult to obtain in same packaging and labeling • Differences in odor or color
	Blinding just prior to administration	• Unblinded pharmacy personnel prepare injectable dosage form • Additional opportunity for communication of actual treatment to trial personnel
Topical, including skin patches	Matching product without active ingredient	• Difficult to match packaging, unless prepared by manufacturer • Odor, texture, or color may differ between products

Adapted from Carney CF, Killeen MJ, Galloway-Ludwig S. *Pharm Eng* 1995; 15(3):42.

these alternatives, while helping to minimize dosing errors. For example in a trial comparing clozapine versus haloperidol, blister card dosing allowed for combinations of active and placebo capsules to be included in each daily dosing regimen.[16,23] Since patients received dosages based upon symptoms of schizophrenia, dosages could range from 100 to 1200 mg per day for clozapine or from 5 to 30 mg for haloperidol. Patients received from 4 to 9 matching capsules daily with combinations of active and placebo capsules of 3 strengths of clozapine (12.5 mg, 25 mg, or 100 mg) and one strength of haloperidol (5 mg) or placebo. Patients randomized to clozapine or haloperidol received matching placebo capsules of the other drug. The use of combinations of active and placebo capsules allowed for blinded dosing adjustments to be made as well as induction and taper dosing. Through a computerized assignment system, specific cards were assigned according to the clinical criteria established in the protocol. Once the card was assigned, dosage errors were minimized because all patients took the same number of capsules daily regardless of drug treatment.

Blister card dosage packages can also help improve adherence with orally administered drug, because dosage times can be specified on the cards. In addition, the cards provide direct and timely feedback to patients and clinical trial personnel regarding adherence. Pharmaceutical potency and stability are further considerations for clinical trial drug packaging. Any drug product not stored in the original manufacturers' packages should be subjected to periodic, scheduled testing (potency, dissolution) to verify stability during the clinical trial.

Regulations Governing the Conduct of Clinical Trials

Prior to initiation of any trial among human subjects, approval must be obtained from the investigator's local institutional review board (IRB). Composed of experts and laymen with varying backgrounds, IRB committees critically review clinical protocols to ensure patient safety and institutional, regulatory, and professional acceptability. IRBs also assess the trial protocol regarding scientific validity and whether the study involves unwarranted risks to the patients. The IRB also will determine if the protocol includes appropriate patient populations and whether inducements to participate in the trial are reasonable and non-coercive. Approval signals that the IRB has determined that the trial is appropriate and does not involve undue risks to the participant. IRB approval must be renewed annually for the trial to continue.

A critical aspect of clinical trial conduct is informed consent from participants. Participants must be informed of all aspects of the trial including the rationale and previous research, potential risks and benefits, treatment alternatives, the likelihood of being randomized to a particular treatment, discomforts associated with the trial, that they may voluntarily dis-enroll at any time, and their rights for future treatment should they be affected adversely by the trial. Informed consent documents must be at a reading level understandable by patients. IRB committees review and approve these documents. In addition to written informed consent, the trial must be dis-

cussed verbally with the patient. Each page must be initialed and dated by the patient and clinical personnel, as well as signatures on the final page of the document. A copy of this legal document is given to the patient as well maintained in patient records throughout the trial.

In April 2003, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) was implemented. This act provides that patients be informed of their rights to maintain the privacy of their health information. Data collection for clinical trials is impacted by HIPAA in that patients must be informed of their rights and provided written consent to researchers to access their medical records. Researchers must verify that they will not allow data collected during the trial to be distributed with patient-identifiable information. HIPPA requirements can be addressed within the informed consent process. More information is available at www.cms.hhs.gov/hipaa.

GOOD CLINICAL PRACTICE MONITORING

FDA regulations governing the conduct of clinical trials, referred to as Good Clinical Practices (GCP), are specified in 21 CFR Sections 50, 56, 312, and 314. In addition, the International Conference on Harmonization has established guidelines to assure patient safety during clinical trials at an international level (www.ich.org). GCP training is necessary for all personnel who are involved in the conduct of a clinical trial.

In addition to addressing patient safety, GCP regulations also help protect against fraud and falsification of trial data. There are significant incentives to health care professionals to assure that patients are enrolled and complete all follow-up visits and that positive trial results are achieved. These incentives include direct financial gain because some trial sponsors reimburse based upon per capita enrollment and/or per follow-up visit. In addition, future funding may be discontinued if results are negative. Sometimes clinical researchers may have financial investments in the company sponsoring the trial. There are also academic pressures to achieve positive results, as trials with positive results tend to more likely be published in prestigious journals. Failure to attempt to publish negative results has been considered a form of scientific misconduct.[24] Fraud and falsification of data have been identified in published literature.[25,26]

The GCP monitoring of clinical trials involves outside reviewers who monitor trial conduct and data collection. Reviewers are specially trained to match trial data with source documentation (data that is not collected as part of the trial) to identify fraud and falsification of data. GCP monitoring is required for any trial that will be used commercially to gain FDA approval or change the labeling or advertising of a drug product. FDA inspections of study sites are also conducted after completion of the trial to verify the appropriate conduct of the trial and the veracity of its results. The FDA requires that all trial records be maintained and accessible at the trial sites for a minimum of 2 years after marketing or change in labeling of a drug product. If marketing or change in labeling is not pursued, records must be maintained for 2 years after completion of the study and FDA notification.

Monitoring and Reporting Adverse Events during Clinical Trials

Safety data are important outcomes of clinical trials. Due to randomization, blinding, and placebo control, trials can provide unbiased reports of prevalence and incidence rates of adverse events. FDA regulations specify how adverse events should be reported. Serious adverse events (SAEs) are defined as those that result in death, are life threatening, cause hospitalization or prolong hospitalization, cause cancer or congenital abnormalities, or require extensive treatment to prevent hospitalization. Unexpected adverse events are defined as events that are not previously identified as associated with the drug by nature of the event, its severity, or its frequency. Unexpected SAEs must be reported to the FDA within 7 calendar days of disclosure to the trial sponsor. They also must be reported to site investigators who are required to report them to their local IRB. SAEs are summarized in the IND annual report that is submitted to the FDA. Furthermore, SAEs resulting in patient's termination from the trial are summarized in the IND annual report. All clinical and subjective information relevant to the event are reported in the SAE reports. For ongoing SAEs, follow-up reports are completed.

Other adverse events (AEs) are also collected regularly during clinical trials. Although these are less severe, they provide important information regarding the impact of drug therapy. AEs are usually coded to a common glossary, so that, although clinicians may use different descriptors for similar events, the events can be consolidated. The FDA has adopted the Medical Dictionary for Drug Regulatory Affairs (MedDRA) as the standard coding system for AE reports. AEs can be categorized by type of event, severity, relatedness to study treatment, intervention used to treat the event, and outcome. Comparisons of incidence rates (number of events per person-years) between drug treatment groups are specified in clinical trial publications. AE data from a minimal number of patients are required for NDAs. However, the limited number of patients exposed at the approval stage, usually about 3000 to 5000, is insufficient for determination of rare adverse events.[27] Thus, postmarketing studies of adverse events are used to identify rare events. The reporting of unusual AEs to the FDA during clinical trials help provide additional data on rare events.

For trials over 1 year in duration, monitoring of the results of the trial is conducted periodically. An impartial group, such as a Data Safety and Monitoring Board (DSMB), provides this oversight. Monitoring usually includes both clinical efficacy and adverse events. Interim reports are usually provided to the DSMB group in a blinded format so that although the treatment groups are compared, the DSMB cannot determine which group is better or worse in terms of efficacy or adverse events. The DSMB has the power to recommend discontinuance of the trial and will do so if there is clear evidence that it may be detrimental to patients assigned to one of the treatment groups if the trial is continued. This may be due to strong evidence of efficacy or safety differences between the groups. Interim statistical analyses that are provided in DSMB reports are preplanned and included in the overall plan for statistical testing.[28]

Overview of Statistical Analysis of Clinical Trial Data

It is not possible to provide comprehensive descriptions of statistical methodologies in this chapter; the reader is referred to statistical textbooks for further information.[29,30] However, certain general statistical issues will be discussed in brief.

Good clinical research will always be conducted using an intention to treat analysis (ITA).[31] This means that even if the patient has stopped taking the medication, did not complete the assigned treatment, or has been switched to an active alternative therapy, the data from the patient is included in the original treatment group to which the patient was randomized. The impact of ITA is to lessen the likelihood of finding a difference between the treatments. However, the ITA is more analogous to what happens outside of the clinical trial situation. Patients typically do not fully comply with therapy or may change therapies. Thus ITA is a key statistical feature of clinical trials.

Adjustment for multiple comparisons is another statistical consideration of clinical trials. The adjustment involves lowering the statistical boundary at which the researcher will consider the results significantly different. When the same data are used for multiple statistical tests, such as in provision of multiple reports to the DSMB, there is an increased likelihood

that a significant difference will be found by chance. If one considers alpha = 0.05 to be acceptable, this means the researcher is willing to accept a 1 in 20 chance that a significant finding will be in error. By doing multiple tests, for example four tests on the same data, the alpha level changes to 4/20 or 1 in 5. A conservative adjustment of alpha for multiple tests is Bonferroni correction, which involves dividing the alpha level by the number of tests. For example, performing four tests at an overall alpha = 0.05 would change to alpha = 0.0125, thus the researcher would not consider the result significant unless the statistical finding was $p \leq 0.0125$.

Another statistical consideration in clinical trials is subgroup analysis. Once the data are obtained, researchers sometimes re-analyze data from many different perspectives, for example, dividing the data into several different patient groups. Pre-planned comparisons, such as those in secondary objectives, are acceptable. However, results of comparisons conducted post-hoc should be interpreted cautiously, especially if based upon trends in the data, as the findings may be misleading. Some potential causes of the deceptive findings are: (1) the trial was not designed to assure there was adequate sample size for the subgroup analysis, (2) potentially confounding variables were not measured or controlled, and (3) insufficient theoretical underpinnings for the test. The number of subgroup analyses should be minimized, and if results of subgroup analyses are published, these limitations should be clearly stated as speculative.

SUMMARY

In the United States, new drug products must be shown to be safe and effective before they are approved by the FDA for marketing. This chapter outlined the various stages involved in new drug development, including the milestones of IND and NDA submission. The costs associated with the development of new drug products are substantial and the most significant expenditures occur during clinical testing. Thus, the design and conduct of clinical trials are critical to successful drug product development. Several considerations in clinical trial design have been highlighted. The reader is encouraged to refer to specific FDA guidance documents and other referenced materials for further information.

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CHAPTER 49

Biotechnology and Drugs

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In medical and pharmaceutical history, the last 30 years ultimately will be regarded as the dawn of the age of biotechnology. Previously rare or even unattainable pharmaceuticals can now be produced in useful quantities by harnessing the power of molecular biology. Interestingly, the term *biotechnology* was first coined in 1919 by the Hungarian engineer, Károly (Karl) Ereky, to describe how products could be produced from raw materials with the aid of living organisms as agriculture began to join forces with industry following World War I.[1] Hence, biotechnology is not a new concept. Humans have been manipulating living organisms over the millennia to solve problems and improve the quality of life. But today, especially in the context of science and health, the term biotechnology is used interchangeably with "genetic engineering." The concept of DNA manipulation is central to most modern references to biotechnology.

The practical realization of this technology has followed from our ability to now detect, isolate, produce, and characterize the various proteins that coordinate the numerous functions essential to human life and health. Processes that precede or are causative in pathophysiology cannot only be identified, but also now manipulated in an attempt to restore normal function. This relatively new methodology involves the synergism of discoveries in recombinant DNA methodology, DNA alteration, gene-splicing, genetic engineering, immunology, and immunopharmacology, with advances in automation and data analysis to create a cogent, high-technology industry. Overall, biotechnology has led to the creation of new products for home and industry, improvement of agricultural yields, diagnosis of genetic disorders, and the enhancement of our medical arsenal against disease. The publications in February 2001, of the virtually complete sequence of the human genome[2,3] will certainly accelerate the application of these technologies. While the close of the last millennium has clearly witnessed the benefits resulting from the proliferation of biotechnology-derived products, new questions have arisen regarding issues of ethics and pharmacoeconomics. Nonetheless, it is clear that the benefits of biotechnology already have far outweighed the drawbacks.

BACKGROUND

As biotechnology-derived pharmaceuticals have become commonplace in healthcare, pharmacy practitioners should have a detailed knowledge of the manufacture and use of these newer agents.[4,5] As a backdrop to understanding modern biotechnology, it will be instructive to review some of the basic biological milestones that precede it. Table 49-1 provides a compilation of milestones in biotechnology, both in general and as they relate specifically to the pharmaceutical sciences. It is clear that technology is proceeding at a rate that is already threatening to bypass our ability to manage the ethical dilemmas presented by these advances. Fortunately, visionaries such as Nobel laureate James Watson have used their positions to encourage the proper and ethical use of genetic information and technology. As the initial director of the publically funded Human Genome Project, Watson announced 15 years ago a plan to set aside 3% of the project budget (now 5%) devoted to ethical, legal, and social implications (ELSI) research, a decision he recently deemed, "probably the smartest thing I did."[6]

Nature has for some 3.5 billion years been conducting what we may call natural genetic experiments. These include mutation (random heredity alteration), crossing-over (breakage and exchange of corresponding segments of homologous chromosomes), and recombination at meiosis (fertilization). These processes all have contributed to the current diversity of life on this planet. In addition, it is well known that humans have been manipulating genetic characteristics of different species for over 10,000 years through inbreeding and cross-breeding experiments. To cite a few examples, one can point to the modern robust strains of wheat or corn, which are a far cry from their puny ancestors. Similarly, the varied breeds of dogs, cats, poultry, and cattle may be mentioned. These manipulative efforts continue, and in less than a lifetime, the development of larger and sweeter oranges, seedless watermelons, and flamboyant ornamental plants has occurred. Also familiar are such hybridizations as the tangelo (crossing the tangerine and the grapefruit) and the mule (crossing a donkey and a horse).

All cell structures and functions begin with proteins, and the code for building the proteins is found in deoxyribonucleic acid (DNA). This is why the discovery of the double-helix structure of DNA by Watson and Crick, in 1953, fundamentally began the unraveling of the mystery of cell processes. (The 50th anniversary of publication of their model was celebrated in 2003, with some exceptional retrospective documentation published in print and on the Internet by Cold Spring Harbor Laboratory and the journals, *Science* and *Nature*). DNA, the genetic blueprint of an organism, is made up of building blocks known as nucleotides (molecules containing a sugar, nitrogen-containing purine or pyrimidine bases, and a phosphate group) that are connected in a very long ladder-like structure. When this rubber-like twisted-ladder structure is coiled tightly, it is referred to as a two-stranded, or double, helix.

There are four different nucleotides (containing the bases adenine, cytosine, guanine, and thymidine) with a total of about 3 billion nucleotide units in the human genome, tightly packed into chromosomes. These include the genetic code for a large number of genes, originally estimated at 100,000 in the human but downgraded to roughly 30,000 as a result of the Human Genome Project. Each of these genes controls the synthesis of a protein made up of a long strand of 50 to 3000 amino acids. Nirenberg and Matthei, in 1961, and others later, elucidated how the nucleotide sequence of a gene regulates the particular

Table 49-1. Milestones in Biotechnology

The recent explosion of growth in the development and application of biotechnology may be traced to a number of successive, discrete, milestone discoveries and events.

1. X-ray diffraction data and proposed double-helix model for the 3-dimensional structure of DNA (RE Franklin and MH Wilkins; JD Watson and FH Crick, 1952–1953).
2. Site-specific recognition and cleavage of DNA by restriction endonucleases (W Arber, 1962; M Meselson and R Yuan, 1968; HO Smith, 1970; D Nathans, 1971).
3. Determination of the genetic code (M Nirenberg, S Ochoa, and P Leder, 1966; HG Khorana, 1966).
4. Identification of DNA ligase (M Gellert, 1967).
5. Identification of RNA-directed DNA polymerase (reverse transcriptase) (HM Temin and S Mizutani, 1970; D Baltimore, 1970).
6. DNA cloning techniques (HW Boyer, S Cohen, and P Berg, 1971–1972).
7. Formal discussions on emerging rDNA technologies (Gordon Conference on Nucleic Acids, June 1973).
8. Asilomar Conference and self-imposed standards for rDNA research (Feb 1975).
9. Hybridoma created (C Milstein and G Kohler, 1975).
10. Recombinant Advisory Committee (RAC) issues guidelines (1976).
11. DNA sequence technologies (F Sanger, 1977; W Gilbert, 1977).
12. US Supreme Court rules that microorganisms are patentable (General Electric *superbug,* 1980).
13. US approval of first diagnostic kit using MAb technology (anti-C3d BioClone: Ortho Diagnostics, 1981).
14. US approval of first ethical pharmaceutical produced by using rDNA technologies (Humulin (human insulin): Genentech and Eli Lilly & Co, 1982).
15. Expression of a foreign gene in plants (bacterial antibiotic resistance gene expressed in tobacco plants: Monsanto Co. Washington University and Max Planck Institute, 1982).
16. The polymerase chain reaction (PCR) methodology enables targeted amplification of DNA sequences (KB Mullis; Cetus Corp., 1983, use of thermostable DNA polymerase, 1988)
17. FDA approval of first recombinant vaccine (for hepatitis B virus; Chiron Corp., 1986)
18. US Patent and Trademarks Office issues first patent for genetically engineered mammal (transgenic mouse: P Leder and Harvard University, 1988).
19. Formal launch of Human Genome Project, 1990
20. First human gene therapy patient (for adenosine deaminase deficiency, WF Anderson, 1990)
21. Dolly the sheep becomes the first cloned mammal (I Wilmut, 1997)
22. Simultaneous publication of human genome sequence by Human Genome Project and Celera Genomics, 2001

sequence in which the 20 different amino acids will be united to produce a particular protein. A single codon is made up of units of three adjacent nucleotides; each codon specifies one amino acid. The arrangement of codons in the DNA, following transcription into messenger RNA (mRNA), determines the sequence of amino acids that will form a particular protein. The detailed understanding of how these genes and their proteins govern basic cellular processes is the underpinning of molecular biology and biotechnology.

Because each of the major organs of the body (brain, liver, blood, tissue, etc) has a specified set of tasks to perform, certain specific sets of genes in each organ (collection of specialized cells) must be activated and deactivated, that is, turned *on* and *off* as needed. Following the directions laid down by the genetic code of DNA and mediated by mRNA, each cell type continuously produces a unique and characteristic array of proteins. Each cell type maintains a complement of transcriptional activating and repressing proteins whose actions balance to create the specific gene expression profile of a particular tissue. Moreover, epigenetic processes such as gene methylation and histone acetylation status also contribute to tissue-specific gene expression. Expressed proteins are then secreted into the extracellular milieu, while many are used within the cell itself. The number of possible biosynthetic permutations is very high if one considers that a typical protein can be made up of some 500 amino acids and, further, that every one of these sites may be occupied by any one of 20 different amino acids. It is likely that over the long periods of evolution of each organism, given the vast array of possible combinations of these amino acids, a multitude of unique proteins with all sorts of optimized functions have developed.

The concept that genetic information flows from DNA to RNA to proteins has become a fundamental milestone of modern biology. Thus, with the discovery of reverse transcriptase (from an RNA virus) by Temin and Baltimore, in 1970, which could convert its own genomic RNA into double-stranded RNA, a second milestone was reached. Modern biotechnology relies heavily on this enzyme. Examples of cellular catalysts, or enzymes, include those that are involved in the digestion of food, and others that produce the chemical building blocks of cell life such as sugars and lipids, hormones for organism regulation, fuel for energy production, and important molecules such as DNA.

Proteins also make up the cell cytoskeleton providing an organized three-dimensional structure. They permit directed transport and movement of molecules throughout the cell. They are embedded in the outer cell membrane and pump nutrients and ions across the membranes. They serve as receptor sites for hormones that finitely adjust the functions of the cell according to changing bodily needs. Another group of proteins regulates gene activities by binding to DNA and activating or repressing gene transcription. Still other proteins, and their smaller fragments (peptides), are secreted by cells as neurotransmitters or hormones like insulin. Some serve as carrier molecules like hemoglobin, the body's oxygen carrier.

As is well recognized, these hormones and various related peptide molecules hold enormous power, and because they can act on numerous specific cell surface receptors, they can influence virtually all bodily functions from the nervous system to the immune system. It is obvious that their selectivity, potency, and often-desired evanescent effects on selective target cells make them enormously attractive candidates as a new generation of drugs in the *magic bullet* concept of Paul Ehrlich. Further, when administered parenterally, hormones have the potential to reach target receptors on the surface of cells, without the need to penetrate membranes. Not unlike the normal bodily processes, they can bind to cell surface receptors and activate the cell's particular function. An example of one such approach is seen with the anticancer drug interleukin-2, which can stimulate some immune cells to attempt to overcome cancerous cell growth.

The body's specific defense response to invading organisms is due to the immune system. Normally, phagocytes called to a site of inflammation induced by pathogens mount a generalized attack response. Indiscriminately, they engulf cellular debris as well as anything recognized as foreign. Occasionally, however,

this is not enough, and illness ensues. At this point, several more focused counterattacks proceed by the three types of white blood cells known as macrophages, T lymphocytes, and B lymphocytes. The key features of the immune system are specificity (the ability to focus on specific pathogens) and memory (the ability to recognize and respond rapidly to previously encountered infections). About 1% of the blood cells are white blood cells. The ones that are central to the immune responses are

B Cells—Lymphocytes that produce antibodies (antibody-mediated immune response).

Macrophages—Phagocytic cells that alert helper T cells of the presence of pathogens.

Helper T Cells—*Master switches* of the immune system that stimulate the rapid division of both killer T cells and B cells.

Suppressor T Cells—Lymphocytes with regulatory functions; ie, they slow down or prevent immune responses.

Killer T Cells and Natural Killer (NK) Cells—Lymphocytes that directly destroy body cells that already have been infected by pathogens (or cancer cells).

Memory Cells—A group of the T cell and B cell population that was produced during the primary encounter with a pathogen but was not used in the battle. These circulate through the body ready to respond rapidly to later attacks by the same organisms.

As a further refinement in the understanding of the immune system, several key weapons are involved in the process. These include the antibodies, which are circulating freely or membrane-bound receptor molecules that bind specific foreign invaders and thereby tag them for destruction by the complement system or phagocytes. There are the perforin proteins, which are secreted by certain T cells and kill their cellular targets by punching holes in them. Finally, there are the lymphokines and interleukins that are secretions by which white blood cells communicate with each other. Thus, the immune system has two fighting branches with specificity, and often both are employed against infections and antigens in general. The T cells dominate one part of the system, and when they are activated it is referred to as a *cell-mediated* response. The B cells dominate the other branch, and events associated with their activation are referred to as *antibody-mediated* response.

An edition of *Science*[4] was devoted to the frontiers in biotechnology for the 1990s. It provided articles on new shortcuts of immediate practicality and great interest in understanding the human genome via expressed sequence tags (ESTs) of complementary DNA that has uncovered a large number of new genes (mainly in the brain). Similarly, *lighthouses* have been developed along the chromosomes to guide the way for sequencing dim restriction maps. DNA research using the polymerase chain reaction (PCR) has become a powerful tool in forensic and research applications.

New publications described how modern metabolic engineering has brought intermediary metabolism back to life through techniques involving enhancing copies of a gene at a rate-controlling point, adding a gene to remove a poisonous product, or adding several genes to introduce a new pathway into an organism that stops short of the desired product. This metabolic engineering has had numerous practical results in addition to helping develop new theories. DNA technology has been applied to metabolic pathways so that branch point control problems can be solved. Even the insertion of similar enzymes from different species into the studied organism has introduced new flexibility and better metabolic characteristics into the older organism.

This issue also covered the recent developments of the vaccinia virus, so that it now can serve as a molecular vehicle for carrying foreign genes into other organisms. As a means for research, this recombinant vaccinia vector has served as a vehicle for producing live vaccines that would otherwise be difficult to produce. Also discussed is the use of monoclonal antibodies in diagnosis and therapy. The monoclonal antibody OKT3 has been approved by the FDA for treatment of acute renal allograph rejection. Antibody power has been enhanced by attachment of a biological poison such as ricin, a cytotoxin such as calicheamycin, or a physical agent such as an alpha emitter. The latter can be used to damage tissue adjacent to that with which the antibody interacts. These are all good examples of combined basic research followed by rapid practical application.

BIOTECHNOLOGY DRUGS

In terms of drug therapy, the body's ability to remember and identify previous infections already has been exploited through the vaccination technique. This relatively simple procedure involves injecting the person with a weakened or killed pathogen that induces an effective immune response without causing the disease. The procedure gives a lasting immunity through the formation of the memory cells mentioned above. Continued advantage of these natural phenomena (normal immunization through infection) is being taken through the application of molecular biology and biotechnology. Among the recent and significant developments are the novel vaccines (eg, Recombivax HB *(Merck),* a hepatitis B vaccine), which are highly specific antibodies that are intended to act like *magic bullets,* and protein drugs that are duplicates of the chemical messages or secreted factors (interleukin-2) through which immune cells communicate with each other. Figure 49-1 shows the production of a genetically engineered vaccine.

As of 2003 it can be said that more biotechnology medicines are in development than ever before. Holmer[7] reported in the 2002 survey of the Pharmaceutical Research and Manufacturers of America (PhRMA) that over the next decade or so, we will see the results of this biotechnology research infrastructure in the forms of cures and treatments for many age-old diseases. These advances will serve to complement the 95 biotechnology products already FDA-approved for therapeutic indications.

This 2002 survey of the PhRMA showed that 371 biotechnology medicines and vaccines are in human clinical trials or are at the FDA awaiting final approval; in 1988 (the first year of the survey) there were 81 biotechnology products, in 1991 there were 132, in 1993 there were 143, and in 1996 there were 284. Even more striking, biotechnology medicines comprise one-third of *all* drugs currently in clinical trials. The growth rate of the industry has increased dramatically, to 77% between the last two surveys and by 100% between 1993 and 1996. This rate of growth has not escaped Wall Street, but investors are now somewhat cautious because of some failures and corporate scandals that have terminated the programs of some companies. The 10–40% annual returns on biotechnology stocks seen in the late 90s had all but evaporated by 2000. However, long-awaited successes in some key therapeutic areas (ie, anti-angiogenic therapies for cancer) has rekindled investor enthusiasm for pharmaceutical biotechnology as the sector is on target to post a nearly 60% return in 2003.

Further study of the 371 biotechnology products now in development showed 144 companies now engaged in treatments for nearly 200 diseases. Fully 48% of the products were in development for cancer treatment, and another 13% are for treating or preventing infectious diseases excluding AIDS/HIV, 7% for autoimmune disorders, and 6% for AIDS/HIV and related disorders. In the mid-1990s, the fastest growing category of biotechnology products had been gene therapy; however, the death of an 18-year-old Phase I gene therapy trial participant, Jesse Gelsinger in 1998 led to a sober reassessment of strategies, precautions, and controls in such trials.[8] The currently fastest growing segments are monoclonal antibodies and vaccines. Vaccine targets are cancer, AIDS, rheumatoid arthritis, and multiple sclerosis. Monoclonal antibodies have also been instrumental in treating various forms of cancer and autoimmune disorders. Product candidates that are nearly approved also are increasing. The number of products in Phase III clinical studies has nearly tripled since 1993 (from 33 to 87). A total of 95 products have been approved by the FDA as of 2002.

