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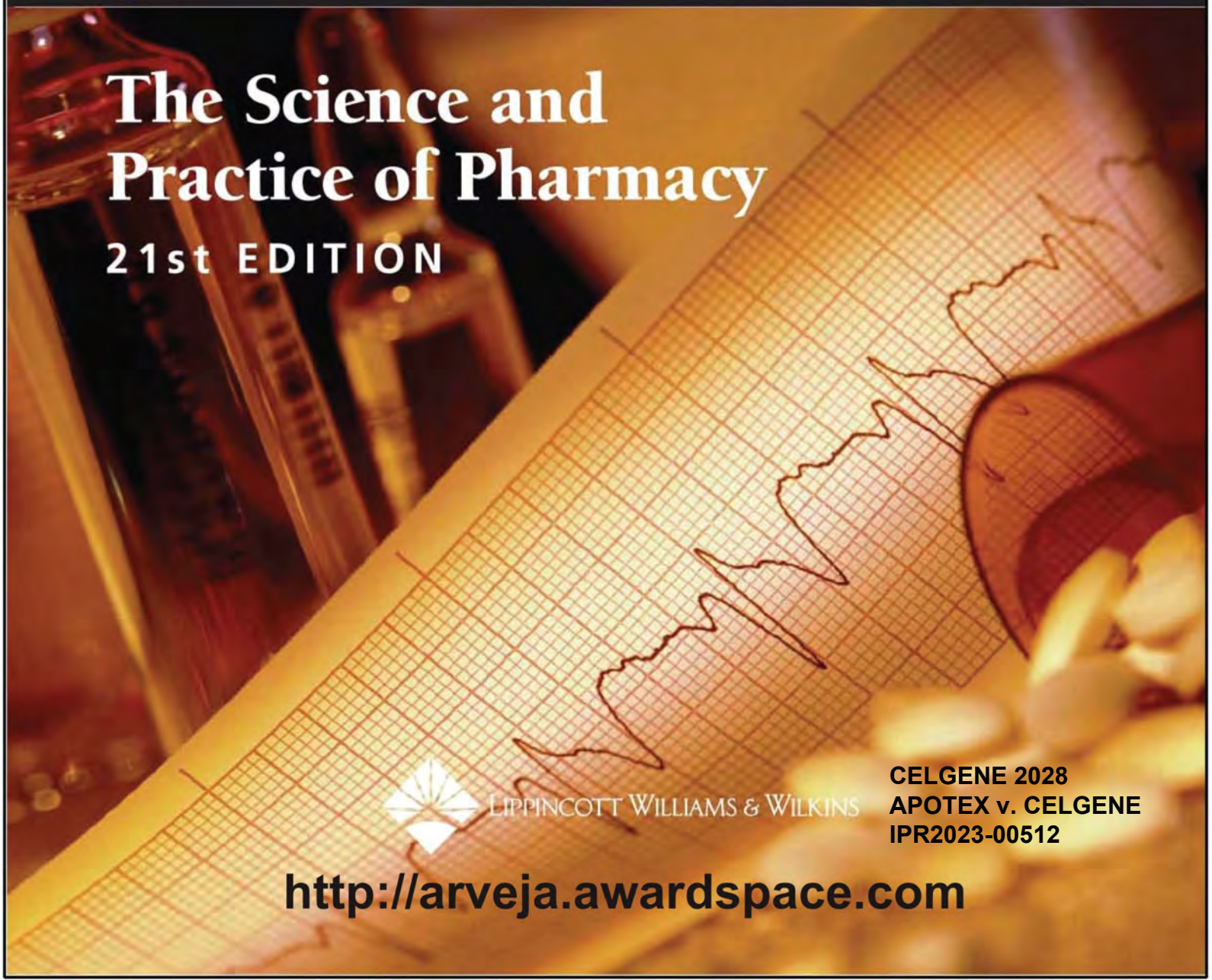

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The Science and Practice of Pharmacy

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CHAPTER 41

Parenteral Preparations

Michael J Akers, PhD

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 bactericidal 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).

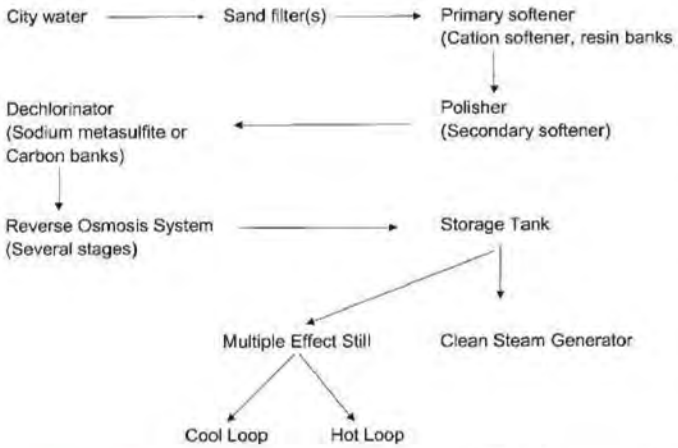


Figure 41-1. Water for injection system. Example of flow from source to end.

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-

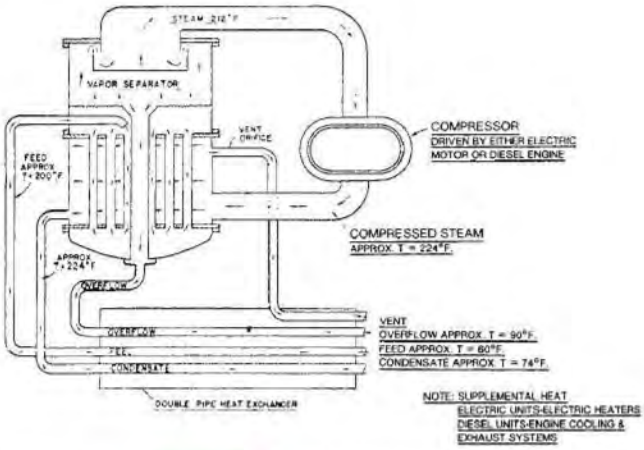


Figure 41-2. Vapor compressor still.

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 wherease 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).

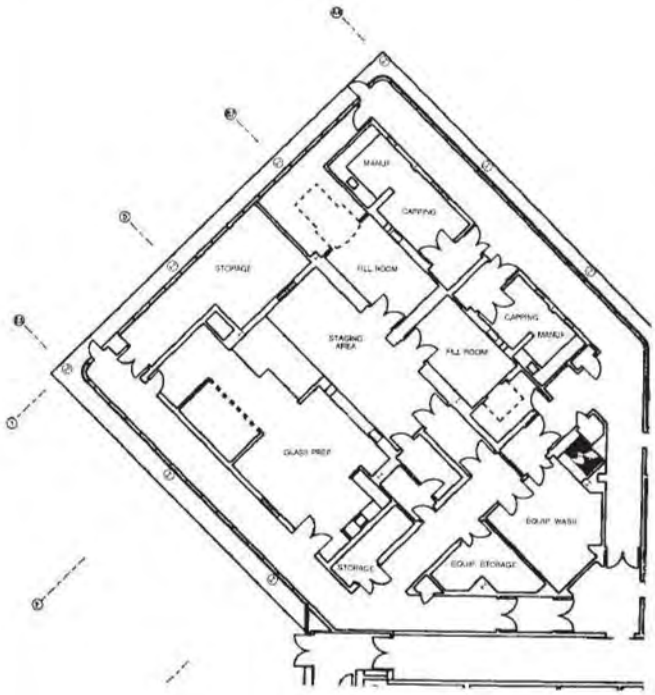


Figure 41-6. Floor plan of aseptic filling rooms and staging room with adjacent support areas (courtesy, Glaxo).

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.

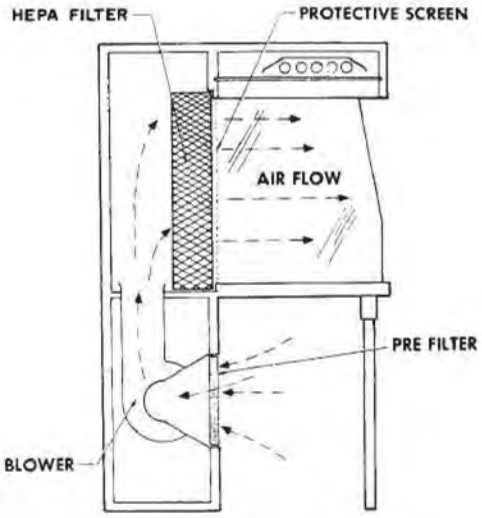


Figure 41-8. Horizontal laminar-flow workbench (courtesy, adaptation, Sandia).

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).

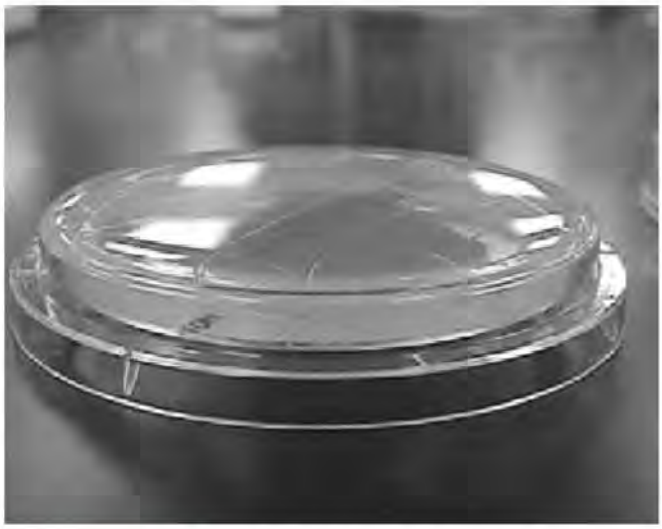


Figure 41-15. Example of a Rodac plate (courtesy, Baxter).

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

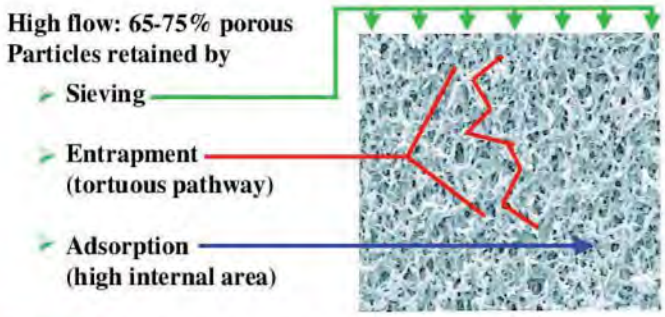


Figure 41-19. Mechanisms of microbial retention on membrane filters (courtesy, Millipore). See Color Plate 10.

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-

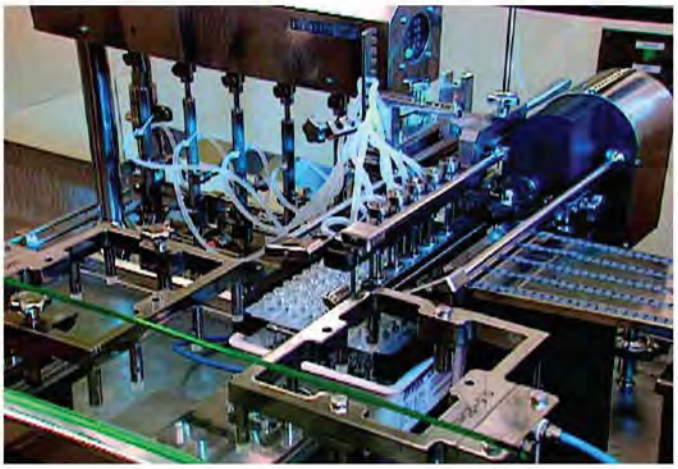


Figure 41-21. Syringe filling machine (courtesy, Baxter). See Color Plate 11.

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.

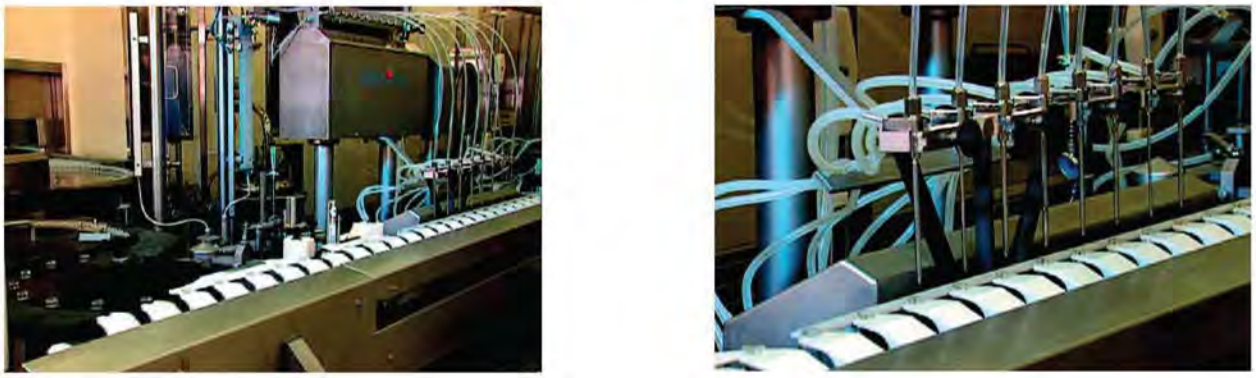
When high-speed filling rates are desired but accuracy and precision must be maintained, multiple filling units often are joined together in an electronically coordinated machine, such as shown in Figures 41-21 and 41-22. When the product is sensitive to metals, a peristaltic-pump filler may be used 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.

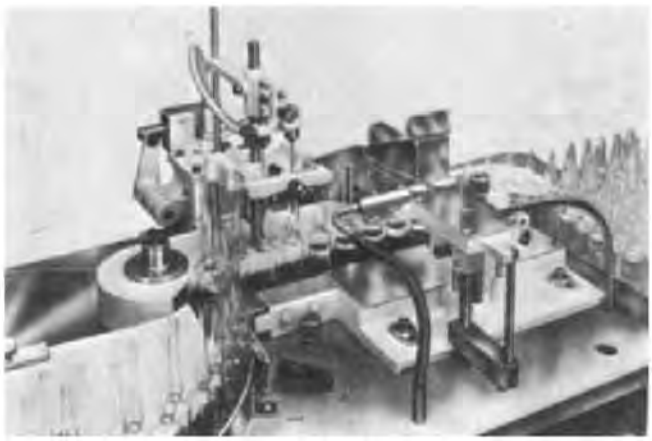


Figure 41-24. Automatic filling and pull-sealing of ampoules (courtesy, Cozzoli).

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 tamperproof. Therefore, an intact aluminum cap is proof that the closure has not been removed intentionally or unintentionally. Such confirmation is necessary to ensure the integrity of the contents as to sterility and other aspects of quality.

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

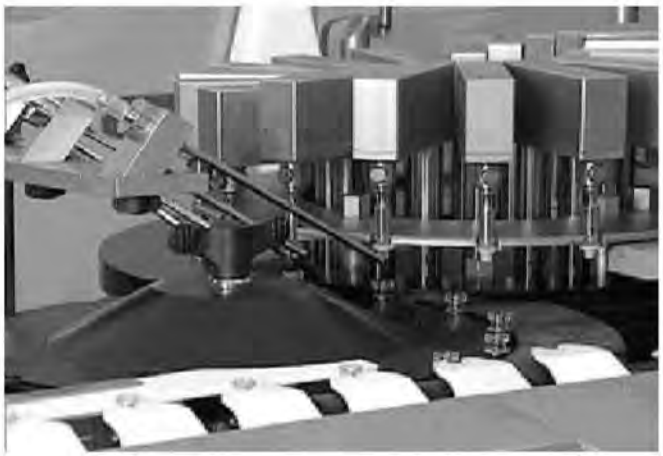


Figure 41-25. Mechanical device for inserting rubber closures in vials (courtesy, Baxter).

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.

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 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

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

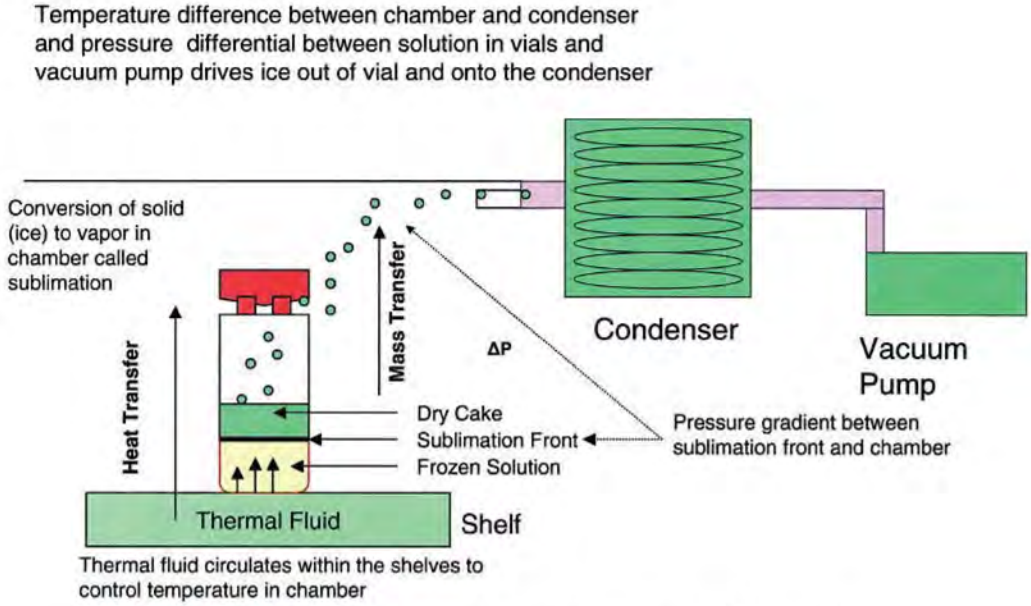


Figure 41-29. Heat and mass transfer in the freeze-dryer. See Color Plate 15.

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.

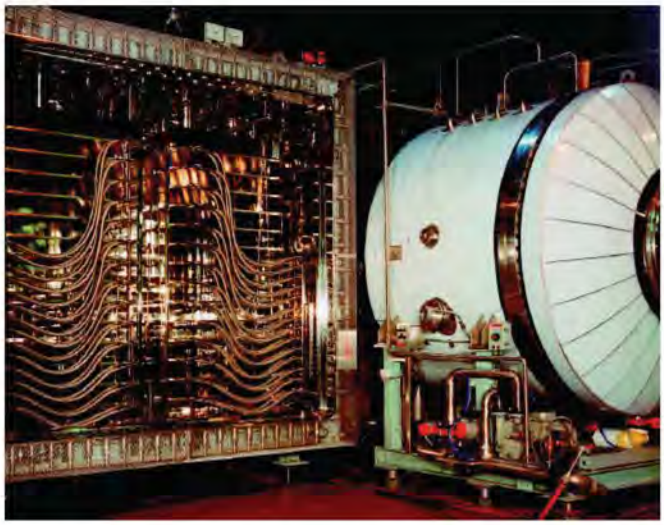


Figure 41-31. Inside view of a production freeze-dryer (courtesy, Edwards). See Color Plate 17.

- 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 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-

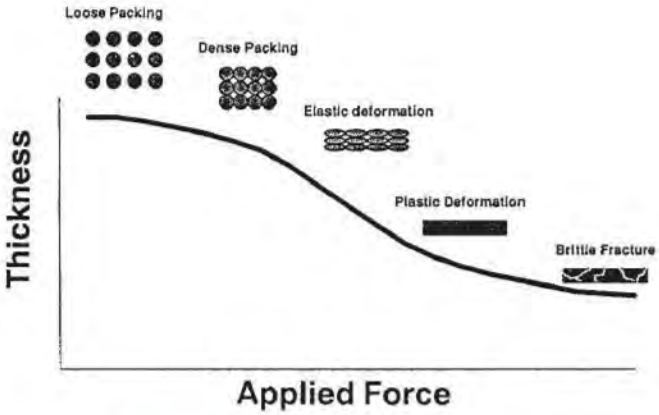


Figure 45-3. The stages of powder compaction.