Interestingly, several products are being tested for the first time against certain diseases: the common cold due to rhinovirus, Huntington's disease, Parkinson's disease, sickle cell anemia, lupus nephritis, and osteoporosis. In addition, all of

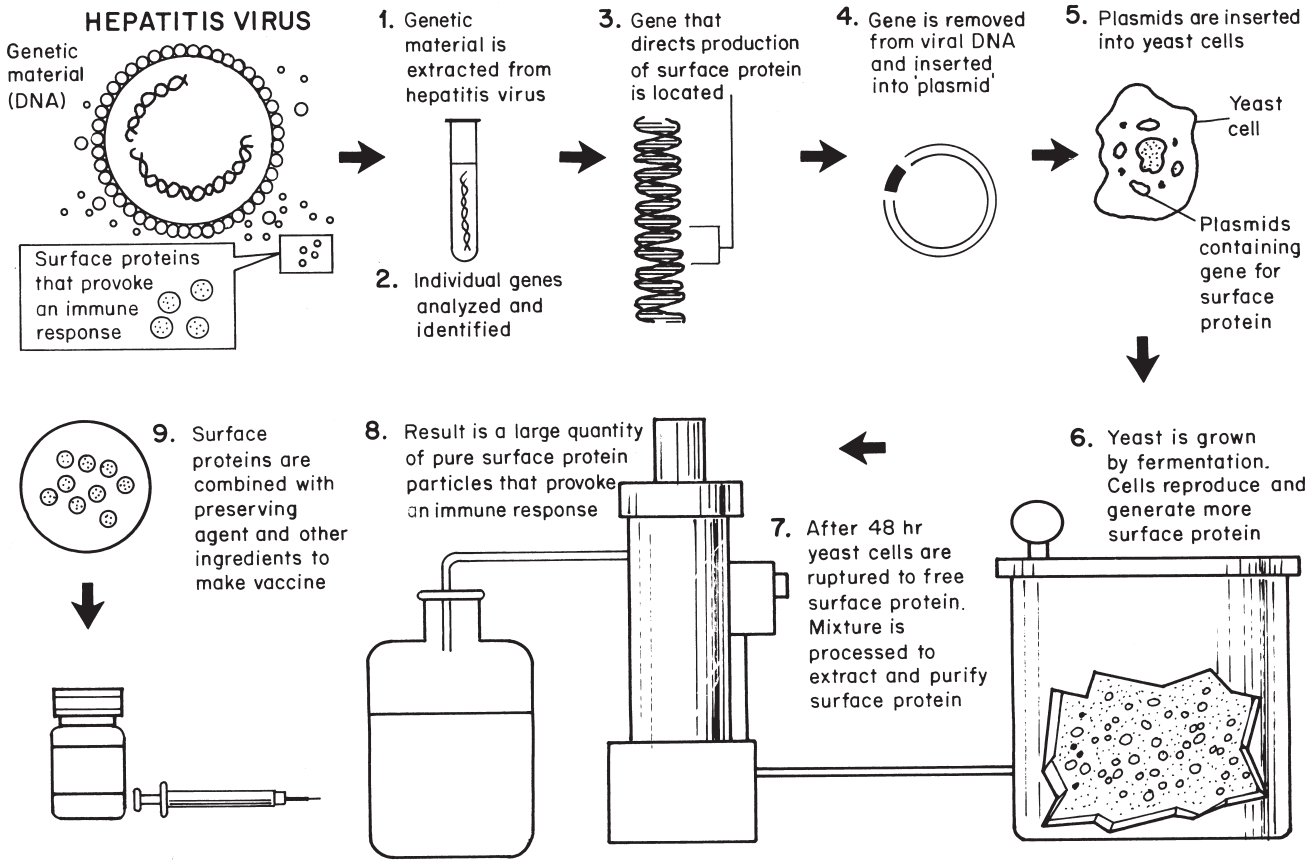

Figure 49-1. Making a genetically engineered vaccine.

these data show that the US pharmaceutical industry continues to hold a worldwide lead in biotechnology research, drugs, and patents. The 1999 figures of the US Office of Patents and Trademarks reveal that the US was the country of origin for 63% of the biotechnology patents issued that year. Japan followed with 13%, the United Kingdom with 10%, and Germany with 7%.With the explosive growth of products in development, space limitations allow us to display only already approved biotechnology products in Appendix A. A glossary of terms also is provided.

All of these agents have been made possible through the biotechnology techniques that allow the isolation, identification, and production of normally minute amounts of proteinaceous *signal agents* found in the extracellular fluids of the body. Once the composition and sequence of amino acids is determined for a protein, that protein can be reproduced in the laboratory. Even better, the protein precursor, DNA, now can be analyzed readily and sequenced, allowing another organism to use that part of the code that determines the protein. This has been made possible through the discovery and use of restriction enzymes by HO Smith, which make specific reproducible cuts along DNA strands. Frederick Sanger et al devised procedures for quickly determining the nucleotide sequence of DNA fragments. This allowed the identification of the DNA sequence of complete genes. Also, the discovery of reverse transcriptase by Temin et al became important in biotechnology because it allowed the mass production of genes from mRNA, which led to increased production of a desired protein. Through these procedures it became possible to determine the amino acid sequence of entire proteins via inference of the genetic code.

The 1972–1973 landmark experiments of Stanley Cohen, Herbert Boyer, and Paul Berg applied this technology to produce recombinant plasmid DNA molecules for propagation in *E coli* and are recognized as the first creation of a genetically engineered organism capable of producing proteins from another species. This hybrid plasmid now could be grown in the common and rapidly producing bacterium, *E coli*. A plasmid is a circular DNA molecule that carries a few genes that the bacterium perpetuates and is replicated in addition to its own normal chromosomes. More than any other technique, this really heralded the birth of recombinant DNA (hybrid DNA is produced by joining pieces of DNA from different sources; also designated rDNA) technology. This permitted, for the first time, rapid isolation of unique proteins and their mass production by rapidly growing microorganisms. In addition, new organisms having specifically inserted and desired characteristics could be engineered for medical, agricultural, and ecological uses.

Another important aspect of recombinant DNA technology is the use of antibodies in biotechnology, therapy, and diagnosis. Antibodies are produced by plasma cells (B cells) and are made up of four protein chains interconnected by disulfide bonds. The surface of the antibody possesses a highly specific indentation, or *lock* that can recognize the specific foreign particle (key) with which it complexes or binds. It long has been known that different antibodies are produced in each individual for their particular immunological experience with antigens. Hence, perhaps millions of different antibodies may be found in any given individual. For a long time it was not known how the B cells were capable of producing this diversity of antibodies that possessed the ability to recognize almost every possible foreign invader. It also was not known whether each B cell secreted a single or many different antibodies.

Fortunately, through the early *clone selection* theory of MacFarlane Burnet in 1957 came the idea that one cell produces only one type of antibody. And, in 1975, Kohler and Milstein devised a method of growing very large numbers of antibody-

producing cells from a single B cell. They did this by the ingenious technique of fusing the B cell to a myeloma cancer cell. The resulting *hybridoma* (Fig 49-2) retained two main features from its two parent cells. It could grow indefinitely like the cancer cell, yet also produce and secrete antibodies like the B cell. This was the main discovery leading to hybridoma technology and earned Kohler and Milstein (together with Niels Jerne) the 1984 Nobel Prize in Physiology or Medicine.

The antibodies produced by these hybridomas are called monoclonal antibodies (MAbs) because they are derived from a single hybrid cell. Using the ability to identify directly the genes that code for antibodies, it was found that the antibodies are put together from a large number of different gene fragments. When combined in different ways they can produce a large number of different antibodies. Those portions of the antibody that contain the antigen-binding site are coded by a combination of hundreds of different gene fragments that get reshuffled and permanently fixed in the B cells. Hence, it has become possible to produce MAbs as key reagents in biotechnology procedures as well as exquisite diagnostic tools and specific drugs of great selectivity.

It already has become possible to tag monoclonal antibodies with radioisotopes that make possible the detection of very small levels of proteins and peptides in body fluids and tissues. The limits of detection are often as low as one billionth of a milligram (picogram) in the procedure widely used and known as radioimmunoassay (RIA). This is sufficient to detect low levels of hormones and other protein substances in body fluids. Figure 49-2 shows the basic procedures involved in hybridoma technology.

The power of molecular biology, combined with pressure from the animal rights lobby, led to a search for methodology to produce antibodies without the use of animal hosts. In 1989, this goal was realized when monoclonal antibodies were first isolated from a combinatorial antibody library. This approach, described in detail by Rader and Barbas,[9] employs the selectable expression of recombinant antibody molecules on the surface of bacteriophage particles. In this procedure, bacteriophage DNA constructs are made that encode human antibody heavy- and light-chain fragments. They then are combined randomly, and the phage are propagated by bacterial infection, allowing each phage to display a unique antibody with a specific antigen-binding site on its surface. Following several rounds of selection of phage particles with high affinity for a specific antigen, the phage DNA can be modified to produce soluble antibodies. An endless supply of antibody is guaranteed by simply repropagating the selected bacteriophage.

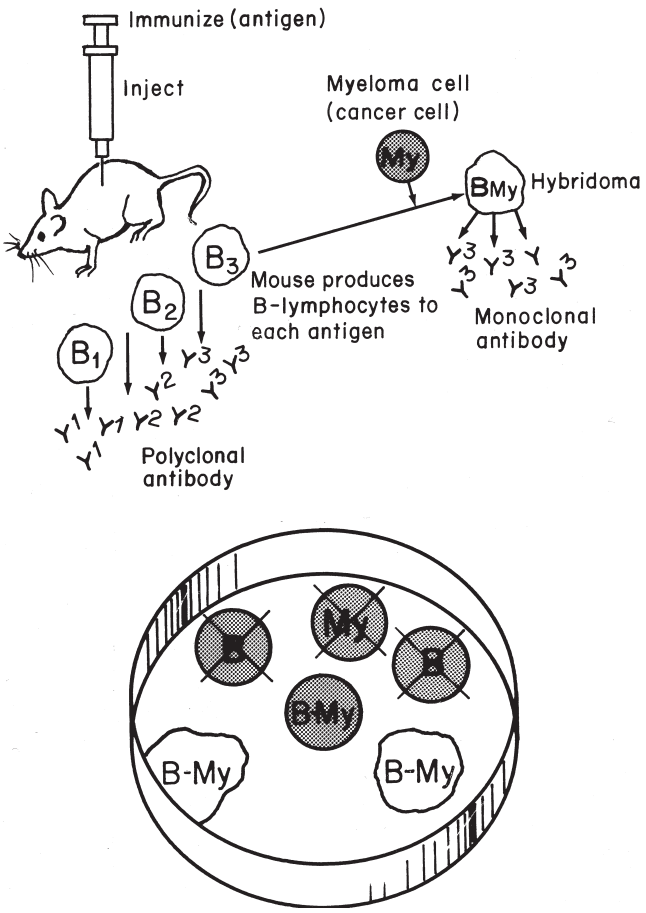

Figure 49-2. Hybridoma manufacture (courtesy, Armour Pharm).

Another exciting area of research is that of gene diagnostics and therapy. It is believed that there are as many as 4000 locations in the human genome that are related to different genetic diseases. Of this number some 1200 have been mapped and characterized to various degrees of detail. Some of the abnormalities found on the genes are called point mutations, and they involve cases where a single nucleic acid base in a gene is substituted by a different one. This irregularity results in the exchange of a single amino acid in the encoded protein. Too many changes may result in genetic disorders. For example, in the genes encoding the hemoglobin protein sequences, there have been located at least 40 point mutations. Sickle-cell anemia is related to one of these. It is hoped that detailed knowledge of this type at the molecular level will allow the development of agents that can prevent the typical alteration in the shape of blood cells in sickle-cell anemia. Molecular probing or screening at this level also will reveal such disorders prenatally, or early in life, so that appropriate remedial action or preventative measures can be instituted (*viz,* gene therapy). Figure 49-3 shows how genetic defects may be detected.

Pharmacogenomics, or pharmacogenetics, is another research area that has sprung from the observation of mutations in key genes among a subset of the population that confer relative resistance or hypersensitivity to certain drugs. In the pharmacogenomic context, these mutations are more commonly referred to as polymorphisms and are often observed in genes encoding drug metabolizing enzymes, transporters, receptors, or other drug targets. These variations in DNA sequence are often single-nucleotide polymorphisms (SNPs) and can occur in either the coding region of a gene causing an amino acid change, or in the regulatory region of a gene thereby causing an alteration in the absolute amount of protein produced. For example, a patient with a polymorphism in one or both copies of a gene encoding a drug-inactivating enzyme would be at risk for exaggerated pharmacological action and potential toxicity for that drug. These pharmacogenetic differences are likely at the heart of most of the heterogeneity of drug responses observed among large populations and have significant impact on the ordinary practice of medicine and in clinical trials. Specific examples of known polymorphisms and the altered effects they confer are delineated in an excellent review article[10] from a premier PharmD pharmacogenomics expert and a table is available online at http://www.sciencemag.org/feature/data/1044449.shl.

Advances in DNA technology also have made this procedure more rapid, particularly when looking for any one of many individual mutations within a single gene that can give rise to disease. This technology, called high-density DNA affinity arrays,[11] or microarrays, is becoming more widespread and financially accessible to even small research institutions. Individual DNA targets that each contain one of these mutations are adsorbed onto a glass substrate in an array pattern and then hybridized with a fluorescently labeled probe generated from the gene expressed in the individual being tested. Another adaptation of this technology is to investigate the relative expression level of genes implicated in various disease processes. Some diseases are not due to gene mutations, but rather to

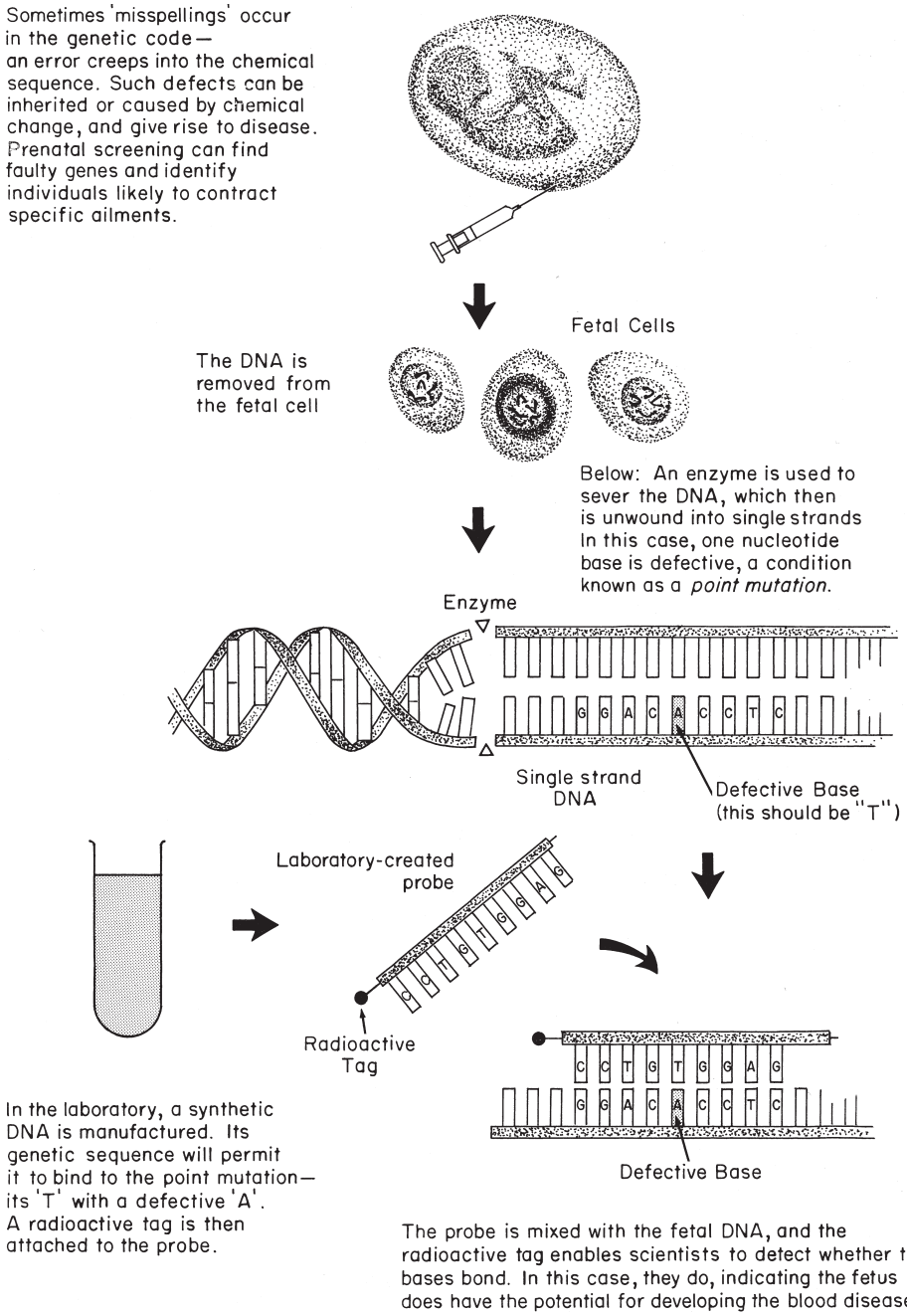

Figure 49-3. Searching for genetic defects.

abnormal over- or underproduction of certain regulatory proteins. DNA arrays permit the screening of literally thousands of genes in a single experiment by comparing genes expressed in normal versus diseased individuals. In fact, the expressed mRNAs from the entire human genome can now be screened on two commercially available "chips" and the race is on for the first manufacturer to put the entire expressed human genome on a single chip. Availability of such technology is expected to allow early diagnosis of many diseases that are due to multiple genetic abnormalities, such as cancer. In one specific case of diffuse B-cell lymphoma patients, microarrays have been used to subclassify the disease to understand which patients will respond best to chemotherapy.[12] In this manner, patients at greatest risk can be given the most aggressive therapy, while those at lower risk can be spared unnecessary toxicity. Microarrays of gene expression can also be applied in drug discovery; a recent application of this technology has been used to predict the general therapeutic classes into which psychotropic medications fall.[13]

One drawback to microarrays in diagnosis and drug treatment is that gene expression is not always predictive of the amount of protein produced. Moreover, it completely ignores post-translational modification of proteins that can vastly influence biological responses. With advances in mass spectrometry instrumentation, the field of proteomics has emerged as the next means to secure a snapshot of cellular activities and correlate the pattern with specific drug responses or disease processes. Researchers at the US Food and Drug Administration and the National Institutes of Health have recently shown the power of proteomics in early detection of ovarian cancer using simple blood samples.[14] It was demonstrated that cancerous alterations in organ function causes an altered profile of proteins in serum, allowing this disease to be caught long before patients are symptomatic and with a high degree of ac-

curacy, thereby minimizing the false-positive rate associated with many clinical diagnostic tests. The pharmacy practitioner is wisely advised to keep abreast of developments in proteomic technologies as these advances are quite likely to influence other therapeutic areas with equal magnitude.

As the ability to determine genetic defects that cause a variety of disorders emerges, health care will improve. However, society must develop policies governing the use and misuse of this information. Baum has reviewed this problem and provides information on some of genetic screening's serious implications. For instance, the use of DNA fingerprinting bothers some observers who question the reliability of such an analysis carried out on a large scale. Results may affect civil liberties, insurability, guilt or innocence, etc. The 1996 Health Insurance Portability and Accountability Act (HIPAA) prohibits group health insurance providers from using genetic information for determining eligibility or setting premiums, but provides no protection for the millions of Americans with individual insurance policies.[15]

As the technique known as restriction fragment length polymorphism (RFLP) analysis develops,[2] it provides markers throughout the genome that vary among individuals. The identification of particular RFLPs that are tightly associated with genes responsible for certain diseases has become possible. Thus, RFLPs provide markers that identify the chromosome that carries the defective gene. But the presence or absence of the marker does not necessarily indicate disease. RFLP analysis must be performed on both parents or two or more grandparents to determine the status of a disorder. Furthermore it is an expensive and complex analysis.

In the mid-1990s, public attention was raised to the applications of genetic polymorphisms for forensic purposes in criminal investigations. However, RFLP analysis has considerable drawbacks for this purpose. The need for relatively large amounts of nondegraded DNA and the time necessary for multiple allelic comparisons led to a search for other methods of individual genotyping. The most popular recent technology[9] analyzes interindividual differences in the variable number of tandem repeats (VTNRs), or *DNA fingerprinting,* as it is known to the lay public. A similar name for the same method is amplified fragment length polymorphisms (AMP-FLPs). We each possess in our genome a variable number of repeated DNA sequences that, when measured in combination, provide a unique *fingerprint* of our DNA. These repeated sequences are referred to as minisatellites or microsatellites, depending on their size, and are often made up of repeated sequences of 2 to 70 base-pair-length monomeric sequences. Since the location of many of these polymorphisms is known, the polymerase chain reaction (PCR) can be used to amplify these repeated sequences from even the extremely small amounts of blood, tissue, or semen found at crime scenes. Depending on the number of satellite sequences analyzed, the individual source of the DNA can be identified with near absolute certainty. So useful is this technique that it was employed in 1994 to positively identify the remains of the Romanovs, using mitochondrial DNA isolated from the bones of the Russian royal family who were murdered by the Bolsheviks in 1918.[16]

So, while many tests will be devised to predict genetic risk factors for complex diseases, what one does with the knowledge remains to be worked out, and undoubtedly society will grapple with this issue for many years to come. Even the magazine *Consumer Reports* provides the lay person with a guide to genetic screening and discusses who's testing what, the possible problem of genetic discrimination, genetic screening's limited powers of prediction, the role of genetic tests in preemployment screening, the presence of few legal safeguards, how some inherited adult-onset disorders may be preempted, remembering that genetic testing is a tool, knowing that the demand for genetic services likely will increase, the role of individual decisions, the pace of change, how to prepare for genetic testing, etc.

The major diseases of mankind owe much of their origin to heredity, so that it will be exciting in the decades to come to see how molecular biotechnological techniques will allow for early detection, prevention, or even possible cures for many of the maladies of old age such as cardiovascular disease, Alzheimer's disease, diabetes, and cancer. These approaches also are allowing us to understand previous unrecognized causes of diseases. For many years, it has been known that many human leukemias could be diagnosed microscopically on the basis of specific translocations, or rearrangements, of the chromosomes. Today, the abnormal proteins made as a result of these translocations can be identified. Look[17] provides a striking review on the function of these aberrant proteins in leukemogenesis. While many of these proteins lead to uncontrolled growth of leukemia cells, some have been shown to cause leukemia by inhibiting the normal cell death that usually occurs in white blood cell populations. This had led to our reclassification of cancer as a disease not necessarily of abnormal cell division, but instead, in some cases, of loss of appropriate cell death. Other articles in the same 1997 issue of *Science* deal with more frontiers in cancer research, showing that molecular biology also has led to our understanding of how cancer can be prevented.

It is hoped that continued approaches based on reverse genetics will be fruitful. So far, these methods have allowed researchers to produce a compilation of the exact locations and even the molecular arrangements of several defective genes that are felt to be responsible for Huntington's disease, retinoblastoma, Duchenne's muscular dystrophy, and polycystic kidney disease, among others. From these studies will come specific and reliable tests for the abnormal genes that will allow genetic counselors to make appropriate recommendations for action. Further in the future will come the new therapeutic models and molecules that eventually will translate into clinically effective drugs.

So far, at least two basic approaches in *genetic medicine* can be envisioned. One involves possible replacement of the defective protein by producing it biotechnologically outside the body (eg, insulin, as has already been done with Humulin *(Lilly),* human insulin produced by DNA). The same can be done with replacing defective or missing enzymes or altering one that should not be produced. The other basic approach is much more complicated and involves replacing the defective gene entirely. In the case of gene therapy that involves germ-line cells (sperm and eggs), once a gene is introduced stably into the germ line, every cell of the individual will bear this gene.

Presently, this type of therapy poses enormous unresolved ethical and scientific questions and is restricted. However, the inclusion of genes in somatic cells (specific body organ cells) is different because these genomes cannot be inherited and stay with the treated individual. One of the ways to accomplish this would be to use *harmless* viruses to insert a corrected gene into the human genome. Unfortunately, in most cases, it is not yet understood how the inserted gene will be expressed in these tissues, only where and when they are needed. Some ways to circumvent these difficulties have been found, but they are limited. For example, one way to produce tissue specificity is to take out the tissues to be altered, insert the corrected gene, and place the corrected cells back into the body. Alternatively, tissue-specific genetic control elements have been identified and can be used to restrict expression of the recombinant gene.

So far, bone marrow cells can be handled in this manner, and they have been the first somatic cell type submitted to clinical testing of this gene-transfer technique. In one example, the goal is the treatment of an inborn disease affecting bone marrow function and involving an enzyme (adenosine deaminase) deficiency that produces severe weakening of the immune system.

One of the goals in biochemistry and pharmacology is to understand the molecular features of cell receptors. These are the *locks* into which the *keys* (drugs) fit that alter or control the function of the cell. While now there exists the capability to determine the basic genetic code and thus learn the sequence of the amino acids that make up the protein, its spatial configuration

still is not known. This is called the tertiary structure of the protein, the functional form of the protein after the proper folding of a simple straight-chain of amino acids.

The novel combination of x-ray crystallography, molecular mechanics, calculations, and supercomputers are brought to bear to reveal the folded or three-dimensional arrangement. From this 3-D picture of the *lock,* researchers can design specifically shaped drugs that fit the active sites of the folded protein. This computational chemistry methodology is a leap forward and truly a rational approach in drug design. In like manner, the possibility of cloning *receptor sites* of specific design and function provides the pharmacologist with excellent *in vitro* test systems for pharmacological screening and understanding of the mechanisms of actions of drugs. For example, the solution of the x-ray crystal structure of the HIV protease has led to the rapid development of four FDA-approved drugs that have revolutionized our treatment of AIDS. A similar approach with thymidylate synthase was used to produce a unique inhibitor of this enzyme for cancer chemotherapy.[18]

In the past few years, several publications have dealt specifically with the pharmacist's role in implementing pharmaceutical care with regard to biotechnology agents. Tami and Evens[19] recently presented an overview on the evaluation of biotechnology products. The authors first discuss the manufacturing, pharmacokinetics, and stability issues that we present in greater detail forthcoming. They specifically made the point that biotechnology product costs often can account for 10% of a pharmacy's total budget. In addition, they discuss pharmacoeconomic studies, availability of alternative agents, concomitant drug costs, special pharmacy procedures, reimbursement, and manufacturer's support. Pharmacists are a particularly important link in assisting patients with reimbursement issues for these expensive drugs.

UNIQUE PHARMACEUTICAL CHALLENGES OF BIOTECHNOLOGY-DERIVED THERAPEUTICS

The transition of biotechnology from theory to pharmaceutical practicality has posed a whole new series of challenges to those involved in drug development. With classical small molecules possessing formula weights less than 1000, a series of chemical compounds normally are screened for a particular pharmacological activity and assessed for specificity. The results of these findings then guide fine-tuning of the chemical entity. As advances in combinatorial chemistry are now generating thousands of compounds in a given class, the rate-limiting step in drug development has shifted to high-throughput screening technologies. Natural products are also regaining prominence in drug discovery because they often possess greater molecular diversity than can be obtained with combinatorial compound libraries. It is now rare that pharmaceutical formulation and drug-delivery problems limit the success of small molecules.

In contrast, macromolecular agents (eg, recombinant proteins and vaccines, antisense DNA, gene therapy constructs) already have the advantage, in theory, of possessing inherent selectivity for a particular biological process. By and large, the limitation to the utility of these agents rests with problems related to drug delivery and stability. In fact, it is no surprise that most biotechnology drugs currently approved in the US act at extracellular sites and/or in compartments that are easily accessible, such as the blood-forming elements. In addition, each type of biotechnology agent also is subjected to unique considerations based on our emerging biological understanding of each system. The discussion that follows attempts to address the obstacles to successful therapeutic use of biotechnology products.

Recombinant proteins almost exclusively constitute the currently approved list of biotechnology-derived agents in the US.[7] These proteins usually have resulted from a search for endogenous agents acting by a newly identified physiological mechanism (such as the stimulation of red blood cell production by erythropoietin manufactured in the kidney). Since the therapeutic administration of a recombinant molecule that mimics an endogenous protein carries with it a naturally inherent specificity, it is no surprise that development times for these agents has been considerably shorter than for most conventional small molecules. The probability of regulatory success with recombinant proteins also has been more favorable.[20] While a new, small, organic molecule may have a 10% chance of achieving NDA status, this percentage is near 40% for recombinant proteins. When compared with conventional small molecules, recombinant products reaching the clinical trials in Phase I (25% versus 71%) or Phase III (66% versus 93%) are much more likely to become successful therapeutic agents. Nonetheless, Cho and Juliano[21] state,

> "The main challenge encountered in development is not so much identifying a bioactive molecule but, rather, how to maintain a therapeutically meaningful concentration of the macromolecule in the vicinity of its target for the desired period of time."

Recombinant protein drugs are produced in various host cells from carefully designed expression systems. For monoclonal antibodies, production is enabled by the highly specialized hybridoma systems described earlier. But for the bulk of the other recombinant protein drugs, the exploitation of any one of these protein *factories* begins in a similar fashion. As addressed earlier in the section on gene splicing, the complementary DNA encoding a particular protein product is spliced (or subcloned) into a circular DNA vector. This recombinant vector contains gene regulatory sequences that enable highly efficient transcription and translation of the recombinant gene once the construct is introduced into the appropriate host.