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.

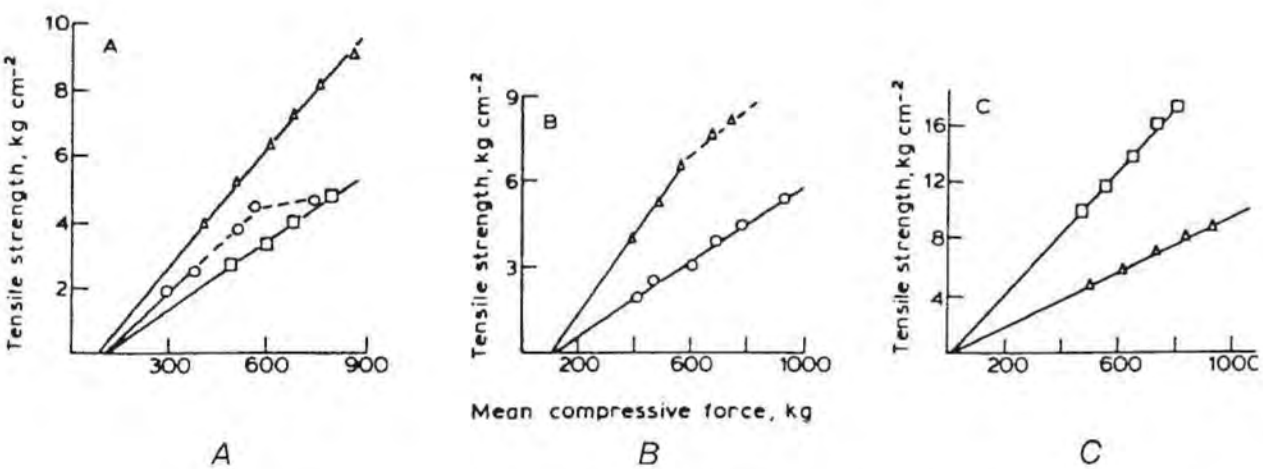


Figure 45-4. Tensile strength of compacts prepared from different crystal forms. *A:* Barbitone (104–152 μm)—○, Form I; □, Form II; △, Form III. *B:* Sulfathiazole (104–152 μm)—○, Form I; △, Form II. *C:* Aspirin (250–353 μm)—△, Form I; □, Form IV. (From Summers MP, Enever RP, Carless JE. *J Pharm Sci* 1977; 66:1172.)

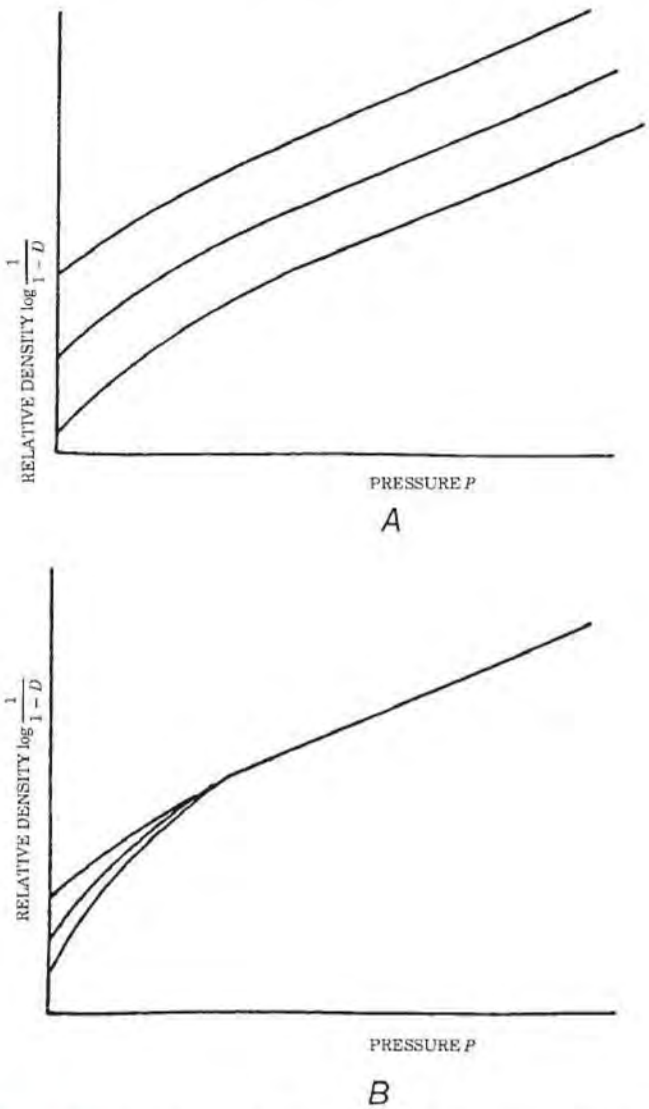


Figure 45-5. Heckel plots. *A:* Type I. *B:* Type II. (From Jones TM. *Acta Pharm Tech* 1978.)

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

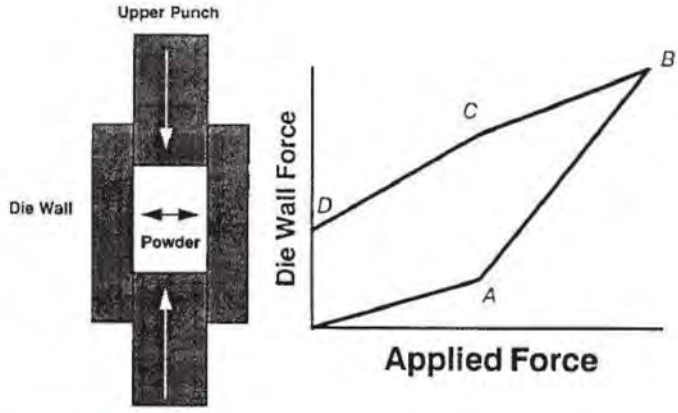


Figure 45-6. Transmitted stresses during tablet compaction.

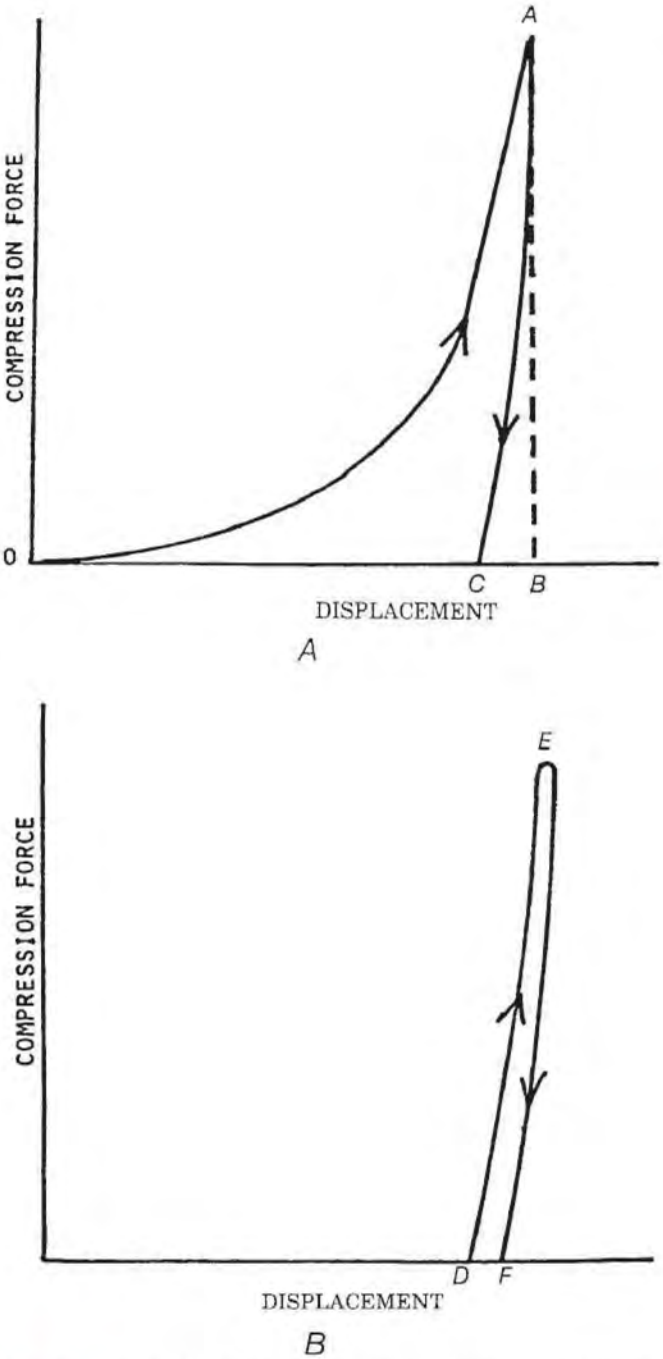


Figure 45-7. Typical forces. *A:* Displacement (F–D) curve; *B:* displacement (F–D), second compression. (From Jones TM. *Acta Pharm Tech* 1978.)