The choice of host system (bacteria, yeast, or mammalian cells) depends highly on the biological requirements of the protein. One major consideration is whether the protein product requires glycosylation, the specific addition of certain sugars, for biological activity.[20] Bacteria like *E coli* are unable to conjugate such carbohydrates onto recombinant proteins, but yeast possesses a limited ability for glycosylation. However, mammalian cell systems such as Chinese hamster ovary cells have the full complement of glycosyltransferase enzymes. For molecules such as the interferons and filgrastim (G-CSF), glycosylation is not necessary for biological activity; therefore these proteins can be produced in less expensive *E coli* systems. However, erythropoietin requires mammalian glycosylation and must be produced in the more costly Chinese hamster ovary cell system. Hamilton and colleagues[22] have recently reported the heroic engineering of the yeast *Pichia pastoris* to encode the entire complement of human N-glycosylation enzymes while deleting the yeast's own glycosylation pathways. Such an organism might represent a more cost-effective host for future manufacture of human therapeutic proteins requiring glycosylation.

These modern protein expression systems have several advantages over trying to isolate the corresponding protein from the organs or tissues of other mammals. First, immune reactivity to a nonhuman protein (human insulin versus porcine insulin) is largely obviated (with exceptions described later). Also, protein drugs can be produced that could never be made by conventional methods (interferons, G-CSF) or in quantities previously only available in limited amounts (insulin, growth hormone). Finally, the protein is inherently free of potentially pathogenic human viruses (factor VIII or hepatitis vaccines), although treatments to destroy any zoonotic pathogens are often employed in subsequent processing.

As the biotechnology drug sector has matured, manufacturers have begun to follow conventional, small-molecule pharmaceuticals in the production of second-generation agents with improved bioavailability and/or safety. While the cynic might argue that these innovations are merely spurred by pending patent expiration of first-in-class agents, it seems that most second-generation biotech drugs represent true advances. For example, the treatment of anemia due to kidney disease or cancer chemotherapy has been improved by increasing the

bioavailability of erythropoietin in the second-generation drug, darbepoietin. Recognizing that N-linked oligosaccharides are essential to the activity of erythropoietin, scientists altered two amino acid residues to accept two additional sialic acid chains. The resulting darbopoietin molecule possesses a 3-fold improvement in serum half-life (26.3 hr relative to 8.5 hr for erythropoietin). This alteration reduces the number of injections necessary for patients to maintain therapeutic hemoglobin levels. While regimens vary by patient and indication, the general rule has been that if a patient had been stabilized previous with three erythropoietin injections per week, only one weekly injection of darbopoietin is now required. From the standpoint of patient quality of life and burden on pharmacy and nursing staff, less frequent dosing has a number of significant advantages.

While scale-up of recombinant protein expression and purification is becoming more routine, these drugs present other challenges not seen with small molecule agents. Issues of proper protein folding, formulation, and stability are proving as labor-intensive as the initial cloning of the gene itself. Betaseron (human recombinant interferon β) required modification of one amino acid to enhance the yield of properly disulfide-linked protein after renaturation processing.[20] This processing modification reflects another advantage of recombinant protein expression that can be employed quite easily, so long as the pharmacological activity of the protein is not compromised. In fact, optimizing the cDNA sequence (and the resulting encoded amino acids) of a recombinant product has resulted recently in the approval of consensus interferon, a single molecule that incorporates the combined activities of multiple interferons.

Manipulation of the expressed gene also can involve the deletion of regions dispensable for biological activity, to optimize therapeutic utility. Human tissue plasminogen activator (tPA) has been used since 1987 for thrombolytic therapy following myocardial infarction. However, tPA is poorly soluble and must be administered in relatively high concentrations, since it is cleared rather rapidly from plasma. Structure-function analysis of individual tPA protein domains allowed the construction of a smaller molecule (reteplase or recombinant plasminogen activator; rPA) that possesses superior solubility and also can be manufactured in *E coli*.

The effects of changes in protein formulation or amino acid substitutions can now be assessed rapidly as a result of advances in protein analytical methodology. Protein secondary structure can be monitored quickly and accurately by such techniques as circular dichroism (CD) spectroscopy and Fourier-transformed infrared spectroscopy (FTIR). This technology has been quite useful in that the structural fidelity of the protein drug can be ensured prior to the initiation of more costly pharmacological evaluation. FTIR also has the advantage of being able to detect protein structure in the lyophilized state, greatly facilitating the optimization of formulations capable of maximal stability.

Pharmacokinetic evaluation of recombinant proteins is also an emerging field of significant relevance to pharmacy.[23] Since most protein drugs cannot be given orally, the impact of other routes of administration must be assessed. It also must be appreciated that for most biotechnologically derived agents, there is a preexisting and nonconstant concentration of the corresponding endogenous molecule present in plasma. Bioanalytical techniques for monitoring concentrations of the agent require optimization for specificity. Unfortunately the specificity of any one method often depends on the particular matrix in which analysis is performed (blood, urine, or the initial formulation).

In addition, the prediction that recombinant human molecules would not be immunogenic has not proven to be the case.[23] Antibodies to several recombinant drugs now are known, but not all neutralize the pharmacological activity of the agent and, in some cases, they can decrease clearance of the agent. These factors obviously complicate the interpretation of pharmacokinetic data. The immunogenicity of a particular protein also may depend on the route of administration. Protein aggregation, known to occur after subcutaneous or intramuscular injection, leads to a greater antigenic response than soluble protein. Finally, the influence of the lymphatic system on protein pharmacokinetics should not be underestimated. After subcutaneous administration, absorption via the lymphatics becomes quantitatively more important than that of blood capillaries as the molecular weight of the drug increases. Since several recombinant protein drugs act primarily through the lymphatics (interferons and interleukins), blood concentrations may be irrelevant to pharmacological activity.

Obviously, there remain immunologic concerns in any instance when a recombinant analog of an endogenous protein is fashioned into a drug product. Known as neoantigenicity, altered protein structure due to amino acid changes, chimeric products (ie, humanized mouse monoclonal antibodies), or fusion with other constituents could trigger antibody-mediated inactivation of the therapeutic molecule as well as its endogenous counterpart. In some instances, the very same modification in one context can result in the opposite effect in another. For example, *E coli* asparaginase had been used to treat certain leukemias based on the observation of their need for the amino acid asparagine. However, some patients experienced immunological reactions to the bacterial protein, and a new product was produced, pegaspargase, where the enzyme was modified by covalent attachment of polyethylene glycol (PEG) molecules. This approach, now known as PEGylation, is also known to improve the bioavailability of a number of proteins by reducing their renal clearance.[24] However, this same strategy used to reduce antigenicity in one context recently caused an immunogenic response with another product, megakaryocyte derived growth factor or thrombopoietin. This product had been in development to treat bleeding disorders due to platelet loss in some disease and with chemotherapy and a PEGylated form being tested in normal volunteers caused inactivating antibodies to be made to their own endogenous thrombopoietin.[24] This example should serve as a reminder that protein modifications do not always have the intended consequences.

The future of recombinant biological agents continues to evolve. To date, most approved agents have been recombinantly expressed, naturally occurring proteins. To a limited extent, some approved agents represent our venture into *protein engineering,* in which chimeric or fusion proteins (immunotoxin conjugates) or mutated or deleted proteins (consensus interferon and rPA) have been developed as a result of our experiences with first-generation agents. A number of other biotechnology approaches are currently under investigation, often in human clinical trials, and their success remains to be fully realized. These agents include antisense RNA and DNA, small interfering RNA (siRNA), ribozymes, aptamers, and gene therapy.

In 1978, the first *in vitro* experiments in which *antisense DNA* was used for specific repression of gene expression opened the door to the opportunity to block disease-causing genes selectively. The antisense nucleotide approach is based on the use of short oligonucleotides (10–20 base pairs) complementary to a specific mRNA whose protein product is implicated in a disease such as cancer or viral infection.[25] Binding of the antisense molecule to its target mRNA is then believed to inhibit protein translation by interfering with ribosomal function. In addition, the resulting DNA-RNA duplex recruits the activity of RNase H, a ubiquitous enzyme that degrades the RNA itself. This approach meets the two crucial criteria in the design of any successful therapeutic agent: the identification of a target implicated in disease etiology and the ability to find a molecule capable of high affinity and selectivity for the target. Although problems of stability, delivery, and specificity have somewhat dulled the initial promise of these agents, several second-generation antisense molecules are in late clinical trials, and the first antisense drug (to prevent blindness due to cytomegalovirus infections in HIV-positive patients) was approved in 1997.

All antisense DNA molecules in these trials possess a modified phosphodiester backbone in which one of the nonbridging oxygens on the phosphate has been replaced with sulfur. The resulting phosphorothioate molecules possess enhanced stability to DNA-degrading nucleases, enabling *in vivo* administration, and effectively penetrate cells and bind target mRNAs.

However, there are numerous reports of antisense efficacy, particularly in inhibiting cancer and other abnormal cell growth, that are due to nonantisense mechanisms.[26] These nonantisense actions may be due to the fact that phosphorothioates have enhanced affinity for polyanions including heparin, growth factors (bFGF, PDGF, EGF, and VEGF), and enzymes required for cell growth (PKC and phospholipase A_2). Other non-sequence-specific actions of phosphorothioates *in vivo* may be due to their enhancement of immune system function by increasing production of immunoglobulins and interferons and by activation of natural killer cell activity. It should be noted that these nonspecific actions may not necessarily be deleterious, especially when the target mRNA is viral or involved in cancer. Nonetheless, antisense molecules with other backbones or backbone combinations currently are being evaluated for greater specificity for their target mRNAs.

Another encouraging adaptation of antisense therapies is an approach that takes advantage of the Nobel prize–winning discovery of Thomas Cech and Sidney Altman, who demonstrated that certain RNA molecules possess an enzymatic RNA-degrading activity. The RNAs, called *ribozymes,* are directed toward a specific disease-causing RNA by the sequence homology used by antisense molecules. However, the promise of ribozymes relates to their catalytic nature; one ribozyme molecule can lead to the destruction of thousands of target RNA molecules. In addition, ribozyme technology appears to possess greater specificity over some antisense nucleotides. Nonetheless, the instability of RNAs as therapeutic agents is one hurdle that must be overcome before the promise of ribozymes can be fully realized.

Other RNA technologies also being investigated take advantage of the three-dimensional nature of RNA molecules. Aptamers are RNA molecules specifically selected for high affinity to certain molecular targets. *In vitro* selectivity of these molecules is quite impressive; affinity-selected RNAs can distinguish between theophylline and caffeine, hypoxanthine molecules that differ by only one methyl group.[27] The hope is that such selectivity can be applied to closely related enzymes (ie, COX-1 and COX-2) or receptor family subtypes.

The most recent, highly-hyped technology to emerge in the late 1990s is the use of small, double-stranded RNA molecules to specifically turn off expression of genes involved in pathogenesis (reviewed in [28]). In 1998, this pathway was first shown to exist in an invertebrate model dear to geneticists, the worm *C elegans*. Shortly thereafter, it was recognized that mammalian cells possess a similar regulatory mechanism for silencing endogenous genes called RNA interference (RNAi). But most commonly, the pathway seems to exist to fight retroviral infections whereby a type III RNase enzyme (appropriately called "Dicer") is activated to cleave viral RNA genomes into 21–28 basepair fragments which then hybridize to other copies of viral RNA to catalyze their degradation. Based on these observations, small, interfering RNA molecules (siRNA) could be synthesized and have now been shown in a number of systems to selectively "knockdown" gene expression. A number of companies have sprung up hoping to exploit this technology in treating viral diseases, especially HIV/AIDS, and other disorders caused by overactivity of an enzyme or protein. The challenges facing siRNA technology are not dissimilar from those of antisense oligonucleotides, focusing primarily on efficient delivery of the molecules or expression vectors capable of producing the siRNA molecules intracellularly. Another problem is specificity and the potential for "off-target" gene silencing. Researchers using microarray technology have recently published conflicting reports on this issue with one showing alterations in dozens of genes using a single targeted siRNA while another group observes no off-target silencing across 20,000 human genes studied.[29,30] As with other revolutionary technologies that propose to realize Ehrlich's dream of the magic bullet, only time and experience will determine the true clinical utility of these agents.

Until the unexpected death of Jesse Gelsinger in a Phase I recombinant adenovirus trial in 1998, the next wave of products seemed destined to be directed toward *gene therapy*.[31] Many different approaches constitute gene therapy, but the most common is to attempt to replace a nonfunctioning or mutated gene product by the directed expression of a new, nonmutated copy of that gene. In other cases, genes are being introduced to make drug therapy more effective (eg, HSV thymidine kinase, p53) or gene therapy is combined with other aforementioned approaches (eg, intracellular expression of antisense RNA to the K-*ras* oncogene). In general, the DNA encoding these new genes is encoded on a plasmid molecule or is part of a retroviral vector that can infect cells with the appropriate desirable gene without causing viral disease. (The Gelsinger case points out that the recombinant virus might still be lethal via other mechanisms.) Delivery methods for these gene sources usually either exploit the DNA delivery tactic of the virus itself or employ cationic liposomal complexes with the DNA to mask the plasmid's negative charge. Obviously, there is substantial concern over the use of modified retroviruses or adeno-associated viruses as gene delivery systems for fear that important host cell genes might be disrupted if the viral DNA is integrated into the host genome. Cationic liposomal strategies have made substantial leaps in the last several years, but their efficiency of gene delivery pales in comparison with viral delivery. Nonetheless, liposome/DNA complexes are amenable to lyophilization and reconstitution, and advances are being made in maximizing the efficiency of these stabilized preparations.[32]

Finally, a new area has emerged for the potential application of biotechnology products against bioterrorism. Following the September 11, 2001 terrorist attacks in New York, Washington, DC, and Pennsylvania and the subsequent anthrax scare, Congress earmarked $37 billion toward homeland defense of which $6 billion is targeted to developing biodefense strategies. A little-known provision of new FDA guidelines are that counter-terrorism agents are eligible for expedited review, as seen now for drugs to treat AIDS or cancer. Biotechnological approaches have already been proposed for both the detection and treatment for biological agents most likely to be used in terrorist attacks.

PHARMACOGNOSTICAL APPLICATIONS

In regard to the applications of biotechnology in pharmacognosy (drugs from natural sources) Cordell[33] reports that major efforts in this field are under way in Germany, Japan, and the People's Republic of China. These countries are attempting to use manipulated plant-cell cultures to produce otherwise difficult to extract natural products. In Germany, which has a substantial number of efficacious prescription natural products not available in the US, the pharmaceutical industry and government have joined together to form an institute designed specifically to produce natural products commercially through cell-free systems and gene technology of medicinal plants. One company in Japan reported that it can produce ginseng extract, identical in chemical composition with that from mature 6-year-old root, in 20,000-gal fermenters.

Davies summarized the application of genetic engineering to the production of pharmaceuticals. He pointed out that new drugs traditionally have come from natural product sources, usually followed by improved growing techniques or chemical synthesis. However, while the plant or microorganism strain-improvement procedures have resulted in up to 1000-fold increases in yield, the techniques largely have been empirical. Furthermore, these methods have virtually no genetic or biochemical pedigree for successive improvements.

The organisms currently used to produce antibiotics (eg, penicillin and tetracycline) on a commercial scale are the same species as those originally collected from the natural state and really have been modified only through forced genetic manipulations (by virtue of the media, etc), based on strain improvement. Of paramount importance is the fact that while gene cloning and recombinant DNA techniques have been successful

for proteins and peptides, the higher plants and microbes producing antibiotics have not been manipulated similarly. This is because an entirely different situation exists when more complex genetic and biochemical processes need to be manipulated. As discussed later, there are also some regulatory assurances that remain to be met, particularly in using transgenic plants as a source of pharmaceuticals.

Antibiotics and alkaloids usually are biosynthesized through multistep pathways possessing complex biogenesis and regulatory circuits. The numerous genes involved in the synthesis of a simple antibiotic are not necessarily present as a single genetic linkage group. Thus, cloning the genes needed would require numerous operations, often without the advantage of selective procedures to detect the presence of the cloned genes. Similarly, the same technical problems associated with multiple components of antibiotic synthesis apply to the genetic engineering of improved yields of many secondary metabolites like alkaloids from plants. Further complicating the issue is that suitable host-vector systems need to be developed fully for the application of recombinant DNA techniques to plants. However, if there is a single rate-limiting step in the pathway of antibiotic biosynthesis, it might be possible to clone the gene for this step by selecting for increased antibiotic production by *shotgun* cloning back into the producing organism.

An alternative way to achieve increased levels of antibiotic production might be to clone appropriate genes on multicopy or high-expression vectors. Another idea would be to engineer antibiotic-producing organisms to produce hybrid or specifically modified antibiotics. This would result in several model compounds that might have more desirable or better properties than the parent antibiotic. For example, Hailes[34] outlined the directed biotransformation of opiate analogs including morphine and hydromorphone using genetically engineered bacteria and discussed the application of this method toward biosynthesis of novel alkaloids. Marsden[35] reported the engineering of broader substrate specificity into a macrolide antibiotic-producing polyketide synthase from the erythromycin producer, *Saccharopolyspora erythraea*. These investigators modified the carboxylic acid acceptor unit of this multicomponent enzyme complex to utilize over 40 alternative branched-chain starter carboxylic acids (as opposed to the two straight chain acids utilized normally). In doing so, a vast number of novel, macrolide antibiotics can now be synthesized.

In the case of plant tissue culture, many compounds such as secondary metabolites have been produced with yields that are equal to or greater than that of parent plants. Staba[36] reports on at least 30 natural products that have been generated through plant-cell culture. Among these are included several well-known, but still difficult to obtain, drugs such as diosgenin-derived steroid hormone precursors, the opium alkaloids, digitalis glycosides, several different essential oils, and the *Catharanthus* alkaloids, vincristine, and vinblastine. However, it has been pointed out that these methods still are not economical when compared with the traditional methods used currently, *viz,* direct extraction from whole plant materials.

Thus far, only one Asiatic drug, known as shikonin (from *Lithospermasm erythrorhizon*), has been produced through plant-cell culture methodology in greater quantities and with substantially lower costs than usual extraction procedures.[37] Certainly, continued efforts expended in the biotechnological manipulation of plant genes will prove more successful as research continues in this area. Table 49-2[38] shows established hairy root cultures (the result of genetic transformation of the plant by *Agrobacterium rhizogenes*) and examples of secondary product formation.

Finally, even though many efforts are oriented toward the cheap, controlled, pharmaceutical production of secondary plant products, it should be remembered that this new approach can offer a valuable system for basic plant biosynthesis. These techniques offer a means quite suitable for physiological studies as well as for genetic manipulation. For once, it will be possible to have a powerful tool for the study of the control of gene expression at both the cellular and whole plant or organ levels. Beyond this, the increased efficiency with which biosynthetic pathways for desired compounds may be expressed makes plant DNA promising material as a source of mRNA for cloning operations directed at the transfer of specific plant enzymes into microorganisms.[38]

Awad[39] has provided an overview on plant biotechnology that he feels is a field fertile for pharmaceutical research. In addition to providing two tables listing both microorganisms and plants that have been used in agricultural, horticultural, and

Table 49-2. Established Hairy Root Cultures with Examples of Secondary Product Formation

FAMILY	SPECIES	MAJOR SECONDARY PRODUCTS
Solanaceae	*Atropa belladonna*	Atropine
	Datura stramonium	Hyoscyamine
	Hyoscymus muticus	Hyoscyamine
	Nicotiana rustica	Nicotine, anatabine
	N tabacum	Nicotine, anatabine
	N hesperis	Nicotine, anabasine
	N cavicola	Nicotine, nornicotine
	Scopolia japonica	Hyoscyamine
	Solanum laciniatum	Steroidal alkaloids
Apocynaceae	*Catharanthus roseus*	Ajmalicine, serpentine, vindolinine, catharanthine
Chenopodiaceae	*Beta vulgaris*	Betacyanin, betaxanthin
Polygonaceae	*Polygonum hydropiper*	
Boraginaceae	*Lithospermum erythrorhizon*	Shikonin
Compositae	*Tagetes patula*	Thiophenes
Rubiaceae	*Cinchona ledgeriana*	Quinoline alkaloids

From Hamill J, Parr A, Robins R, et al. *Bio/Technology* 1987; 5:800.

pharmaceutical research in biotechnology, he shows the major groups of compounds of commercial importance that are derived from plants. These include pharmaceuticals (alkaloids, steroids, anthraquinones), enzymes (papain), latex (rubber), waxes (jojoba, carnuba), pigments (food dyes), oils (olive oil, corn oil, etc), agrochemicals (pyrethrins), cosmetic substances (essential oils and perfumes), food additives (flavor compounds, nonnutritive sweeteners), and gums (gum acacia and tragacanth). He perceives the major trends in plant biotechnology to include plant-microbe interactions, gene delivery and manipulation, diversity of gene engineering, and microbial and plant secondary metabolites.

Constabel [40] reviewed medicinal plant biotechnology as a revolutionary methodology useful in enhancing the formation and accumulation of desirable natural products and a possible product-modification method. He describes advances in micropropagation that involve plant regeneration from *in vitro* cultured cells. Here the multiplication factor can be high and of great advantage to speed up slow-growing important medicinal plants. Recent studies with ipecac *(Cephaelis ipecacuanha)* yielded 100 plantlets per shoot-tip explant per year or 600 plantlets per axenic shoot. Similarly, *Digitalis lanata* cultivars with high cardenolide content were obtained by inbreeding and subsequent crossing of selected genotypes. The isolation and *in vitro* culture of shoot tips led to the formation of adventitious shoots. Following short- and long-term culture, rooting of these shoots on solid medium established plantlets that were transferred to soil. The cardenolide yields equaled those of the parent plants.

Similar studies showed that axenic shoot-tip cultures also can be stored for long periods of time and even be cryopreserved for gene banks. Some studies also are focusing on overcoming somaclonal variation, so that stable, high-yield chemovariants can be developed. In terms of enhancement of productivity, gene technology has allowed true transgenic plants. Their uniqueness is shown as a change, ie, enhancement, in plant performance (insect resistance, herbicide) and productivity (storage proteins, pigmentation). Transgenic cell cultures of drug plants with modified or increased productivity and microorganisms producing phytochemicals are conceivable and may further increase the feasibility of phytochemical production by *in vitro* methods. Already key enzymes for biosynthetic pathways in plants have been identified and related to isolated DNA clones and genes. Schell described plant biotechnology as a powerful tool to use plant resources and to improve the environmental impact of agriculture. He described how transgenic plants can be developed to promote insect tolerance, virus resistance, and tolerance to fungal diseases in crop plants. Critics of plant biotechnology raise legitimate concerns over the potential immunogenicity of foreign proteins expressed in foodstuffs. The European Union nations have been particularly opposed to the marketing of these so-called "Frankenfoods" but these genetically engineered food crops have now grown to represent more than 40% of the corn and soybeans harvested annually. Similarly reviewed are the enhancement of stress tolerance, development of hybrid seeds, and improvement of nutritional-quality plants. For example, Miller and Ackerman[41] also provided new perspectives on food biotechnology, describing tomatoes that are rot resistant and animal foods being modified by genetic means.

Plant biotechnology has also been used to omit products that are undesirable in a particular crop. Of greatest pharmaceutical relevance is the presence of caffeine in the coffee plant.[42] Those who wish to avoid the hypertensive and CNS-stimulating effects of this methylxanthine must resort to coffee products that have been decaffeinated by chemical processes that either employ organic solvents which also remove some components of flavor and aroma. However, Japanese researchers[43] have now succeeded in using RNA interference technology to downregulate one of the three N-methyltransferase enzymes required for caffeine biosynthesis in the non-commercial plant, *Coffea cenephora*. The resulting transgenic plants exhibited a 50–70% decrease in caffeine content. The remaining challenge is to cross these plants with the more economically important *Coffea arabica* and achieve a 97% reduction in caffeine content as required in the US for "decaffeinated" labeling.

The use of transgenic plants or animals in producing recombinant proteins for pharmaceutical use is called "pharming," a term accepted in the 2001 release of the *The Columbia Encyclopedia*. A 2003 survey by the Pew Initiative on Food and Biotechnology revealed that while 81% of Americans favored tinkering with plant genes to produces medicines, only half felt comfortable making transgenic animals for the same purpose. Proponents of transgenic plants as pharmaceutical sources point out that production of recombinant proteins requires a specialized facility costing $300–$500 million and roughly 5 years of set-up. In contrast, transgenic plant or animal scale-up can be done on the scale of tens of millions of dollars and in half the time. However, no recombinant product produced in plants or animals has yet made it to market, and only three plant-produced products are currently in clinical trials. The industry has suffered numerous setbacks,[44] not the least of which relate to concerns on the contamination of food crops with plant-made pharmaceuticals, particularly since some companies are using plants to produce orally-active vaccines. In late 2002, a Texas plant biotechnology company was cited for twice contaminating soybean crops in Nebraska and Iowa with transgenic corn harboring either a pig vaccine or a human protease inhibitor. Plants clearly hold great promise for producing biotechnology drugs, but several hurdles must be overcome before this idea is practically implemented.

PHARMACOLOGICAL APPLICATIONS

Pharmacologically directed biotechnological methodology also holds much promise for the medical field. Even before completion of the Human Genome Project, genes had been isolated for literally dozens of neurochemical receptor drug targets, ion channels, and transporters. With these sequences in hand, target proteins could be produced in vitro or in cellular systems for high-throughput drug screening. Not only do these expressed proteins provide tools for identifying drug molecules active against a certain system, but the availability of other similar gene sequences enable determination of molecular specificity (eg, dopamine D2 antagonism vs dopamine D1 antagonism). Moreover, these potent drug discovery technologies are no longer exclusive to pharmaceutical companies. Academic researchers in the neuropharmacology area now have access to recombinant protein screening services of the National Institute for Mental Health (NIMH) for novel CNS-active agents. Through an NIMH contract, Drs. Linda Brady and Bryan Roth at Case Western Reserve University maintain cellular systems for assaying drug activity against over 70 neurochemical receptors and transporters. In fact, this system has recently been used in an attempt to resolve the controversy over the active antidepressant component(s) of extracts from the herbal remedy, St. John's wort.[45]

It should be mentioned that long before their testing as therapeutic agents, antisense oligonucleotides were used experimentally to advance our understanding of physiology and pharmacology. As an example, Pasternak and Standifer[46] have outlined their exploitation of antisense molecules in elucidating the functional biology of opioid receptor subtypes. Using antisense molecules to down-regulate certain opioid receptor subtypes (or mRNA-splicing variants of the same receptors), these investigators have been able to differentiate between receptors responsible for morphine-induced spinal analgesia, morphine-induced supraspinal analgesia, and the supraspinal analgesia induced by the active glucuronide conjugate of morphine. A similar approach has been used to investigate dopamine, muscarinic acetylcholine, and NMDA receptors.

Huber[47] provides an excellent review on the therapeutic opportunities involving cellular oncogenes because of the novel ap-

proaches fostered by biotechnology. Oncogenes can serve as novel therapeutic targets for cancer diagnosis, prognosis, and treatment. Marx[48] provides another perspective on oncogenes by detailing advancements made in our understanding of tumor suppressor genes whose function is inactivated in carcinogenic progression. Tumor suppressor genes are obviously excellent candidates for reintroduction strategies in treating cancer.

PHARMACEUTICAL MANUFACTURING APPLICATIONS

The use of genetically modified bacteria also has played a part in increasing the efficiency of producing certain pharmaceutically important synthetic organic compounds. For example, researchers have isolated a gene from a species of *Corynebacterium* that codes for 2,5-diketo-D-glucose reductase. This particular enzyme catalyzes the conversion of 2,5-diketo-D-glucose to 2-keto-L-gulose, which is an intermediate in ascorbic acid (vitamin C) production. The scientists successfully have inserted the gene into *Erwinia herbicola* bacteria, via a plasmid. Unchanged *E herbicola* has the ability to ferment D-glucose into 2,5-diketo-D-glucose. Inserting the new gene provides the changed bacterium with the ability to ferment D-glucose to 2-keto-L-gulose in one step. The second step involved in the production of vitamin C is base- or acid-catalyzed cyclization of 2-keto-L-gulose to the acid. Thus, the genetic engineering process saves at least four steps, compared with the previous procedure. The older Keichstein-Grussner process involves six steps in the synthesis of ascorbic acid.[49]

ORGANIC SYNTHESIS APPLICATIONS

In an interesting synthesis application, Iverson and Lerner[50] report on sequence-specific peptide cleavage catalyzed by an antibody. The monoclonal antibodies necessary for this procedure were produced by immunizing with a Co(III) triethylenetetramine (trien)-peptide hapten capable of catalyzing specific hydrolysis of the Gly-Phe bond of peptide substrates at a neutral pH with a metal complex cofactor. As a group, these antibodies are able to bind trien complexes of not only Co(III), but also numerous other metals. At least six peptides were studied as possible substrates with these antibodies as well as various metal complexes. The results of these studies demonstrate the feasibility of using cofactor-assisted catalysis in an antibody-binding site to achieve successful results in difficult chemical transformations.