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,

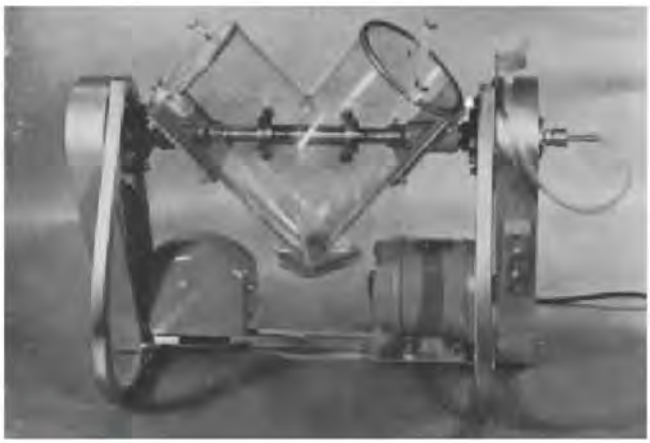


Figure 45-8. Twin-shell blender for solids or liquid-solids blending (courtesy, Patterson-Kelley).

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.

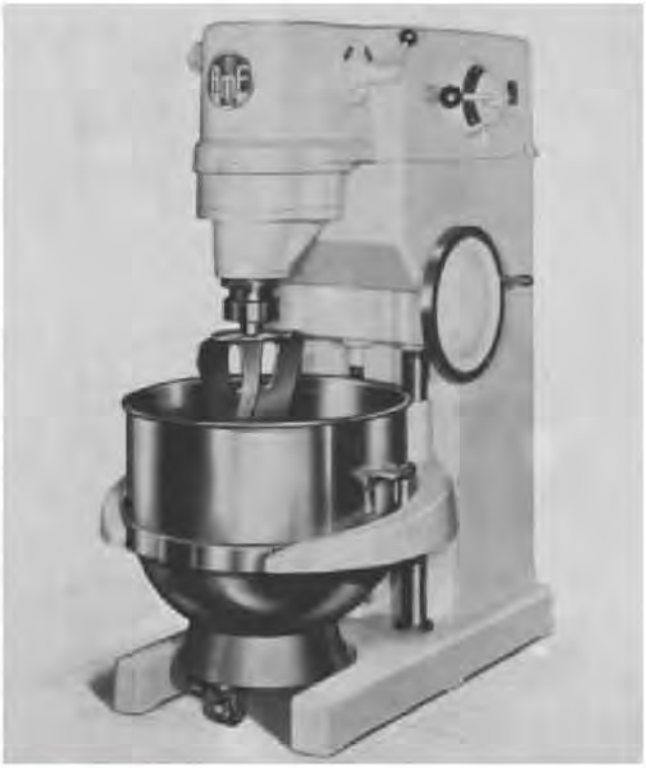


Figure 45-9. The Glen powder mixer (courtesy, Am Machine).

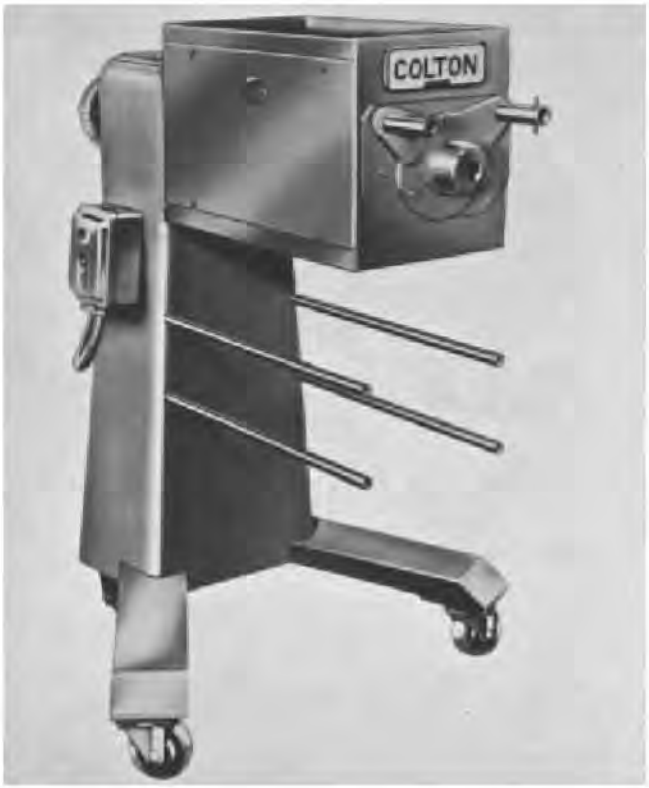


Figure 45-10. Rotary granulator and sifter (courtesy, Vector/Colton).

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

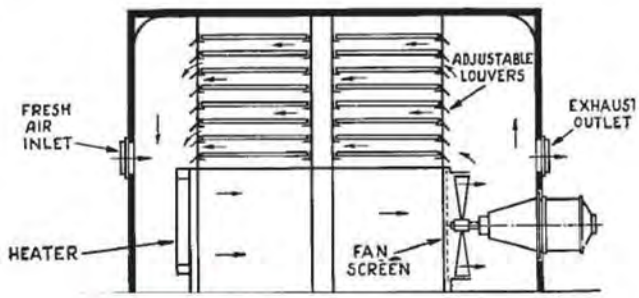


Figure 45-11. Cross-section of tray dryer.

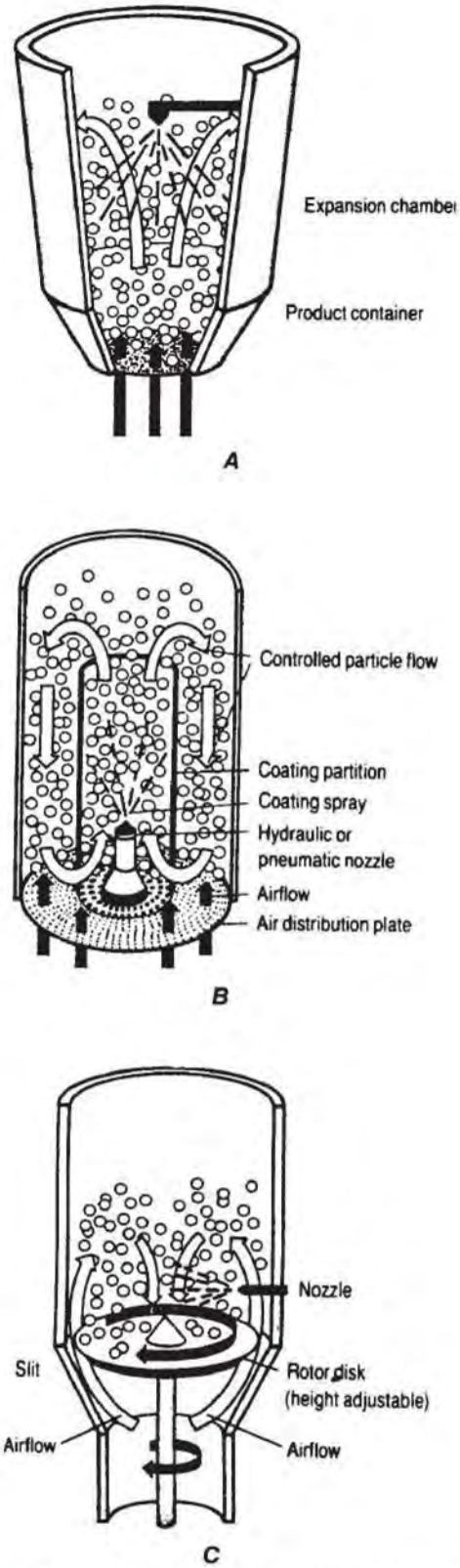


Figure 45-12. Three versions of fluidized-bed granulation and drying. *A:* Top-spray method used in conventional fluid-bed granulation coaters; *B:* bottom-spray method used in Wurster air- suspension columns; *C:* tangential-spray method used in rotary fluid-bed coaters/granulators. (Courtesy, Aster 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.

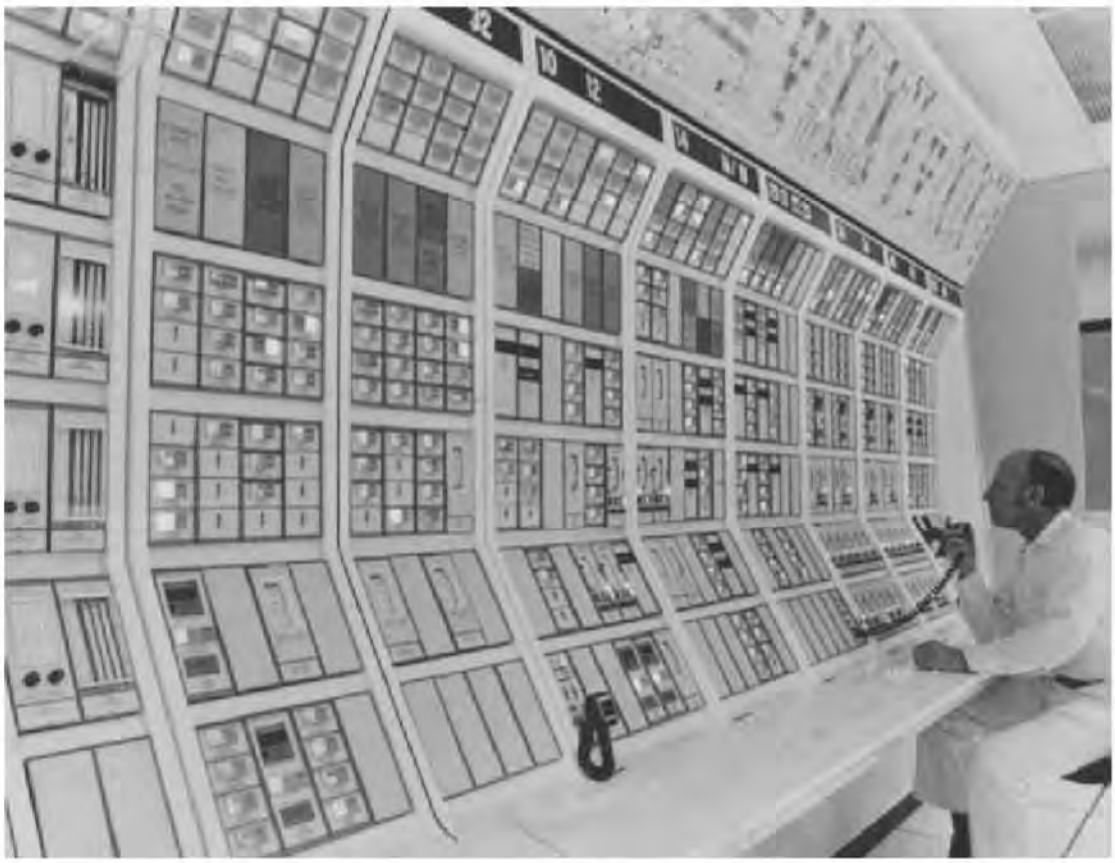
Equipment suppliers work closely with individual pharmaceutical companies in designing specialized and unique systems.

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

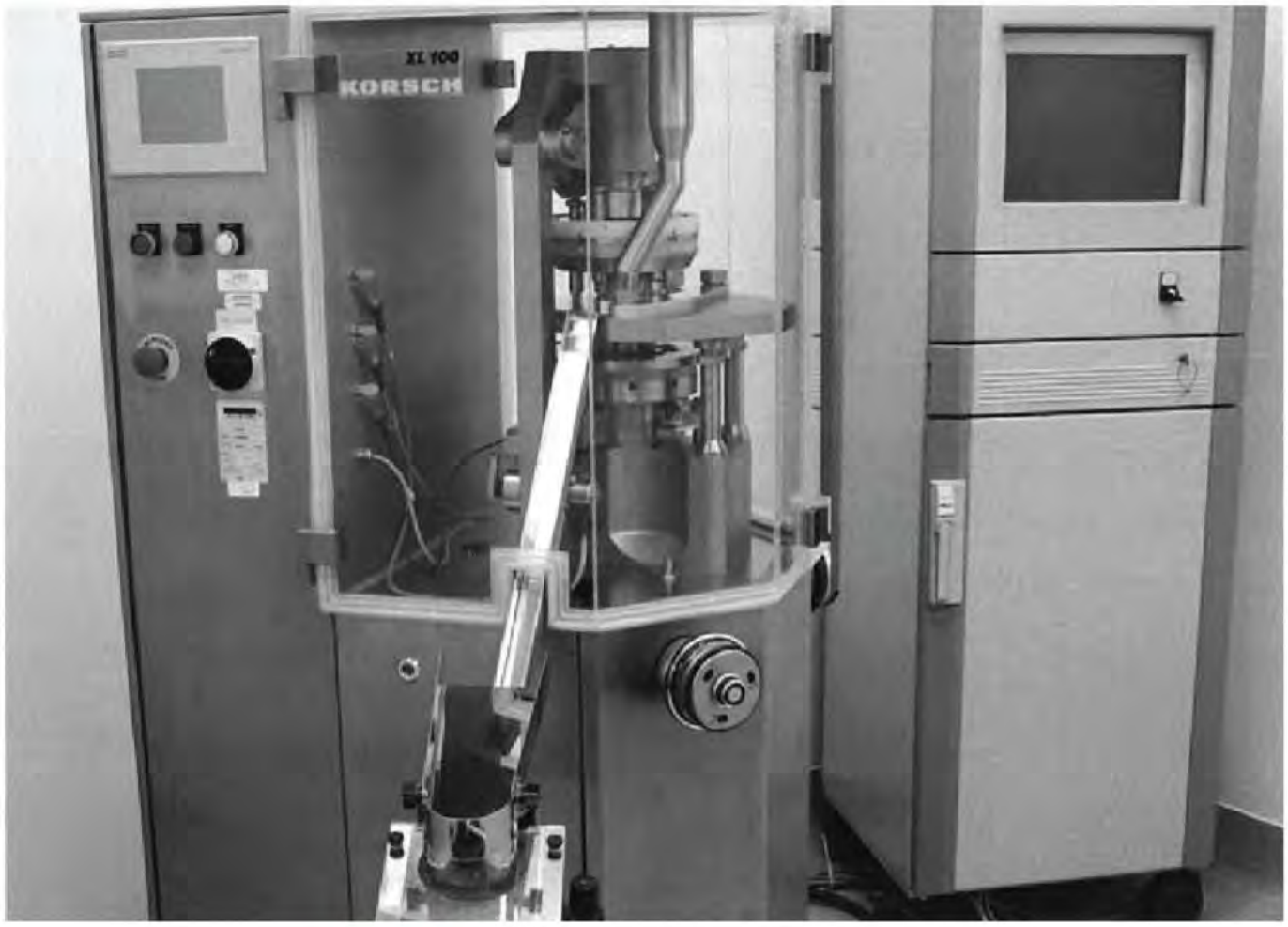
Figure 45-13. *(continued)* **c.** Computer-controlled/monitored granulation.

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

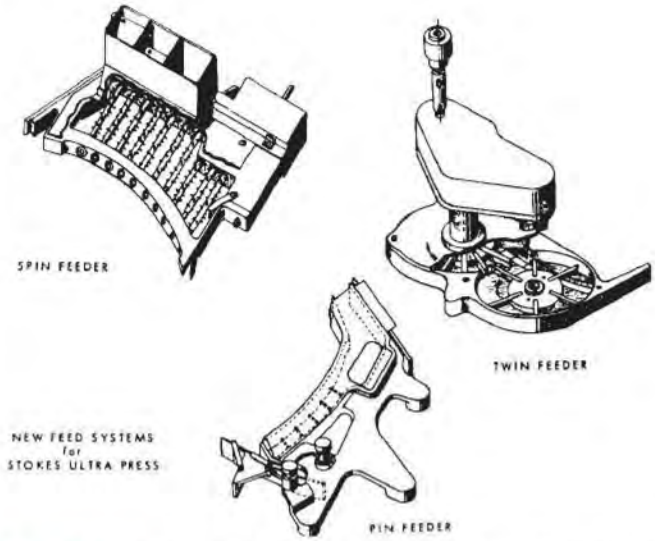


Figure 45-14. Feeding devices designed to promote flow of granulations for high-speed machines (courtesy, Stokes/Pennwalt).

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).

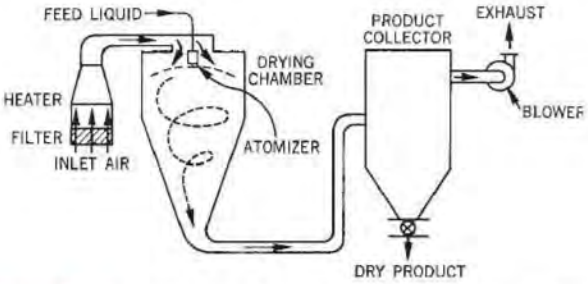


Figure 45-16. Typical spray-drying system (courtesy, Bowen Eng).

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

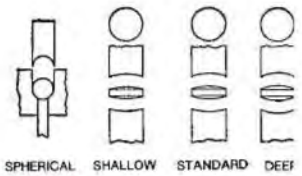


Figure 45-17. Concave punches.

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 45-19. Collection of punches (courtesy, Stokes/Pennwalt).

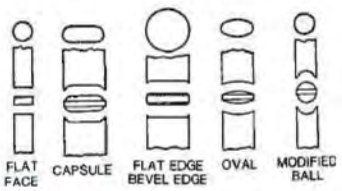


Figure 45-18. Specially shaped punches.

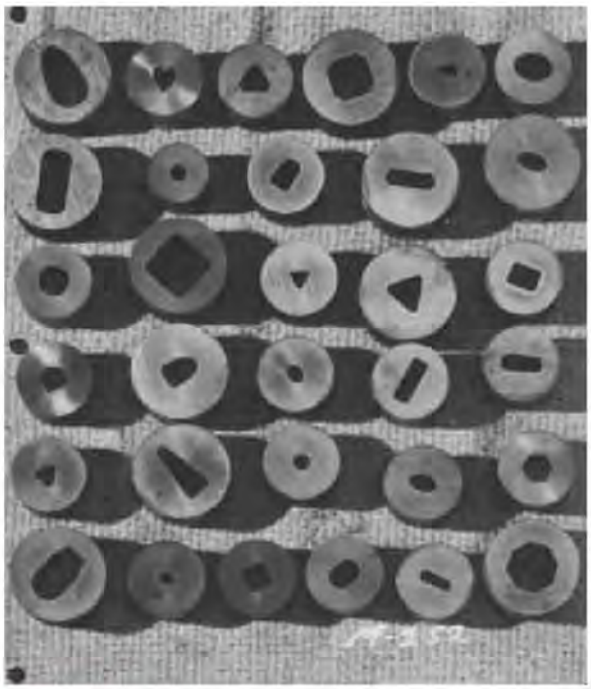


Figure 45-20. Collection of dies (courtesy, Stokes/Pennwalt).

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	1⅝
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.

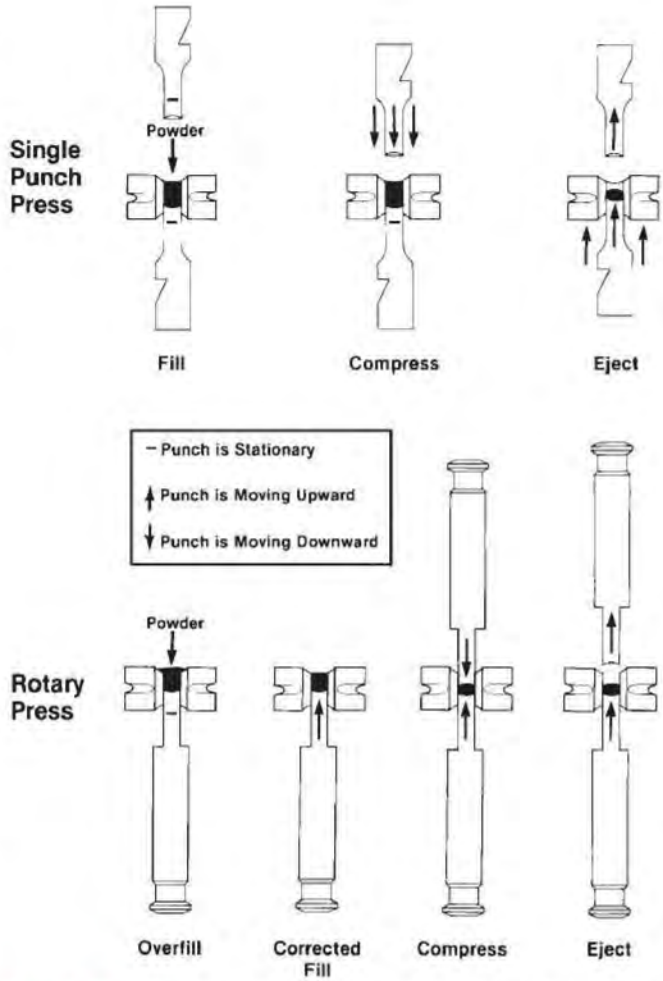


Figure 45-21. The steps associated with single-punch and rotary tablet machines.