MORAL AND ETHICAL QUESTIONS

On the matter of moral and ethical questions of biotechnology applications in medicine, numerous articles appear periodically[8,15,51] to debate the issue. Francis Collins, Director of the National Human Genome Research Institute (NHGRI) has written,

"It is estimated that all of us carry dozens of glitches in our DNA–so establishing principles of fair use of this information is important for all of us."

There are many questions such as

Does genetic testing constitute invasion of privacy?
Will there be an increase in abortions that discriminate against the *genetically unfit*?
Should those destined to be stricken with a fatal genetic disease be informed of their fate, especially if there is no remedy available?
Will these decisions become mandated legally and ultimately demean humans or create a new underclass of the genetically less-fortunate?
Should gene therapy be used only for treating disease or also for *improving* an individual's genetic legacy?

Currently, most protections on the use of genetic information are regulated at the state level, resulting in uneven application across the population. Senators Jeffords and Daschle recently outlined their respective views on the passage of federal laws that protect the collection and use of genetic information, particularly relating to employment and health insurance.[15] The Human Genome Project's ELSI program (Ethical, Legal, and Social Implications of Human Genetics Research) is now charged with addressing issues that appear as daunting as the sequencing of the genome itself. The benefits of biotechnology in disease prevention and treatment are numerous and the decoding of the human genome will continue to produce new opportunities to improve our quality of life. But as with all technological advances, safeguards are required to prevent discriminatory and unethical use of this new information.

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Yoxen E. *The Gene Business. Who Should Control Biotechnology*. New York: Oxford University Press, 1983, p 230. [*Note:* This reference provides a detailed analytical study of the corporate agenda for biotechnology. It is a readable account of how genetic engineering evolved from a pure science into a profitable business. The structure and function of the multinational gene business, the effects to date, and the economic, scientific, social, and political implications are examined in detail.)

Biotechnology Medicines Approved and in Development

APPENDIX **A**

The content of this chart has been obtained through government and industry sources, based on the latest information. Chart is current as of September 27, 2002. The information may not be comprehensive. For more specific information about a particular product, contact the individual company directly. This table on the entire series of "New Medicines in Development" is available on PhRMA's web site at http://www.phrma.org. Provided as a Public Service by PhRMA. Founded in 1958 as the Pharmaceutical Manufacturers Association.

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PRODUCT NAME	COMPANY	INDICATION (DATE OF US APPROVAL)
Actimmune interferon gamma-1b	Genentech, San Francisco, CA	Management of chronic granulomatous disease (12/90) Osteopetrosis (2/00)
Activase alteplase (recombinant)	Genentech, South San Francisco, CA	Acute myocardial infarction (11/87) acute massive pulmonary embolism (6/90) acute myocardial infarction, accelerated infusion (4/95) ischemic stroke within 3 to 5 hours of symptom onset (6/96)
AcuTect Tc-99m apticide	Berlex Laboratories, Montville, NJ	Scintigraphic imaging of acute venous thrombosis in the lower extremities of patients who have signs and symptoms of acute venous thrombosis (9/98)
Adagen injection pegademase bovine	Enzon, Bridgewater, NJ	Treatment of severe combined immunodeficiency disease (SCID) (9/90)
Alferon N interferon alfa-n3 (injection)	Interferon Sciences, New Brunswick, NJ	Genital warts (10/89)
Apligraf graftskin	Novartis Pharmaceuticals, East Hanover, NJ	Treatment of venous leg ulcers (5/98)
Aranesp darbopoietin alfa	Amgen, Thousand Oaks, CA	Treatment of anemia in chronic renal failure (9/01) Treatment of chemotherapy-induced anemia (7/02)
Argatroban	GlaxoSmithKline, Philadelphia, PA/Res. Triangle Park, NC Texas Biotechnology, Houston, TX	Heparin-induced thrombocytopenia (HIT) syndrome (6/00)
Avonex beta interferon 1a (recombinant)	Biogen, Cambridge, MA	Relapsing multiple sclerosis (5/96)
BeneFIX recombinant human factor IX	Wyeth Pharmaceuticals, Philadelphia, PA	Treatment of hemophilia B (2/97)
Betaseron recombinant interferon beta-1b	Berlex Laboratories, Wayne, NJ Chiron, Emeryville, CA	Relapsing, remitting multiple sclerosis (8/93)
BioTropin human growth hormone	Bio-technology General, Iselin, NJ	Growth deficiency in children (5/95)
Campath alemtuzumab	Berlex Laboratories, Montville, NJ ILEX Oncology, San Antonio, TX	treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy (5/01)
Carticel autologous cultured chondrocytes	Genzyme Tissue Repair, Cambridge, MA	Repair of clinically significant, symptomatic cartilaginous defects of the femoral condyle (medial, lateral, or trochlear) caused by acute or repetitive trauma (8/97)
CEA-Scan technetium-99m-arcitumomab	Immunomedics, Morris Plains, NJ	presence, location and detection of recurrent and metastatic colorectal cancer (6/96)
Cerezyme imiglucerase (recombinant)	Genzyme, Cambridge, MA	Gaucher's disease (5/94)
Comvax haemophilus b conjugate (meningococcal protein conjugate) and hepatitis b recombinant vaccine	Merck, Whitehouse Station, NJ	vaccination of infants beginning at two months of age against both invasive *Haemophilus influenzae* type b diseases (Hib) and hepatitis B (10/96)
DACS SC stem cell enrichment device	Dendreon, Seattle, WA	Rescue therapy following high-dose chemotherapy (8/99)
Eliteck rasburicase	Sanofi-Synthelabo, New York, NY	Prophylaxis for chemotherapy-induced hyperuricemia, treatment of cancer-related hyperuricemia (7/02)

continued

PRODUCT NAME	COMPANY	INDICATION (DATE OF US APPROVAL)
Enbrel etanercept	Amgen, Thousand Oaks, CA Wyeth Pharmaceuticals, Philadelphia, PA	Moderate to severe rheumatoid arthritis (11/98) Moderate to severe active juvenile rheumatoid arthritis (5/99) Disease modification of active rheumatoid arthritis and psoriatic arthritis (1/02)
Engerix-B hepatitis B vaccine (recombinant)	GlaxoSmithKline, Philadelphia, PA/Res. Triangle Park, NC	Hepatitis B (9/89)
EPOGEN epoetin alfa (rEPO)	Amgen, Thousand Oaks, CA	Treatment of anemia associated with chronic renal failure, including patients on dialysis and not on dialysis, and anemia in Retrovir-treated HIV-infected patients (6/89) treatment of anemia caused by chemotherapy in patients with non-myeloid malignancies (4/93) prevention of anemia associated with surgical blood loss, autologous blood donation adjuvant (12/96) anemia in children with chronic renal failure who are currently undergoing dialysis (11/99)
PROCRIT epoetin alfa (rEPO)	Ortho Biotech, Raritan, NJ	Treatment of anemia associated with chronic renal failure, including patients on dialysis and not on dialysis, and anemia in Retrovir-treated HIV-infected patients (6/90) treatment of anemia caused by chemotherapy in patients with non-myeloid malignancies (4/93) prevention of anemia associated with surgical blood loss, autologous blood donation adjuvant (12/96) anemia in children with chronic renal failure who are currently undergoing dialysis (11/99) [PROCRIT was approved for marketing under Amgen's epoetin alfa PLA. Amgen manufactures the product for Ortho Biotech.] Under an agreement between the two companies, Amgen licensed to Ortho Pharmaceutical the U.S. rights to epoetin alfa for indications for human use excluding dialysis and diagnostics.
Follistim recombinant follicle-stimulating hormone	Organon, West Orange, NJ	infertility (10/97)
GenoTropin somatotropin (rDNA origin) for injection	Pharmacia, Peapack, NJ	Short stature in children due to growth hormone deficiency (8/95) Growth failure due to Prader-Willi syndrome (6/00) Long-term treatment of growth failure in children born small for gestational age (7/01)
Geref human growth hormone-releasing factor	Serono, Rockland, MA	Evaluation of the ability of the somatotroph of the pituitary gland to secrete growth hormone (12/90) Pediatric growth hormone deficiency (10/97)
GlucaGen glucagon (rRNA origin) for injection	Novo Nordisk Pharmaceuticals, Princeton, NJ	Treatment of hypoglycemia and for use as a diagnostic aid (6/98)
Gonal-F recombinant follicle-stimulating hormone (r-FSH)	Serono, Rockland, MA	Female infertility (9/97)
Helixate FS antihemophilic factor (recombinant)	Aventis Behring, King of Prussia, PA	Treatment of hemophilia A (6/00)
Hepsera adefovir dipivoxil	Gilead Sciences, Foster City, CA	Treatment of chronic hepatitis B (9/02)
Herceptin trastuzumab	Genentech, South San Francisco, CA	Treatment of HER2 overexpressing metastatic breast cancer (9/98)
Humalog insulin lispro	Eli Lilly, Indianapolis, IN	Diabetes (10/82)
Humatrope somatotropin (rDNA origin) for injection	Eli Lilly, Indianapolis, IN	Human growth hormone deficiency in children (3/87)

continued

PRODUCT NAME	COMPANY	INDICATION (DATE OF US APPROVAL)
Humulin human insulin (recombinant DNA origin)	Eli Lilly, Indianapolis, IN	Diabetes (10/82)
Infergen interferon alfacon-1	Amgen, Thousand Oaks, CA	Treatment of chronic hepatitis C viral infection (10/97)
Intron A interferon alfa-2b (recombinant)	Schering-Plough, Kenilworth, NJ	Hairy cell leukemia (6/86), genital warts (6/88), Kaposi's sarcoma (11/88), hepatitis C (2/91), hepatitis B (7/92), malignant melanoma (12/95), follicular lymphoma in conjunction with chemotherapy (11/97)
Kineret anakinra	Amgen, Thousand Oaks, CA	Signs and symptoms of rheumatoid arthritis (11/01)
KoGENate antihemophiliac factor (recombinant)	Bayer, West Haven, CT	Treatment of hemophilia A (2/93)
KoGENate-FS rFVIII	Bayer, West Haven, CT	Hemophilia A (6/00)
Leukine sargramostim (GM-CSF)	Berlex Laboratories, Montville, NJ	Autologous bone marrow transplantation (3/91), neutropenia resulting from chemotherapy in acute myelogenous leukemia (9/95), allogenic bone marrow transplantation (11/95), peripheral blood progenitor cell mobilization and transplantation (12/95)
LYMErix Lyme disease vaccine (recombinant OspA)	GlaxoSmithKline, Philadelphia, PA/Rsch. Triangle Park, NC	Prevention of Lyme disease (12/98)
Mylotarg gemtuzumab ozogamicin for injection	Wyeth Pharmaceuticals, Philadelphia, PA	Treatment of patients 60 years and older in first relapse with CD33-positive acute myeloid leukemia (AML) who are not considered candidates for cytotoxic chemotherapy (5/00)
Natrecor nesiritide	Scios, Sunnyvale, CA	Acute decompensated congestive heart failure (8/01)
Neulasta pegfilgrastim	Amgen, Thousand Oaks, CA	Chemotherapy-induced neutropenia (1/02)
Neumega oprelvekin	Wyeth Pharmaceuticals, Philadelphia, PA	Prevention of severe chemotherapy-induced thrombocytopenia (11/97)
NEUPOGEN filgrastim (rG-CSF)	Amgen, Thousand Oaks, CA	Chemotherapy-induced neutropenia (2/91), autologous or allogenic bone marrow transplantation (6/94), chronic severe neutropenia (12/94), support peripheral blood progenitor cell transplantation (12/95), acute myelogenous leukemia (4/98)
Norditropin somatropin (rDNA origin) for injection	Novo Nordisk Pharmaceuticals, Princeton, NJ	Treatment of growth failure in children due to inadequate growth hormone secretion (5/95)
Novolin 70/30 70% NPH human insulin isophane suspension & 30% regular human insulin (rDNA origin)	Novo Nordisk Pharmaceuticals, Princeton, NJ	Insulin-dependent diabetes mellitus (6/91)
Novolin L Lente human insulin zinc suspension (rDNA origin)	Novo Nordisk Pharmaceuticals, Princeton, NJ	Insulin-dependent diabetes mellitus (6/91)
Novolin N NPH human insulin isophane suspension (rDNA origin)	Novo Nordisk Pharmaceuticals, Princeton, NJ	Insulin-dependent diabetes mellitus (7/91)
Novolin R regular human insulin (rDNA origin)	Novo Nordisk Pharmaceuticals, Princeton, NJ	Insulin-dependent diabetes mellitus (6/91)
NovoLog insulin aspart (rDNA origin) injection	Novo Nordisk Pharmaceuticals, Princeton, NJ	Treatment of adult diabetes mellitus (6/00)
NovoLog Mix 70/30 70% insulin aspart (rDNA origin) protamine suspension and 30% insulin aspart (rDNA origin) injection	Novo Nordisk Pharmaceuticals, Princeton, NJ	Treatment of adult diabetes mellitus (11/01)
NovoSeven coagulation factor VIIa (recombinant)	Novo Nordisk Pharmaceuticals, Princeton, NJ	Treatment of bleeding episodes in hemophilia A or B patients with inhibitors to factor VIII or factor IX (3/99)
Nutropin somatropin (rDNA origin) for injection	Genentech, South San Francisco, CA	Growth failure in children due to chronic renal insufficiency, growth hormone inadequacy in children (3/94), Turner's syndrome (12/96), growth hormone inadequacy in adults (12/97)
Nutropin AQ somatropin (injection/liquid)	Genentech, San Francisco, CA	Growth failure in children caused by chronic renal insufficiency

continued

PRODUCT NAME	COMPANY	INDICATION (DATE OF US APPROVAL)
		Growth hormone inadequacy in children (12/95), Turner's syndrome (12/96), growth hormone inadequacy in adults (12/97)
Nutropin Depot somatropin (rDNA origin) for injection (suspension)	Alkermes, Cambridge, MA Genentech, South San Francisco, CA	Growth failure in children due to chronic renal insufficiency, growth hormone inadequacy in children (3/94), Turner's syndrome (12/96), growth hormone inadequacy in adults (12/97)
OncoScint CR/OV satumomab pendetide	CYTOGEN, Princeton, NJ	Detection, staging, and follow-up of colorectal and ovarian cancers (12/92)
Oncospar PEG-L-asparaginase	Enzon, Bridgewater, NJ	First-line treatment of acute lymphoblastic leukemia (2/94)
Ontak denileukin diftitox	Ligand Pharmaceuticals, San Diego, CA Seragen, Hopkinton, MA	Persistent or recurrent cutaneous T-cell lymphoma (2/99)
ORTHOCLONE OKT 3 muromonab-CD3	Ortho Biotech, Raritan, NJ	Reversal of kidney transplant rejection (6/86), reversal of liver and heart transplant rejection (6/93)
PEG-Intron A interferon alfa-2b	Enzon, Bridgewater, NJ Schering-Plough, Kenilworth, NJ	Hepatitis C (8/01)
Proleukin aldesleukin (interleukin 2)	Chiron, Emeryville, CA	Renal cell carcinoma (5/92)
ProstaScint capromab pentetate	CYTOGEN, Princeton, NJ	Detection, staging and follow-up of prostate adenocarcinoma (10/96)
Protropin somatrem for injection	Genentech, San Francisco, CA	Human growth hormone deficiency in children (10/85)
Pulmozyme DNase dornase alpha	Genentech, San Francisco, CA	Cystic fibrosis (12/93), management of advanced cystic fibrosis (12/96)
Rebetron ribavirin/interferon alfa-2b, recombinant combination	Schering-Plough, Kenilworth, NJ	Treatment of chronic hepatitis C in patients who have relapsed following alpha interferon therapy (6/98), treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with alpha interferon therapy (12/99)
Rebif interferon beta-1a	Serono, Rockland, MA	Relapsing forms of multiple sclerosis (3/02)
Recombinate antihemophiliac factor rAHF (recombinant)	Baxter Healthcare, Deerfield, IL Wyeth Pharmaceuticals, Philadelphia, PA	Prevention and control of bleeding episodes in patients with hemophilia A (12/92)
RECOMBIVAX HB hepatitis B vaccine (recombinant), MSD	Merck, Whitehouse Station, NJ	Hepatitis B prevention (7/86)
ReFacto antihemophilic factor VIII (recombinant)	Wyeth Pharmaceuticals, Philadelphia, PA	Hemophilia A (3/00)
Refludan lepirudin (rDNA) for injection	Berlex Laboratories, Montville, NJ	Heparin-induced thrombocytopenia type II (3/98)
Regranex becaplermin	Ortho-McNeil Pharmaceuticals, Raritan, NJ	Chronic diabetic ulcers (12/97)
Remicade infliximab	Centocor, Malvern, PA	Short-term use in Crohn's disease (8/98), reduction in signs and symptoms in rheumatoid arthritis (11/99), inhibit the progression of structural damage in patients with rheumatoid arthritis (1/01), improve physical function in rheumatoid arthritis (2/02), long-term remission-level control of Crohn's disease (7/02)
ReoPro abciximab	Centocor, Malvern, PA Eli Lilly, Indianapolis, IN	Antiplatelet prevention of blood clots in the setting of high risk percutaneous transluminal coronary angioplasty (12/94), refractory unstable angina when percutaneous coronary intervention is planned (11/97)
Retavase reteplase	Centocor, Malvern, PA	Treatment of acute myocardial infarction (10/96)
Rituxan ritixmab	Genentech, South San Francisco, CA IDEC Pharmaceuticals, San Diego, CA	Treatment of relapsed or refractory low-grade or follicular CD20-positive B-cell non-Hodgkin's lymphoma (11/97)
Roferon-A interferon alfa-2a (recombinant)	Roche, Nutley, NJ	Hairy cell leukemia (6/86), AIDS-related Kaposi's sarcoma (11/88), chronic myelogenous leukemia (11/95), hepatitis C (11/96)

continued

PRODUCT NAME	COMPANY	INDICATION (DATE OF US APPROVAL)
Saizen somatropin (rDNA origin) for injection	Serono, Rockland, MA	Pediatric growth hormone deficiency (11/96)
Serostim somatropin (rDNA origin) for injection	Serono, Rockland, MA	Treatment of AIDS-associated catabolism/wasting (8/96), pediatric HIV failure to thrive (2/98)
Simulect basiliximab	Novartis Pharmaceuticals, East Hanover, NJ	Prevention of renal transplant rejection (5/98)
Synagis palivizumab	MedImmune, Gaithersburg, MD	Respiratory syncytial virus (6/98)
Thymoglobulin thymocyte globulin (rabbit)	SangStat, Menlo Park, CA	Prevention of kidney transplant rejection (12/98)
Thyrogen thyrotropin alfa for injection	Genzyme, Cambridge, MA	Detection and treatment of thyroid cancer (11/98)
TNKase tenecteplase	Genentech, South San Francisco, CA	Acute myocardial infarction (6/00)
Velosulin BR buffered regular human insulin injection (rDNA origin)	Novo Nordisk Pharmaceuticals, Princeton, NJ	Treatment of diabetes mellitus (7/99)
Verluma nofetumomab	DuPont Merck Pharmaceutical, Billerica, MA	Detection of small-cell lung cancer (8/96)
Viread tenofovir disoproxil	Gilead Sciences, Foster City, CA	HIV infection (10/01)
Vistide cidofovir injection	Gilead Sciences, Foster City, CA	Cytomegalovirus retinitis in AIDS patients (6/96)
Visudine verteporfin	QLT, Vancouver, British Columbia	Minimally classic age-related macular degeneration (4/00)
Vitravene fomviren sodium injectable	Ciba Vision, Duluth, GA Isis Pharmaceuticals, Carlsbad, CA	Treatment of cytomegalovirus retinitis in patients with AIDS (8/98)
Xigris drotrecogin alfa	Eli Lilly, Indianapolis, IN	Severe sepsis (11/01)
Zenapax daclizumab	Roche, Nutley, NJ Protein Design Labs, Fremont, CA	Prevention of acute kidney transplant rejection (12/97)
Zevalin ibritumomab	IDEC Pharmaceuticals, San Diego, CA	Treatment of relapsed or refractory low grade, follicular, or transformed B-cell non-Hodgkin's lymphoma (2/02)

APPENDIX B

A Guide to Understanding the New Biotechnology[a]

Appendix A lists a large number of major types of therapeutic products produced using genetic engineering. Many of these terms are new or unfamiliar to all but specialists. To help understand them, the following is an explanation of these new classes of products and the therapeutic benefits they may provide:

ANTICOAGULANTS/THROMBOLYTIC AGENTS—Inappropriate or unnecessary clotting of the blood is responsible for more deaths than cancer. The body's own clot-dissolving process begins with formation of the enzyme plasmin. Substances that activate plasmin are found in the body only in minute amounts. As a result of biotechnology, sufficient quantities of these substances are available and are being developed.

COLONY-STIMULATING FACTORS—The production of white blood cells is controlled by proteins called colony-stimulating factors (CSFs). Cancer chemotherapy and inherited disorders are among the causes of low white blood counts, which lower resistance to infection. CSFs are being investigated not only as a way to counteract low white blood cell counts generally but also as a way to produce specific types of white blood cells. In addition, there is hope that CSFs can stimulate the body to produce additional bone marrow as well as cause some cancer cells to stop dividing.

DISMUTASES—Dismutase, an enzyme, is important in organ transplantation and in treating heart attack when tissues have been deprived of blood for a short time. When the blood flow is restored to the transplanted organ or to the heart muscle after a clot is dissolved, the cells in the organ can be damaged by the excessively oxygen-rich blood. Dismutases prevent this *reperfusion injury* by allowing the oxygen-deprived tissues to recover their normal state in a more orderly manner.

ERYTHROPOIETIN (EPO)—Kidney disease often impairs the body's ability to produce this hormone, causing anemia, a deficiency in red blood cell production. Frequent blood transfusions or restoration of the missing hormone, EPO, can add more red blood cells to correct chronic anemia. Since transfusions may expose those who receive them to infectious agents, such as hepatitis and AIDS, EPO may provide major gains in safety and efficiency. Through genetic engineering, it is now possible to obtain EPO in large amounts, a development of great importance to the 225,000 Americans who rely on kidney dialysis machines. Researchers also are looking into ways to use EPO to treat other types of anemia, including those resulting from arthritis and the side effects of the AIDS drug Retrovir (AZT). Further, since EPO can cause a tenfold increase in red cell production, it is possible that blood banks may be turned into blood farms.

HUMAN GROWTH HORMONE—Our growth is regulated by human growth hormone (hGH) secreted by the pituitary gland. A child whose body produces insufficient hGH will be limited to an adult height of about 4 feet. It is estimated that as many as 15,000 American children suffer from hGH deficiency. Beginning in the late 1950s, such children were treated with hGH extracted from cadaver pituitaries. This not only was extraordinarily expensive but also exposed the children to the risk of infection from viral contamination of the hormone. Now, genetic engineering technology makes available pure supplies of hGH. Research is continuing to find other beneficial applications of this new product.

INTERFERONS—In 1957 it was discovered that a glycoprotein naturally produced by the cells apparently could interfere with the ability of a virus to reproduce after it invaded the body. By the mid-1970s it appeared that this protein, interferon, might also curtail the spread of certain types of cancer. The application of recombinant DNA techniques provided sufficient interferon for useful research. While much more needs to be learned about the interferons, they hold great promise. The alpha group has proved effective against hairy cell leukemia, once a lethal disease. It normalizes blood counts and controls tumor growth in 90% of patients. Alpha interferon is being investigated and has approval applications at FDA for other cancers.

INTERLEUKINS—In the 1960s it was discovered that interleukin, a natural substance occurring in the body, transmits signals between types of white blood cells, or leukocytes. While the full therapeutic potential of the interleukins is only beginning to be explored, interleukin-2 has been used to fight cancer. A patient's T cells, specialized white blood cells involved in ridding the body of diseased cells, are exposed to interleukin outside the patient's body, to activate them against the cancer. The activated T-cells are then given back to the patient, where they are much more effective in finding and destroying the cancer cells.

MONOCLONAL ANTIBODIES—Antibodies, often referred to as the body's missile defense system, are large protein molecules produced by white blood cells. They seek out and destroy harmful foreign substances. Such foreign cells are recognized by telltale surface proteins, called antigens. After the invader has been destroyed, the antibodies remain in the blood, on instant alert should a similar antigen arrive. Antibodies also are useful in matching donors and recipients in organ transplantation, in blood typing, and in measuring and identifying hormones, toxins, and various antigens in blood and fluids. In addition to their extraordinary diagnostic capability, monoclonals can be used alone for a pinpoint attack on a cancerous cell or to mop up cancerous cells remaining after conventional chemotherapy. They also can be enlisted as porters (adjuvants or adjuncts) to transport drugs, toxins, or radioactive particles to such cells.

PEPTIDES—Proteins are made of simple organic molecules called amino acids. When the amino acids are *knitted* together, they form peptide links. As more amino acids are combined, the chain of the peptide becomes longer. At a certain point, when about 40 or 50 amino acids are joined together, the peptide becomes a protein. Thus, peptides and proteins only differ by the length of their amino acid chain. The body often uses peptides as special messenger substances for specific purposes such as increasing heart beat or body temperature and turning on or off a cell that secretes an important substance. Because peptides are smaller, they travel around the body more efficiently than larger proteins. Once the peptide reaches its target and does its job, it is broken down easily by the body to stop the process. Scientists also have learned that only portions of a protein are involved in biological activity. By making the peptide portion of the protein that shows biological activity, a number of peptide drugs have been discovered.

TUMOR NECROSIS FACTOR—As far back as the 1700s, a few physicians noted that cancer regression sometimes ac-

[a] Courtesy, PhRMA, 1996.

companied an infection. In 1975 it was learned that in response to some bacterial infections, the body produces peptides that permit cells to transmit signals to one another. One such intercellular messenger, tumor necrosis factor (TNF), triggers the deployment of immune defenses that can destroy tumors. By damaging the blood vessels that nourish the tumor, it is, in effect, starved to death. Research continues on how it works and how best to control it.

VACCINES—When a virus or other germ invades the body, its immune system produces antigens to protect it by attaching to the protein coat on the surface of the virus. Genetic engineering allows large-scale production of the protein components of a virus. A vaccine using only the protein coat of the virus will still activate antigen production to neutralize the real, full virus. The *protein coat* vaccine is incapable of reproducing like the virus and therefore cannot cause the disease.

Glossary[a]

APPENDIX C

ACTINIC KERATOSES–Roughness and thickening of the skin caused by overexposure to the sun's ultraviolet rays. It can degenerate into a skin cancer called squamous cell carcinoma.

ADENOCARCINOMA—Technical name for a malignant tumor derived from a gland or glandular tissue, or a tumor of which the gland-derived cells form gland-like structures. Examples include most cancers of the colon, breast, pancreas, and kidney and many of the other organs.

ADJUNCT—An auxiliary treatment that is secondary to the main treatment.

ADJUVANT—Substance or drug that aids another substance in its action.

AIDS—Acquired immune deficiency syndrome.

ALLOGENEIC (transplantation)–Refers to having cell types that are distinct and cause reactions in the immune system.

AMYLOIDOSIS–A disease in which amyloid, an unusual protein that normally isn't present in the body, accumulates in various tissues. There are many forms of the disease. In primary amyloidosis, the cause isn't known, but it is associated with abnormalities of plasma cells. In secondary amyloidosis, the disease is secondary to another disease, such as tuberculosis. A third form is hereditary and affects nerves and certain organs.

AMYOTROPHIC LATERAL SCLEROSIS (ALS)—Also known as Lou Gehrig's disease, the most common of the motor neuron diseases, a group of rare disorders in which the nerves that control muscular activity degenerate within the brain and spinal cord, causing weakness and wasting of the muscles.

ANAPLASTIC ASTROCYTOMAS—Fast-growing primary brain tumors that originate in nerve tissue. They can produce signs of abnormal brain function, such as weakness, loss of sensation and an unsteady gait.

ANGIOPLASTY—A technique to open up blocked coronary arteries with a catheter tube.

ANKYLOSING SPONDYLITIS–An inflammatory disorder of unknown cause that primarily affects the spine. The vertebrae may fuse together and form a rigid back that is impossible to bend. The arthritis may involve large joints, such as the hip.

ANTISENSE—An antisense drug is the mirror, or complementary image, of a small segment of messenger RNA (mRNA), the substance that carries instructions *(sense)* from the genes to the cell's protein-making machinery. The antisense drug readily binds to the mRNA strand, keeping it from transmitting its instructions to the cell and thus inhibiting the production of an unwanted protein.

ATOPIC DERMATITIS—A chronic form of eczema characterized by an intensely itchy skin rash occurring in people who have an inherited tendency toward allergies, such as asthma or allergic rhinitis. It is common in babies, often appearing between the ages of 2 and 18 months.

AUTOLOGOUS (TRANSFUSION; TRANSPLANTATION)—An autologous blood transfusion uses the patient's own blood. An autologous transplantation refers to a graft in which the donor and recipient areas are in the same individual.

B- AND T-CELL LYMPHOMAS—Cancers caused by proliferation of the two principal types of white blood cells, B and T lymphocytes.

BIOTECHNOLOGY—The collection of industrial processes that involve the use of biological systems. For some of the industries, these processes involve the use of genetically engineered organisms. For the purpose of this chart, only those products that involve recombinant DNA, monoclonal antibody/hybridoma, continuous cell lines, cellular therapy, and gene therapy technology are included.

CLOTTING FACTORS—Proteins involved in the normal clotting of blood.

CLONE—A group of genetically identical cells or organisms asexually descended from a common ancestor. All cells in the clone have the same genetic material and are exact copies of the original. An additional molecular biological use of the word is to refer to a DNA plasmid construct used as the source for generation of protein/peptide pharmaceuticals.

CMV (CYTOMEGALOVIRUS)—A DNA virus related to the herpes virus, affecting mostly neonatal infants and immunocompromised individuals. CMV is sexually transmitted and can occur without symptoms or result in mild flu-like symptoms. As an opportunistic infection in AIDS patients, it can cause *CMV retinitis,* an inflammation of the retina that can lead to blindness if left untreated.

COLITIS—Inflammation of the colon or large intestine.

COLONY STIMULATING FACTOR (CSF)–Protein responsible for the production of white blood cells.

CONGESTIVE HEART FAILURE—The end result of many different types of heart disease. The heart cannot pump blood out normally. This results in congestion (water and salt retention) in the lungs, swelling in the extremities, and reduced blood flow to body tissues.

CROHN'S DISEASE–A subacute chronic gastrointestinal disorder, involving the small intestine, characterized by deep patchy ulcers that may cause fistulas and a narrowing and thickening of the bowel.

CYSTIC FIBROSIS—A genetic disorder of the exocrine glands that causes abnormal mucous secretions that obstruct glands and ducts in various organs, particularly the lungs. It is the most common fatal hereditary disorder of US Caucasians and the most common cause of chronic lung disease in children and young adults.

CYTOKINES—Substances secreted usually by cells of the immune system that can produce an effect on other cells. Chemically consist of protein hormones. Are normally involved in common and pathological functions of the immune system.

DYSPLASIA—Any abnormality of growth, such as abnormal cell features including the size, shape, and rate of multiplication of cells.

ENDOGENOUS—Arising from within the body.

ENZYME REPLACEMENT THERAPY—A therapeutic procedure in which an isolatable or genetically engineered protein is used to replace a defective or missing human enzyme.

EX VIVO—Occurring outside the body.

FUSION GENE—Made up of two or more gene-coding DNA molecules commonly fused together via DNA ligase enzyme or by a modification of the polymerase chain reaction. This results in a union of individual genetic elements that can be used in genetic engineering of a recombinant molecule designed to produce a polypeptide coded by the combined gene units.

[a] Compiled from past and current PMA/PhRMA surveys.

GENOME—The entire DNA capable of expressing all the genetic information in the cell.

GAUCHER'S DISEASE—A group of inherited diseases caused by a lack of, or deficient amount of, an enzyme *(glucocerebrosidase)* that causes an accumulation of effects throughout the body that usually results in death.

GENE THERAPY—Therapy at the intracellular level to replace or inactivate the effects of disease-causing genes or to augment normal gene functions to overcome disease.

GRAFT VS HOST DISEASE (GVHD)—A complication in bone marrow transplants in which immune system cells attack the transplant recipient's tissue.

GROWTH FACTORS—Factors responsible for regulating cell proliferation (rapid and repeated reproduction), function, and differentiation.

HEMOPHILIA A AND B—Hemophilia A, the *classic* hemophilia, is a genetic bleeding disorder caused by deficiency of the coagulation factor VIII. Hemophilia B, or *Christmas* disease, is caused by deficiency of coagulation factor IX.

HEMATOLOGICAL NEOPLASMS—Tumors of the blood-forming organs.

HEPATITIS–Inflammation of the liver with accompanying liver cell damage or death, caused most often by viral infection, eg, hepatitis A, B, and C.

HERPES SIMPLEX 2—A strain of herpes virus that may lie dormant in nerve tissue and can be reactivated to produce painful sores of the anus or genitals.

HIV—Human immunodeficiency virus (the virus that causes AIDS).

HUMAN PAPILLOMAVIRUS (HPV)—Viral agent of warts, believed to be contagious, affecting only the skin's topmost layer. Associated with human cervical cancer, since the cervix contains keratin-expressing cells.

HUNTINGTON'S DISEASE—Huntington's chorea is an uncommon, inherited disease in which degeneration of the basal ganglia results in rapid, jerky, involuntary movements and dementia (progressive mental impairment). Symptoms do not usually appear until age 35 to 50.

HYBRIDOMA—A cell culture consisting of a clone of fused cells of different kinds, eg, mouse myeloma cells and lymphocytes. A cell that produces antibody can be rendered *immortal* by fusing it with a tumor cell (see *Monoclonal*).

INFLAMMATORY BOWEL DISEASE—Term for inflammatory disorders affecting the small and/or large intestine.

INTERFERON—A glycoprotein naturally produced by cells that interferes with the ability of a virus to reproduce after it invades the body. Interferon potentially might also curtail the spread of certain types of cancer.

IN VIVO—Within the body.

ISCHEMIA—Insufficient supply of blood to an organ or tissue, which can cause damage such as an *ischemic stroke*.

IV—Intravenous.

KAPOSI'S SARCOMA—A rare, malignant skin tumor, which occurs in some AIDS patients. It can be accompanied by fever, enlarged lymph nodes, and gastrointestinal problems.

LEUKEMIA—Form of cancer in which the white blood cells are dedifferentiated and grow abnormally.

LUPUS NEPHRITIS—Inflammation of the kidney(s) caused by systemic lupus erythematosus.

LYMPHOKINE—Cytokine derived from a lymphocyte.

LYMPHOMA—Cancer in which the cells of lymphoid tissue, found mainly in the lymph nodes and spleen, multiply unchecked. Lymphomas fall into two categories: One is called *Hodgkin's disease,* characterized by a particular kind of abnormal cell. All others are called *non-Hodgkin's lymphomas,* which vary in their malignancy according to the nature and activity of the abnormal cells.

MONOKINE—Cytokine derived from a monocyte, usually a macrophage.

MALARIA VIVAX—Vivax is one of the four species of the genus *Plasmodium* responsible for human malaria, which is transmitted from human to human by the bite of infected female *Anopheles* mosquitoes.

MALIGNANT MELANOMA—A cancer made up of pigmented (usually brown-colored) skin cells anywhere in the body.

METASTASES—Secondary cancers that have spread from the primary or original cancer site.

MONOCLONAL—Derived from a single cell; pertaining to a single clone. *Monoclonal antibodies* are produced from hybrid cells by use of hybridoma technology; these antibodies can be traced back to production by a single cell.

MULTIPLE MYELOMA—A malignant condition characterized by uncontrolled proliferation of plasma cells (a class of white blood cells) in bone marrow. Symptoms include pain and destruction of bone tissue, numbness and paralysis, kidney damage, anemia, and frequent infections. The condition is rare and affects those of middle to older age groups.

MULTIPLE SCLEROSIS (MS)—Progressive disease of the central nervous system in which scattered patches of the covering of nerve fibers (myelin) in the brain and spinal cord are destroyed. Symptoms range from numbness and tingling to incontinence and paralysis.

MYELODYSPLASTIC SYNDROMES—A group of acquired blood disorders, often referred to as *preleukemia,* which ultimately are fatal, as patients usually succumb to infections or bleeding.

MYELOGENOUS LEUKEMIA—One of the many forms of cancer of the blood-forming organs in the bone marrow. The blood cells are not complete and do not function properly.

MYOCARDIAL INFARCTION—Damage to the heart muscle caused by stoppage or impairment of blood flow to the heart, also known as a heart attack.

NECROTIZING FASCIITIS–An extremely severe form of cellulites (bacterial skin infection) that destroys infected tissue under the skin. Some refer to it as the "flesh-eating disease."

NEUROBLASTOMA—A tumor of the adrenal glands or sympathetic nervous system. Neuroblastomas are the most common extracranial (outside the skull) solid tumor of childhood.

NEUTROPENIA—Caused by an abnormally low neutrophil count (certain white blood cells), leaving a patient vulnerable to bacterial infections.

ONCOLYTIC VIRUSES–The use of viruses to preferettially infect and kill cancer cells while not harming healthy cells. Oncolytic refers to lysis or breakdown of cancer cells through the process of apoptosis. There are many methods of oncolytic virus therapy, all of which involve the virus becoming active in cancer cells that have specific genetic and metabolic transformations.

OSTEOMYELITIS—Infection of bone and bone marrow, usually caused by bacteria.

OXYGEN TOXICITY IN PREMATURE NEONATES—Incomplete development of the lungs in premature babies causes damage from high oxygen levels.

PARKINSON'S DISEASE—Chronic neurological disease of unknown cause, characterized by tremors, rigidity, and an abnormal gait. There is an imbalance of dopamine and acetylcholine, brain neurotransmitters. Some patients with advanced disease develop dementia. It is a common chronic disease of later life.

PERIPHERAL NEUROPATHY—Disease, inflammation, or damage to the peripheral nerves, which connect the central nervous system to the sense organs, muscles, glands, and internal organs.

PERTUSSIS—Also called *whooping cough,* which mainly affects infants and young children.

PHASE I—Safety testing and pharmacological profiling in humans.

PHASE II—Effectiveness testing in humans.

PHASE III—Extensive clinical trials in humans.

PRADER-WILLI SYNDROME–A genetic disorder characterized by short stature, mental retardation, abnormally small

hands and feet, hypogonadism, and uncontrolled appetite leading to extreme obesity.

PROPHYLAXIS—Preventive treatment; intended to preserve health and prevent the spread of disease.

PSEUDOMONAS INFECTIONS—Refers to infections caused by a genus of bacteria called *Pseudomonas*.

PULMONARY EMBOLISM—A blood clot that obstructs the pulmonary artery, which transports blood from the heart to the lungs. More than 90% of pulmonary emboli originate as clots in the deep veins of the lower extremities (deep vein thromboses). They can result in sudden death.

RECOMBINANT DNA—The hybrid DNA produced by joining pieces of DNA from different sources. Usually designated as rDNA.

RECOMBINANT SOLUBLE RECEPTORS—Synthetic version of cellular receptors manufactured with recombinant DNA technology, used as decoys to attract pathogens that otherwise would bind to cellular receptors and cause disease. They are *soluble* because they are freestanding and not attached to cells.

RESPIRATORY SYNCYTIAL VIRUS DISEASE (RSV)—One of the most important causes of lower respiratory tract disease in children, accounting for more than 90% of cases of bronchiolitis.

RENAL ALLOGRAFT REJECTION—Rejection of a transplanted kidney.

RENAL FAILURE—Kidney failure.

RHINITIS—Inflammation of the membranes of the nose.

SEPSIS—A condition associated with the presence of bacteria in the blood. *Gram-negative sepsis* is caused by a particular kind of bacteria.

SEPTIC SHOCK—Blood poisoning due to reaction to toxins made by bacteria. The effects of shock include a sudden drop in blood pressure and changes in heart rate and temperature.

SCLERODERMA—Shrinkage and hardening of the skin anywhere in the body.

STROKE (CEREBRAL THROMBOSIS)—Usually caused by atherosclerosis, a blood clot obstructs a major blood vessel of the brain, resulting in death or serious brain damage.

THALASSEMIA—An inherited blood disorder in which the abnormal production of hemoglobin causes fragile and broken blood cells leading to anemia.

THROMBOCYTOPENIA—A reduction in the number of platelet cells in the blood, which causes a tendency to bleed, especially from the smaller blood vessels.

TISSUE PLASMINOGEN ACTIVATOR (TPA)—tPA is a substance produced in small amounts by the inner lining of blood vessels that prevents abnormal blood clotting by converting plasminogen (an inactive protein in the blood) to the active enzyme plasmin.

TURNER'S SYNDROME—Females born with a missing X chromosome are characterized by shortness of stature, webbed neck, absence or very retarded development of secondary sexual characteristics, absence of menstruation, narrowing of the aorta, eye and bone abnormalities, some mental retardation, and infertility.

UNSTABLE ANGINA—An accelerating pattern of chest pain in cases of previously stable angina, which is caused by insufficient oxygen in the heart muscle.

VENOUS STASIS—Diminished or complete stoppage of blood flow through one or more veins.

WASTING SYNDROMES—Any number of conditions, such as anorexia and cachexia, resulting in a loss of body mass, notably protein.

CHAPTER 50

Aerosols

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Inhalation therapy has been used for many years, and there has been a resurgence of interest in delivery of drugs by this route of administration. The number of new drug entities delivered by the inhalation route has increased over the past 5 to 10 years. This type of therapy also has been applied to delivery of drugs through the nasal mucosa, as well as through the oral cavity for buccal absorption. Originally, this type of therapy was used primarily to administer drugs directly to the respiratory system (treatment of asthma); inhalation therapy is now being used for drugs to be delivered to the bloodstream and finally to the desired site of action. Proteins (insulins), steroids, cardiac agents, immunizing agents, etc, are being developed for delivery in this manner.

Drugs administered via the respiratory system (inhalation therapy) can be delivered either orally or nasally. Further, these products can be developed as a:

nebulizer/atomizer
dry powder inhaler
nasal inhaler
metered dose aerosol inhaler

Drugs delivered via a nebulizer/atomizer are generally formulated as aqueous solutions (or suspensions) and are inhaled by the patient through an atomizer, nebulizer, or other similar devices. These products are not included in this chapter.

Dry powders have been used for inhalation therapy for over 75 years. The active ingredients were packaged in capsules, representing a single dose of drug. The capsule was punctured and a small amount of powder fell into a chamber while the patient inhaled. The procedure was repeated until all of the powder was inhaled. While these dry powders were somewhat popular during the early 1940s–1950s, they fell into disuse with the introduction of the aerosol metered dose inhaler, which became available around 1955. This first generation MDI was formulated with chlorofluorocarbons (CFC), was compact, and contained epinephrine hydrochloride or albuterol as the active ingredient. These MDIs quickly became the dosage form of choice for inhalation therapy, especially for the treatment of asthmatics. With the phase out of CFC's starting in 1996, dry powders containing about 25–30 to 60 doses of active ingredient were developed and became commercially available from 2000 to 2003. Several dry powder inhalers currently available include salmeterol, fluticasone, and budesonide. Mometasone dry powder inhaler is available in Europe while insulin dry powder inhaler is presently in the final stages of development and submitted to the Food and Drug Administration for review. These dry powder inhalers do not contain a propellant. These consist of active, very potent drugs that are dispensed from a specially designed package. An accurate amount of drug as a dry powder is released while the patient inhales deeply. The dry powder will then travel to the lungs along with the inspired air. The technology of dry powders is not a part of this chapter.

The nasal metering drug delivery system produces an aqueous spray consisting of active ingredient and excipients. The drugs used can act locally within the nasal mucosa or systemically by passing through the nasal mucosa and enter the general circulation system. This occurs via numerous capillary vessels present in the mucosa. These nasal sprays can also be formulated similar to MDIs using propellants and a nasal adapter. The latter type of nasal inhaler is included in this chapter.

The development of the metered-dose inhaler (MDI) in the mid 1950s made possible a convenient dosage form for the delivery of medication to the respiratory system. Atomizers and nebulizers were cumbersome to use and in many instances did not offer convenience of use, so that administration of drugs by atomizers/nebulizers was generally left to hospital or at-home use. While many improvements were made to these nebulizers and atomizers, they lacked the convenience of use especially as to their portability and use outside of a hospital and/or home setting.

Metered Dose Inhalers consists of a pressurized container filled with active ingredient, excipients and propellant, and a metered-dose valve. The pressurized container is placed within an oral adapter (mouthpiece), and when the unit is dispensed, an exact amount of drug is expelled in the proper particle size distribution to achieve maximum deposition of drug into the lungs. The aerosol dosage form (MDI) has become the dosage form of choice for delivery of drugs to the lungs. Metered dose inhalers are formulated as solutions or suspensions of active drug in a mixture of solvents, dispersing agents, and liquefied gas propellants.

Topical pharmaceutical aerosols can be formulated as a spray, foam, and semisolid and can be used to deliver therapeutic agents topically to the skin surface, rectally, and vaginally. They consist of a liquid, emulsion, or semisolid concentrate and liquefied gas or compressed gas propellant. Each of these systems is discussed in later parts of this chapter.

Many therapeutically active ingredients have been administered or applied to the body by means of the aerosol dosage form. This dosage form has been used orally to dispense a variety of agents such as budesonide, salmeterol xinafoate, fluticasone propionate, fenoterol, epinephrine hydrochloride, albuterol, albuterol sulfate, metaproterenol sulfate, cromolyn sodium, flunisolide hemihydrate, ipratropium bromide, beclomethasone dipropionate, and triamcinolone acetonide. These MDIs were formulated using a CFC propellant and are currently in widespread use in the United States even though the use of CFCs has been phased out throughout the world. Some exemptions have been granted to Third World Countries

and "essential use" exemption has been granted to MDIs, which were commercially available prior to the year 2000.

Oral aerosols have been used mainly for the symptomatic treatment of asthma as well as for the treatment of several other ailments. These aerosols have been readily accepted by both physician and patient.

ADVANTAGES—One of the main reasons for the rapid and widespread acceptance of the MDI dosage form for the administration of therapeutically active agents is that it affords many distinct advantages to the user. These advantages have been described by various investigators and, for MDIs, include:

Rapid onset of action
Circumvention of the first-pass effect and avoidance of degradation in the GI tract
Lower dosage that will minimize adverse reactions, especially in the case of steroid therapy where most of the steroid reaches the respiratory tract and less is swallowed
Dose titration to individual needs and ideal for prn medication
Alternate route when therapeutic agent may interact chemically or physically with other medicinals needed concurrently
Viable alternative when the drug entity exhibits erratic pharmacokinetics upon oral or parenteral administration
Container and valve closure are tamperproof

The pressure package is convenient and easy to use. Medication is dispensed in a ready-to-use form at the push of a button. There is generally no need for further handling of the medication. Since the medication is sealed in a tamperproof pressure container, there is no danger of contamination of the product with foreign materials, and at the same time, the contents can be protected from the deleterious effects of both air and moisture. Easily decomposed drugs, such as epinephrine, lend themselves to this type of package as oxygen is excluded from the headspace.

Sterility is always an important consideration with certain pharmaceutical and medicinal preparations. While initial sterility is generally no problem to the manufacturer, there is concern for the maintenance of the sterility of the package during use as, for example, with ophthalmic preparations. When necessary, the aerosol package can be prepared under aseptic conditions, and sterility be maintained throughout the life of the product. For those products requiring regulation of dosage, a metering valve can be used. An accurately measured dose of therapeutically active drug can be administered quickly and, in the case of drugs for inhalation, buccal or nasal application, in the proper particle-size range.

There are many advantages to the administration of medicinal agents by inhalation, buccally and nasally. Response to drugs administered by inhalation, buccally and nasally, is prompt, often very specific and with minimal side effects, faster in onset of activity than drugs given orally and, with most drugs, approaches intravenous therapy in rapidity of action. Drugs that normally are decomposed in the GI tract can be administered safely by inhalation, buccally and nasally. The use of the self-pressurized aerosol package makes this type of therapy simple, convenient, and acceptable, compared with the use of atomizers and nebulizers, which are bulky and require cleaning.

DEFINITIONS—The term *aerosol* is used to denote various systems ranging from those of a colloidal nature to systems consisting of *pressurized packages*. Aerosols have been defined as colloidal systems consisting of very finely subdivided liquid or solid particles dispersed in and surrounded by a gas. Originally, the term *aerosol* referred to liquid or solid particles having a specific size range, but this concept has fallen into disuse.

The present-day definition refers to those products that depend upon the power of a liquefied or compressed gas to dispense the active ingredient(s) in a finely dispersed spray, foam, or semisolid. Pump systems that also dispense the active ingredient(s) in the form of a finely dispersed mist (although of greater particle size) often are classified as aerosols. These pump systems generally are used to dispense medication intranasally.

In 1978, the use of certain chlorofluorocarbons (CFCs) was curtailed by the FDA, EPA, and CPSC. These restrictions applied to the use of Propellants 11, 12, and 114 (CFCs) for use in all aerosol products. Exemptions were granted to MDIs and a few other essential uses. Because of these restrictions, new valve systems and dispensing systems, which allowed greater use of liquefied hydrocarbons and compressed gases, were developed for non-MDIs. While newer HFA propellants were developed for use with MDIs, CFC propellants still can be used to produce medicinal aerosols that are currently commercially available in the US. These regulatory requirements are discussed in greater detail in the *Propellant* section of this chapter.

MODE OF OPERATION

Liquefied-Gas Systems

Liquefied gases have been used widely as propellants for most aerosol products. These compounds are useful for this purpose, since they are gases at room temperature and atmospheric pressure. However, they can be liquefied easily by lowering the temperature (below the boiling point) or by increasing the pressure. The compounds chosen generally have boiling points below 70°F (21°) and vapor pressures between 14 and 85 psia at 70°F (21°). When a liquefied-gas propellant is placed into a sealed container, it immediately separates into a liquid and a vapor phase.

Since these materials are liquefied gases, some of the molecules will leave the liquid state and enter the vapor state. As molecules enter the vapor state, a pressure gradually develops. As the number of molecules in the vapor state increases, the pressure also will increase. An equilibrium soon is attained between the number of molecules changing from a liquid to a vapor and from a vapor to a liquid. The pressure at this point is referred to as the vapor pressure (expressed as psia) and is characteristic for each propellant at any given temperature. The term psig (pounds/square inch gauge) represents the uncorrected gauge pressure and is to be distinguished from psia (pounds per square inch absolute), which is corrected to include atmospheric pressure (0 psig, which equals 14.7 psia). This vapor pressure is exerted equally in all directions and is independent of the quantity of liquefied gas present.

The pressure exerted against the liquid phase is sufficient to push the latter up a dip tube and against the valve. In cases when there is no dip tube (MDIs) the container is used in the inverted position so that the liquid phase is in direct contact with the valve. When the valve is opened, the liquid phase is emitted and comes into contact with the warm air at atmospheric pressure. The liquid propellant immediately reverts to the vapor state, since its boiling point is substantially below room temperature. As the contents of the container are expelled, the volume within the container occupied by the vaporized propellant increases, causing a temporary fall in pressure. However, as soon as the pressure decreases, a sufficient number of molecules change from the liquid state to the vapor state and restore the original pressure. When a compressed gas is used as the propellant, the relationship is quite different, and there is a drop in pressure as the contents are used.

TWO-PHASE SYSTEM—This is the simplest of all aerosol systems. It consists of a solution or a suspension of active ingredients in liquid propellant or a mixture of liquid propellant and solvent. Both a liquid and a vapor phase are present, and when the valve is depressed, liquid propellant containing dissolved active ingredients and other solvents are released. Depending on the nature of the propellants used, the quantity of propellant present, and the valve mechanism, a fine mist or wet spray is produced because of the large expansion of the propellant at room temperature and atmospheric pressure. This system is used to formulate aerosols for inhalation or nasal application.

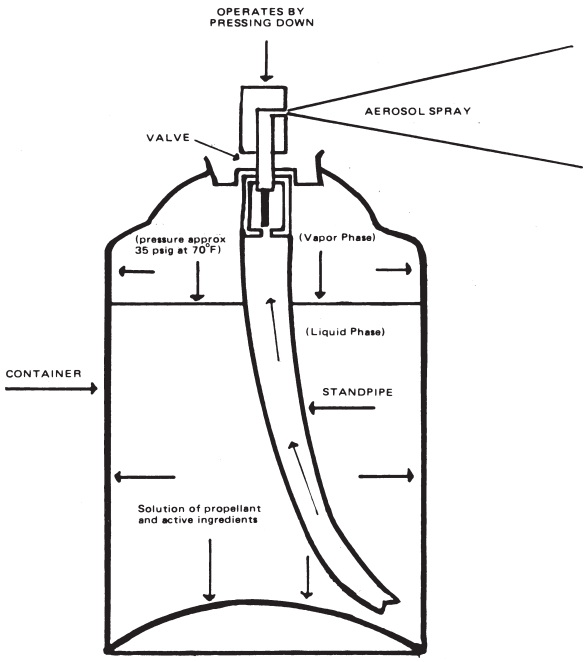


Figure 50-1. Cross-section of a typical space or surface-coating aerosol spray.

Fluorocarbon propellants, primarily trichloromonofluoromethane (P-11), dichlorodifluoromethane (P-12), and dichlorotetrafluoroethane (P-114), are used for MDIs provided that they currently have been approved under an NDA or ANDA. All new products must use other fluorocarbon propellants that are environmentally acceptable, a hydrocarbon propellant, or a compressed gas. The section dealing with propellants indicates those that are useful for this purpose.

A *space spray* generally contains from 2 to 20% active ingredients and from 80 to 98% propellant. While the pressure of space sprays is in the range of 30 to 40 psig, the particles that are produced range from less than 1 to 50 μm. These particles remain suspended in air for relatively long periods of time. Space insecticides, room deodorants, and vaporizer sprays are examples of this type of system. MDIs formulated with a non-CFC propellant will generally have a internal pressure of about 50 to 70 psig.

A *surface-coating spray* (a relatively wet or coarse spray) can be achieved by decreasing the amount of low-boiling propellants and increasing the ratio of active ingredients and solvents. The product concentrate can vary from 20 to 75%, and the propellant from 25 to 80%. Particles are produced ranging in size from 50 to 200 μm. Products such as hair sprays, residual insecticides, perfumes, colognes, paints, protective coatings, and topical sprays are formulated in this manner. The pressure of this system is generally lower than that in the space spray.

Figure 50-1 shows a cross-section of a typical space or surface-coating aerosol spray.

The liquefied gas propellants widely used for MDIs include those shown in Table 50-1. Combinations of these propellants are used to achieve the desired spray characteristics. In certain instances the nature of the product will determine the propellant combination. Dispersion or suspension sprays used for MDIs are similar to space sprays in that they are two-phase systems, in which the active ingredients are either dissolved or suspended, in the liquid propellant phase. At the present time Propellants 12, 12/11, or 12/114, are used for these inhalation aerosols that are exempted from the CFC ban. Propellant 134a is used to formulate the only non-CFC MDIs approved by the FDA for use in the U.S. Propellant 227 also can be used to formulate aerosols with a non-CFC propellant. Their properties are shown in Table 50-2. Propellant 152a can be used in topical aerosols along with hydrocarbons, dimethyl ether (DME), and compressed gases. The properties of these propellants are included in Tables 50-3 to 50-5.

THREE-PHASE SYSTEM—This system is useful for topical pharmaceutical aerosols in that it allows a greater use of liquid components not miscible with the propellants. Water is not miscible with liquefied-gas propellants and, in many instances, presents a problem, since active ingredients are soluble in water. With the increased emphasis upon the decrease of volatile organic compounds (VOCs) in all products, these systems are finding increased use. These problems have been overcome to a large extent by use of the three-phase system. Depending on the nature of the formulation, one of the following two systems may be employed. Dimethyl ether is most useful for products containing large amounts of water.

Two-Layer System—In this system the liquid propellant, the vaporized propellant, and the aqueous solution of active ingredients make up the three phases. Since the liquid propellant and water are not miscible, the liquid propellant will separate as an immiscible layer. When a hydro alcohol mixture is used, the propellant and hydro alcohol solution will mix and form a single layer. When this propellant is of the fluorocarbon type, being denser than water, it will fall to the bottom of the container. Hydrocarbons, on the other hand, are lighter than water and, when used in this manner, will float on top of the aqueous layer. A spray is produced by the mechanical action of an exceedingly small valve orifice through which the liquid and some vaporized propellant are forced by the vapor pressure of the propellant. The vapor layer is replaced continuously by vaporization of the liquid layer of propellant. This action results in the maintenance of a constant vapor pressure in the headspace.