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.

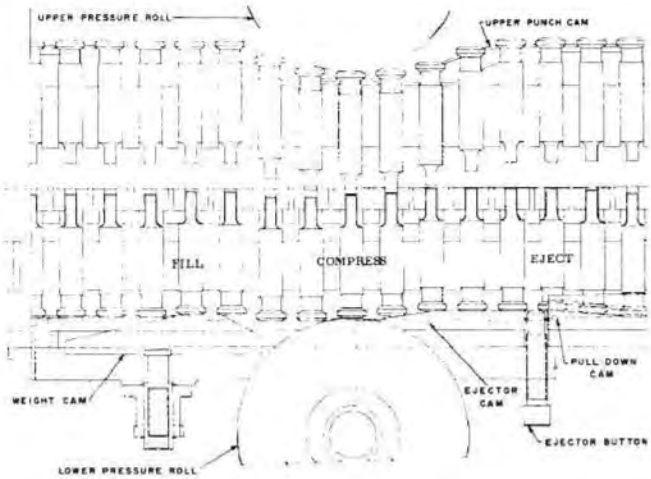


Figure 45-23. Tooling for a 16-station rotary press showing positions of the cycle required to produce one tablet per set of tooling (courtesy, Vector/Colton).

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).

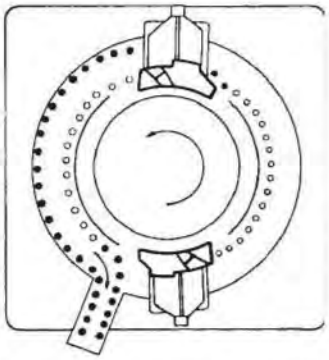


Figure 45-26. The movement of tablets on die table of a double rotary press (courtesy, Vector/Colton).

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).

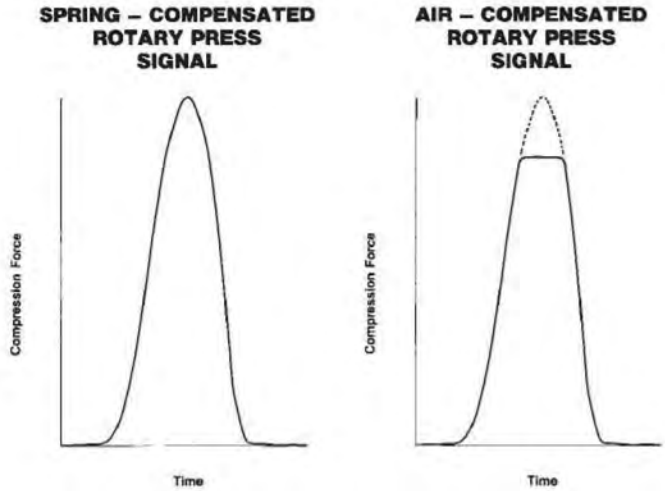


Figure 45-29. Force-time curves for two types of tablet press.

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

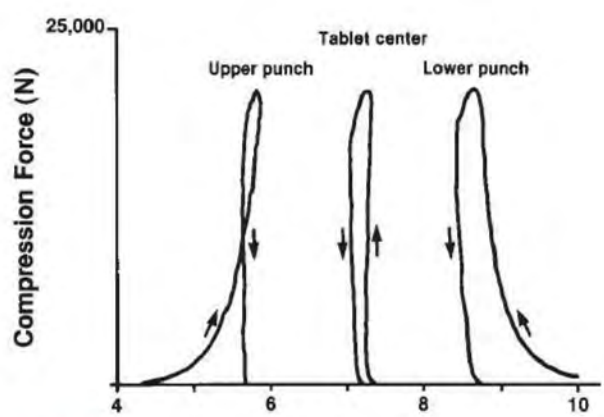


Figure 45-30. Plot showing the upper and lower punch forces as functions of the position of the punch face within the die. A biaxial force/displacement curve also shown is a plot of the position of the tablet center as a function of the compression force.

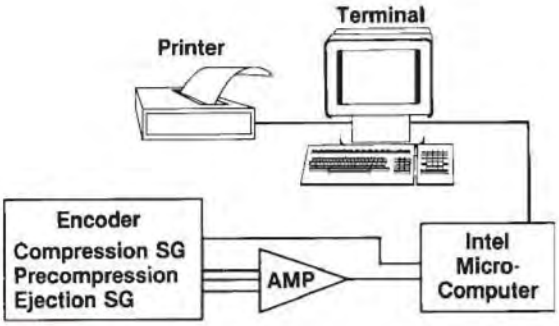


Figure 45-31. Schematic of an instrumentation system using a microcomputer as developed by Schering-Plough.

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 ⅜-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 5/32-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 7/16-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 ⅝-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, 13/32-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 9/32-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.

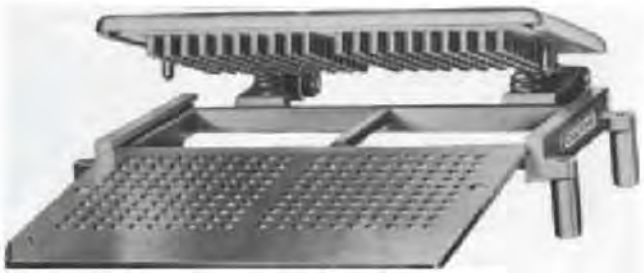


Figure 45-34. Tablet triturate mold (courtesy, Vector/Colton).

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.

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 45-40. Manufacture of hard gelatin capsules by dipping stainless steel pins into gelatin solutions (courtesy, Lilly).

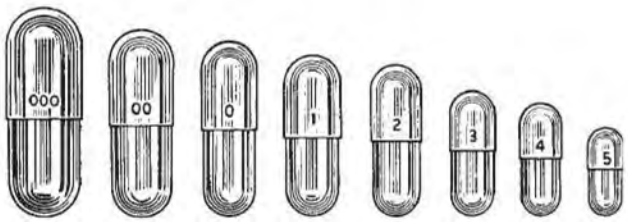


Figure 45-39. Hard gelatin capsules showing relative sizes (courtesy, Parke-Davis).

Figure 45-41. Formed capsules being dried by rotating through a drying kiln (courtesy, Lilly).

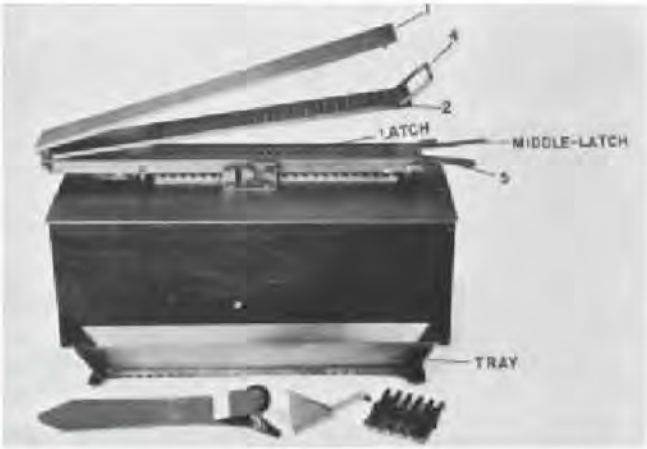


Figure 45-42. Hand-operated capsule machine (courtesy, Chemi-Pharm).

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,

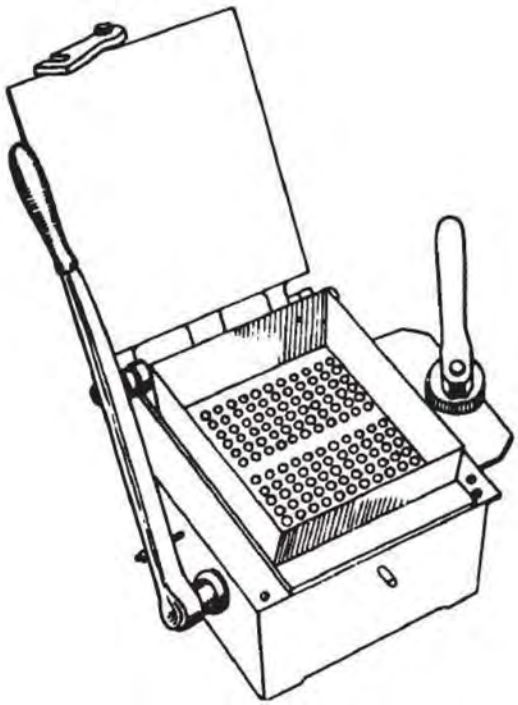


Figure 45-43. Hand-operated capsule machine, Model 300 (courtesy, ChemiPharm).

Table 45-5. Capsule Fill Chart

CAPSULE FILL WEIGHTS (MG) BASED ON SIZE AND DENSITY

	CAPSULE VOLUME (mL)									
	0.95	0.78	0.68	0.54	0.5	0.37	0.3	0.25	0.21	0.13
POWDER DENSITY	CAPSULE SIZE									
(g/ml)	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

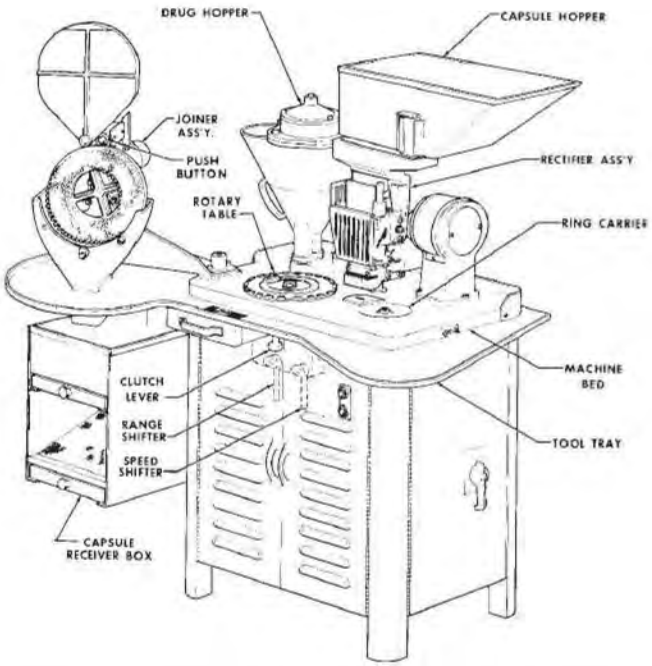


Figure 45-44. Schematic of Type 8 capsule-filling machine (courtesy, Parke-Davis).

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,

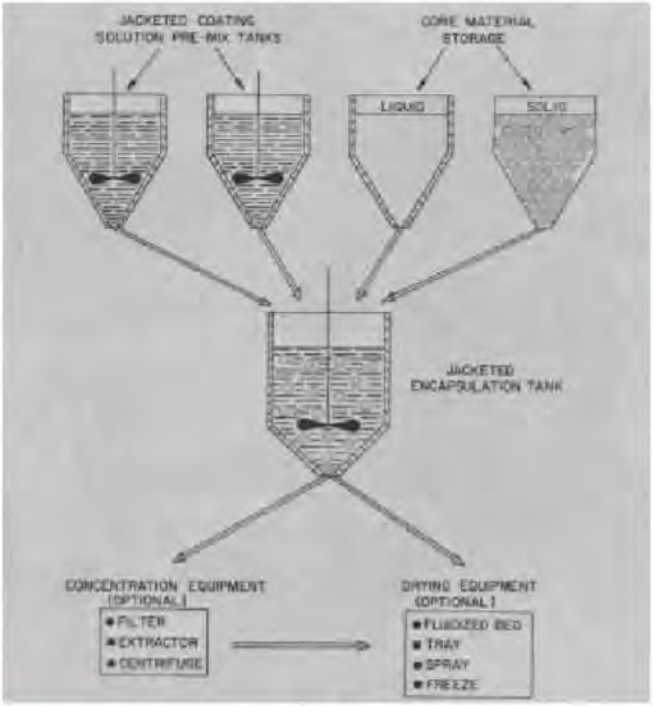


Figure 45-51. Production installation for the microencapsulation process (courtesy, NCR).

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,

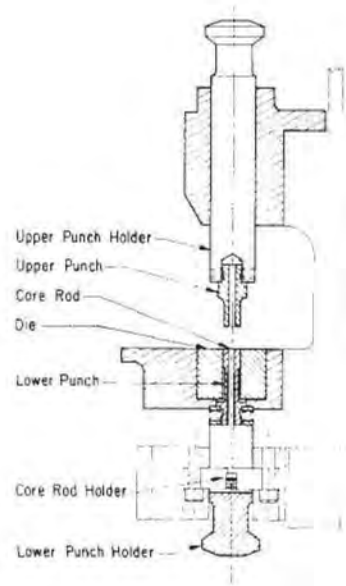


Figure 45-52. Core-rod tooling for compressing troches or candy pieces with hole in center (courtesy, Vector/Colton).

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-

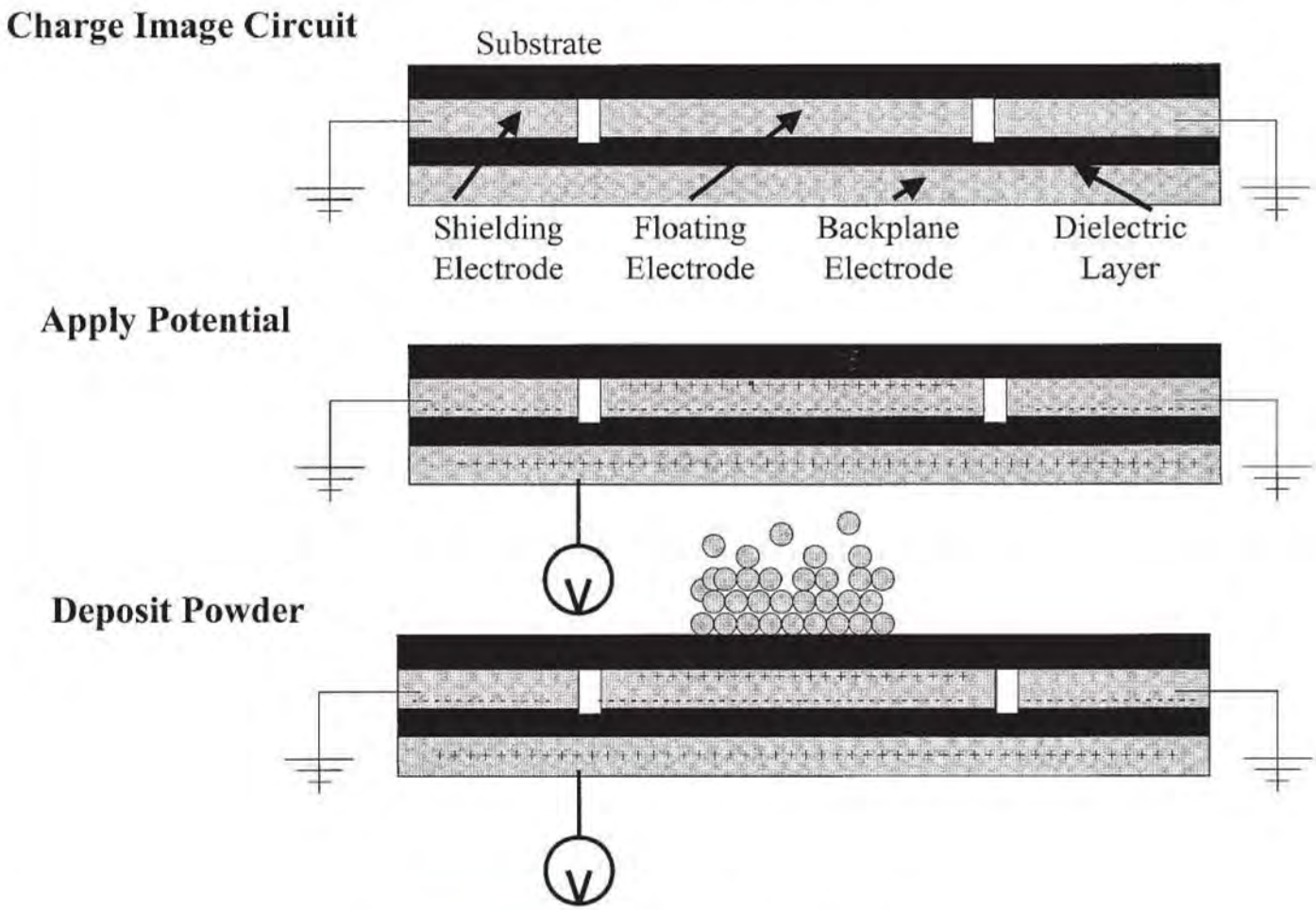


Figure 45-53. Electrostatic powder deposition process.

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.

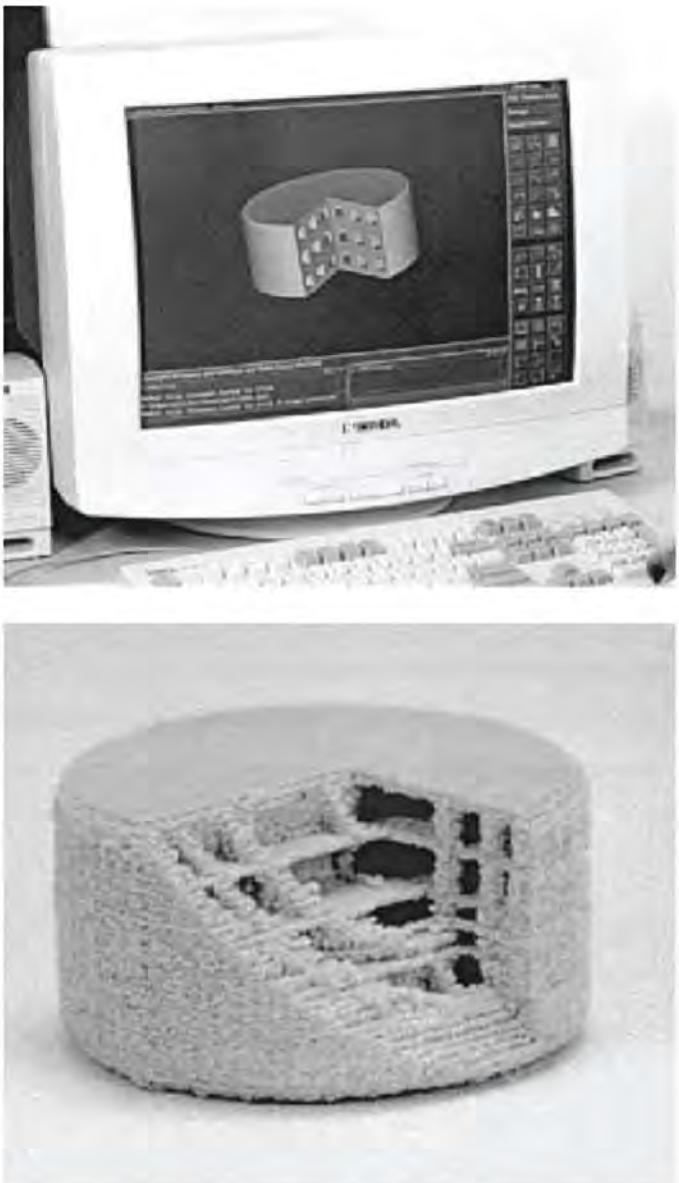


Figure 45-55. Design versatility of three-dimensional printing.