An important characteristic of this system is that the propellant layer can be adjusted by varying the components so its specific gravity is almost equal to, but does not exceed, that of the hydroalcoholic phase. The propellant floats on top of the hydro alcoholic phase and, when shaken, is dispersed easily. When the valve is depressed, sprays are produced of varying

Table 50-1. Properties of Fluorocarbons (CFCs)

PROPERTY		TRICHLOROMONOFLUOROMETHANE	DICHLORODIFLUOROMETHANE	DICHLOROTETRAFLUOROETHANE
Molecular formula		CCl_3F	CCl_2F_2	$CClF_2CClF_2$
Numerical designation		11	12	114
Molecular weight		137.28	120.93	170.93
Boiling point (1 atm)	°F	74.7	−21.6	38.39
	°C	23.7	−29.8	3.55
Vapor pressure (psia)	70°F	13.4	84.9	27.6
	130°F	39.0	196.0	73.5
Liquid density (g/mL)	70°F	1.485	1.325	1.468
	130°F	1.403	1.191	1.360
Solubility in water (weight %)	77°F	0.11	0.028	0.013

Table 50-2. Properties of Hydrofluorocarbons (HFCs)

PROPERTY		TETRAFLUOROETHANE	HEPTAFLUOROPROPANE
Molecular formula		CF_3CH_2F	CF_3CHFCF_3
Numerical designation		134a	227
Molecular weight		102	170
Boiling point (1 atm)	°F	−15.0	−3.2
	°C	−26.2	−16.5
Vapor pressure (psig)	70°F	71.1	43 at (20°)
	130°F	198.7	—
Liquid density (g/mL)	21.1°	1.22	1.41
Flammability		Nonflammable	Nonflammable
Solubility in water	% w/w	0.150	0.058

Table 50-3. Properties of Hydrochlorofluorocarbons (HCFCs)

PROPERTY		DIFLUOROETHANE
Molecular formula		CH_3CHF_2
Numerical designation		152a
Molecular weight		66.1
Boiling point (1 atm)	°F	−12.0
	°C	−11.0
Vapor pressure (psia)	70°F	63.0
	130°F	176.3
Liquid density (g/mL)	70°F	0.91
	130°F	—
Solubility in water (weight %)	77°F	<1.0

Table 50-4. Properties of Hydrocarbons and Ethers

PROPERTY	PROPANE	ISOBUTANE	*N*-BUTANE	DIMETHYL ETHER
Molecular formula	C_3H_8	C_4H_{10}	C_4H_{10}	CH_3OCH_3
Molecular weight	44.1	58.1	58.1	46.1
Boiling point (°F)	−43.7	10.9	31.1	−13
Vapor pressure (psig at 70°F)	110.0	30.4	16.5	63.0
Liquid density (g/mL at 70°F)	0.50	0.56	0.58	0.66
Flash point (°F)	−156	−117	−101	—

Table 50-5. Properties of Compressed Gases

PROPERTY	CARBON DIOXIDE	NITROUS OXIDE	NITROGEN
Molecular formula	CO_2	N_2O	N_2
Molecular weight	44	44	28
Boiling point °F	−109[a]	−127	−320
Vapor pressure, psia, 70°F	852	735	492[b]
Solubility in water,[c] 77°F	0.7	0.5	0.014
Density (gas) g/mL	1.53	1.53	0.96699

[a] Sublimes
[b] At the critical point (−233°F)
[c] Volume of gas at atmospheric pressure soluble in one volume of water.

characteristics depending on the nature of the formulation. This system is designed to dispense pressurized products efficiently and economically using relatively small amounts of hydrocarbon, HFA, or HCFC propellants.

The vapor phase of the propellant and the product concentrate enter the mixing chamber in the actuator through separate ducts or channels. The vaporized propellant enters, moving at tremendous velocity, while the product is forced into the actuator by the pressure of the propellant. It is at this point that product and vapor are mixed with violent force, resulting in a uniform, finely dispersed spray. Depending on the configuration of the valve and actuator, either a dry or a wet spray can be obtained.

Water-based aerosols developed for use in this system have the advantage that the chilling effect associated with liquefied-gas systems is eliminated. Since only vaporized propellant is dispensed, less propellant is required in the container. With greater use of water as a solvent for active ingredients a greater range of products can be developed. Because the use of volatile organic compounds (VOCs) is now being curtailed, water is being used, when possible, as an alternative to some solvents such as alcohol. The use of P-152a and/or DME as a propellant also helps to reduce the VOC content of some aerosols such as hairsprays. Table 50-3 and Table 50-4 illustrates the properties of these propellants.

Foam System—Foam aerosols, which often are classified separately, consist of three-phase systems in which the liquid propellant, which normally does not exceed 10 to 15% by weight, is emulsified with the propellant. When the valve is depressed, the emulsion is forced through the nozzle, and in the presence of warm air and at atmospheric pressure; the entrapped propellant reverts to a vapor and whips the emulsion into a foam. The use of a dip tube is optional with this type of system, and when present, the container is designed for upright use. For those containers where the dip tube is omitted, the container must be inverted prior to use.

Foam valves have been developed that are applicable to both types of packages. Foam products operate at a pressure of about 30 to 45 psig at 70°F (21°) and generally contain about 4% to 7% propellant, depending upon the nature of the propellant. Hydrocarbon propellants are used at the lower percentage, since their density is much lower than that of their fluorocarbon counterparts. A typical foam-type aerosol can be seen in Figure 50-2. Shave creams, suntan foams, as well as several topical dermatological aerosols have been formulated as foam aerosols. Generally, a blend of propane/isobutane or propane/isobutane/butane or isobutane alone is used for foam aerosols.

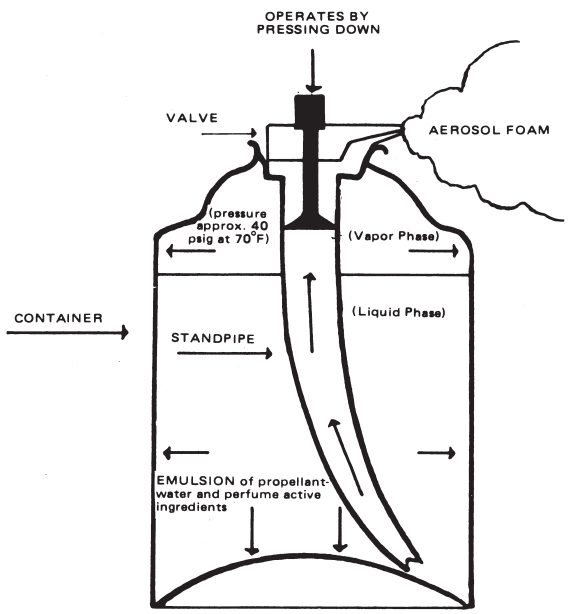


Figure 50-2. Foam-type aerosol.

Some foams use P-152a as the propellant, since this propellant will produce a somewhat more stable foam and is less flammable than hydrocarbons. It is also possible to use the non-CFC propellants for foams. Depending on the formulation, some aerosols use nitrous oxide, carbon dioxide, or a mixture of both as the propellant. Contraceptive foam aerosols are formulated with a hydrocarbon, generally A-31, as the propellant.

Compressed-Gas Aerosols

Aerosols using compressed gases as the propellant are finding increased use. These propellants, especially nitrogen, carbon dioxide, and nitrous oxide, are acceptable for use with pharmaceuticals. Compressed gases are used to dispense the product as a solid stream, wet spray, or foam. These aerosol products use an inert gas such as nitrogen, carbon dioxide, or nitrous oxide as the propellant. The gas is compressed in the container, and it is the expansion of the compressed gas that provides the push or the force necessary to expel the contents from the container. As the contents of the container are expelled, the volume of the gas will increase, causing a drop in pressure according to Boyle's law. This enables one to calculate the drop in pressure as the contents of a compressed-gas aerosol are used. Table 50-5 indicates some of the more important properties of these compressed gases. Depending upon the nature of the formulation and the type of compressed gas used, the product may be dispensed as a semisolid, foam, or spray.

Semisolid Dispensing—The concentrate generally is semisolid in nature, and since the gas is insoluble and immiscible with the concentrate, the product is dispensed in its original form. This system is applicable to the dispensing of dental creams, hairdressings, ointments, creams, cosmetic creams, foods, and other products. Compressed-gas aerosols operate at a substantially higher initial pressure of 90 to 100 psig at 70°F (21°). This pressure is necessary to ensure adequate pressure for the dispensing of most of the contents from the container. The amount of product retained in the unit after exhaustion of the pressure varies with the viscosity of the product and loss of pressure due to seepage of gas during storage. Since the concentrate generally is semisolid in nature and the dispensing characteristics depend largely on the viscosity of the product and the pressure within the container, the viscosity of the product concentrate must be adjusted accordingly.

Foam Dispensing—Soluble compressed gases such as nitrous oxide and carbon dioxide can be used to produce a foam when used with emulsion products. This system is typical for whipped creams and toppings and several pharmaceutical and veterinary products. When this system is used, the gas dissolved in the concentrate will be evolved and cause a whipping of the emulsion into a foam. To facilitate the formation of a foam this system is shaken prior to use, to disperse some of the gas throughout the product concentrate.

Spray Dispensing—This system is similar to a space or surface spray except that a compressed gas is used as the propellant. Since these gases do not possess the dispersing power of the liquefied gases, a mechanical breakup actuator is used. The product is dispensed as a wet spray and is applicable to solutions of medicinal agents in aqueous solvents.

Another application for this type of system is found in the contact lens saline solutions. These consist of a normal saline solution packaged in an aluminum aerosol container and pressurized with nitrogen. Since these solutions may come in contact with the eye, they are sterilized using cobalt-60 gamma irradiation.

Barrier-Type Systems

These systems separate the propellant from the product itself. The pressure on the outside of the barrier serves to push the contents from the container. The following types are available.

PISTON TYPE—Since it is difficult to empty the contents of a semisolid from an aerosol container completely, a piston-type aerosol system has been developed. This uses a polyethylene piston fitted into an aluminum container. The product is placed into the upper portion of the container. The pressure from nitrogen (about 90 to 100 psig) or a liquefied gas pushes against the other side of the piston, and when the valve is opened, the product is dispensed. The piston scrapes against the sides of the container and dispenses most of the product concentrate. The piston-type aerosol system is shown in Figure 50-3. This system has been used successfully to package cheese spreads, cake decorating icings, and some ointments and creams. Since the products that use this system are semisolid and viscous, they are dispensed as a lazy stream rather than as a foam or spray. This system is limited to viscous materials, since limpid liquids, such as water or alcohol, will pass between the wall of the container and the piston. The piston type system has also been used to formulate post-foaming type gels.

PLASTIC-BAG AND BAG-IN-BAG TYPE—This system consists of a collapsible plastic bag fitted into a standard, three-piece, tinplate or aluminum container as shown in Figure 50-4. The product is placed within the bag, and the propellant is added through the bottom of the container. Since the product is placed into a plastic bag, there is no contact between the product and the container wall except for any product that may escape by permeation through the plastic bag. A variation of this system is shown in Figure 50-5. The valve and a collapsed inner bag is inserted into a container. A compressed or liquefied gas is added at the same time as the valve/bag is inserted and then the valve is crimped. The product is forced through the valve and into the bag. The bag expands and will compress the propellant resulting in an increase in pressure. As the valve is opened, the product will be dispensed. Ointments, creams, and gels can be packaged in this system.

Limpid liquids, such as water, can be dispensed as either a stream or a fine mist, depending on the type of valve used, while semisolid substances are dispensed as a stream. To prevent the gas from pinching the bag and preventing the dispensing of product, the inner plastic bag is accordion-pleated.

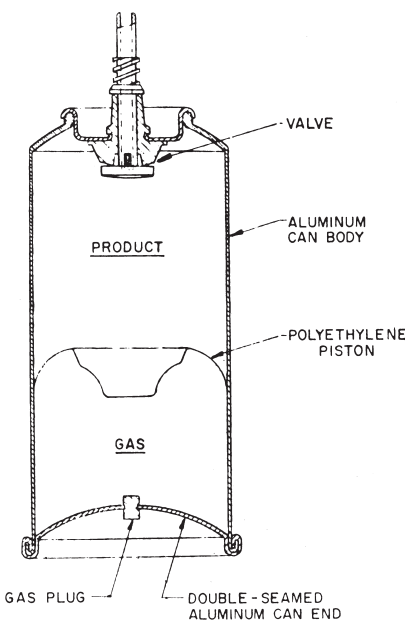


Figure 50-3. Free-piston aerosol system.

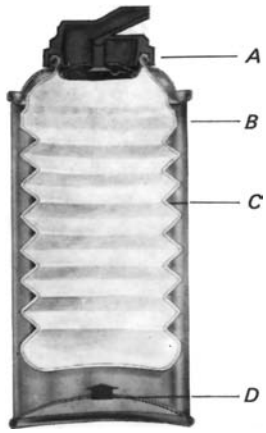


Figure 50-4. Plastic Bag Aerosol System.

This system can be used for a variety of different pharmaceutical and nonpharmaceutical systems, including topical pharmaceutical products as a cream, ointment, or gel.

A modification of the barrier system dispenses the product as a gel that will then foam. By dissolving a low-boiling liquid such as isopentane or pentane in the product, a foam will result when the product is placed on the hands and the warmth of the hands will cause vaporization of the solvent. This system, as well as the piston system, is used in post foaming shave gels.

CAN-IN-CAN SYSTEMS—Figure 50-6 illustrates a system consisting of an aluminum can into which an aluminum thin-walled can has been inserted. This inner can is glued to the outer can at the neck and forms a gas-tight seal. Then, the neck of the can is fabricated. The propellant (liquid or compressed) is added through a small opening in the bottom of the can that is sealed with a rubber plug. A recent addition to this system includes replacement of the inner aluminum pouch with an inner plastic bag made of organic polymers. Sufficient space remains between this bag and the walls and the bottom of the outer container to accommodate sufficient propellant to evacuate the product completely. Systems illustrated by Figure 50-6 can be used with a continuous or metered dose valve to dispense medicated solutions, gels, creams, and lotions.

Figure 50-5. Bag-in Can System–ABS (courtesy, CCL Container, Aerosol Division).

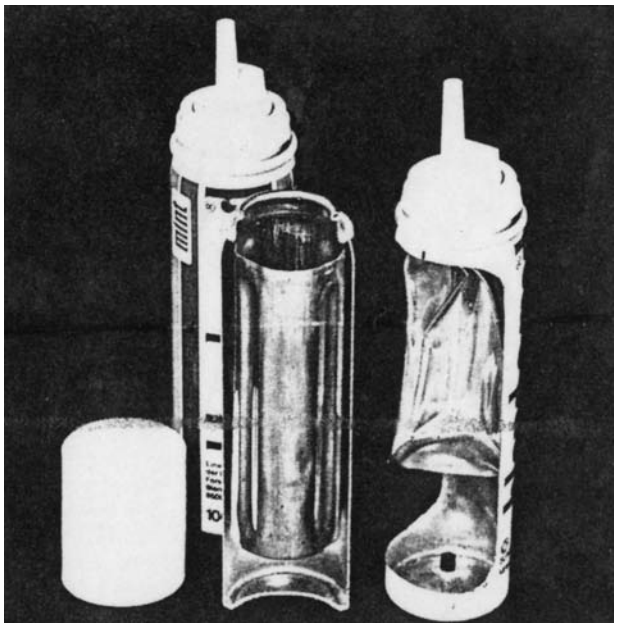


Figure 50-6. Cross-section of the Lechner barrier pack. It consists of a rigid or flexible inner bag that can be evacuated more than 95%, depending upon the viscosity of the product (courtesy, Lechner GMBH).

PROPELLANTS

The propellant generally is regarded as the *heart* of the aerosol package. In addition to supplying the necessary force to expel the product, the propellant must also act as a solvent and diluent and has much to do with determining the characteristics of the product as it leaves the container. Various chemical compounds have been used as aerosol propellants.

Compounds useful as propellants can be classified as:

Liquefied gases
Chlorofluorocarbons (CFC)
Hydrochlorofluorocarbons (HCFC)
Hydrofluorocarbons (HFC)
Hydrocarbons (HC)
Hydrocarbon ethers
Compressed gases

Liquefied Gases

The liquefied-gas compounds have widespread use as propellants, since they are extremely effective in dispersing the active ingredients into a fine mist or foam, depending on the form desired. In addition, they are relatively inert and nontoxic. They have the added advantage that the pressure within the container remains constant. Two types of liquefied gases are used. The chlorofluorocarbons (CFCs) and hydrofluorocarbons (HFCs) find greater use since they are nonflammable in contrast to the flammable hydrocarbons. The hydrocarbons are advantageous since they are less expensive than any of the fluorocarbons and generally are environmentally acceptable.

CHLOROFLUOROCARBONS (CFCS)—These compounds have been implicated in causing a depletion of the ozone layer and for responsibility for the *greenhouse* or for the *global warming* effect (increase in earth's temperature, rising sea levels, and altered rainfall patterns). Depletion of the ozone layer is also alleged to have resulted in an increase in the incidence of skin cancer. This is due to a greater penetration of the ozone layer by the skin-cancer-causing UV radiation from the sun (the ozone layer will prevent these rays from penetrating the earth's atmosphere). In 1974, the Environmental Protection Agency (EPA), Consumer Product Safety Commission (CPSC), and the FDA promulgated a *ban* on the use of chlorofluorocarbons, namely Propellants 11, 12, and 114, in most aerosol products. Certain pharmaceutical aerosols for inhalation use (MDIs) were exempted from this ban. According to the Montreal Agreement reached in 1988, beginning in 1989, the production of these propellants was restricted worldwide. Starting January 1, 1996, worldwide production of CFCs was reduced to only the amount needed for certain exempted uses that included MDIs for the treatment of asthma and chronic obstructive pulmonary disease (COPD). CFC propellants are used in all of the metered dose inhalers in the US. MDIs have been classified by the Environmental Protection Agency and Food and Drug Administration as "essential use" and as such are exempted from the ban on the use of CFCs. The EPA granted allocation of CFC 11, 12, and 114 to those manufacturers of MDI inhalers currently being sold so that these products can continue to be manufactured and available in the US marketplace. At the present time, no firm date has been issued by the EPA as to when CFCs will no longer be available; however, EPA regulations prohibit the granting of a CFC allocation for any MDI classified as essential use and not approved by the FDA prior to December 31, 2000. Essentially this ruling prevents the development and sale of a generic version of these CFC containing MDIs. MDIs containing Albuterol are the only MDI products available in generic form. All other CFC propelled MDIs can continue to be sold in the marketplace free from generic product competition.

Generic MDI products containing Albuterol and those containing Epinephrine have been developed since the late 1990s and are currently marketed by generic pharmaceutical companies. No other generic version of an MDI product is available in the US.

In the latter part of the 1990s, FDA issued a ruling to encourage the development of ozone-friendly propellants (HFAs) so that essential use designation could be removed. This ruling allowed for the removal of essential use designation from existing MDIs containing CFCs if the following conditions are met:

- At least one non-CFC product with the same active drug is marked with the same route of administration, for the same indication, and with approximately the same level of convenience of use as the CFC product containing that active moiety (while these alternatives are not required to be MDIs, the presumption is that HFA-MDIs would most easily fit criteria compared to, for example, dry powder inhalers);
- Supplies and production capacity for the non-CFC products(s) exist or will exist at levels sufficient to meet patient need;
- Adequate US postmarketing use data are available for the non-CFC product(s); and
- Patients who medically required the CFC product are adequately served by the non-ODS product(s) containing that active moiety and other available products.

The FDA Pulmonary-Allergy Drugs Advisory Committee met on June 10, 2004 to consider removing "Essential Use" designation for Albuterol MDI's containing CFCs. The committee was in agreement that Albuterol MDI met the first three criteria but were not in agreement as to the last criteria. Concern was raised as to the effect of removal of Albuterol MDIs containing CFCs from the market place and what effect their replacement with an HFA Albuterol would have upon the cost to the consumer. Albuterol MDI is available in the US as a generic product while the HFA Albuterol will not be available as a generic until either 2010 or 2015 depending upon which patent(s) are upheld. This has caused concern to the committee members. While no final decision has been made, the FDA has suggested a phase out date of December 31, 2005 after which date no Albuterol CFC MDIs can be legally marketed in the US. This rule making has not been published in final form and is currently under discussion.

While MDIs are currently being formulated with a HFC propellant in place of the CFC, only two drug entities have received FDA approval for marketing in the US. These include Albuterol and Beclomethosone Propionate. In contrast to Europe and the rest of the world, almost every CFC metered dose inhaler has been replaced with a HFC propellant. These replacements will be discussed in greater detail in another section of this chapter.

Since the early 1990s topical aerosol products have been reformulated using a hydrocarbon or a compressed gas propellant in place of the CFC. Compressed gasses, hydrocarbon, and HFC propellants are the suggested alternative propellant.

Since CFC propellants are in widespread use for most of the MDIs currently in use, the properties of the CFCs remain important and are covered in the next section of this chapter. Other than some of the specific properties of the CFCs and the HFCs, the principles of use in dosage form development remain essentially the same.

Liquefied gases provide a nearly constant pressure during packaging operations and have a large expansion ratio. Several of the fluorinated hydrocarbons have an expansion ratio of about 240, that is, 1 mL of liquefied gas will occupy a volume of approximately 240 mL if allowed to vaporize. Dimethyl ether has a value over 350. On the other hand, compressed gases expand only to the extent of 3 to 10 times the original volume.

The physicochemical properties of these compounds are of prime importance in the formulation and manufacture of aerosol products. The solvent power, stability, and lack of reactivity of the propellants have made them extremely useful for this purpose.

Nomenclature—To refer easily to the fluorinated hydrocarbons a relatively simple system of nomenclature was developed some time ago by the refrigeration industry. A numerical designation is used to identify each propellant.

All propellants are designated by three digits (000). When the first digit is zero, the propellant is designated by the last two digits and zero is assumed to be the first digit (ex: Propellant 011 is Propellant 11).

The first digit is one less than the number of carbon atoms in the compound. When there are only two digits, (0) is understood to be the first digit and indicates a methane derivative. When this first digit is (1), the propellant is an ethane derivative, when (2) it is propane, and when (3) it is a butane derivative.

The second digit is one more than the number of hydrogen atoms in the compound.

The last digit represents the number of fluorine atoms.

The number of chlorine atoms (for CFCs) in the compound is found by subtracting the sum of the fluorine and the hydrogen atoms from the total number of atoms that can be added to saturate the carbon chain.

In the case of isomers, each has the same number, and the most symmetrical one is indicated by the number alone. As the isomers become more and more asymmetrical, the letter a, b, c, etc, follows the number.

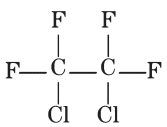
For cyclic compounds, a C is used before the number.

The use of this system can be exemplified as follows:

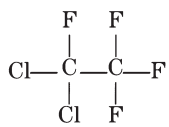
For CFC 114–Dichlorotetrafluoroethane

Propellant 114 is an ethane derivative, has no hydrogens, and contains 4 fluorine atoms.

Since 6 atoms are required to saturate the carbon chain, of necessity there must be 2 chlorine atoms. These can be arranged in two different ways; however, since there is no letter following the numerical designation, the symmetrical structure refers to Propellant 114.



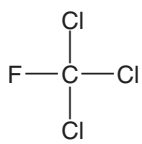
Propellant 114



Propellant 114a

For CFC 11–Trichloromonofluoromethane

The designation is 0 for methane (first digit)
1 for number of fluorine atoms (third digit)
1 for one more than number of hydrogen atoms (second digit)
3 chlorine atoms required to saturate molecule.

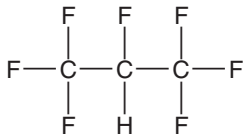


Propellant 11

For HFC-227–Heptafluoropropane

The designation is 2 for propane (first digit)
7 for number of fluorine atoms (third digit)
2 for one more than number of hydrogen atoms (second digit)

Since there is no letter following the third digit, the one H atom must be on the #2 carbon as this is the most symmetrical configuration.

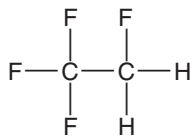


Propellant 227

For HFC-134a–Tetrafluoroethane

The designation is 1 for ethane (first digit)
4 for number of fluorine atoms (third digit)
3 for one more than number of hydrogen atoms (second digit)

There are two possibilities for the 2 hydrogen atoms (one on each carbon or two on one carbon). Since this designation has an "a" following the last digit, it is the unsymmetrical compound.



Propellant 134a

Physical Properties—Table 50-1 shows some of the more useful physicochemical properties of CFC propellants. Propellants 11, 12, and 114 are included in the latest issue of the USP/NF and the British Pharmacopoeia. Specifications for these propellants, hydrocarbons, as well as the HFCs, HCFCs and compressed gases can be found in the *Handbook of Pharmaceutical Excipients,* Fourth Edition.

From a solubility standpoint, the CFC, HFC, and HCFC propellants, which are nonpolar, are miscible with most nonpolar solvents over a wide range of temperature. They also are capable of dissolving many substances. For the most part the propellants are not miscible with water, although the degree of miscibility depends on the individual propellants. A cosolvent such as ethanol, 2-propanol, or DME, must be used when water is present, to produce a clear solution. However, when one considers that these propellants are used for metered-dose aerosols, the choice of cosolvent is extremely limited and, in many cases, to the use of ethyl alcohol. The alternative is to form an emulsion for topical aerosol pharmaceuticals.

One of the most important physicochemical properties of a propellant is its vapor pressure, which may be defined as the pressure exerted by a liquid in equilibrium with its vapor. When the vapor pressure exceeds atmospheric pressure, boiling and vaporization take place. However, if the vaporized molecules are prevented from leaving the container (by placing the propellant into a sealed container), they will fill the head space and eventually cause an increase in pressure. The pressure developed at equilibrium is the vapor pressure. The vapor pressure of a liquefied gas is independent of the quantity used but is influenced by temperature changes. Assuming ideal behavior for the liquefied gas, the effect of temperature on the vapor pressure can be calculated from

$$\log P = -\frac{\Delta H_{vap}}{2.303\,RT}$$

where P is the vapor pressure, H is the heat of vaporization, R is the gas constant (generally 1.987 cal deg^{-1} $mole^{-1}$), and T is the absolute temperature.

Since

$$\ln P = -\frac{\Delta H_{vap}}{RT} + C$$

a plot of log P versus $1/T$ should yield a straight line, and from this the heat of vaporization may be calculated.

$$\Delta H_{vap}\,(cal\ mole^{-1}) = -(\text{slope})(2.303R)$$

These equations can be used to predict the behavior of pure propellants at elevated temperatures. When one considers that an aerosol preparation consists of a propellant and solvents or mixtures of these, the vapor pressure considerations are somewhat different. By mixing various propellants such as Propellants 11 and 12 or Propellants 12 and 114, a range of vapor pressures is obtained. This is not possible when the HFCs are used, since the range in pressure between P-134a and P-227 is relatively small (about 26 psig compared with about 70 psig between P-11 and P-12). The vapor pressure of a mixture of propellants may be calculated from Raoult's law, which states that the *vapor pressure of a solution is dependent upon the vapor pressure of the individual components. For ideal solutions, the vapor pressure is equal to the sum of the mole fractions of each component present times the vapor pressure of the pure compound at the desired temperature.*

Mathematically, this law may be expressed as

$$p_A = \frac{n_A}{n_A + n_B} p_A^\circ = N_A p_A^c$$

where p_A = partial vapor pressure of Component *A*, p_A° = vapor pressure of pure Component *A*, n_A = mols of Component *A*, n_B = moles of Component *B*, and N_A = mol fraction of Component *A*.

$$p_B = \frac{n_B}{n_B + n_A} p_B^\circ = N_B p_B^\circ$$

The total vapor pressure of the system is obtained by

$$P_{total} = p_A + p_B$$

When the mole fraction of one component is large, the other component has a small mol fraction, and as such, it does not appreciably affect the vapor pressure. This system approaches ideal behavior.

When the components are of similar physical and chemical nature, the experimentally determined values and the calculated values are approximately the same. In the case of the fluorinated hydrocarbons, the deviation from ideal behavior is not great, and the results are approximately equal or within 5%. When other solvents are present, such as alcohols, the vapor pressures can be calculated in a similar manner.