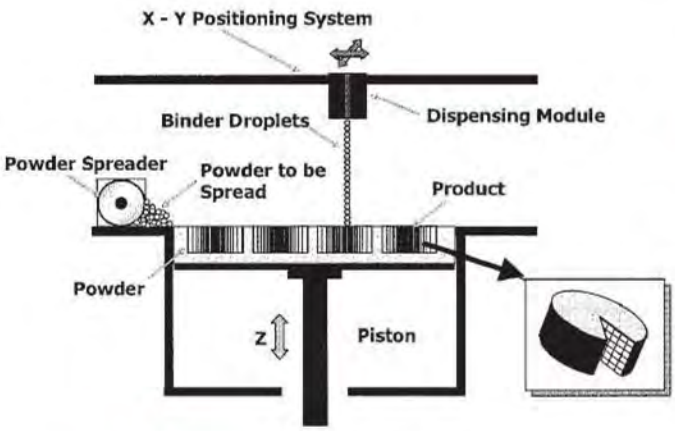


Figure 45-54. Three-dimensional printing process.

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

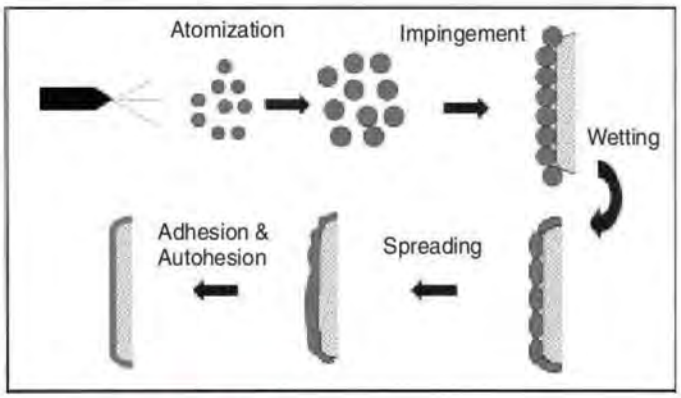

Figure 46-2. The film-coating process.

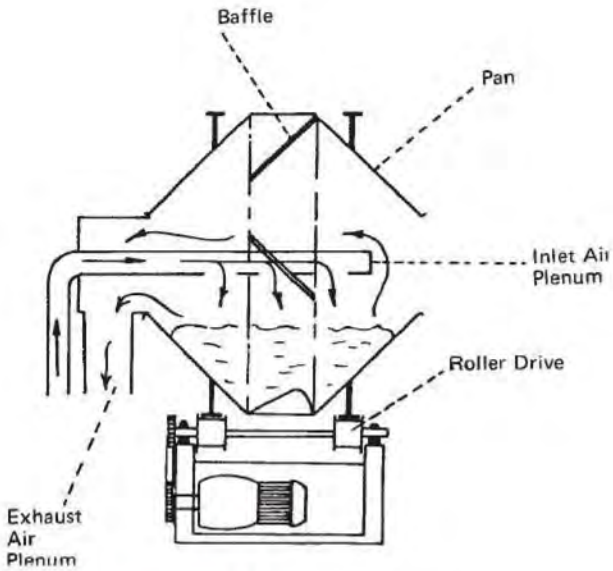

Figure 46-3. A Pellegrini coating pan.

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*

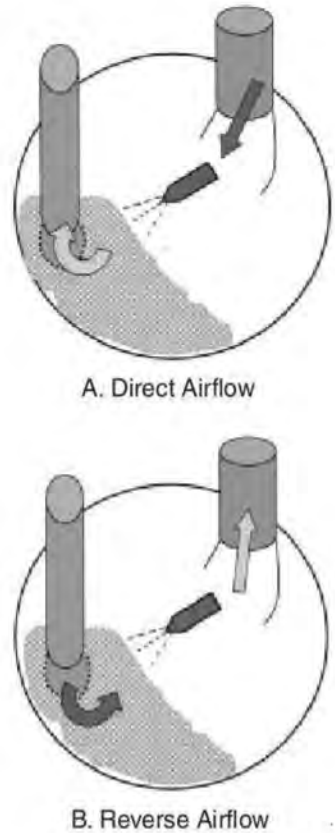

Figure 46-4. Upgraded conventional coating pans. **A.** Direct airflow. **B.** Reverse airflow.

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.

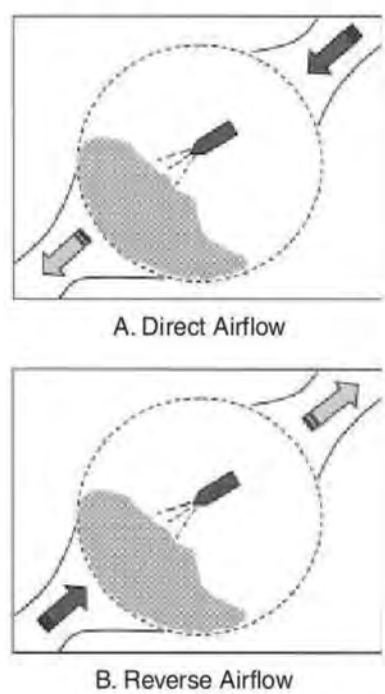

Figure 46-5. Side-vented coating pans. **A.** Direct airflow. **B.** Reverse airflow.

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-

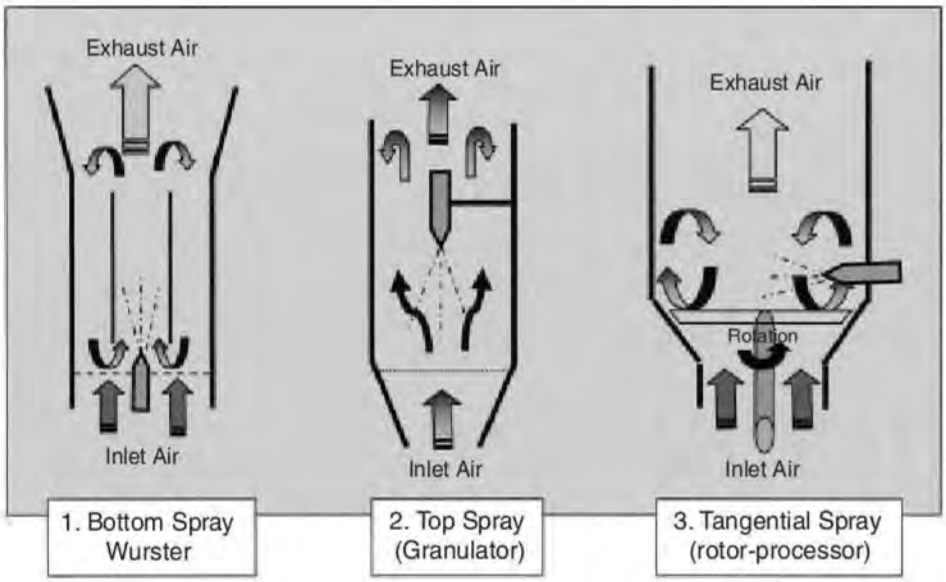

Figure 46-6. Three basic processes used for fluid-bed film coating.

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.

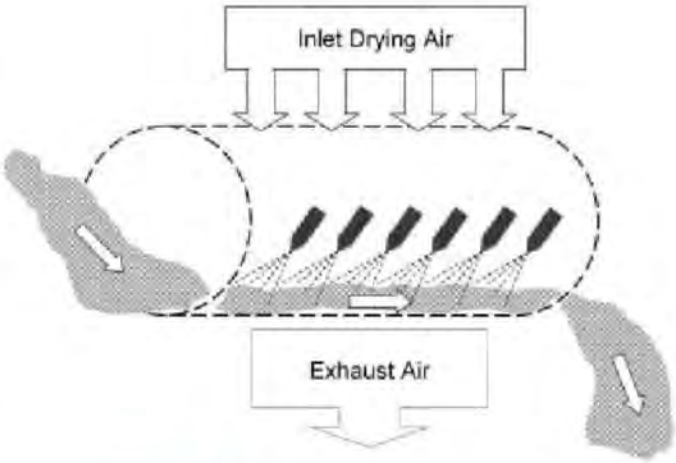

Figure 46-7. Continuous film-coating process.

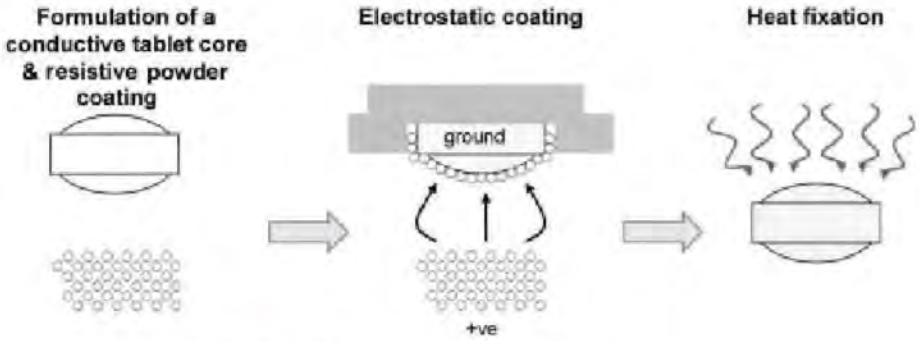

Figure 46-8. Electrostatic powder coating process.

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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