Chemical Properties—The fluorinated hydrocarbons have been widely used as aerosol propellants because they generally are considered to be chemically inert. From the standpoint of formulation, the only chemical property that need be considered is hydrolysis in regard to Propellant 11. While addition of fluorine to a carbon atom generally increases stability, a propellant such as trichloromonofluoromethane may undergo hydrolysis with the formation of hydrochloric acid. Propellant 11 is not used with aqueous products, as hydrolysis will occur; Propellant 114 generally is used instead. For topical and cosmetic aerosols, hydrocarbons, or hydrochlorofluorocarbons are used (Propellants 152b, or DME). Propellants 134a and 227 have properties similar to those of P-12 except for their solubility characteristics.

HYDROCARBONS—Hydrocarbon propellants have replaced CFCs for topical pharmaceutical aerosols. Their low-order toxicity makes them suitable, while their flammability tends to limit their use. With the development of newer types of dispensing valves, the flammability hazard has been reduced considerably. The advantage of hydrocarbons is their greater range of solubility and a lower cost than CFCs. To date they represent a readily available replacement for CFCs as propellants, provided that the flammability hazard can be reduced. The HFC propellant used for MDIs are also applicable to topical aerosol pharmaceuticals with the added advantage of nonflammability.

In addition to having the proper vapor pressure, hydrocarbons have other properties that make them useful as propellants. Their density of less than 1 and their immiscibility with water make them useful in the formulation of three-phase (two-layer) aerosols. Being lighter than water, the hydrocarbon remains on top of the aqueous layer and serves to push the contents out of the container. Not being halogenated, hydrocarbons generally possess better solubility characteristics than the fluorinated hydrocarbons.

As with CFCs, a range of pressures can be obtained by mixing various hydrocarbons in varying proportions. As the composition of the hydrocarbons is likely to vary somewhat, depending on their source, blending of hydrocarbons must be based on the final pressure desired and not on the basis of a stated proportion of each component, whose pressure will depend on its purity. Table 50-6 lists some commonly used blends that are commercially available.

Finally, it should be indicated that the hydrocarbons are characterized further by their extreme chemical stability. They are not subject to hydrolysis, making them useful with water-based aerosols. They will react with the halogens but only under severe conditions.

Alternative Propellants (HCFCs and HFCs)

Many pharmaceutical aerosols were developed originally using chlorofluorocarbons (CFCs) 11, 12, and 114. These propellants have found widespread use because of their inertness, nonflammability, and nontoxicity. Unfortunately, the CFCs have been implicated in depleting the ozone layer, and their use as aerosol propellants has practically been eliminated, except for exempted medical uses which included MDIs.

Topical pharmaceutical aerosols have been successfully reformulated with Propellants 152a, DME, hydrocarbons, and compressed gases. Suitable valves are available that, together with modifications in formulation and propellant blends, produce topical aerosol pharmaceuticals that are satisfactory and acceptable.

Several new liquefied-gas materials have been developed to replace the CFCs as refrigerants and foaming agents and in other nonpharmaceutical uses. Propellant 134a and Propellant 227 have been developed as substitutes for Propellant 12 in MDIs and have survived many of the short- and long-term toxicity studies. To date, no suitable replacement has been found for Propellants 11 and 114. Propellant 114 is not essential for use with MDIs, but most of the present suspension formulations require a minimum amount of Propellant 11. Propellant 11 is used to form a slurry with the active ingredient and dispensing agent. This is impossible to accomplish with Propellants 134a and P-227 (unless these propellants are chilled well below their boiling point and handled as a cold fill). Propellant 11 also has been used to dissolve the surfactants that have been used with CFC MDIs. The HFCs are extremely poor solvents and will not dissolve a sufficient amount of the currently used

Table 50-6. Commonly Used Hydrocarbon Blends

		COMPOSITION (mol %)		
DESIGNATION[a]	PRESSURE (psig AT 70°F)	*n*-BUTANE	PROPANE	ISOBUTANE
A-108	108 ± 4	Traces	99	1
A-31	31 ± 2	3	1	96
A-17	17 ± 2	98	Traces	2
A-24	24 ± 2	49.2	0.6	50
A-40	40 ± 2	2	12	86
A-46	46 ± 2	2	20	78
A-52	52 ± 2	2	28	70
A-70	70 ± 2	1	51	48

[a] Designations used by Phillips Chemical Co, Bartlesville, OK.
Other designations include: Aeron—Diversified CPC International, Inc., Channahon, IL

FDA-approved surfactants (oleic acid, sorbitan trioleate, and soya lecithin).

It also has been noted that some of the currently used valves are not compatible with these newer HFC propellants. The gaskets and sealing compounds used in metered-dose valves may present compatibility problems to the formulator; however, other gasket materials (EPDM) have been developed and found to be satisfactory. Several of the critical properties of these newer propellants are shown in Table 50-2. Additional details about their use in formulation of MDIs is included in a later part of this chapter.

Compressed Gases

The compressed gases such as nitrogen, nitrous oxide, and carbon dioxide have been used as aerosol propellants. Depending on the nature of the formulation and the valve design, the product can be dispensed as a fine mist, foam, or semisolid. However, unlike the liquefied gases, the compressed gases possess little, if any, expansion power and will produce a fairly wet spray and foams that are not as stable as liquefied-gas foams. This system has been used for the most part to dispense food products and for nonfoods, to dispense the product in its original form as a semisolid. Compressed gases have been used in products such as dental creams, hair preparations, ointments, and aqueous antiseptic and germicidal aerosols and are extremely useful in contact lens cleaner saline solution and barrier systems.

CONTAINERS

Metal

TIN-PLATED STEEL—To produce an aerosol container that was light and relatively inexpensive, tin-plated steel was used for aerosol containers. This resulted in the large-scale production of aerosol containers. For certain products the tin affords sufficient protection, so that no further treatment is necessary. For additional protection to either the drug product or container, a coating, usually organic in nature, may consist of an oleoresin, phenolic, vinyl, or epoxy coating. The liner (single or double coat) is added to the container prior to fabrication; that is, it is applied to the flat sheets of tin plate.

ALUMINUM—Many MDIs and pharmaceutical aerosols use an aluminum container. Aluminum containers (sometimes referred to as canisters) are produced by an impact extrusion process so that the container is seamless. These containers are extremely strong and will withstand relatively high pressures. A variety of different aluminum aerosol containers ranging in size from 10 mL to 45 fl oz is available. While aluminum is less reactive than other metals used in can manufacture, added resistance can be obtained by coating the inside of the container with organic materials such as epoxy, vinyl, phenolic, or polyamide resins. Many of the MDIs will use an anodized or nonanodized internal surface, with or without an organic inner coating. Most of the aluminum containers for MDIs formulated with an HFC propellant are coated with an organic inner coating.

GLASS—For pharmaceuticals and medicinals, glass is preferred because of the absence of incompatibilities, as well as for its esthetic value. The use of glass containers is limited to those products having a lower pressure and lower percentage of propellant. While glass is basically stronger than most metallic containers, a potential hazard is present if, and when, the container is dropped with subsequent breakage. Two types of glass aerosol containers are available. The uncoated glass container has the advantage of decreased cost and high clarity. The contents can be viewed at all times. The plastic-coated glass containers are protected by a plastic coating that prevents the glass from shattering in the event of breakage. The plastic coated glass container is used for some topical and MDI aerosols.

VALVES

Probably the most basic part of any aerosol or pressurized package is the valve mechanism through which the contents of the package are emitted. Together with the formulation, the valve determines the performance of a pressurized package. The interaction of these two components is such that one cannot readily be discussed without reference to the other.

The primary purpose of the valve is to regulate the flow of product from the container. It provides a means of discharging the desired amount when needed and prevents loss at other times. The valve also exerts a major effect on the character of the dispensed product. For example, a product formulated to produce a foam can be dispensed as a spray or as a wet stream by the use of different actuators or push buttons on the valve. The selection of proper propellants also governs whether a foam, spray, or wet stream will be produced.

Continuous-Spray Valves

Figure 50-7 illustrates the basic subcomponents used in aerosol valves. A fully assembled valve is shown in Figure 50-8.

A small hole about 0.013 to 0.020″ in diameter sometimes is placed in the valve body as seen in Figure 50-7. This allows the escape of a small quantity of vaporized propellant along with the product. This gives a greater degree of dispersion to the emitted spray as well as cleaning the valve orifices following discharge. However, since a greater amount of propellant is used than with nonvapor-tap systems, care must be exercised during formulation of the product to take this into account. One may also note a change in spray pattern from start to finish because of the change in propellant composition that takes place as the contents are used. Vapor-tap valves are used with powder aerosols, water-based aerosols, aerosols containing suspended materials, and other agents that would tend to clog the valve. They currently are used with hydrocarbon aerosols since

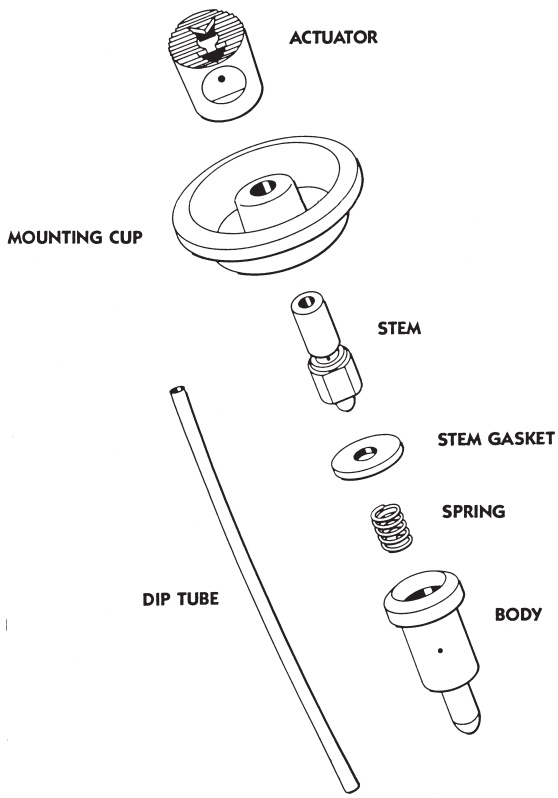


Figure 50-7. Continuous-spray aerosol valve, showing subcomponents used for sprays, foams, and semisolids (courtesy, Precision Valve).

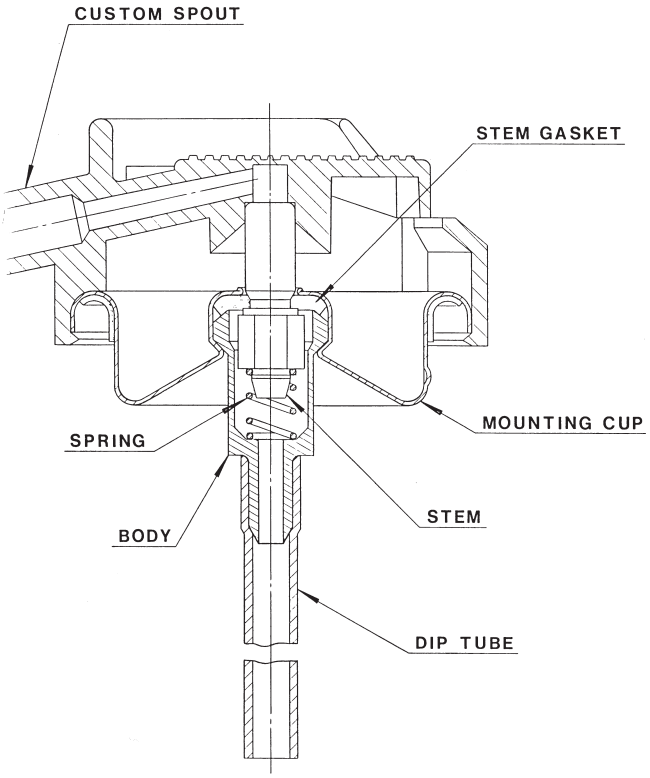


Figure 50-8. Assembled continuous-spray valve (courtesy, Precision Valve).

the flame extension of the spray can be reduced substantially through use of a vapor-tap valve. This is accomplished by balancing the size of the vapor-tap opening and the valve orifice.

Foam Valves

Valves for foam or aerated products usually have only one expansion orifice, the one at the seat. Following this is a single expansion chamber that serves as a delivery nozzle or applicator. It is sufficiently large in volume to permit immediate expansion of the pressurized product to form the familiar ball of foam. As demonstrated earlier, the same formulation will be discharged as a solid stream when dispensed with a valve and actuator having small orifices and expansion chambers. Under these latter conditions, the ball of foam will begin to develop where the stream impinges on a surface. This rather interesting performance is used in some pressurized surgical soaps on the market. These products are preferred for use by surgeons and other operating room personnel since when applied; the foam breaks down easily and is rubbed into large areas of the hands and arms. Another similar product contains ethyl alcohol made into a similar foam and is used as a skin disinfectant or sprayed onto instruments, etc.

Because of their large openings, foam valves may lend themselves to use with viscous materials such as syrups, creams, and ointments. Foam valves also have been used to dispense rectal and vaginal foams. Metered valves are discussed later in this chapter.

ACTUATORS

The actuator provides a rapid and convenient means for releasing the contents from a pressurized container. It provides the additional functional use in allowing the product to be dispensed in the desired form, that is, a fine mist, wet spray, foam, or solid stream. Mechanical breakup actuators are used for three-phase or compressed-gas aerosols. In addition, special actuators are available for use with pharmaceutical and medicinal aerosols that allow dispensing of products into the mouth, nose, throat, vagina, or eye.

PACKAGING

Two methods have been used to package aerosol products. Unlike nonaerosol products, part of the manufacturing of necessity takes place during the filling operation. The propellant and product concentrate must be brought together in a way, which ensures uniformity of product.

Depending on the nature of the product concentrate, the aerosol can be filled by a cold-filling or a pressure-filling process. There are advantages and disadvantages to both methods, and there are many factors that must be considered before deciding which process to use. Since aerosol packaging is a very specialized procedure; many of the pharmaceutical aerosols are manufactured and packaged at commercial contract filling facilities. A typical unit used to fill MDIs in the laboratory is shown in Figure 50-9, while Figure 50-10 and 50-10a illustrates

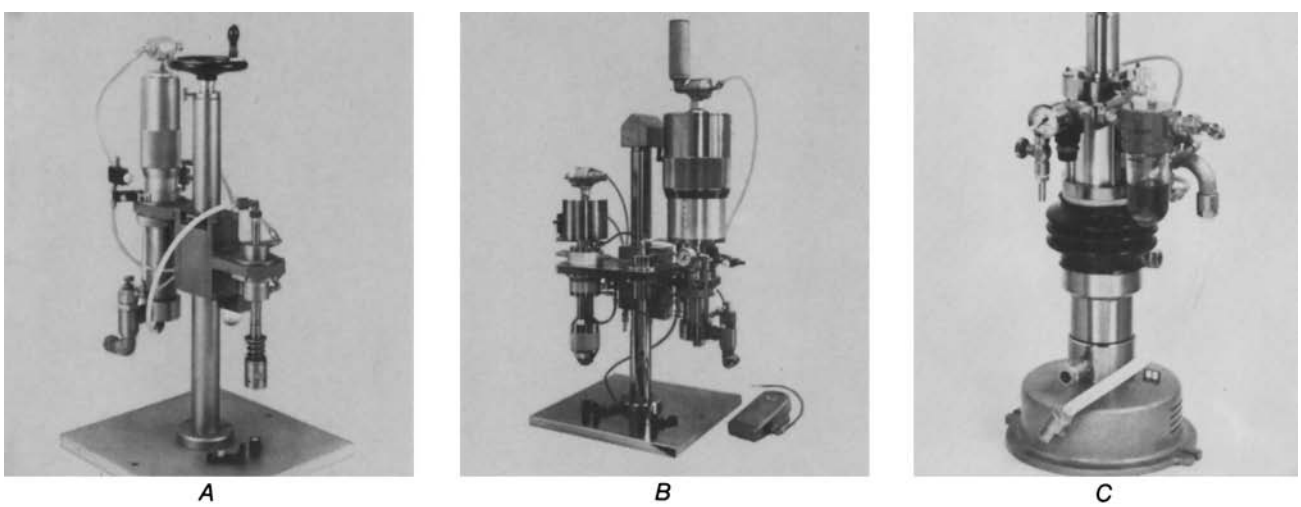


Figure 50-9. Aerosol laboratory and pilot-sized filling equipment. *A*, Product filler. *B*, Crimper and pressure filler for propellant. *C*, Propellant pump (courtesy, Pamasol Willi Mader AG).

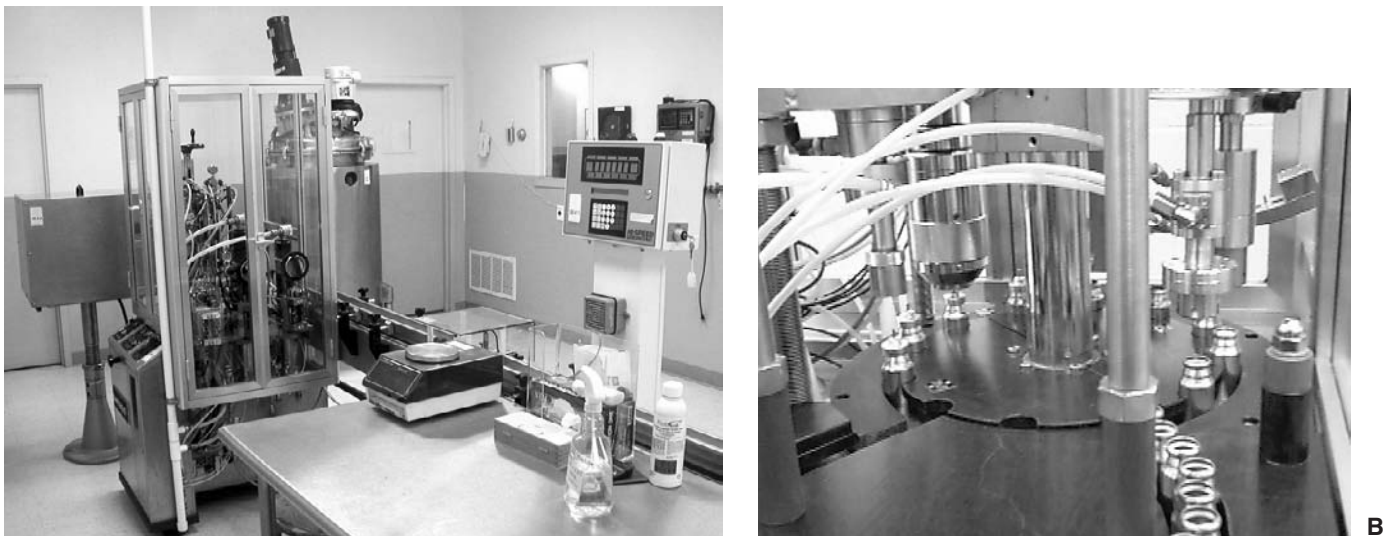


Figure 50-10. (A) Commercial Aerosol filling and packaging Pamasol line for MDIs (courtesy, Sciarra Laboratories, Inc.) (B) Detail of crimping and pressure filling head.

a typical Pamasol aerosol packaging line for MDIs. Figure 50-11 shows a Terco filling and packaging line for topical pharmaceutical aerosols.

APPLICATIONS

Aerosol technology has been applied to the formulation of products containing therapeutically active ingredients. A pharmaceutical aerosol may be defined as an aerosol product containing therapeutically active ingredients dissolved, suspended, or emulsified in a propellant or a mixture of solvent and propellant and intended for oral or topical administration or for administration into the nose, eye, ear, rectum, or vagina.

MDIs are intended for administration as fine, solid particles or as liquid mists via the respiratory system or nasal passages. They are used for their local action in the nasal areas, throat, and lungs, as well as for prompt systemic effect when absorbed from the lungs into the bloodstream (inhalation therapy). The particle size must be considerably below 10 μm and, in most instances, should be between 3 and 6 μm for maximum therapeutic response.

Figure 50-11. Aerosol filling and packaging Terco line for Topical Aerosols (courtesy, Sciarra Laboratories, Inc.)

An alternative definition of this dosage form includes: *Pharmaceutical aerosols are products that are packaged under pressure and contain therapeutically active ingredients that are released upon actuation of an appropriate valve system. They are intended for topical application to the skin as well as local application into the nose (nasal aerosols), mouth (lingual aerosols) or lungs (inhalation aerosols).*

Aerosol Formulation

Topical pharmaceuticals may be formulated as aerosols using solutions, suspensions, emulsions, powders, and semisolid preparations while MDIs are formulated as solutions or suspensions. Table 50-7 illustrates the basic formulation of aerosol products for use as metered-dose inhalants.

SOLUTION AEROSOLS—Topical aerosols consist of a solution of active ingredients in pure propellant or a mixture of propellant and solvents. The solvent is used to dissolve the active ingredients and/or retard the evaporation of the propellant. Solution aerosols are relatively easy to formulate, provided the ingredients are soluble in the propellant. However, the propellants are nonpolar in nature and in most cases are poor solvents for some of the commonly used medicinal ingredients. Through use of a solvent that is miscible with the propellant, one can achieve varying degrees of solubility of the active ingredient. For topicals, (isopropyl alcohol, isopropyl myristate, polyethylene glycols, etc.) ethyl alcohol has found the greatest use, although some other solvents may be of limited value. For those substances that are insoluble in the propellant or propellant/solvent system, a dispersion or suspension can be produced. In this case the drug must be micronized so that the particles are less than 10 μm in average diameter.

The usual fluorocarbon propellants used in currently available MDIs are blended as indicated in Table 50-7 or used alone when appropriate. Propellant 11 is used often when solubility of the drug and solvents presents a problem, as it is a better solvent than either Propellant 12, 114, 134a, or 227. Additionally, Propellant 11 may be required to prepare a suitable slurry when preparing a dispersion aerosol. Generally the propellant represents upward of 60 weight-percent of the final formulation and, in most cases, may be as high as 99.9%. Propellant 12 may be used alone or in combination as indicated. The proportion of each propellant is varied to obtain the desired pressure within the container and the proper particle-size distribution.

Table 50-7. Metered-Dose Inhalants (Solution and Suspensions): Prototype Formulation

Solution (CFC, HFC)[a]
Active ingredient(s): solubilized
Antioxidants: ascorbic acid
Solvent blends: water, ethanol, glycols
Propellants: 12/11, 12/114 or 12 alone; 134a, 227, 134a/227
Suspensions (CFC)
Active ingredient(s): micronized and suspended
Dispersing agent(s): sorbitan trioleate, oleyl alcohol, oleic acid, lecithin, etc.
Propellants: 12/11, 12/114, 12 or 12/114/11
Suspensions (HFC)[a]
Active ingredient(s): micronized and suspended
Solvent: ethanol
Dispersing agent(s): sorbitan trioleate, oleyl alcohol, oleic acid, lecithin, etc.
Propellants: 134a, 227, 134a/227
or
Active ingredient(s): micronized and suspended
Propellants: 134a, 227, 134a/227

[a] The reader is directed to the patent literature to ensure that the formulations are not covered by a patent.

Topical pharmaceutical solutions are formulated using the hydrocarbon propellants, butane, isobutene, and propane. Although butane and isobutene can be used individually, the hydrocarbons are generally used as a blend as shown in Table 50-6. Other non-MDIs are formulated as aqueous solutions (eye care, etc.) and utilize nitrogen as the propellant. These are packaged as a conventional aerosol or utilize a barrier system.

DISPERSIONS OR SUSPENSIONS (POWDER AEROSOLS)—These aerosols are similar to solution aerosols except that the active ingredients are suspended or dispersed throughout the propellant or propellant and solvent phase. This system is useful with antibiotics, steroids, and other poorly soluble compounds. Problems associated with the formulation of this system include agglomeration, caking, particle-size growth, and valve clogging. Some of these problems have been overcome through use of lubricants such as isopropyl myristate, sorbitan trioleate, oleic acid, or other substances that provide slippage between particles of the compound as well as lubricating component parts of the valve. Surfactants also have been used to disperse the particles. The use of dispersing agents such as sorbitan trioleate, oleic acid, or lecithin is useful in keeping the suspended particles from agglomerating. Thought also should be given to both the particle size and the moisture content of the powder. The moisture content should be kept between 100 and 300 ppm or less, depending upon the type of product, and the propellants and solvents must be dried by passing them through a drying agent. The particle size for metered-dose inhalants should remain in the micrometer range and should be between 2 and 8 μm or less, with a mass median diameter of between 3 and 6 μm.

FORMULATION OF MDIS USING HFCS AS THE PROPELLANT:

Several new environmentally acceptable propellants are available worldwide as replacements for CFCs in MDI inhalers. Among the alternatives is Tetrafluoroethane (HFC 134a), which is available as Dymel 134a/P from *DuPont Fluoroproducts*; Solkane 134a pharma from *Solvay;* and Zephex 134a from *Ineos Fluor*.

Tetrafluoroethane (P-134a) is a hydrofluorocarbon (HFC) or hydrofluoroalkane (HFA) aerosol propellant (contains hydrogen, fluorine, and carbon) as contrasted to a CFC (chlorine, fluorine, and carbon). The lack of chlorine in the molecule and the presence of hydrogen reduce the ozone depletion activity to practically zero, therefore, tetrafluoroethane can be considered an alternative to CFCs in the formulation of metered dose inhalers. It has replaced CFC-12 as a refrigerant since it has essentially the same vapor pressure. Its very low Kauri-butanol value and solubility parameter indicate that it is not a good solvent for the commonly used surfactants for MDIs. Sorbitan trioleate, sorbitan sesquioleate, oleic acid, and soya lecithin show limited solubility in tetrafluoroethane and the amount of surfactant that actually dissolves may not be sufficient to keep a drug readily dispersed. Tetrafluoroethane has been used as a replacement for CFCs in MDIs containing Albuterol. Two such products containing Albuterol Sulfate and one product containing Beclomethasone Dipropionate are currently available in the US. Outside the US, this propellant has found greater use in Europe and the rest of the world, where many MDIs have been developed using Tetrafluoroethane.

The use of tetrafluoroethane as a propellant for MDIs has been the subject of numerous patents throughout the world. These patents cover the formulation of MDIs, use of specific surfactants, cosolvents, etc. Many of these formulation patents are no longer valid in many countries of the world. The US patents have not been challenged to date.

US Patent No. 5,605,674 claims *a self-propelling aerosol formulation which may be free from CFCs which comprises a medicament, 1,1,1,2-tetrafluoroethane, a surface active agent, and at least one compound having a higher polarity than 1,1,1,2-tetrafluoroethane.*

The formulator is referred to the patent literature prior to formulating an MDI with tetrafluoroethane and/or heptafluoropropane (P-227) as the propellant. The use of an HFC as the propellant may also requires a change in manufacturing procedure that necessitates a redesign of the filling and packaging machinery for an MDI.

One commercially available MDI is Proventil HFA *(Schering),* which contains albuterol sulfate suspended in ethanol, oleic acid, and tetrafluoroethane (P-134a). Each actuation delivers 108 μg of albuterol sulfate equivalent to 90 μg of albuterol from the mouthpiece. To date this MDI and one containing beclomethasone propionate are the only non-CFC MDI available in the United States. Similar versions of this product are available in the United Kingdom and the rest of the world. In 1998, 3M released Qvar for sale in the United Kingdom. This MDI contains beclomethasone in solution form. Since the respiratory fraction of the product is substantially higher than the current CFC product, according to the literature, a 200-μg dose of Qvar achieved a total beclomethasone level comparable to a 400-μg dose of the CFC-containing beclomethasone formulation. An NDA for Qvar has since been approved by the FDA and Qvar MDI is now available commercially in the US.

Another replacement for CFCs in metered dose inhalers is Heptafluoropropane (P- 227), which is available as Dymel 227 ea/P from *DuPont Fluoroproducts;* Solkane 227 pharma from *Solvay;* and Zephex 227ea.

Heptafluoropropane is classified as a hydrofluorocarbon (HFC) aerosol propellant since the molecule consists only of carbon, fluorine, and hydrogen atoms. It does not contain any chlorine and consequently does not affect the ozone layer, nor does it have an effect upon global warming. It is therefore considered as an alternative propellant to CFCs for metered dose inhalers. The vapor pressure is somewhat lower than that of tetrafluoroethane and dichlorodifluoromethane, but considerably higher than the vapor pressure used to formulate most MDIs. Similar to tetrafluoroethane, heptafluoropropane is not a good solvent or medicinal agents used in the formulation of MDIs. Its use as a propellant is included in US Patent 5,605,674.

Although there are no MDIs formulated with this propellant currently available in the US, the rest of the world–including Europe and Asia–have many MDIs that contain P-227. There are several MDIs formulated with P-227 currently under review by the FDA.

EMULSIONS—An emulsion system is useful for a great variety of topical pharmaceutical products. Since these systems

contain a relatively small amount of propellant (4 to 10%), there is little if any chilling effect. Active ingredients that may be irritating if inhaled can be used as a foam. Depending on the nature of the formulation and the manner in which the product is to be used, the foam is aqueous or nonaqueous and can be stable or quick-breaking.

Emulsions can be dispensed from an aerosol container as a spray, stable foam, or quick-breaking foam, depending on the type of valve used and the formulation. Two types of emulsions can be formulated for use in an aerosol. A W/O emulsion is one in which the water phase is dispersed throughout the oil phase; an O/W emulsion is one in which the water is the continuous phase.

If the product concentrate is dispersed throughout a propellant, the system behaves similarly to a W/O emulsion. However, since the propellant is in the external phase, the product is dispersed as a wet stream rather than as a foam. When the propellant is in the internal phase (O/W), a foam will be produced. The consistency and stability of the foam can be modified by choice of surfactants and solvents used.

Many water-based aerosols are of the W/O type, in which the propellant is in the external phase. Stable shave-cream foams, on the other hand, are produced by keeping the propellant in the internal phase.

The stable foam is similar to a shaving-cream formulation into which therapeutically active ingredients are incorporated. The foam is dispensed and rubbed into the skin or affected area. By substituting glycols and glycol derivatives for the water in an emulsion, a nonaqueous foam is obtained. The foam stability can be varied by the choice of surfactant, solvent, and propellant. It has been suggested that these foams are applicable to ointment bases, rectal and vaginal medication, and burn preparations.

A quick-breaking foam allows convenient and efficient application of medication. In certain instances the product was dispensed as a foam that quickly collapsed. This was useful in covering large areas with no rubbing necessary to disperse the medication. These quick-breaking foams consist of alcohol, surfactant, water, and propellant.

Container and Valve Components

PHARMACEUTICAL CONTAINERS—Aluminum is used as the material of construction for most metered-dose aerosols. While aluminum can be used without an internal organic coating for certain aerosol formulations, many containers are available that have been anodized or may have an internal coating made from an epoxy, epoxy phenolic, or polyamide resin.

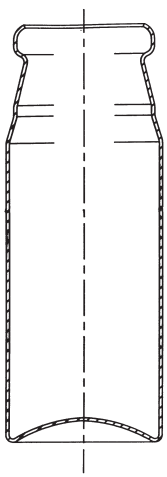


Figure 50-12. Typical aluminum aerosol container, cut-edge type used with an O ring (courtesy, Presspart).

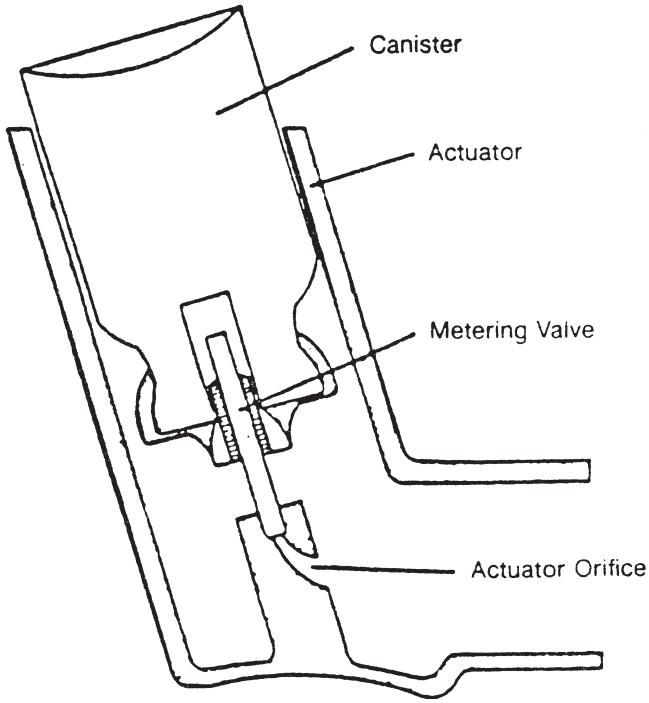


Figure 50-13. Typical metered-dose aerosol delivery system.

Aluminum containers are produced with a 20-mm opening so as to receive the standard metered 20mm and non-metered valves. These canisters are used for MDIs and are fitted with a 20mm metered dose valve. Albuterol made with a CFC will utilize a non-anodized aluminum canister while other MDIs use an anodized canister or one, which has been coated internally with an organic liner. A variety of openings ranging from 13 to 20 mm are available for special and customized applications. Aluminum containers are manufactured from a *slug* of aluminum and are seamless; therefore, there is virtually no danger of leakage. Figure 50-12 shows a typical aluminum container used for MDIs.

PHARMACEUTICAL VALVES—A typical metered-dose aerosol delivery system is illustrated in Figure 50-13. Metering valves fitted with a 20-mm ferrule are used with the above containers for all metered-dose inhalation, nasal aerosols, and oral products.

The metering valve delivers a measured amount of product and the amount delivered is reproducible not only for each dose delivered from the same package but from package to package. Two basic types of metering valves are available, one for inverted use and the other for upright use. Generally, valves for upright use contain a thin capillary dip tube and are used with solution-type aerosols. On the other hand, suspension or dispersion aerosols use a valve for inverted use that does not contain a dip tube. Figures 50-14 and 50-15 illustrate both types of valves and are typical of those commercially available.

An integral part of these valves is the metering chamber that directly is responsible for the delivery of the desired amount of therapeutic agent. The size of the chamber can be varied, so that from about 25 to 150 μL of product can be delivered per actuation. Most of the products commercially available use dosages in the range of 25 to 75 μL. The chamber is sealed via the metering and stem gasket. In the actuated position, the stem gasket will allow the contents of the metering chamber to be dispensed while the metering gasket will seal off any additional product from entering the chamber. In this manner the chamber always is filled and ready to deliver the desired amount of therapeutic agent.

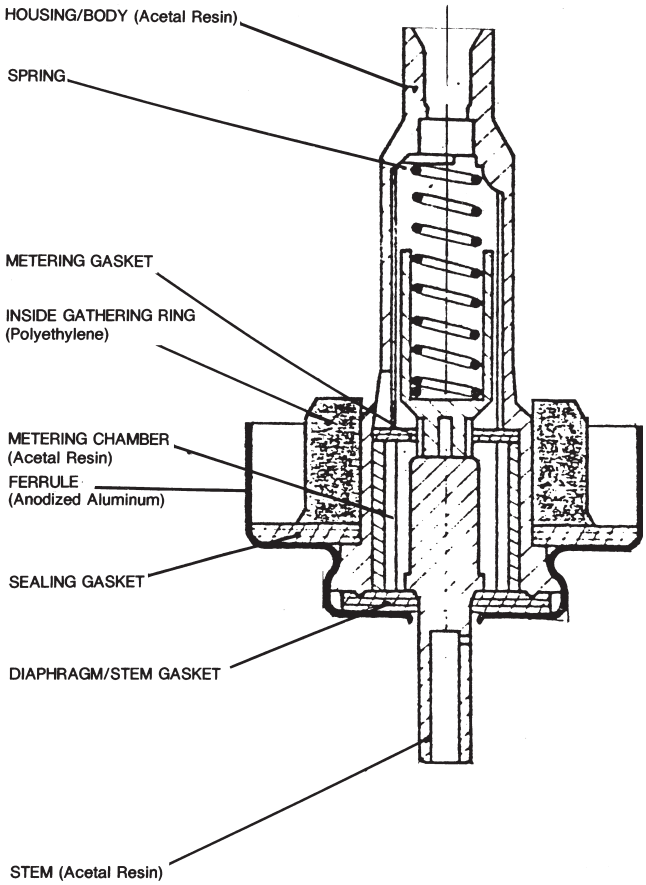


Figure 50-14. Metering valve—inverted (courtesy, Valois).

These valves should retain their prime over fairly long periods of time. However, it is possible for the material in the chamber to return slowly to the main body of product in the event the container is stored upright (for those used in the inverted position). The degree to which this can occur varies with the construction of the valve and the length of time between actuations.

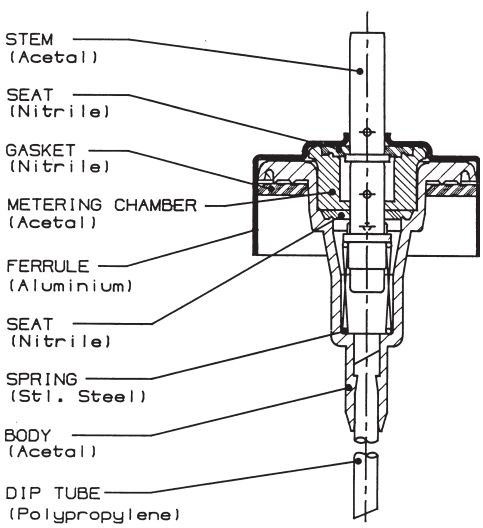


Figure 50-15. 20-mm metered-dose valve showing the subcomponent parts and metering chamber. It is used in the upright position (courtesy, Bespak).

Both types of valves currently are used on commercially available oral inhalation aerosols. During the development stage, the compatibility of the valves should be determined with the exact formulation to be used, to determine the accuracy of the metered dose in regard to doses delivered from the same container of product and from different containers. Additionally, one should ensure that there is no interaction between the various valve subcomponents and the formulation. If distortion or elongation of some of the plastic subcomponents occurs, this may result in leakage, inaccurate dosage, and/or decomposition of the active ingredients.

There also have been instances in which the therapeutic agent was adsorbed or absorbed onto the various plastic components, and a lower than normal dose of the active ingredient was dispensed. For these reasons, one must not only determine the total weight of product dispensed per dose but also the actual amount of active ingredient in each dose. Some test procedures use the results obtained by taking 10 doses of material and determining the average amount present in one dose. When possible and when the analytical procedure permits detection of fairly small amounts of active ingredients present per dose, multiple single-dose assays should be performed. Using the average of 10 doses may fail to reveal problems of variations in each of the individual doses dispensed.

Evaluation of MDIs and Topical Pharmaceuticals

Various tests have been devised to ensure the integrity of the aerosol package. These aerosol products are said to be tamperproof, since they cannot be opened and closed in the usual manner. Because these products are all under pressure, it is very difficult to add any foreign material to the product once the entire package is assembled. This also makes it rather difficult to obtain suitable samples for an analysis. Special sampling procedures and test methods have been developed and are used to determine the suitability of the product.

Topical pharmaceutical aerosols do not present any special problems other than the sampling procedure. The USP includes several tests under the specific monographs for the topical aerosols. These include delivery rate, leak testing, microbial limit test, and assay. While several of these products are dispensed as sprays, no special emphasis or consideration is given to the particle size of the droplets or particles emitted. The spray may be defined as a fine, dry, or wet spray. Of special interest for topical spray products is the concern that some of the smaller particles may be inhaled by the user.

MDIs require a greater amount of testing since the metered valve, oral adapter, and the formulation are collectively responsible for delivering the therapeutically active ingredient to the appropriate site in the respiratory passages. This assumes that the patient will administer the product properly, so that both the dose and depth of penetration of the medication can be ensured. Unfortunately, this is not always done. Both the physician and the pharmacist have provided a most valuable service to the patient by taking the time to demonstrate the correct use of these inhalers.

Many of the tests required for the evaluation of MDIs are similar to those used for other dosage forms. These include description, identification, and assay of the active ingredient; microbial limits; moisture content; net weight, degradation products and impurities (if any); extractables; and any other tests deemed appropriate for the active ingredient.

Other tests specific for MDIs include:

DOSE UNIFORMITY OVER THE ENTIRE CONTENTS–(MDIS ONLY)—This test is described in the USP/NF and determines the amount of active ingredient delivered through the mouthpiece (oral adapter) per a specified number of actuations (dose taken by patient).

LEAKAGE RATE—This test is also available in the USP/NF and is used to estimate the weight loss over a 1-yr period. Since

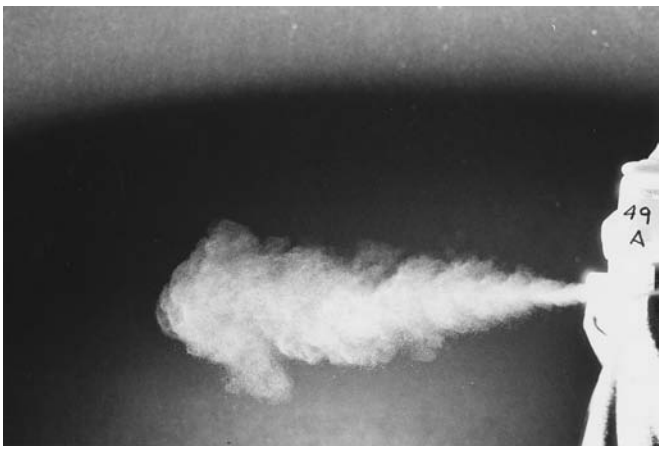


Figure 50-16. Plume emitted from a solution type MDI.

there are several sealing gaskets present in a metered-dose valve, this test determines the integrity of the gaskets as well as the proper crimping of the valve onto the container.

TOTAL NUMBER OF DISCHARGES PER CONTAINER—This is defined as the number of actuations per container and is not less than the label claim.

SPRAY PATTERN AND/OR PLUME GEOMETRY—This test evaluates the type of spray pattern emitted for the MDI and relates to the characteristics of the metering valve and oral adapter as well as to the formulation. Figure 50-16 illustrates a typical cloud or plume emitted from a solution type MDI.

It is beyond the scope of this chapter to discuss these tests in greater detail. The reader is referred to the USP/NF for specifics on each test. However, particle-size distribution is covered in greater detail because of its relationship to deposition of particles of drug in the respiratory system.

Particle-Size Distribution

Particle-size distribution is probably one of the most important characteristics of an MDI. To be effective, the particles emitted from the spray must be below 10 μm and in most cases between 2 and 8 μm in diameter. Several methods are available for the determination of the particle-size distribution for MDIs. A common method includes a cascade impactor that depends upon the principle of carrying particles in a stream of air through a series of consecutively smaller jet openings. The heavier and larger-diameter particles are impacted on a slide under the larger opening, and as the openings get smaller, the velocity of the stream increases and the next larger particles are deposited on the next slides. Figure 50-15 illustrates a cascade impactor that can be used to indicate the particle-size distribution of MDIs.

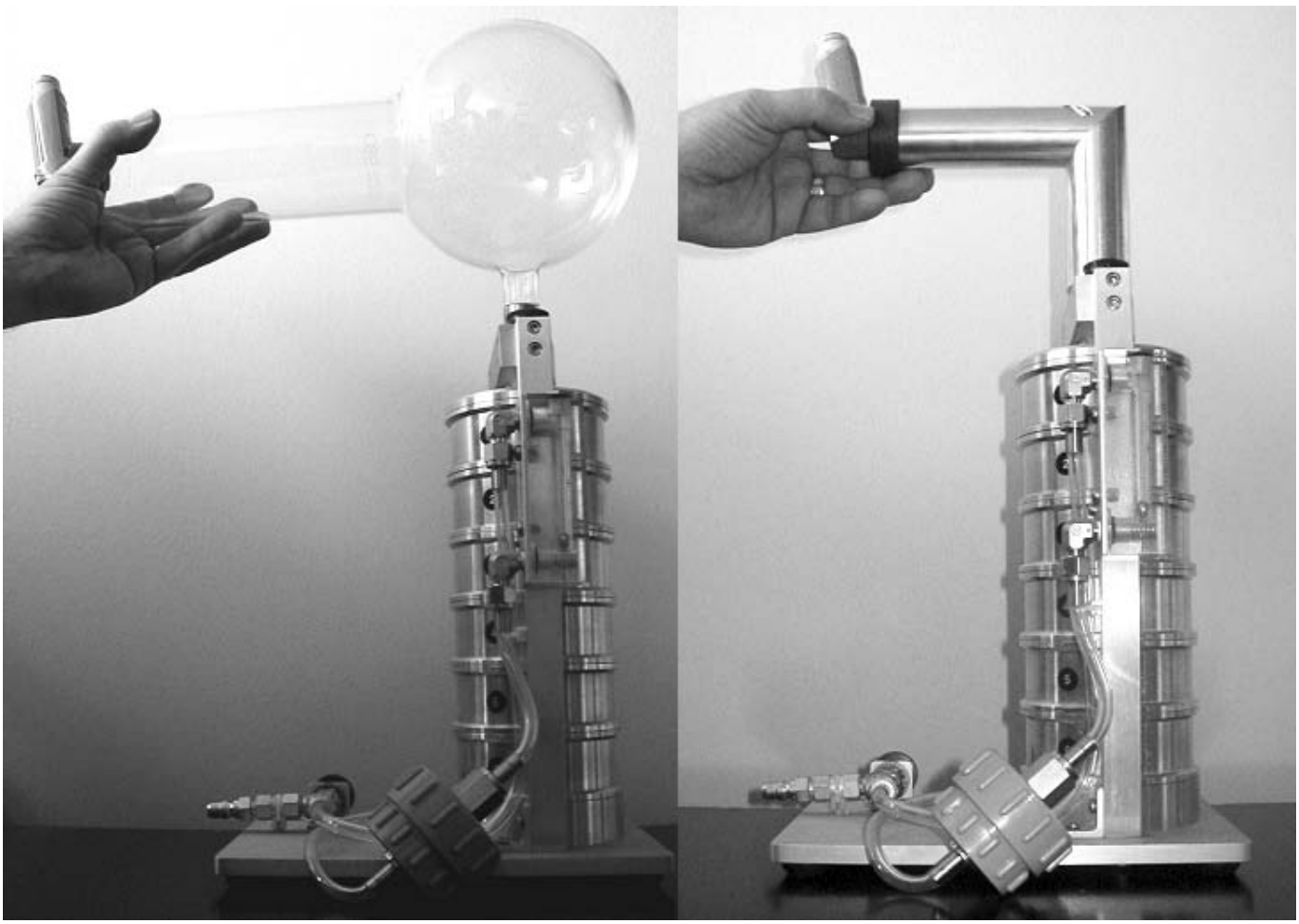


Figure 50-17. Cascade impactor (Impaq AS-6) used for particle-size distribution of MDIs (left-fitted with a 1000ml sampling throat; right-fitted with USP throat).

Figure 50-18 and Table 50-8 give a typical analysis of a suspension MDI. Table 50-9 gives a full analysis of the particle size for a solution MDI. Other methods include the use of a microscope or instrumentation based on the use of laser technology. The reader is referred to the USP/NF for a more comprehensive review of this subject.

FORMULATION FACTORS—Included among formulation factors are the physicochemical characteristics of the active ingredients, the particle size and shape of the drug, the type and concentration of surface-active agent used, and, to some extent, the vapor pressure and the metered volume of propellants. In terms of physicochemical properties, the lipoidal solubility and pulmonary absorption rates of the active ingredient are of utmost importance. Another physicochemical factor governing the biopharmaceutics of a drug is its dissolution characteristics in pulmonary fluids. Drugs having a rapid dissolution rate in pulmonary fluids predictably produce much more intense and rapid onset of action, having a shorter duration than their less soluble derivatives. Therapeutic agents that exhibit very poor solubility in pulmonary fluids are to be avoided, since they are likely to serve as irritants and precipitate bronchial spasms.

The selection of the appropriate surface-active agent (required in most pressurized inhalation suspension aerosols) is another important consideration, since the surfactant will influence droplet evaporation, particle size, and overall hydrophobicity of the particles reaching the respiratory passageways and pulmonary fluids. Solubility of these dispersing agents or surfactants is limited when formulating with an HFC propellant. Ethyl alcohol has been added to increase their solubility.

The effects of propellant vapor pressure and the metered volume of propellants on drug deposition in the lungs recently have been studied using rather large, specialized, plastic adapters. Findings in this area have demonstrated that the amount of material deposited in the mouth, tube, and actuator (likely sites of material loss) increased as the vapor pressure was decreased and the metered volume increased.

COMPONENT DESIGN—Component design, specifically that of the actuator and adapter, also has been shown to alter the particle size and the penetration and deposition of drugs into the lungs. Numerous studies have demonstrated that a complex set of interactions exist between the actuation type, valve dimensions, distance from actuator, and other component variables and that particle size (mass median diameters) could vary up to 40% by altering one or more of the aforementioned components.

One component that has undergone enormous modification in the last few years to improve drug delivery is the adapter or mouthpiece. Up to about the mid 1970s, almost all adapters were short and rather simplistic so as to minimize possible holdup of material in the adapter. The holdup in the short-stem adapters averages anywhere from 5 to 20%. Recently, however, numerous customized adapters having specific designs and dimensions have entered the marketplace.

Interest in the larger adapters (often referred to as tube spacers) can be attributed to any one or more of the following reasons. The larger adapter designs permit a complete evaporation of propellant, reducing initial droplet velocity and particle size. This reduction of particle size improves depth of drug penetration into the lungs, while a lower initial velocity decreases product impaction to the back of the esophagus (whiplash effect), common to short-stem adapters. The larger adapter designs also permit a decrease in pressure and increased volume flow that also has been reported to increase penetration of particles into the lungs. It should be pointed out that the larger tube spacers are not without problems. They are inconvenient because of their size, are expensive, and are somewhat difficult to clean. They also present the manufacturer with the problem of assessing product holdup in a rather complex device.

ADMINISTRATION TECHNIQUES—The metered-inhalation aerosol dosage form, although popular, generally is

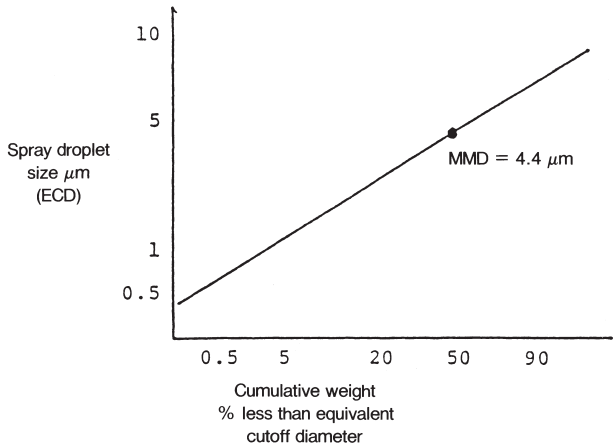


Figure 50-18. Log probability plot of data from the cascade impactor (MMD, mass median diameter).

Table 50-8. Cumulative Particle-Size Distribution

SLIDE NO.	PARTICLE SIZE (μM)	CUMULATIVE PARTICLE SIZE DISTRIBUTION (%)
Filter	Less than 0.5	0.55
6	0.5–1	5.35
5	1–2	18.98
4	2–4	61.59
3	4–8	90.20
2	8–16	96.67
1	16–32	100.00

Table 50–9. Particle Size Distribution of Solution Type MDI

COLLECTION UNIT	MASS FOUND μg	MASS FOUND %	CUMULATIVE PARTICLE SIZE DISTRIBUTION %
Valve stem	38.7	1.43	—
Mouthpiece	298.3	11.02	—
Collar	27.6	1.02	—
Induction Port	1057.8	39.07	—
Filder—(0.3 μm)	70.2	5.46	5.46
Stage 6—(0.5 μm)	66.3	5.16	10.61
Stage 5—(1.0 μm)	151.4	11.77	22.39
Stage 4—(2.0 μm)	303.8	23.64	46.02
Stage 3—(4.0 μm)	408.8	31.80	77.83
Stage 2—(8.0 μm)	204.4	15.90	93.73
Stage 1—(16.0 μm)	80.6	6.27	100.00
Total A	2300.7		
Total B	1285.4		
Total C	2707.8		
Total R	1204.7		

Respirable Dose (μg) = 120.47
Respirable Fraction = 52.36%
Mass Median Aerodynamic Diameter (MMAD) (μm) = 1.95
Geometric Standard Deviation (GSD) = 2.81
Mass Balance = 99.73%

A = Total Mass of Drug found on the collar, induction port, filter, and stages 1–6.
B = Total Mass of Drug found on the filter and stages 1–6.
C = Total Mass of Drug found on the valve stem, mouthpiece, collar induction port, filter and stage 1–6.
R = Total Mass of Drug found on stages 2–6 and filter.

considered one of the most complicated to use drug-delivery systems currently marketed by the pharmaceutical industry. It is viewed by many as being only slightly simpler to use than an injectable, since inhalation products often require up to 10 to 15 maneuvers by the patient during use. Failure of the patient to perform any one of these maneuvers correctly may alter significantly the deposition of the drug into the appropriate portion of the lungs.

Differences in the directions for use of each inhalation product are a result of the product formulation and actuator design that the manufacturer deemed most appropriate for the particular product. In light of this, it is not surprising to find patients who require two or more aerosol inhalation products or who are constantly changing their medication (such as the asthmatic patient) occasionally experiencing difficulties in complying with the suggested method of application.

These problems present a unique opportunity for the pharmacist to counsel the patient on the correct use of these inhalers. Several manufacturers will provide placebo inhalers for this purpose. Others will provide videotapes that can be used by the pharmacist and other health professionals to teach the correct use of these inhalers. Brown bag and senior citizen programs, health seminars, and other similar programs can provide a suitable audience for group presentations. However, the most successful programs are conducted on a one-to-one basis in the privacy of the pharmacy.

Many attempts have been made to overcome these problems and increase the efficacy of this dosage form. A breath- activated inhaler has been developed by 3M Pharmaceuticals and is used as an integral part of their pirbuterol acetate inhalation aerosol. They found that in a study of 70 patients, the use of the breath-activated inhaler increased the efficient use of these inhalers from 50 to 91%. These patients were given both written and verbal instructions. Reading instructions alone increased the efficiency from 39 to 63%. Many other devices, including tube spacers, breath activated, and electronic devices have been under study for numerous years. To date none of these units have become commercially available other than one breath activated (Maxair Autohaler–3M) and one spacer (Azmacort Inhalation Aerosol–*Aventis Pharmaceuticals*).

Tube spacers also increase the efficiency of drug delivery via MDIs. These spacers permit atomization of the delivered dose in a confined chamber or bag and eliminate the need for the precise synchronization of actuations and deep breathing with inspiration. Triamcinolone acetonide MDI is available as an MDI and is fitted with a tube spacer instead of the conventional short-stem actuators. Figure 50-19 illustrates several metered-dose aerosols with short-stem actuators. Patients must check with their physician before using these spacers, since the particle- size distribution of the drug being dispersed through one of these spacers may be substantially different from those emitted from a short-stem actuator. Certainly, the deposition pattern will change, and the efficiency of the delivered dose reaching the proper pulmonary airways will be increased.

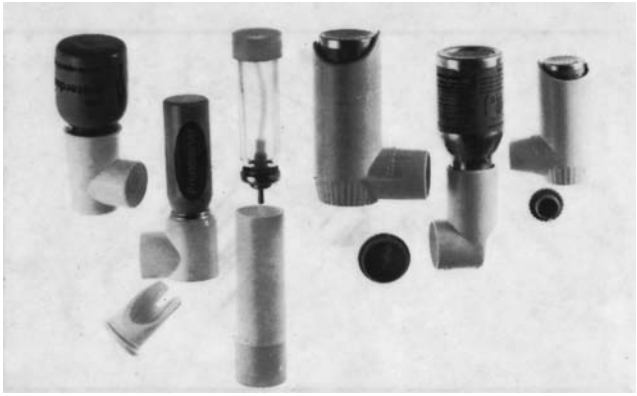


Figure 50-19. Medicinal aerosols with short oral applicators.

NEWER DEVELOPMENTS

At present, there is much interest in developing MDIs for a variety of conditions including asthma, emphysema, diabetes, aids, cancer, heart disease, and cystic fibrosis. Many of these compounds have been developed using biotechnology processes, and their delivery to the respiratory system via an MDI is an extremely challenging undertaking. With the introduction of newer, alternative propellants, the challenge becomes even greater and presents a unique opportunity for the delivery of these compounds. There is very little interest by manufacturers of currently available MDIs formulated with a CFC to convert the existing therapeutic agents to a HFC product. As indicated previously, Albuterol and Beclomethasone Propionate are the only two drug entities available in the US with a HFC propellant. It is doubtful if any others will ever be converted to a HFC. Manufacturers are currently discovering newer therapeutic agents for development as an MDI using the environmental acceptable HFA propellant. Several "second generation steroids" are currently under development and are formulated with a HFA propellant.

The valve and container suppliers are cooperating with the industry to develop much-needed hardware to accommodate this change. At present, there is no specific scheduled date when manufacturers can no longer use CFCs for their metered dose inhalers. As long as CFCs remain available, the changeover will continue at the current slow pace.

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